Antidepressant Medications: Treatment Options

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How to Take This Course
Please take a look at the steps below; these will help you to progress through the course material, complete the course examination and receive your certificate of completion.

1. **REVIEW THE OBJECTIVES**

   The objectives provide an overview of the entire course and identify what information will be focused on. Objectives are stated in terms of what you, the learner, will know or be able to do upon successful completion of the course. They let you know what you should expect to learn by taking a particular course and can help focus your study.

2. **STUDY EACH SECTION IN ORDER**

   Keep your learning "programmed" by reviewing the materials in order. This will help you understand the sections that follow.

3. **COMPLETE THE COURSE EXAM**

   After studying the course, click on the "Course Exam" option located on the course navigation toolbar. Answer each question by clicking on the button corresponding to the correct answer. All questions must be answered before the test can be graded; there is only one correct answer per question. You may refer back to the course material by minimizing the course exam window.

4. **GRADE THE TEST**

   Next, click on "Submit Test." You will know immediately whether you passed or failed. If you do not successfully complete the exam on the first attempt, you may take the exam again. If you do not pass the exam on your second attempt, you will need to purchase the course again.

5. **FILL OUT THE EVALUATION FORM**

   Upon passing the course exam you will be prompted to complete a course evaluation. You will have access to the certificate of completion **after you complete the evaluation**. At this point, you should print the certificate and keep it for your records.

Course Introduction

JK is a 37 year old female who has been experiencing significant anxiety, irritability and depressed mood over the course of the last several years. She initially sought treatment because her sister had been treated for similar symptoms and was thriving. JK thought she should also have a psychiatric evaluation because her own symptoms were so much like those her sister had prior to treatment. During the assessment, the nurse practitioner discovered that the patient had had moderate symptoms of depression as a young adult, but she had not received treatment; in fact, JK had a low level of depression chronically. Despite this chronic depression, she was able to work and care for her family (which includes 2 adolescent children); she even was able to have fun on occasion. JK has been having increasing conflicts with her husband and has felt like she's not sure that it's worth continuing to struggle.

GH is a 48 year old male who experienced depressive symptoms in response to conflicts at work and marital problems. He had been working long hours for the past several years to clear up the family debts. This has had significant negative impact on his marriage. His wife has asked for a divorce and GH has been devastated. He has no history of previous depression; no family history of depression. He was prescribed a selective serotonin reuptake inhibitor (SSRI) and had a very good response. He felt so well after 4 months that he stopped taking the medication. Two months after stopping the antidepressant his depressive symptoms returned. When he went back on the SSRI, he did not have as good a response as he experienced previously.

AB is a 54 year old woman who has experienced depressive and anxiety symptoms since childhood. She experienced verbal and emotional abuse in childhood, having a mother who herself had untreated anxiety and depression. AB has held a variety of jobs in the same large organization for over 20 years; however, she has taken medical leaves every several years, due to depression during her entire employment history. Her functional abilities have been impaired, having missed out on multiple promotions due to her illness; two failed marriages and a significant lack of enjoyment in most things. She is often overwhelmed by her feelings of depression and anxiety. She has been treated for depression with medication and therapy over much of the course of her life. She was treated for many years with tricyclic antidepressant medications and therapy. She was often non-adherent to treatment because she felt that she just needed to work harder at being happy and not so negative. In recent years she took several different antidepressants, mainly the selective serotonin reuptake inhibitors, but continues to feel significantly depressed and is currently on a medical leave from her job.

CD is a 61 year old female who has been unable to maintain a job as an editor, despite her graduate education. She is now doing free lance work; however, she is clearly underemployed. She has suffered from depression since childhood; her father was also chronically depressed. CD has been treated for depression since adolescence with only modest improvement. She is generally motivated to continue to seek treatment alternatives. CD has been treated aggressively with medications and psychotherapy; however, her depression has been very treatment resistant. She has had trials of just about all of the possible antidepressants. Although she currently feels better than she ever has, she continues to struggle, at times, with overwhelming feelings of depression.

EF is a 26 year old male who has been unable to maintain employment since graduating from college 4 years ago due to significant symptoms of depression. He is now again living with his parents and EF fears that he will never be able to lead a "normal" life of marriage, children and successful employment; which has precipitated thoughts of suicide. He has been in treatment with the same psychiatrist and psychologist since late adolescence, he is not always forthcoming with either of his treatment providers; EF often minimizes his symptoms during sessions. EF had a maternal grandfather who committed suicide due to depression; no one else in the family suffers from depression. EF has been on the same selective serotonin reuptake inhibitor for the past several years.

These people have something in common. They all have been diagnosed with a depressive disorder and they all present a challenge for the prescribing mental healthcare provider. The advent of antidepressant medications has been extremely beneficial for millions; people who would have been disabled by crippling depression are leading productive lives. However, like all medications, antidepressants may not be beneficial for all patients; they also potentially can cause serious side effects. An understanding of depressive disorders and the medications used to treat them are critical to a nurse's practice.

The World Health Organization has rated depression as the leading cause of disability in lost years of productive life in market economies. Depression causes disability at rates greater than cancer, diabetes, asthma, and HIV/AIDS!

Depression, as well as all of the psychiatric illnesses, has long been misunderstood and those who suffer from it have long been stigmatized. Current research confirms that depression is not a matter of will, or "trying harder", depression is clearly an outcome of multiple factors including neurochemical, environmental and genetics. Currently, depression is conceptualized as a chronic illness, and like all chronic illnesses, it must be managed over time.

Depression is a treatable medical condition that affects millions of people. The advent of antidepressant medications changed treatment and recovery. There are many medications available with many more being produced and marketed. Tricyclic agents (TCAs) were the first medications used and are still effective. The often disturbing side effects are the usual reason for discontinuation of therapy. The monamine oxidase inhibitors (MAOIs) were developed next and are useful for patients with atypical depression. Serious drug and food interactions occur with this class of medication and have prohibited their widespread use. In the late 1980s the introduction of selective serotonin reuptake inhibitors (SSRIs), with their treatment success rates and low incidence of side effects, saw a new drug, Prozac, become one of the most widely prescribed medications in the country. Since the introduction of Prozac, newer drugs in this class have been introduced and are widely used. Selective norepinephrine/serotonin reuptake inhibitors, or dual action anti-depressants, are also used in the primary treatment of depression, and development of additional antidepressants continues.

This course will provide current information about depression diagnoses and the pharmacological treatment of depressive disorders. The choice of an antidepressant medication depends on the symptoms the patient exhibits and the side effect profile of each drug. Usual drug dosages are explained as well as strategies when the prescribed medication is not working. Patient education information is also included. While the course has most applicability to advance practice nurses, registered nurses also can benefit from the information provided.

Objectives

At the completion of this learning activity the learner will be able to:

- Define the depressive disorders that benefit from treatment with antidepressant medications.
- List factors to include in an assessment for depressive disorder.
- Explain the three stages of treatment of depression using antidepressant medications.
- Identify major classes of drugs used to treat depression.
- Describe rationale for choosing specific antidepressant medications for specific patients.
- Discuss the most commonly prescribed antidepressants: actions, side effects, and usual dosages.
- Discuss alternatives that can be used when patients are not responding to a single drug or cannot tolerate side effects of prescribed treatment.
- Identify information to include in patient teaching for patients on antidepressant medications.

About the Authors

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Ms. Beaupre is a board certified psychiatric nurse practitioner in private practice. Ms. Beaupre has worked in a variety of clinical settings, treating a range of psychiatric illness, from the chronically and persistently mentally ill in inpatient settings to treating adult patients in private out-patient settings. Her specialty area of focus is mood disorders in women. She has been an educator in the classroom and in the clinical setting for nursing students at associate's, bachelor's, and master's degree levels. She also has extensive experience in staff development and clinical supervision.

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What is Depression?

Depression is a condition that affects 18.8 million adults in the US every year (National Institute of Mental Health [NIMH], 2004) that translates to almost 10% of the population. Nearly twice as many women (12.0 percent) as men (6.6 percent) are affected by a depressive disorder each year. These figures translate to 12.4 million women and 6.4 million men in the U.S. (NIMH, 2004).

Depression is unrelated to ethnicity, education, income, or marital status. It is twice as common in women as in men. Depression is a public health problem and is costly to society. It is associated with high disability, mortality, suffering and decreased physical, social, and role functioning and is an enormous cost to society in both dollars and lost productivity.

The last half of the twentieth century has been marked by a dramatically increased understanding of mood disorders. And yet defining depression can be confusing. The term depression is often used by the general public to indicate feeling "down" or "blue". Healthcare professionals can also be confused by the many presentations and diagnoses that are referred to as depressive disorders or mood disorders. Depressive disorders can be characterized by a broad spectrum of symptoms, from the hallmark symptoms of depressed mood and anhedonia to aches, pain, fatigue and gastrointestinal disturbances. These variations in the presentation of depression can make diagnosis difficult, particularly in primary care settings, where the focus of the healthcare provided is physical in nature.

The various depressive disorders include: Major Depressive Disorder, Dysthymic Disorder, Double Depression, Atypical Depression, Seasonal Affective Disorder, Major Depression with Psychotic Features, Depressive Disorder due to General Medical Condition, Post-Partum Depression, Cyclothymic Disorder, Bipolar Disorder I and II, Adjustment Disorder with Depressed Mood, Adjustment Disorder with Depressed and Anxious Mood, Premenstrual Dysphoric Disorder, as well as depressive symptoms associated with Anxiety Disorders, Borderline Personality Disorder, Post-Traumatic Stress Disorder and Somatoform Disorders.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM IV-TR) (APA, 2000a) identifies the following disorders (Please see DSM IV-TR for full diagnostic criteria):

Major Depressive Disorder

Major depressive disorder is a syndrome consisting of a constellation of signs and symptoms that are not normal reactions to life's stress. A sad or depressed mood is only one of the several possible signs and symptoms of major depressive disorder.

For major depressive disorder, at least five of the following symptoms are present during the same time period, and at least one of the first two symptoms must be present. In addition, symptoms must be present most of the day, nearly daily, for at least 2 weeks.

- Depressed mood most of the day, nearly every day.
- Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time).
- Significant weight loss/gain.
- Insomnia/hypersomnia.
- Psychomotor agitation/retardation.
- Fatigue (loss of energy).
- Feelings of worthlessness (guilt).
- Impaired concentration (indecisiveness).

- Recurrent thoughts of death or suicide.

Bipolar Disorder

A small percentage of patients with major depressive disorder have bipolar illness. These patients experience mood cycles with discrete episodes of depression and mania. In between episodes, they may feel perfectly normal.

For mania, at least four of the following symptoms, including the first one listed, must be present for a period of at least 1 week.

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood.
- Less need for sleep.
- Talkative or feeling pressure to keep talking.
- Distractibility.
- Flight of ideas.
- Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
- Inflated self-esteem or grandiosity.
- Excessive involvement in pleasurable activities which have a high potential for painful consequences (buying sprees, sexual indiscretions, or foolish business investments).

Dysthymic Disorder

Characterized by at least two years of depressed mood for more days than not, accompanied by additional depressive symptoms that do not meet criteria for a Major Depressive Disorder.

Adjustment Disorder with Depressed Mood

This is a subtype of adjustment disorder, which is a psychological response to an identifiable stressor that results in the development of clinically significant emotional or behavioral symptoms, with the predominant symptoms including depressed mood, tearfulness and feelings of hopelessness.

Adjustment Disorder with Depressed and Anxious Mood

As above, but with predominant manifestation of a combination of depression and anxiety.

Seasonal Affective Disorder

Essential feature is the onset and remission of Major Depressive Episode at characteristic times of the year, most often episodes begin in fall or winter and remit in the spring.

Post-Partum Depressive Disorder

Depressive Disorder that occurs within four weeks after childbirth; may include fluctuations of mood, mood lability, preoccupation with infant well-being such as over concern or frank delusions.

Cyclothymic Disorder

The essential feature is a chronic, fluctuating mood disturbance involving numerous periods of hypomanic symptoms and numerous periods of depressive symptoms insufficient enough in number, severity, pervasiveness and duration to meet criteria for Manic Episodes or Major Depressive Episodes.

Premenstrual Dysphoric Disorder

The essential features are markedly depressed mood, marked anxiety, marked affective lability and decreased interest in activities regularly occurring during the last week of the luteal phase in most menstrual cycles. Symptoms begin to remit within a few days of the onset of menses and are always absent in the week following menses.

Depressive Disorder Not Otherwise Specified

Depressive Disorder Not Otherwise Specified (NOS) are those disorders with depressive features that do not meet criteria for the depressive disorders listed above.

Double Depression

Although not included in the DSM IV-TR, it is commonly referred to as concurrent Dysthymia and Major Depressive Episode.

In addition to the generally accepted diagnoses of depression listed above, there has been a greater recognition among clinicians and researchers that for some people, depression manifests more as a physical illness rather than a psychiatric illness. These individuals suffer from more somatic symptoms such as aches, pain, dizziness, and fatigue. These patients generally present for treatment to their primary care providers because of a physical complaint, rather than a psychiatric complaint. Patients who primarily experience depression as physical symptoms may not even be aware of any mood problems, rather they experience fatigue or lack of motivation and energy.

It should also be acknowledged that the DSM-IVTR is a work-in-progress. In the late 70s, it was the DSM-II that clinicians used to make psychiatric diagnoses. The collective understanding of depressive disorders as well as psychiatric illness in general continues to evolve. As knowledge is gained, our conceptualizations regarding illness changes. The physiology of the brain and the complex neurochemical interactions among the structures and functional components of the brain, their interrelationship with the physical body, and cultural and sociological changes, all impact on how psychiatric illness, including the various kinds of depression, are identified and defined. It is likely that the above categories of depression will change with updated versions of the DSM.

It should also be mentioned that antidepressant medications are being used to treat a variety of disorders that do not necessarily have a depressive component. Some new indications for antidepressants are: generalized anxiety disorder, obsessive-compulsive disorder, social phobia, smoking cessation, and panic disorder. Other potential indications include: eating disorders and obesity, alcoholism, pain management and chronic fatigue syndrome (Schatzberg, 2000).

The Cost of Depression

Cost in Disability

In *Global Burden of Disease* (1990), the World Health Organization, Harvard University and the World Bank studied the burden of mental illness on health. The study developed a single measure to allow comparison of the burden of disease across many different disease conditions by including both death and disability. This measure was called Disability Adjusted Life Years (DALYs). DALYs measure lost years of healthy life regardless of whether the years were lost to premature death or disability. The disability component of this measure is weighted for severity of the disability. For example, disability caused by major depression was found to be equivalent to blindness or paraplegia whereas active psychosis seen in schizophrenia produces disability equal to quadriplegia.

Using the DALYs measure, major depression was the leading cause of disability in magnitude of disease burden in established market economies. For women throughout the world as well as those in established market economies, depression is the leading cause of DALYs.

Cost in Suicide

Thoughts of death and suicide are a symptom of major depressive disorder. In 2003, suicide was the 10th leading cause of death in the US, up from the 11th leading cause of death in the years 1999-2002 (NCIPC, 2004). Psychological autopsy studies indicate that up to 86% of suicides are persons who were experiencing major depressive disorder at the time of the suicide (Coryell & Young, 2005).

Many risk factors that have been identified for suicide,

- Current suicidal plan
- A history of suicide attempts
- Living alone
- Isolation and lack of support
- Being male
- Being over the age of 65

Retrospective studies have only clearly identified having a current suicidal plan and having a history of suicide attempts as predictive of suicide (Coryell & Young, 2005).

Other researchers have looked at variables that point to a higher suicide rate in the first year after diagnosis as compared to suicides that occur later in the illness. Fawcett et al. (1990) identified that suicides early in treatment are associated with:

- Alcohol abuse
- Anhedonia
- Psychic anxiety
- Decreased concentration
- Insomnia

Suicides that occurred 10 years after diagnosis were associated with:

- Hopelessness
- Suicidal ideas

Monetary Cost

Depression has the highest medical benefit costs for all behavioral conditions and results in more days of disability than chronic medical conditions such as heart disease, hypertension, diabetes and lower back pain (NCQA, 2002). Depression costs the U.S. $44 billion annually (AHRQ, 1999): $23.8 billion in indirect costs and $19.9 billion in direct costs in 1990 (Greenberg et al., 1993). More than 200 million days of work are lost each year due to depressive disorders, with employers bearing an average of 55 percent of the costs because of absenteeism and lost work productivity (Greenberg et al., 1993). In 1995, the annual economic cost of depression was $600 per depressed worker; one third of these costs were for treatment and 72 percent were related to absenteeism and lost productivity.

Etiology of Depression

Depression is a syndrome with many likely causes. Research has been effective in increasing knowledge of brain functioning and the mechanism of antidepressant drugs. Genetic studies have shown that depression is three times more likely to occur in first degree relatives of persons with depression than in the general population.

Interpersonal theories link stress and environment with onset of depression. Biochemical theories discuss the role of serotonin, norepinephrine, dopamine, GABA and substance P.

In research utilizing neuroimaging techniques, the brains of persons with depression show signs of neurobiological changes. The amygdala, cingulate cortex, and hippocampus of the brain are all impacted by depression (Shelton, 2004). Research also indicates that the hippocampus atrophies in response to depression (Sheline et al., 2003). This same research identified a correlation between the volume of the hippocampus and the duration of the depression, as well as with the number of days of untreated depression. There is also some evidence in the research that points to early depressive episodes' neurobiological changes that may impact the development of future depressive episodes through a process of sensitization, or "kindling" (Shelton, 2004).

Unfortunately, we do not yet fully understand how depression develops or what accounts for the range of presentations of depression.

What is clearly understood about the depressive disorders is that they are **NOT** a result of not trying hard enough, being lazy, or having a moral failing. Depression is currently conceptualized as a medical illness, with biological, genetic and well as environmental links.

Additionally, supported by recent research, depression is now being conceptualized as a chronic illness. Most people who have depression, have multiple episodes of significant symptoms with accompanying functional impairments in many aspects of their lives. Because of the ongoing and recurring nature of depression, it should be conceptualized as a chronic disease and managed as such.

Beginning Antidepressant Treatment

Before beginning treatment with antidepressant medication a thorough assessment should be done. This should include a physical assessment to rule out any physiological basis for depressive symptoms. Then a thorough psychiatric assessment needs to be performed, including a careful history of the presenting problem, social history (including family of origin, educational, work, legal, relationship aspects of the individual's life, especially any past or current trauma history), drug and alcohol use and medication and other treatment histories. The psychiatric assessment will include the formulation of a diagnosis, likely one of the previously mentioned diagnoses. Once this is completed and a diagnosis of a depressive disorder is made, antidepressant medication can be considered, along with other treatments for depressive disorders.

Multiple treatments for depressive disorders exist, among them are: psychotherapy from a variety of theoretical perspectives, medication, behavioral treatments, physical treatments, and electroconvulsant therapy. Use of antidepressant medications as a treatment option must be considered in the context of multiple interacting variables including: simplicity or complexity of presenting depression, prior treatment history, patient preference, preference of the treatment provider, possible formulary limitations, cost of treatment and cost of not providing treatment. As with any use of medications, the risk must be weighed against the benefits.

The following factors may preclude the prescription of antidepressants and should be considered before deciding to initiate psychopharmacologic treatment:

- the diagnosis is unclear
- symptoms are very mild
- current use of other contraindicated medications or substance abuse
- risk of side effects or concomitant medical complications is present
- the patient objects to the use of medication

Depressive disorders have been treated with antidepressant medications when:

- the depression is characterized by moderate to severe symptoms
- potential for suicide or other harm is present
- when maintenance treatment is expected or relapse likely
- when there is history of previous medication use and response
- inter-episode recovery has been poor
- there has been failure to respond to psychotherapy

Depressive disorders tend to be chronic in nature. Antidepressant medications can remit the depression or control many depressive symptoms, but there is often a high rate of relapse if medication is discontinued. Treatment should be viewed as a long-term process and maintenance therapy is often necessary.

The current approach to antidepressant medication is to treat to remission and then provide maintenance treatment (APA, 2000b). This includes ongoing assessment for recurrence of symptoms over time.

Kupfer (1991) described a treatment model, which consists of three stages: an acute treatment phase, a continuation phase, and a maintenance phase. The stages are defined in relation to symptomatology and involve treatment response, remission, relapse, recurrence, and recovery. This classic treatment model is relevant still today; however, time frames have been updated, as medications have been added, as has the concept of chronicity relative to depression.

Acute Treatment Phase

Treatment in the acute treatment phase focuses on selecting the appropriate medication, titrating the dose to a therapeutic level, monitoring side effects, maintaining compliance, and determining response. During the acute treatment phase, a period of 6-12 weeks, patients are usually seen very regularly for medication management. If there is adequate response the continuation phase will begin. If the response is inadequate or it is necessary to change drugs a new "acute treatment phase" will begin. It has been thought that the antidepressant medications require continuous dosing for 2-3 weeks before improvement is evident, however some research indicates that response can be dramatically earlier.

This is not related to the time required to reach therapeutic blood levels, but is thought to be due to a time-dependent process of neuronal adaptation. Raising the dose does not speed up response and can increase side effects, therefore, titration and monitoring response are essential. For some drugs it is interesting to note that higher than usual doses can actually be associated with a lower rate of response.

The most anticholinergic and antiadrenergic drugs require the most care titrating and may be difficult to use because the severity of side effects may prevent adequate dosing. On the other hand, because of the low rate of side effects associated with the SSRIs, they are often started and used at doses higher than actually required for positive response. If a partial response is obtained after 4-6 weeks medication should be continued for at least 12 weeks. During this time, continued improvement and full response usually results. If response is less than desired or a plateau is reached another medication should be considered or another augmenting drug should be added.

Continuation Phase

If satisfactory response is achieved, then the continuation of medication is advised. This phase consists of monitoring response, side effects, and compliance. Discontinuation of medication during this phase is associated with a high rate of relapse. Continuation treatment should last for 6-9 months (Kupfer, 1991). However, APA guidelines for the treatment of depression (2000b) indicate that continuation treatment should last approximately 1 year. If maintenance therapy is not planned, medication should be gradually tapered over a period of 4-6 weeks and should never be abruptly discontinued.

Maintenance Phase

The majority of patients with a mood disorder have more than one episode. Recurrence rates for depression are estimated to be 50% for people who have had one episode and 80-90% for those who have had two episodes (Delgado & Gelenberg, 1996). Because of this possibility of relapse maintenance treatment is used prophylactically to prevent recurrences. It has also been found that maintenance therapy is necessary to maintain the response. Patients who have had more than two episodes of depression or those who are suicide risks should be encouraged to stay on antidepressant medication as a long-term maintenance strategy.

According to Kupfer (1991) maintenance patients should be seen every 4-6 weeks for the first year and every six months thereafter; however many clinicians will see patients frequently when there is a change in symptoms or treatment, but once stable, will see patients who are in remission every 3 months. The frequency of visits should be individualized depending on the psychosocial needs, medication adherence, presence of

any symptoms and side effects. If medication is to be discontinued at any time it must be tapered over at least a four-week period.

Antidepressant Medication

Although recent advances in antidepressant medication have provided greater options for both prescribers and patients, there are limitations as well as benefits with each choice. DeVane (2000) identified the characteristics of an ideal antidepressant. It is suggested that to the degree currently available medications possess these properties, medication selection criteria can be drawn from them. They include: efficacy characteristics, safety and tolerability characteristics and pharmacokinetic characteristics.

The efficacy characteristics include: cures or alleviates symptoms; provides efficacy for most or all patients; provides rapid effectiveness; provides sustained effects with continuation/maintenance treatment; and provides consistent and predictable dose:effect relationship.

The safety and tolerability characteristics include: low incidence of adverse events; minimal overdose toxicity; low or no impairment of cognition; and beneficial effects on wellness.

The pharmacokinetic characteristics include: consistent and predictable disposition, multiple pathways of elimination, convenient dosing schedules, and low propensity to participate in drug-drug interactions.

There are several classes of medications used to treat depression: tricyclic agents (TCAs), monamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), the selective serotonin/norepinephrine reuptake inhibitors (SSNRIs), as well as others. These antidepressants are used as monotherapy or in combination; some are used in combination for the treatment of side effects or when augmentation therapy is needed.

The MAOIs are seldom used because of the serious drug interactions, the necessity of complete washout of other antidepressant drugs, and the need to maintain severe dietary restrictions in order to avoid life-threatening complications.

Tricyclic Antidepressants (TCAs)

TCAs were the first antidepressants, imipramine having been discovered to have antidepressant benefit, while searching for a safer antipsychotic medication. They are still widely used although use has declined because of concern about side effects and the availability of the newer antidepressant medication. The TCAs have a high affinity for many receptors: muscarinic, cholinergic, histaminergic, alpha-adrenergic, and dopamine. The antidepressant effect of TCAs is attributed to inhibition of norepinephrine and serotonin transporters. Side effects of TCAs are thought to be due to their action on the other neuroreceptors (Gumnick & Nemeroff, 2000). TCAs, generic and brand names, and therapeutic dosages follow in Table 1.

Table 1. Commonly Used Tricyclic Agents		
Generic Name	**Brand Name**	**Therapeutic Dose mg/day**
Imipramine	Tofranil	150-300
Amitriptyline	Elavil	75-300
Doxepin	Sinequan	150-300
Desipramine	Norpramin	150-300
Nortriptyline	Pamelor	75-150
Clomipramine	Anafranil	75-300

TCAs have been used successfully for many years and are still often considered the "gold standard" in antidepressant medication treatment. Their efficacy has been proven in multiple controlled studies (Thase, 2003; Gumnick & Nemeroff, 2000). The most common side effects of the TCAs are anticholinergic side effects: dry mouth, urinary retention, constipation, tachycardia, and blurred vision. Sedation and weight gain are thought to be secondary to antihistaminic effects. Orthostatic hypotension is attributed to blockade of alpha-adrenergic receptors. The most dangerous side effect of the TCAs are the cardiovascular side effects. They can cause cardiac conduction delays, particularly first-degree atrioventricular and bundle branch block (Gumnick & Nemeroff, 2000). They should be used very cautiously with people with a history of seizures, glaucoma, urinary retention, heart disease, hyperthyroidism, and dementia.

These drugs are not addictive, but should be tapered at discontinuation due to side effects that may occur if they are discontinued rapidly. Due to the range of side effects, compliance can be poor. Research indicates that approximately 27% of patients who take TCAs discontinue to take the medication due to side effects (Thase, 2003).

TCAs are the number one class of prescription medication most responsible for death by poisoning in the U.S. (Gumnick & Nemeroff, 2000). The danger of suicide must be considered and medication monitored if there is a high risk of suicide attempt.

Recommended doses:

- Amitriptyline (Elavil) is initially started at 75 mg/day and may be increased to 150 mg/day. The usual dose is 40-100 mg/day. It is often given at bedtime because of its sedating effects.
- Nortriptyline (Pamelor) is given initially at a dose of 25 mg three or four times a day. It may be increased to 150 mg/day.
- Imipramine (Tofranil) is started at 75 mg/day and may be increased to 150 mg/day. Doses greater than 200 mg/day should not be used.
- Desipramine (Norpramin) is begun at 100-200 mg/day and may be increased to 200-300 mg/day. Much lower doses of 50-75 mg/day should be used for elderly people.
- Doxepin (Sinequan) often controls mild to moderate depression at doses of 25-50 mg/day. Maintenance therapy of 150 mg/day is used and doses of up to 300 mg/day may be needed for severe depression.
- Protriptyline (Vivactil) is initially started at 15-40 mg/day in divided doses three times a day or four times a day. It may be increased to 60 mg/day with elderly people limited to 15-20 mg/day in three or four divided doses.

Monoamine Oxidate Inhibitors (MAOIs)

During research of an antituberculosis medication, the antidepressant benefit of the MAOIs was observed (Gumnick & Nemeroff, 2000). The antidepressant action is thought to be due to the

potential of monoaminergic neurotransmission. The MAOIs block the action of an enzyme that breaks down the neurotransmitters norepinephrine and dopamine.

This category of antidepressant medications seem to be particularly useful for patients with atypical depression and for patients who cannot tolerate the side effects of the other classes of antidepressants. Because of the possibility of a hypertensive crisis, a patient on MAOIs must follow serious diet restrictions of tyramine and symptathomimetics. Tyramine is found in cheese, red wine, and other foods; pseudoephedrine is a symptathomimetic and must also be avoided. This means that MAOIs are not considered first line treatment options; they are used rarely today. However, the MAOIs continue to offer good benefit to patients who have had unsuccessful trials on the other categories of antidepressants. Their use also requires significant patient education and a commitment from the patient to adhere to the dietary restrictions. Table 2 lists the most common MAOIs.

Table 2. Monamine Oxidase Inhibitors

Generic Name	Brand Name	Therapeutic Dose mg/day
Phenelzine	Nardil	45-60
Tranylcypromine	Parnate	20-40

MAOIs should not be administered in combination with medications that increase serotonin, such as TCAs, SSRIs and some of the SNRIs and other antidepressants, as well as multiple other non-antidepressant medications.

Current research regarding the use of Selegiline, a MAOI, is focused on its administration transdermally rather than orally. This method of providing the medication is approved for the treatment of Parkinson's Disease; however, it's use transdermally as an antidepressant has not yet been approved by the FDA, nor is it yet available. Research has suggested that the dietary restrictions will not be necessary. When available, this may provide another treatment option for both patients and providers (The Brown University Psychopharmacology Update, 2003).

Selective Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs dramatically changed the treatment of depression. Their lower side effect profile as compared to older antidepressants and the ease of once-daily dosing was a significant convenience for patients.

SSRIs act by enhancing the activity of serotonin due to their potent and relatively selective inhibition of serotonin reuptake at presynaptic terminals (Gumnick & Nemeroff, 2000). The lower incidence of side effects such as the weight gain, dry mouth, constipation, drowsiness, and cardiovascular effects which are so troubling to patients on TCAs has increased SSRI acceptance and use. It should also be noted that it is difficult to take a fatal overdose of an SSRI, making these medications a good choice for patients who are suicidal.

The FDA approved fluoxetine (Prozac) in 1987. It quickly became one of the most prescribed drugs in the US and was widely hailed as a miracle drug for depression. Unfortunately, there was also a media backlash regarding the medication. Sertraline (Zoloft) was approved in 1991, paroxetine (Paxil) in 1992; fluvoxamine (Luvox) followed. Citalopram (Celexa) was approved in 1998 and in 2001 a variation of citalopram, escitalopram (Lexapro), was developed by the maker of Celexa.

The SSRIs are the most commonly prescribed antidepressants, because of their effectiveness, lower incidence of distressing side effects, ease of prescribing and convenience of once-daily dosing. The SSRIs are among the first-line medications used in the treatment of depressive disorders. The SSRIs haves received widespread publicity in the general media, as well as

widespread use among practitioners. Table 3 identifies the most commonly used SSRIs and their dosage ranges.

Table 3. Selective Serotonin Reuptake Inhibitors

Generic Name	Brand Name	Therapeutic Dose mg/day
Fluoxetine	Prozac	20-80
Sertraline	Zoloft	50-200
Paroxetine	Paxil	20-60
Paroxetine CR	Paxil CR	12.5
Fluvoxamine	Luvox	50-300
Citalopram	Celexa	20-60
Escitalopram	Lexapro	10-20

Although the SSRIs have less distressing side effects than the TCAs and MAOIs, they do indeed have side effects. Among them are headache, excessive sweating, nausea, upset stomach, diarrhea, sleep disturbance and tremors. A decrease in weight occurs more often initially in treatment, long term use may be associated with weight gain, although at a rate equal to placebo (Fava, 2000). SSRIs may cause serious sexual side effects with 40-50% of users complaining of one or more sexual problems, inability to have orgasm, decreased desire and arousal, erection impairment in men and loss of lubrication in women.

Lower doses are usually indicated in older people and in people with kidney or liver problems. Use of antidepressant medications in pregnant or nursing women or women who might become pregnant presents a difficult clinical decision. Currently no antidepressant has been approved by the FDA for use in pregnancy. However there is considerable anecdotal information on the use of antidepressants during pregnancy. There is retrospective information on the use of antidepressants during pregnancy and breastfeeding.

The use of antidepressant medication in pregnant or nursing women should be discussed with the patient and with the collaborating physician, if applicable, before prescribing. Current literature is focusing on the danger of **not** treating pregnant women for depression, both in the impact of depression on the developing fetus, as well as on the infant after birth. Risks and benefits must be weighed carefully.

SSRIs are among the most commonly prescribed antidepressant medications since the side effects are generally the least troublesome, once daily dosing is more convenient, and generally they are safer in combination with other drugs and pose less risk of overdose than other antidepressants. Ease of prescribing is also a factor in their popularity.

Recommended doses:

- Fluoxetine (Prozac) - 20 mg/day. It may be increased up to a maximum of 80 mg/day.
- Sertraline (Zoloft) - Initial dose of 25-50 mg/day may be increased gradually to a maximum of 200 mg/day.
- Paroxetine (Paxil) - Initial dose of 20 mg/day may be increased to a maximum of 60 mg/day.
- Fluvoxemine (Luvox) - Initial dose of 50 mg given at bedtime. Increase by 50 mg at intervals of 4-7days to a maximum of 300 mg. Doses over 100 mg a day should be given in divided doses.
- Citalopram (Celexa) - Initial dose of 20 mg/day; may be increased if needed to a maximum dose of 60 mg/day.
- Escitalopram (Lexapro) – Initial dose of 10 mg/day, may be increased, if needed to 20-30 mg/day.

Selective Serotonin/Norepinephrine Reuptake Inhibitors

Venlafaxine (Effexor and Effexor XR) was approved in 1993 with a long acting form approved in 1997. It was the first of the serotonin-norepinephrine reuptake inhibitors (SNRIs). It inhibits the reuptake of serotonin and norepinephrine, and is a weak reuptake inhibitor of dopamine. It has no appreciable affinity for muscarinic, cholinergic, histaminic, or alpha-adrenergic receptors. The benefit of using this classification of antidepressant medication is its dual action relative to both norepinephrine and serotonin; both implicated in both depressive and anxiety symptoms.

The most common side effects are nausea, anorexia, insomnia, nervousness, asthenia, sweating, constipation, dry mouth, dizziness, tremors and blurred vision. A unique side effect is a dose-dependent increase in blood pressure, making blood pressure monitoring necessary during venlafaxine administration. Other dose-related side effects include nausea, sexual dysfunction, somnolence and sweating.

Duloxetine (Cymbalta) is the newest dual action agent, an SNRI, approved by the FDA in 2004. Duloxetine has been identified as particularly helpful in the physical symptoms associated with depression (Fava, et. al, 2004), as well as the emotional symptoms. The most common side effect is nausea, generally at the start of treatment. Taking the medication at a low dose to begin treatment may help to minimize the nausea.

Nefazadone (Serzone) is a serotonin and norepinephrine reuptake inhibitor. It does not aggravate sleeping difficulty, which many depressed people have. It also rarely causes sexual problems. Unfortunately, nefazadone has been associated with liver disease. It is no longer available for use in Europe; however, it remains available in the US, with a black box warning to monitor liver functions. More common and less toxic side effects of nefazodone include nausea, somnolence, dry mouth, dizziness, asthenia, and constipation. There is a risk of priapism with this drug; patients should be warned to report erectile problems promptly.

Recommended Dosages:

- Venlafaxine (Effexor) is begun at 75 mg/day in two or three divided doses, taken with food. It may be increased to 225 mg/day, by 75 mg/day at intervals of not less than 4 days, with no more than 375 mg/day at the maximum, in 3 divided doses. Effexor XR, the extended release version of the medication, is started at a single dose of 37.5 or 75 mg. The lower dosage may be necessary to minimize the possibility of side effects. The maximum dose is 375 mg/day. Effexor XR should be swallowed whole and not divided, chewed, crushed or placed in water.
- Duloxetine (Cymbalta) is started at 30 mg/day, generally in the morning. The dosage is increased to 30 mg BID for 1 week and then the patient may take 60 mg q d. This titration of the dosage is meant to decrease the occurrence of nausea. The manufacturer suggests that the maximum daily dosage is 60 mg, however there is safety data up to 240 mg q d. In clinical practice, patients often receive 90 mg/day and reports of up to 120 mg q d are in the literature.
- Nefazadone (Serzone) should be kept at the lowest possible dose. Recommended starting dose is 200 mg/day divided in two doses. It may be increased over several weeks to a maximum of 600 mg/day. Monitoring of liver functions is essential when using nefazadone.

Noradrenergic/Serotonergic Receptor Modulator

Mirtazapine (Remeron) is a noradrenergic and serotonergic receptor modulator. Its modes of actions are thought to be receptor blockade at alpha-adrenergic receptors and blockade at 5-HT2 and 5-HT3 receptors (Gumnick & Nemeroff, 2000). It is often classified as a dual-action agent.

Research has demonstrated the efficacy of Remeron to be equivalent to that of amitriptyline. The most common side effects are sedation, fatigue, increased appetite and weight gain. Other less common side effects include transient neutropenia, transient elevations in liver enzyme levels and elevated serum cholesterol. It does not seem to cause sexual dysfunction.
Recommended Dosage:

- Mirtazapine (Remeron) is started at 15 mg at bedtime and can be increased to 60 mg q hs. Remeron has a half-life of approximately 20-40 hours; dosage changes should be made at intervals of at least 1-2 weeks, if needed.

Selective Norepinephrine Reuptake Inhibitors

Bupropion (Wellbutrin, Wellbutrin SR and Wellbutrin XL) and its long acting form are also among the newer antidepressants. It is a relatively weak inhibitor of dopamine, norepinephrine and serotonin reuptake. A formulation of this drug, Zyban, is being used for smoking cessation. Research has demonstrated that bupropion is comparable in efficacy to TCAs. While this drug is used as a single agent to treat depression it is commonly used as augmentation for other antidepressants or to alleviate sexual side effects of SSRIs. The most serious side effect is its increase in seizure risk, especially in patients with a history of seizure or head trauma or those taking other medications that lower the seizure threshold. Seizure risk is greater with higher doses (Gumnick & Nemeroff, 2000). Common side effects are anxiety, agitation, insomnia and appetite suppression.

Reboxetine, a norepinephrine reuptake inhibitor, is currently being tested in clinical trials and is not available in the US, but is expected to be approved by the Food and Drug Administration in the near future. It is the first selective non-TCA norepinephrine reuptake inhibitor (NRI). It is currently available in Europe. Research is demonstrating that Reboxetine is at least as efficacious as TCAs and SSRIs. It may have greater efficacy in severe depression and have a more rapid onset of action (Gumnick & Nemeroff, 2000). Its most common side effects include: dry mouth, headache, nausea, sweating, constipation and hypotension.

Recommended doses:

- Bupropion (Wellbutrin) is started at 100 mg two times a day in the morning and at bedtime. It may be increased to 100 mg three times a day. No single dose should exceed 150 mg and the maximum daily dose is 450 mg/day. Wellbutrin SR, the sustained release version of Wellbutrin, is given as a single 150 mg dose in the morning. It may be increased to 150 mg bid as early as day four if tolerated. Doses should be given at least eight hours apart and maximum daily dose is 450 mg. Caution patients to not take the 2nd dose too close to bedtime, as it can significantly interfere with sleep. Wellbutrin XL is the once-daily preparation and it is started at 150 mg and may be increased to a maximum of 450 mg.

Choosing an Antidepressant Medication

Many factors influence the choice of antidepressant medication to be prescribed. The decision must be made individually for each person. It is beneficial to identify target symptoms for each individual patient. This can assist the provider in choosing a medication that can specifically target the patient's symptoms.

Stahl (1998) theorized that the neurotransmitters -- dopamine, norepinephrine, and serotonin -- impact mood, and that both norepinephrine and serotonin impact anxiety. Dopamine may preferentially regulate motivation, pleasure, and reward; serotonin may preferentially regulate obsessions and compulsions; and norepinephrine may preferentially regulate alertness and energy. Showing the symptom domains of serotonin and norepinephrine, Stahl placed mood, emotion, anxiety, pain, irritability, and cognitive function in the domain of both neurotransmitters. Vigilance and motivation are in the domain of norepinephrine; and the serotonin domain includes impulsivity, sex, appetite, and aggression.

This theoretical conceptualization has applicability to the clinical situation, as a common intervention when an SSRI is partially effective or creates a certain pattern of side-effects is to add noradrenergic agent. For example, bupropion is a frequent choice for augmentation with SSRI. There are strong indications from clinical experience as well as support from research data that the "broad spectrum" approach (ie, attacking from both the serotonergic and noradrenergic approach) to treatment is valid.

A critical aspect of choosing an antidepressant medication is its side effect profile. Many side effects can be avoided by starting the medication at a low dose and slowly increasing the dosage. Generally, one chooses a medication that is the safest and has the side effect profile most compatible with the patient's specific symptoms. In some practice settings limited formularies may be a constraint. Cost of medications should also be considered, the older TCAs and MAOs are significantly less expensive than the antidepressants developed in the last 15 years. Generally speaking, most antidepressant medications seem to be equally effective.

Recent research (Krell, et. al, 2004) suggests that patients who have a high expectation of improvement prior to antidepressant treatment do have a significantly higher level of response to the medication. This may also be considered in light of the choice of which antidepressant to prescribe. Patients often tell prescribers about family members or friends who are taking a particular medication with good benefit; the prescriber would be wise to at least consider this medication, since the patient has a positive expectation about its efficacy.

Additionally, the choice of which antidepressant medication to prescribe to a particular patient is often limited by the patient’s insurance or managed care provider. Benefit plans vary in which medications they include in their formularies. Some plans allow for only medications that come in a generic preparation; some plans indicate the maximum number of pills the patient is entitled to receive per month; some plans allow for a broader choice of medications, but the patient must pay a higher copay for certain brands; some plans allow the prescriber to appeal to a pharmacy review board, other plans make no exceptions. Clearly, third party payers impact on the choice of medication, except in situations where patients are able to afford the medications out of pocket.

The choice of antidepressant is generally based on the patient's symptoms, the current understanding of the neurobiology of depression, family history, side effect profile of the medication, limits of benefit plans, as well as patient and prescriber preference.

A sample of side effects follows in Tables 4 and 5.

Table 4. Antidepressant Drug Side Effects				
Drug	**Anticholinergy**	**Sedation**	**Hypotension**	**Cardiovascular**
TCAs				
Imiprimine	Moderate	Moderate	High	High
Amitriptyline	High	High	High	High
Doxepine	High	High	Moderate	Moderate
Nortriptyline	Moderate	Moderate	Low	Moderate
MAOIs				
Phenelizine	Low	Low	Moderate	None
Tranylcypromine	Low	Low	Low	None
SSRIs				
Fluoxetine	Low	Low	Low	Low
Sertraline	None	None	None	None
Paroxetine	Low	Low	Low	Low
Fluvoxamine	None	Low	None	None
Citalopram	Low	Low	None	None
Escitalopram	Low	Low	None	None

Table 5. Antidepressant Drug Side Effects				
Medication	**Anticholinergy**	**Sedation**	**Hypotension**	**Cardiovascular**
Selective Norepinephrine/Sertonin Reuptake Inhibitors				
Venlafaxine*	X			X
Nefazodone	X	X		
Selective Norepinephrine Reuptake Inhibitors				
Bupropion**				
Reboxetine	X		X	
Noradrenergic/Serotonergic Receptor Modulator				
Mirtazapine		X		

*Dose-dependent increase in blood pressure is a side-effect.
**Increased seizure risk
(Adapted from Garrett, 1999)

The rule of thumb for prescribing antidepressant medications is to "start low and go slow". This practice allows for patients to adjust to the medications and decreases the likelihood of side effects. The fewer side effects, the more likely the patient will continue taking the medication. Patients who experience even transient side effects are more likely to discontinue medication use.

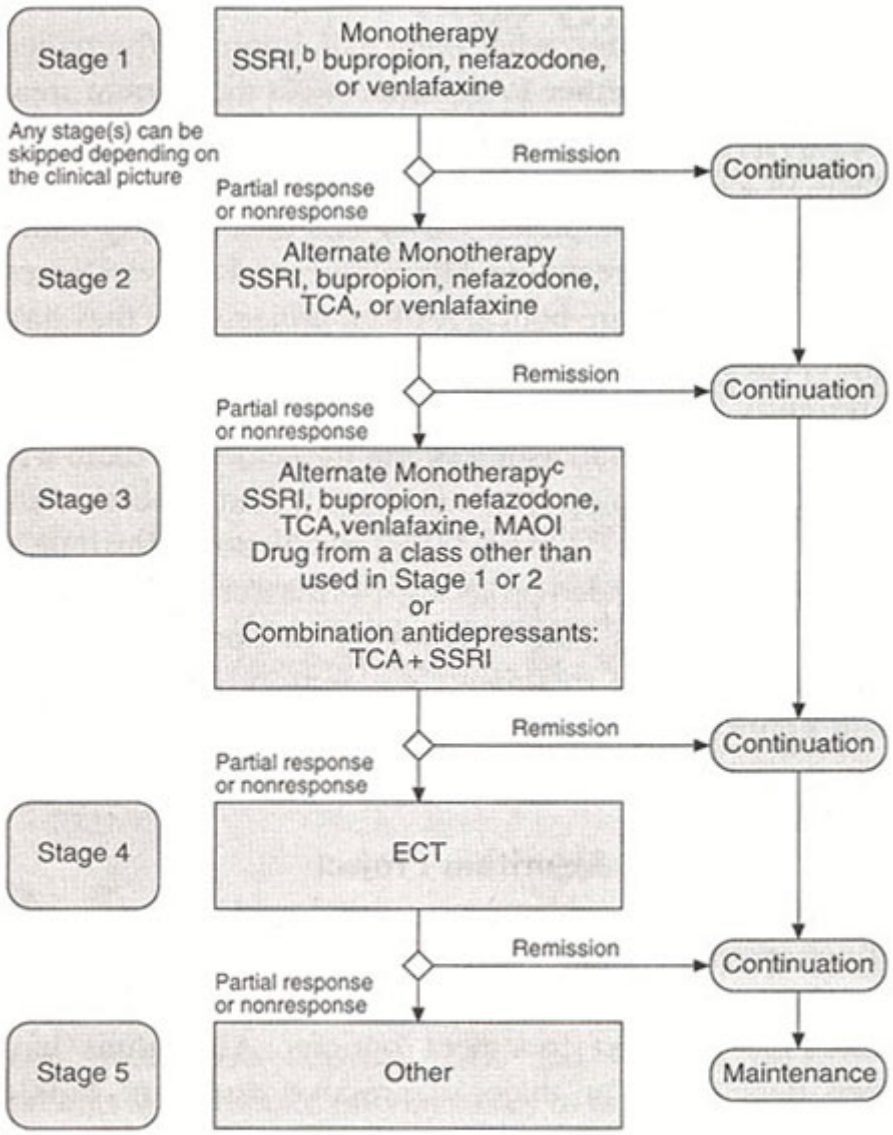
Simple dosing schedules are preferred by most patients. Dosing once daily is more convenient and improves compliance over divided dosing. Monotherapy is preferred over multiple medications.

Treatment Algorithms

Typically, treatment algorithms are decision trees for medication management. Current algorithms have been developed using an evidence-based methodology. Multiple algorithms have been developed or are in development.

One such algorithm is the Texas Medication Algorithm Project (TMAP) (Trivedi, 2003). This decision tree was developed from expert consensus. Monotherapy is the first choice, as it associated with fewer side effects. If this is ineffective, treatment becomes increasingly complex, with increasing risk for adverse events. The patient's progress must be evaluated periodically by the clinician in order to assess the level of response.

Figure 1. Texas Medication Algorithm Project (TMAP): Major Depressive Disorder Without Psychotic Features[a]



[a]Adapted from Crismon et al.[9] The TMAP algorithms are in the public domain, and this figure may be reproduced without permission, but with the appropriate citation. Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]SSRIs preferred.
[c]Consider TCA or venlafaxine if not tried.

Another algorithm is currently being developed by the National Institute of Mental Health, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and remains in the research phase.

When the Medication Doesn't Work

Full remission is the goal of antidepressant medication treatment; that is, the elimination of all symptoms of the original episode of depression and includes the full resolution of all functional impairment (Thase, 2003). Research indicates that only approximately 25-40% of depressed patients achieve this remission with the first course of antidepressant mediation (Thase, 2003). Ideally, treatment occurs with as few medications as possible, as low a dose as possible, and as simple dosing schedule as possible. Despite the array of medication options available, and the excellent results many patients experience, there is no single medication that will help every patient.

The most common cause of ineffective medication is inadequate dosing and inadequate trial length. Some clinicians utilize medications only to the average dosage, but do not maximize the dosage, which for some patients can result in poor effectiveness of the medication. Medication trials must be long enough for adequate assessment of effectiveness. Despite adequate antidepressant trial, generally considered to be at least 4 to 6 weeks (Thase, 2003), and longer trials increase the likelihood of response, some patients will not benefit from a particular medication. Another major reason for the ineffectiveness of antidepressant medication is that some patients cannot tolerate side effects enough to stay on the medication or to have adequate dosage.

Additionally, some patients have treatment-resistant depression. This term is generally reserved for patients who have failed to respond to 2 adequate trials of different antidepressants (Thase, 2003). Treatment-refractory patients may be considered as those who have failed to respond well to multiple antidepressants and electroconvulsive treatment (Thase, 2003).

Manning (2003) identified factors that are associated with treatment resistance to antidepressant medications:

- Medication adherence problems on the part of the patient
- Lack of adequate dose/duration of treatment
- Comorbid medical illness, particularly thyroid illness, hypercortisolism, stroke (particularly in the left middle cerebral artery region) and HIV. Treatment of some comorbid illnesses with centrally acting antihypertensives, corticosteroids, progestins may also be contributing to a limited antidepressant response
- Comorbid substance abuse or dependency- decreased antidepressant efficacy is associated with the use of alcohol
- Axis II Disorders, that is personality disorders, and high stress psychosocial situations
- Biological heterogeneity of depressive illness
- Undiagnosed bipolar depression

Manning (2003) suggests interventions targeting patient education, psychosocial and psychotherapy interventions can be options for treatment. Additionally, he identifies correcting misdiagnoses and the treatment of comorbid illness as necessary; pharmacogenetic research is promising.

A variety of treatment options can be utilized in the management of antidepressant medication treatment. These include: switching to another antidepressant or augmenting with another antidepressant or another medication which is not an antidepressant.

<u>Switching Antidepressants</u>

Switching antidepressants is a common treatment strategy. Switching medications can occur within or across antidepressant classes. Switching can be used to obtain a different neurochemical effect or to resolve side effects (Trivedi, 2003).

For patients on an SSRI, switching to another may be beneficial (Nelson, 2003). Despite having side effects to one SSRI, many patients will not have side effects to another SSRI. Other switching strategies include use of another category of antidepressants, particularly one with a different mechanism of action. Nelson (2003) in reviewing the research literature found that venlafaxine (Effexor) was effective in patients when SSRI treatment was ineffective.

Nelson (2003) defines the term bridging as the addition of a second agent to enhance response with the intent that if the patient does well, the first medication is withdrawn and the patient continues on the second.

Some disadvantages are associated with switching antidepressants. These include: loss of treatment time, since the first agent is generally tapered down while increasing the dose of the second medication, loss of any partial response to the original medication, discontinuation-emergent adverse events, side effects to the new medication and a sense of failure or a contribution to hopelessness on the part of the patient (Trivedi, 2003). It must be emphasized that with some medication, as with a switch from MAOIs to another antidepressant, a long "wash-out" period is needed (generally, at a minimum, 2 weeks).

Augmentation

Augmenting treatment with another medication may be needed if monotherapy is ineffective. Combining therapies can produce benefit by adding additional neurochemical action that is different or greater than is seen with a single agent (Shelton, 2003).

Advantages of augmentation include a potentially rapid response to the new medication with no loss of treatment time and maintenance of any partial response to the initial medication, as it is not necessary to taper down the dosage of the first medication, while increasing the second medication, as is frequently the case with switching (Trivedi, 2003). Lower doses of both drugs may be helpful and will reduce side effects that can result from higher doses of either.

Frequent augmentation agents include: bupropion, lithium, benzodiazapine, or a TCA (Fredman et al., 2000). Research has pointed to the use of thyroid hormones, lithium and buspirone as augmentation strategies (Trivedi, 2003; Shelton, 2003). In clinical practice, multiple other augmentation strategies are utilized and have anecdotal recommendations: mood stabilizers and low-dose novel anti-psychotic medications, Pindolol or other beta blockers (Shelton, 2003). The augmenting drug may also treat a co-morbid condition such as hypothyroidism or bipolar disorder. The use of anxiolytic or antipsychotic medications with antidepressant medications will depend on the condition of the patient and other psychiatric symptoms present.

Disadvantages of augmentation include possible drug interactions, emergence of new side effects and greater cost (Trivedi, 2003).

Combining Antidepressant Medications

It may also be necessary to add a second antidepressant medication to control side effects as well as to augment the action of the first medication, and to target specific symptoms. When the second antidepressant medication has a different mechanism of action, a synergistic effect can be achieved (Trivedi, 2003). The specific combination of a norepinephrine reuptake inhibitor in combination with SSRIs has shown to be more effective than the use of either an NRI or SSRI alone (Shelton, 2003). The combined use of a SSRI with a dual-action agent, or with a dopamine and norepinephrine reuptake inhibitor, such as bupropion, is common.

Decisions to use combination drug therapies depend on each patient's response, side effects, concomitant conditions, and the prescriber's own experience. One caution that cannot be overemphasized is that MAOIs must not be used in combination with other antidepressants and

may be lethal if so used. It is essential that MAOIs not be started until a period of drug wash out has occurred. The half life of the drugs varies and is an important consideration when changing or starting other medications.

Management of Antidepressant Side Effects

Recent research (Hu et al., 2004) indicates that patients may experience more side effects and that they are more bothersome that prescribers believe to be the case. It is important to provide thorough patient teaching regarding side effects at the onset of medication treatment, as patients may experience side effects that they do not understand to be related to the medication. Additionally, the presence of side effects must be assessed at each patient contact. If current research is any indication, prescribers do not fully comprehend the extent and nature of the impact of side effects on patients taking antidepressants.

Often adverse effects can be controlled by a reduction of the dosage of the medication; a change in drugs may not be necessary. This should be tried first if the side effect is not serious. It should also be noted that tolerance can occur if the medication is continued. The patient may no longer be bothered by the adverse effects and the dose may be gradually increased (Prekorn, 1999).

There are other side effects that can be treated if tolerance does not develop. Constipation is helped by the use of bulk-forming stool softeners, increasing water intake and exercise. Occasionally the diaphoresis is so bothersome that beta blockers may be considered. Gastrointestinal upset can occur with all SSRIs and generally occurs early in treatment; it also may be dose dependent. Following the general rule of starting the medication at a low dose and increasing slowing often reduces this side effect. Dry mouth is helped by drinking water, chewing sugarless gum, or sucking on sugarless candies. Sweet snacks should be avoided. Good dental hygiene and flossing are necessary to prevent tooth decay and gum disease that can occur due to the loss of antibacterial saliva. The use of benzodiazepines to combat the nervousness or agitation that can occur in some patients needs careful consideration because of the risk for dependence or abuse; often side effects of nervousness or agitation require a change in medications.

Often sexual side effects are difficult for patients to bring up to nurses. It is necessary for the nurse to bring up the subject. Tolerance usually does not develop and sexual side effects are often a cause of unscheduled medication discontinuation. Dosage reduction is no longer recommended due to the current recommendations for the long-term treatment of depression (i.e. same drug, same dose) (Rothschild, 2000). It usually requires a change to a different medication or addition of a second medication. Some success has been achieved in switching patients from SSRIs to bupropion or nefazodone (Rothschild, 2000). The addition of the following medications drugs has resulted in success for some patients: amantadine, buspirone, cyproheptadine, yohimbine, sildenafil, and topically applied testosterone creams for orgasm in women. Low dose psychostimulants such as dextroamphetamine, methylphenidate and pemoline have been reported to have some success (Rothschild, 2000). The use of gingko biloba at doses beginning at 180 mg q day for decreased libido, to 900 mg q day for anorgasmia, are also being used (Bezchibnyk-Butler & Jeffries, 2001). No single effective approach has been found and research continues.

While some antidepressants, notably the TCAs, nefazodone, trazodone and mirtazapine, have significant sedation side effects, the SSRIs have been associated with both sedation and insomnia. Dosing the medication at bedtime may help to reduce daytime sedation. In the case of once daily dosing, such as with mirtazapine, taking the medication at bedtime is recommended. SSRIs are typically taken in the morning to reduce the possibility of insomnia. The addition of trazodone at low doses is often prescribed to improve sleep, although it is not approved by the FDA for such indication, it is widely used for this purpose. For patients who experience lethargy and sedation with SSRI treatment, the addition of medication that may improve the energy level may be considered. Possibilities include bupropion, which often has an activating effect, or psychostimulants, such as methylphenidate or modenafinil, which is indicated for the treatment of narcolepsy. The prescriber should be aware that some medications may not be approved by the FDA for such use.

Patient Education

Regardless of the antidepressant medication used it is important that nurses and patients form a partnership in treatment. Patients can be excellent partners for the nurse in decision making concerning drug effectiveness, titration of doses, side effects, need to change medications, etc. Building a therapeutic alliance that allows for the patient to recognize that s/he is an important partner in their own treatment is critical. Informed consent is an important aspect of the therapeutic alliance. Patients must be informed of the nature of their diagnosis or condition, the benefits that they can reasonably expect from treatment, the nature and probability of risks, the inability to predict results, the likely results of no treatment, and available alternatives.

Target symptoms that were identified during the course of diagnosing the depression should be shared with the patient. The patient's perspective on the status of target symptoms is important assessment information and should be reviewed with the patient at every visit. Following is a sample you can provide to patients:

Weekly Activity Record

You can make a chart like this to keep a record of your medicines, side effects, how you feel, and activities. Keeping a chart like this and sharing it with your health care provider will help make your treatment more effective.

Day of the Week	**Medicines I took** Name of Medicines I am taking: _____	**Side Effects** How the medicine made me feel	**Target Symptoms** How I feel (hopelessness, fearfulness) on a scale of 0 to 5 0=Bad 5=Good	**Activities** Activities for today: Include plans and "homework" for psychotherapy	**Appointment Schedule**
Sample: Monday, May 15th	Zoloft 200mg	Dry mouth	2 - I feel better about things today.	Went to the grocery store. Made a list of good things about my life.	Dr. Smith 3:00
Sunday					
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					

This record allows patients to track the medications they take, any side effects, the status of target symptoms on a scale of 0-10, daily activities, and appointments. Patients can be urged to utilize this record, besides providing valuable information, it can help patients feel more control over their illness and treatment, as well as providing a framework for their active participation in treatment.

Additional patient education information includes the importance of taking medication as prescribed. Effect on the depression will require continued dosage and effects will generally not be noticed for two weeks or more. The prescriber must elicit information regarding all medical conditions and any other medications, prescribed, over-the-counter, herbal preparations and street drugs that the patient takes. Alcohol or unprescribed medications/substances must be avoided. As stated earlier, patients must understand that the medications cannot be rapidly or suddenly discontinued, but that they must be tapered. They should be informed that the side effects that can occur range from nausea and headache to seizures.

The abrupt discontinuation of SSRIs has been associated with "SSRI discontinuation syndrome". This collection of symptoms can occur within 1 day of abrupt discontinuation of SSRIs. Generally, SSRIs with short half-lives (paroxetine and sertraline) tend to contribute to the discontinuation syndrome more often than do those with longer half-lives such as fluoxetine. The SSRI discontinuation syndrome includes both somatic and psychological symptoms. The somatic symptoms may include: dizziness, paresthesia, lethargy, nausea, vivid dreams, insomnia, headache, and movement-related adverse effects. Psychological symptoms are divided into core symptoms of anxiety/agitation, crying spells and irritability and other reported symptoms such as over activity, depersonalization, decreased concentration/slowed thinking, lowered mood, confusion and memory problems.

Some antidepressant medications may cause drowsiness. Care operating machinery or driving must be taken and it may be necessary to avoid such activities. Dosing medication at bedtime can be helpful. Judgment, alertness and physical coordination may be impaired initially and care should be taken when the medications are begun.

For patients with sleep disturbance, behavioral interventions are more effective than is the use of sedative hypnotics (Thase, 2000). Patients should be instructed to utilize the following guidelines to manage sleep/wake habits: avoid naps, have a light snack, if needed, before bedtime, refrain from exercise or heavy meals 2 hours prior to bedtime, restrict caffeine, avoid late night or shift work, and maintain a cool, dark, quiet sleeping area (Thase, 2000). Utilizing progressive relaxation techniques, including diaphragmatic breathing, may assist in helping patients to fall asleep more easily.

As previously described, it is important for the nurse to bring up the subject of sexual activity as some patients may be unwilling to do so. The discussion provided in the previous section should be included in patient education. Although it has been widely publicized in the media, some patients may not recognize the sexual difficulties as related to medication use.

Patients must understand that side effects should be reported so that the patient and nurse can work together to monitor, change dosing schedule, change medications, or prescribe medication to alleviate some effects.

Conclusion

Although the advent of antidepressant medications has changed the treatment of depression, there is no simple or easy formula for prescribing. There is no single drug or one dose that will help every patient. Prescribing must be individualized and sometimes trial and error is what's often needed. By knowing all one can about each patient, about the medications available and particularly the ones the prescriber frequently uses, a nurse can develop comfort and success treating most depressed patients.

JK is a 37 year old female who has been experiencing significant anxiety, irritability and depressed mood over the course of the last several years. She initially sought treatment because her sister had been treated for similar symptoms and was thriving. JK thought she should also have a psychiatric evaluation because her own symptoms were so much like those her sister had prior to treatment. During the assessment, the nurse practitioner discovered that the patient had had moderate symptoms of depression as a young adult, but she had not received treatment; in fact, JK had a low level of depression chronically. Despite this chronic depression, she was able to work and care for her family, which includes 2 adolescent children; she even was able to have fun on occasion. JK has been having increasing conflicts with her husband and has felt like she's not sure that it's worth continuing to struggle.

After the initial psychiatric assessment, JK was prescribed Wellbutrin XL starting at 150 mg q d, then increased to 300 mg q d. At the time of assessment she presented with no suicidal ideation, but did have significant feelings of hopelessness. She had a very good response to the medication, with no side effects. However, she was not adherent to the recommendation that she begin psychotherapy to address the issues of trust in the marriage. Although she is no longer depressed, she recognizes that she is not happy. She continues to struggle with feelings of hopelessness regarding her marriage and her life in general. She is adamant that she will not participate in psychotherapy.

GH is a 48 year old male who experienced depressive symptoms in response to marital problems. He had been working long hours for the past several years to clear up the family debts. This has had significant negative impact on his marriage. His wife has asked for a divorce and GH has been devastated. He has no history of previous depression; no family history of depression. He was prescribed a selective serotonin reuptake inhibitor and had a very good response. He felt so well after 4 months that he stopped taking the medication. After 2 months his depressive symptoms returned. When he went back on the medications, he did not have as good a result as he experienced previously. The psychiatric nurse practitioner caring for GH initially increased his Prozac from 40 mg q d to 60 mg q d. After one month, GH felt no better, despite weekly therapy. The Prozac was again raised from 60 mg q d to 80 mg q d. After another 4 weeks on the 80 mg q d, the patient was switched to Zoloft, 100 mg and soon started to have remission of his target symptoms. He remained symptom free 8 months later; he was adherent to the NP's recommendation for at least 1 full year of treatment.

AB is a 54 year old woman who has experienced depressive and anxiety symptoms since childhood. She experienced verbal and emotional abuse in childhood, having a mother who herself had untreated anxiety and depression. AB has held a variety of jobs in the same large organization for over 20 years; however she has taken medical leaves every several years, due to depression during her entire employment history. Her functional abilities have been impaired, having missed out on multiple promotions due to her illness; two failed marriages and a significant lack of enjoyment in most things. She is often overwhelmed by her feelings of depression and anxiety. She has been treated for depression with medication and therapy over much of the course of her life. She was treated for many years with tricyclic antidepressant medications and therapy, although she was often non-adherent to treatment, because she felt that she just needed to work harder at being happy and not so negative. In recent years she took

several different selective serotonin reuptake inhibitors, but continues to feel significantly depressed and is currently on a medical leave from her job.

AB was hospitalized briefly; her medication was increased, from Celexa 40 mg to 60 mg q d. Trials of lorazepam 1 mg q d and Zyprexa 2.5 mg q d were added with some benefit in anxiety, but depression was resistant to treatment. Celexa was tapered and discontinued and Prozac was started, titrated up to 80 mg. Augmentation with Wellbutrin XL 300 mg q d achieved remission of depressive symptoms. Patient remained on Prozac 80 mg and Wellbutrin XL 300 mg q d, she also switched therapists to one who had a cognitive-behavioral, as well as humanistic perspective. This patient reported feeling happy for the first time in her life.

CD is a 35 year old female who has been unable to maintain a job as an editor, despite her graduate education. She is now doing free lance work, however she is clearly underemployed. She has suffered from depression since early childhood; her father was also chronically depressed. CD has been treated for depression since adolescence with only modest improvement. In addition to severe mood and anxiety symptoms, this patient also experiences depression in somatic ways. Her experience is one of overwhelming disabling pain. She is generally motivated to continue to seek treatment alternatives. CD has been treated aggressively with medications and psychotherapy; however, her depression has been very treatment resistant. She has had trials of just about all of the possible antidepressants. Although she currently feels better than she ever has, she continues to struggle, at times, with overwhelming feelings of depression.

A trial with lithium augmentation was attempted. She had significant improvement, but she experienced severe tremors, which interfered with her work. Other mood stabilizers were attempted but were also discontinued due to side effects. Multiple other antidepressant medications were attempted over the years, including several TCAs, most of the SSRIs, as well as augmentation with Wellbutrin XL 300 mg q d, which had been mildly beneficial, at varying times with the following single or combinations: Effexor XR 300 mg q d, Zoloft 200 mg q d, and Prozac 80 mg q d. She is currently taking Cymbalta 90 mg q d (above the recommended dosage), Wellbutrin XL 300 mg q d and Prozac 60 mg q d. While this combination has been moderately beneficial to the patient, she continues to struggle with depression, however, her pain symptoms have also moderately improved, and her depressive episodes are shorter with longer periods of mild symptoms between episodes.

EF is a 26 year old male who has been unable to maintain employment since graduating from college 4 years ago due to significant symptoms of depression. He is now again living with his parents and EF fears that he will never be able to lead a "normal" life of marriage, children and successful employment; which have precipitated thoughts of suicide. He has been in treatment with the same psychiatrist and psychologist since late adolescence. He is not always forthcoming with either of his treatment providers, often minimizing his symptoms during sessions. EF had a maternal grandfather who committed suicide due to depression; no one else in the family suffers from depression. EF has been on the same selective serotonin reuptake inhibitor for the past several years.

EF continued to have suicidal ideation and finally became more open with his treatment providers. He was switched from Prozac to Effexor XR, titrating up to 300 mg q d. Additionally, he was placed on Risperdal 1 mg q hs. This switch and the augmentation provided significant improvement his symptoms of rumination over past failures, and overall in his hopefulness about the future. He is now in a day treatment program and participating in multiple group therapies, learning cognitive reframing and coping skills. He has moved out of his parents' home and is living in a supported housing program and has been participating in a structured work program.

From this small sample of patients, it is clear that depression presents in multiple ways and multiple antidepressant medications exist to treat depressive symptoms. It is also clear that

despite some excellent treatment options available today, depression continues to be a chronic medical illness that causes significant disability.

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Antidepressant Medications: Treatment Options
Course Exam

After studying the downloaded course and completing the course exam, you need to enter your answers online. **Answers cannot be graded from this downloadable version of the course.** To enter your answers online, go to e-leaRN's Web site, www.elearnonline.net and click on the Login/My Account button. As a returning student, login using the username and password you created, click on the "Go to Course" link, and proceed to the course exam.

1. In order for a diagnosis of major depressive disorder to be made which of the following symptoms must be present?

   a. History of one or more manic episodes.
   b. Frequent obsessions about sad memories.
   c. Period of at least two weeks of depressed symptoms.
   d. Crying spells which persist.

2. Major depression is more common in:

   a. Men
   b. Women
   c. It occurs equally in females and males.
   d. None of the above.

3. Which of the following are symptoms of depression?

   (1) Insomnia
   (2) Excessive sleeping
   (3) Loss of appetite
   (4) Overeating

   a. 1 and 4
   b. 1, 2, and 3
   c. 1, 3, and 4
   d. All of the above

4. With the SSRIs, improvement in depressed symptoms is always evident within 3-5 days.

   a. True
   b. False

5. The acute treatment phase focuses on all of the following EXCEPT:

   a. Choosing the drug of choice.
   b. Daily increases of dosage.
   c. Assessing side effects.
   d. Patient education.

6. Long term maintenance of antidepressant medications should be continued for patients who:

   a. Think more clearly on medication.
   b. Understand the actions and side effects of the drug.
   c. Have had two or more depressive episodes.
   d. Have had two or more manic episodes.

7. Which of the following classes of antidepressant drugs can cause life-threatening complications if patients do not closely follow dietary restrictions?

    a. MAOIs
    b. TCAs
    c. SSRIs
    d. SNRIs

8. TCAs are used less frequently than SSRIs because:

    a. There have more problematic side effects.
    b. They are less effective.
    c. They only work with the elderly.
    d. They are more expensive.

9. Side effects more common with SSRIs than TCAs include:

    a. Weight gain
    b. Drowsiness
    c. Sexual dysfunction
    d. Constipation

10. Which of the following medications may be better for the depressed patient complaining of severe insomnia:

    a. Fluoxetine (Prozac)
    b. Sertraline (Zoloft)
    c. Phenelzine (Nardil)
    d. Mirtazapine (Remeron)

11. The choice of which antidepressant medication to prescribe is made by indentifying target symptoms and then choosing a medication that impacts those symptoms. In addition, the following must be considered:

    a. Side effect profile.
    b. Benefit plan limitations.
    c. Patient/prescriber preference.
    d. All of the above.

12. Which of the following foods must be avoided by a patient on MAOI therapy?

    a. Bananas
    b. Avocados
    c. Cheese
    d. Sugar

13. The life threatening complication associated with Tyramine ingestion while taking MAOIs is:

    a. Severe hypoglycemia
    b. Insulin reaction
    c. Hypertensive crisis
    d. Epigastric bleeding

14. One of the significant side effects of the SNRI, venlafaxine is

    a. Hypotension
    b. Cardiac arrhythmias
    c. Hypertension
    d. Delirium

15. Elderly patients on TCAs should be monitored closely for:

    a. Confusion
    b. Insomnia
    c. Diarrhea
    d. Urinary frequency

16. Which of the drug classes has the highest potential for causing cardiac arrhythmias:

    a. TCAs
    b. MAOIs
    c. SSRIs
    d. SNRIs

17. Switching to another SSRI is often the first option when the first SSRI is not effective.

    a. True
    b. False

18. Augmentation is a treatment strategy that can be used when monotherapy is ineffective.

    a. True
    b. False

19. Drugs that may be used in combination with SSRIs to augment effects include all of the following EXCEPT:

    a. Lithium
    b. Synthroid
    c. Phenelzine (Nardil)
    d. Bupropion (Wellbutrin)

20. When prescribing antidepressant medications, the best rule to follow is to start with one medication, at a low dose then increase dosage slowly.

    a. True
    b. False