APA Quick Practice Guide

MAXIMIZING PHARMACOTHERAPY IN THE TREATMENT OF MAJOR DEPRESSION: The Case for Maintaining Open Access to Medically Indicated Medications

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Executive Summary

Recent efforts by pharmacy benefit managers to contain increases in the cost of providing coverage for prescription medications have focused on decreasing total expenditures by limiting benefits to medications that are comparatively more cost effective. Two methods have been utilized, "incentive formularies," and "restricted or closed formularies." Both methods reduce both physician and patient choice, potentially leading to decreased quality of care, which over time, results in increased utilization and costs.

Many pharmacy benefit plans, especially state supported Medicaid programs, have implemented preferred drug lists to define their closed formulary. If a medication is not on the preferred drug list, no benefit is paid. Either the physician and patient must choose an alternative medication that is on the preferred drug list, or the patient must cover the cost of the medication out of their own pocket. Some plans include a "prior authorization" procedure in which the plan will allow an exemption to the preferred drug list and cover the cost of the medication if the physician can justify the medical necessity of the higher cost medication. In many plans however, prior authorization is unusually cumbersome, with a low percentage of requests for exemption being granted, and invariably leading to delays in optimal treatment, if at all.

In many cases, closed formularies have severely limited physicians' ability to choose the most effective treatment plan available for each individual patient. In closed formularies, physicians are frequently required to prescribe medications that are considered to be "second line" – clinically less effective than the physician's first choice – simply because of cost concerns. For patients with major depressive disorder (MDD), restrictions in access to the full array of medications proven to be safe and effective in treating the disease results in prolonged illness, decreased patient compliance, worsened outcomes, and ultimately, increased utilization and costs to the healthcare system due to incomplete symptomatic as well as functional recovery and significantly increased risk of relapse.

Central to the concept of restricted formularies is the misguided notion that different members of a specific class of medication are interchangeable. If the different medications within the class are interchangeable, it would be logical to choose the least expensive medication within the class. However, nothing could be farther from the truth in the medications that make up the class of "antidepressants." The concept of interchangeability is based on analyses of clinical trial results collected for approval of medications by the Food and Drug Administration.

Unfortunately, studies designed to meet FDA requirements for approval are based on a narrowly defined efficacy that a growing body of evidence now indicates does not equate to the actual effectiveness of medications in the general population.

The numerous medications used to treat depression are sub-divided into groups, usually by their mechanism of action – such as the widely used selective serotonin reuptake inhibitors or

"SSRIs" – yet substantial evidence now indicates that, while the members of specific sub-classes may be similar, each medication is pharmacologically unique – possessing a specific binding profile – and is not therapeutically interchangeable. Various antidepressant medications have been shown to have significantly variable clinical effects, side effects, and adverse effects in different subpopulations of patients with depression.

Just as the effects of different antidepressant medications are known to be highly variable, the disease of major depression itself is also highly variable between individuals and subpopulations of patients. The signs and symptoms of depression vary extensively from one individual to another, with several sub-types of depression having been identified. In addition, both a patient's symptoms and their likelihood of response to any given antidepressant medication is directly affected by the patient's age, sex, race and ethnic background, and most significantly, their coexisting medical and mental health history.

As a result of the high degree of variability in the disease itself, it is critical that a physician closely match a medication's clinical effect, side effect, and adverse effect profiles to each specific patient's needs. In choosing which antidepressant medication to prescribe for a patient, the physician works through an extremely complex decision tree that matches a patient's particular symptoms and needs to the most appropriate medication.

Restrictive formulary polices directly negate the physician's ability to accomplish this delicate yet vitally important match, resulting in lower quality of care. Formularies that restrict access to just a few of the least costly antidepressant medications result in significantly increased burden and suffering for patients, while failure to treat moderate to severe forms of major depression with the most effective and appropriate medications available results not only in incomplete recovery and potential relapse, but potentially in increasingly severe symptoms, leading to a patient's death by suicide.

If physicians are to achieve the best possible outcomes in the treatment of depression, they must aim optimal treatment toward remission -- the complete absence of symptoms and a full return to normal function for the patient. Restricting access to the wide array of medications, proven to differentially provide the best chance of remission to highly variable populations of patients, results in remission being nearly impossible to achieve.

Introduction

In the last two decades, the costs of insurance coverage for mental health claims have risen for both adult and child and adolescent patients. A significant proportion of these increases has been attributed to escalating utilization and therefore costs of prescription medications. However, this attribution may not be entirely appropriate.

An analysis by the federal Centers for Medicare and Medicaid Services (CMS) determined that during the 11 year period from 1993 to 2003, absolute total expenditures in the United States for prescription drugs indeed rose by almost 200 percent.[i] [ii] However, prescription costs actually comprise only 12 percent of the total health care costs during that time frame.

The U.S. Department of Health and Human Services in 2003 confirmed that four of the top ten leading causes of disability in the United States as well as other countries were psychiatric in origin: major depression, bipolar depression, schizophrenia, and obsessive-compulsive disorder.[iii] The economic burden of major depression alone, which the World Health Organization identifies as the leading cause of global disability[iv], was calculated to be $44 billion in the U.S. in 1990.[v] Of this total, 28 percent represented direct costs of inpatient and outpatient care. Only 3 percent of the total cost of depression was determined to be due to pharmaceutical costs. The remainder was indirect costs of lost work time and productivity.

In spite of evidence indicating that a low proportion of the total cost increases are due to the costs of prescription medications, third party insurance administrators as well as state Medicaid directors have focused cost containment efforts on reducing cost of medications. Pharmacy benefit managers (PBMs) have targeted their efforts on limiting patients' access to medications that are comparatively more cost effective, such as FDA approved generic versions of more expensive brand name products. When generics are not available, PBMs restrict access to brand name medications that are competitively priced – less expensive than other members of the same therapeutic class of medications.

The resulting list of medications accessible to patients through the PBM is commonly referred to as a preferred drug list (PDL), or more simply, a restrictive formulary. PBMs will cover the cost of medications included in the PDL automatically. However, if a patient needs a medication that is not on the PDL, the prescribing physician may be required to seek an exception to the PDL, obtaining prior authorization. Even after going through an often onerous prior authorization procedure, the physician is not assured that their patient will be allowed to take the medication they need, having its cost covered by the PBM. The result is significantly reduced quality of care.[vi] [vii] [viii]

Recent research suggests that even less restrictive incentive formularies – in which physicians and patients are strongly encouraged to choose medications that are more cost effective (again mostly generic formulations or competitively priced brand name products) in order to keep the patient's out of pocket cost at a lower co-payment – may result in decreased quality of care and worsened outcomes when patients switch to lower cost medications. In addition, the data indicate, as a greater percentage of the cost of a medication is shifted from the PBM to the patient when a more expensive medication is

prescribed, many patients simply stop taking medically necessary medications, rather than accept that increased out of pocket expense.[ix]

Major Depressive Disorder

Depression is a word commonly used by many to describe a feeling of sadness or despair, a mood that is often a temporary and quite normal reaction to adversity, difficult or unpleasant life circumstances. The word also describes a pathological disease state, often colloquially referred to as "clinical depression," in an effort to distinguish the disease of depression from the more common emotion. The disease of depression is defined by clear criteria, contained in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition -- Text Revision* [x] or *DSM-IV-TR.* Depression as a disease is chronic, occurring in repeated episodes that often begin in adolescence and continue, producing great dysfunction throughout the patient's life.

Clinical depression, more accurately termed Major Depressive Disorder (MDD or "major depression") is clearly quite different than the relatively common depressed mood sparked by one's life experiences. Unlike ordinary shifts in mood, major depression is characterized by a prolonged episode in which a person's mood noticeably changes. Unlike the normal shifts in mood that most people experience, the symptoms of major depression are more extreme and are frequently incapacitating.

Symptoms of major depression may include a persistent sad mood that is accompanied by several other symptoms, including a loss of interest in, or lack of pleasure from, activities that were previously enjoyed; significant changes in appetite that are often accompanied by a change in body weight; changes in sleep habits; a feeling of physical slowing or agitation; a loss of energy; feelings of worthlessness or inappropriate guilt; difficulty in thinking or concentrating; and recurrent thoughts of death or suicide.

Diagnosing Depression

According to the criteria specified in the *DSM-IV-TR*, a diagnosis of MDD requires that symptoms be either new, or are significantly worse than the person's status quo. In addition, the symptoms must occur for most of the day, nearly every day, and last at least two weeks.

MDD is an episodic disorder, with periods of significant symptoms interspersed with periods where the person's mood and functional level are normal. A key criterion for diagnosing an episode of major depression requires that symptoms be so significant that they impair the individual's ability to function either socially, occupationally, or in other areas, such as education, or within their family. With milder episodes, the level of functioning may appear to be normal, however the individual finds it necessary to put a significantly higher level of effort into maintaining that function.

By definition, a major depressive episode is not due to the direct effects of a drug of abuse such as alcohol or cocaine, or to the side effects of medications like steroids. In addition, the symptoms are not due to another general medical illness, such as hypothyroidism. When symptoms do occur after a major life event, such as the loss of a loved one, a diagnosis of major depression is not made unless the

symptoms are severe (causing significant impairment), and significantly prolonged (lasting for longer than two months, rather than two weeks), without improvement as time passes.

According to the *DSM-IV-TR*, patients with a major depressive episode are likely to be tearful, irritable and may brood, obsess and/or worry. In addition, they may be prone to anxiety, panic attacks, phobias, and commonly complain of pain -- headaches, joint pain, abdominal pain, and back pain. Importantly, recent research has indicated that these body aches -- referred to as somatic complaints -- are the most common symptoms complained of by patients eventually diagnosed with depression.[xi] Patients with major depression commonly have difficulty in intimate relationships, have less satisfying social interactions and may have difficulties in sexual function as well. Marital problems (often leading to separation and divorce) are common, as are occupational difficulties (decreased productivity, job loss), academic difficulties (truancy, failure), and substance abuse (most commonly alcohol).

As implied by the *DSM-IV-TR* terminology "major depressive episode," major depression is a chronic, episodic disorder which often starts early in life,[xii] and produces substantial disability.

In the United States, several studies[xiii] [xiv] have estimated the prevalence of major depression. According to the most recent report, [xv] it is estimated that 16.2 percent of those over the age of 18 will experience a major depressive episode at some point in their lifetime, representing a total of 32.6 million to 35.1 million U.S. adults. That depressive episode will occur in the next 12 months for 6.6 percent of those over 18, meaning that somewhere between 13.1 million and 14.2 million U.S. adults will experience an episode of major depression in the next year. Other studies have determined similar numbers in many countries throughout the world, resulting in a total population in excess of 120 million experiencing major depression during any given year.[xvi] [xvii] [xviii]

The average episode of depression lasts 16 weeks and nearly 60 percent of those individuals will suffer major impairment in their ability to function on a daily basis. In addition, research indicates that in roughly 70 percent of cases, major depression occurs in the setting of another mental disorder, such as an anxiety disorder, substance abuse, or "impulse control" disorder.[xix]

Depression's Impact

The costs associated with depression -- both for the individual and for society -- are enormous. According to the World Health Organization,[xx] major depression is now the leading global cause of disability when measured by the total number of years an individual lives with a disability, outranking all other diseases including heart disease and cancer. Depression is the fourth leading cause of disability resulting in premature death. A recent study[xxi] documented that depression is the cause of 48 percent of lost productivity on the job, resulting in an estimated annual loss of $44 billion to U.S. employers -- an astounding $31 billion more than the cost of lost productivity for all other causes combined.

There is also significant evidence that depression worsens outcomes for many medical illnesses, often by making it more difficult and less likely for patients to comply with their medical treatment.[xxii] For example, patients with depression are three times less likely to comply with their medical regimen than

those without depression. For patients with diabetes who are depressed, that means poorer diet, more problems regulating their blood sugar, greater disability and higher health care costs overall, compared to non-depressed diabetic patients.[xxiii] A similar relationship has been found for patients who have had a heart attack: concurrent depression makes it much less likely that they will follow dietary and lifestyle changes necessary to their recovery.[xxiv] The result is a 3.5 times higher risk of death following a heart attack for those patients who also have depression, compared to those who do not have depression.[xxv] [xxvi] [xxvii] New research also suggests that successful treatment of depression may actually lower death rates from both heart attacks[xxviii] and strokes.[xxix]

The most serious consequence of major depression is suicide. According to the *DSM-IV-TR,* suicide risk is especially high for patients who have psychotic symptoms such as hallucinations or delusions as part of their depression. In addition, patients with substance abuse, a prior history of suicide attempt, or a history of suicide within their family, all have an increased risk of attempting and completing suicide. A recent report by the Institute of Medicine[xxx] found that an estimated 90 percent of all suicides are associated with a mental illness, most commonly depression.
Because major depression is a recurring, episodic disorder, it is vitally important for patients to recognize symptoms and seek appropriate, evidence-based treatment as soon as possible.

Treating the Roots of Depression

While a considerable amount of resources and effort have been devoted to the study of depression over the last five decades, Thomas R. Insel, M.D., director of the National Institute of Mental Health, recently noted that "there has been far more success in treating this illness than in understanding it."[xxxi] Research has shown that antidepressant medications and structured forms of psychotherapy are effective treatments for 60 percent to 80 percent of those who receive them.[xxxii] However, only an estimated 25 percent to 50 percent of those who have depression receive any treatment at all, and of those that do, treatment is adequate in only one out of every four patients.[xxxiii] Studies have also indicated that the earlier treatment begins in a depressive episode, the more successful the treatment is. And treatment reduces the likelihood that an individual will relapse -- experiencing a second episode of depression -- by half. Of those that receive treatment, about 18 percent relapse within two years, while 41 percent of those that do not receive treatment relapse within two years.[xxxiv]

The most prominent current theories of the origin of depression involve complex interactions of biological factors with psychological factors and social factors. Depression is "now recognized as a multi-system disorder affecting brain and body."[xxxv] Studies have indicated that depression tends to run in families and is influenced by both genetic factors and shared environmental factors.

Through the last half of the 20th century, researchers combined the efforts and contributions of diverse fields of study including genetics, basic neuroscience, endocrinology, and brain imaging to advance the understanding of the biological basis of mood disorders. Through family studies, twin studies, and adoption studies, it has become well established that genetic influences undoubtedly play a large role in the development of MDD.[xxxvi] It is through twin studies that researchers have shown that there is no evidence that a shared environment as they grow up has a significant impact on whether or not two

twins will both develop depression. However, those same studies do show a tremendous genetic contribution to the development of major depression.[xxxvii] [xxxviii] [xxxix]

Considerable research to date has found no single "depression gene." However, a number of studies have found genetic markers that have been associated with mood disorders, including major depression and bipolar disorder as well as schizophrenia. All three disorders are now thought to be the result of multiple effects tied to a number of both major and minor gene defects. These genetic defects may predispose an individual to depression, with the disease developing when the individual is confronted with adverse environmental (psychosocial) inputs.

Pharmacologic Interventions in Depression

Today, the vast majority of patients with major depression benefit the greatest from the prescription of antidepressant medications, optimally in combination with various forms of psychosocial and psychotherapeutic interventions. The goal of treatment with antidepressants is to address the biological underpinnings of MDD, aiming for remission of its symptoms. Today, many mental health professionals prefer to begin treatment of moderate to severe MDD with medications, stabilizing the patient from a biological perspective, before pursuing psychosocial interventions to help the patient with adjustment and problem solving skills as well as the development of healthy interpersonal skills. It is thought that in moderate to severe depression, the various forms of therapy may not be as effective until the severity of symptoms can be ameliorated to some degree by medication.[xl]

The biological origins or influences that lead to the development of major depression are thought to involve the physiology and metabolism of several brain chemicals known as neurotransmitters. Early research in the 1950s spawned the "biogenic amine hypothesis" of depression, which suggested that the disease was due to deficiencies in the concentration of one or more of the neurotransmitters norepinephrine (NE), epinephrine (EPI), dopamine (DA) and/or serotonin (5-HT).[xli]

In the 50 years since the birth of the biogenic amine hypothesis, researchers have further defined the biological origins of depression, supporting the fundamental connection of disorders of mood and behavior to specific neurotransmitters. Depression is thought to be primarily mediated by disturbances in the serotonin and norepinephrine systems, with possible lesser contributions by the dopamine, GABA, and acetylcholine (ACh) systems.[xlii] Research has also shown that in addition to changes within systems of nerve cells in the brain which use these neurotransmitters, changes also occur in hormone and protein physiology in the brain.

Many researchers now believe that depression may result not simply from changes in concentration of the individual neurotransmitters, hormones, proteins, and enzymes that occur with depression but also from changes in how those neuro-chemicals function.[xliii] [xliv] Over the last 30 years researchers have discovered that each of the two primary neurotransmitters believed to be involved in depression, for example, are capable of binding to multiple different receptors on the surfaces of nerve cells. In addition, they interact with proteins and enzymes found inside of, as well as in the spaces between, nerve cells (called synapses), potentially changing the functions of those proteins and enzymes.

To date, researchers have identified at least four different cell receptors to which norepinephrine binds and at least 14 different receptors to which serotonin binds. In addition, five unique receptors have been identified for dopamine, at least two receptors for GABA, and two distinct families of receptors with which acetylcholine interacts.[xlv] [xlvi]

During the last decade of the 20th century, in particular, research into the molecular and cellular mechanisms of mood disorders exploded as new methods of study were developed, including brain imaging. It was brain imaging that, for the first time, allowed scientists to study the apparent changes in metabolism within the living brains of individuals with depression compared to those without the disease. Most intriguing were studies which found that the metabolic changes that appeared to be associated with depression[xlvii] returned to normal when the patient was given antidepressant medications.[xlviii] Imaging also allowed investigators to document anatomical changes in various parts of the brain now associated with depression. [xlix] [l] [li]

Driving research into the biological causes and mechanisms of depression was an explosion of research and development into medications to help alleviate the symptoms of depression. Researchers used new brain imaging techniques, for example, to look at the cellular effects of newly developed medications, noting where those medications were localized within the brain and attempting to define what the medications were actually doing -- the direct interactions of the medications with those receptors, proteins and enzymes within the body thought to be involved in mood regulation. By relating the medications' clinical effects -- alleviation of certain symptoms -- backward through a mechanism of action -- particular cellular effects -- researchers have greatly advanced the knowledge base of anatomical and physiological mechanisms involved in depression.

We now know today that antidepressant medications do not only change the amount of a neurotransmitter available to nerve cells, but perhaps more importantly, the medications change the way those neurotransmitters interact with specific receptors, proteins and enzymes within the central nervous system. Most of the medications also interact with similar receptors, proteins, and enzymes found throughout the rest of the human body, leading to side effects and potential adverse events. In this way, each medication has not only primary effects -- directly changing whatever cellular component it is binding to -- but also secondary (and potentially tertiary and on) effects -- through changes in the actions and interactions of those receptors, proteins, and enzymes down the "chemical line", referred to as cascade effects.[lii]

The first medication known to alleviate symptoms of depression was iproniazid, introduced in the early 1950s. Using the "reverse engineering approach,"[liii] the drug would years later be shown to bind to and block an enzyme called monoamine oxidase, which is responsible for breaking down and inactivating biogenic amines. By blocking this enzyme's activity, levels of those amines (serotonin and norepinephrine) increase. The second, imipramine, was introduced shortly thereafter. It would later be identified as a medication that binds to a cellular protein known as a reuptake transporter. Reuptake transporters collect the neurotransmitter from a synapse following a nerve signal, and recycle it back inside the nerve cell to be used again in the next signal. Imipramine binds to both the serotonin transporter and the norepinephrine transporter, inhibiting the reuptake of both neurotransmitters. The result again is elevation of the levels of both neurotransmitters available to the cells to use for signals.

While changes in the levels of neurotransmitters would be considered the medications' primary mechanism of action for many years, further research would show that the two medications also interact with numerous receptors, making the picture much more complex.

Antidepressant medications available today are generally classified as: monoamine oxidase inhibitors (MAOIs); tricyclic and tetracyclic antidepressants (TCAs); selective serotonin reuptake inhibitors (SSRIs); norepinephrine reuptake inhibitors (NRIs); serotonin-norepinephrine (or "combined") reuptake inhibitors (SNRIs); and the "atypical" antidepressants.

Perhaps the most important advance in antidepressant research occurred when it was determined that not all members of a given class of antidepressant are chemically or pharmacologically "created equal." For example, all SSRIs may block the reuptake of serotonin by binding to and inhibiting the serotonin transporter, but each individual medication is structurally different, and therefore binds to a potentially different set of individual receptors, proteins, and enzymes associated with nerve cells that use serotonin -- a property that researchers refer to as the medication's "binding profile." Each medication's binding profile defines that medication's primary therapeutic effects, secondary effects, side effects, and its adverse effects. Each of these categories of effects can, and do, vary significantly from one medication to another, even within the same class of medications.[liv] [lv] Therefore, the members of the class of "antidepressants" may be similar in their use; however, they are pharmacologically unique and not therapeutically interchangeable.

The Physician's Decision Tree

When a physician prescribes an antidepressant for a patient diagnosed with depression, many factors must be taken into account in order to ensure that the best medication is chosen to match the patient's needs. This "matching" is absolutely critical to the success of the individual patient's treatment. Because depression is so highly variable from one patient to another – a phenomenon referred to as heterogeneity – and because each of the antidepressants available has its own therapeutic as well as side effects – based upon its binding profile – the only chance for successful treatment is careful consideration of the freedom to choose the best medication for each patient.

The APA's Practice Guideline for the Treatment of Patients with Major Depressive Disorder says: "The initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for individual patients, patient preference, quantity of clinical trial data regarding the medication and its cost. On the basis of these considerations, the following medications are likely to be optimal for most patients: selective serotonin reuptake inhibitors (SSRIs), desipramine, nortriptyline, bupropion, and venlafaxine." [lvi]

The Practice Guideline emphasizes, however, that the initial selection of medication should be made only after a complete and sound diagnostic workup has occurred. A fundamental question answered during that workup is what type of depression the patient has. Is the depression uncomplicated -- fitting the standard diagnostic criteria, and occurring in the absence of any comorbid psychiatric or medical disorders? Are the patient's symptoms mild, moderate or severe?

Does the patient exhibit psychotic features with their depression, experiencing either delusions or hallucinations? Does the patient show catatonic features, seemingly unable to move and showing an extreme negative outlook? Does the patient appear to have melancholic features to their depression, experiencing a near complete absence of the ability to experience pleasure, waking up early with a sense of slowed body functions and a loss of appetite so severe that the patient has lost significant weight? Is the patient's depression atypical, having moods that actually brighten appropriately with positive input, a tendency to overeat resulting in significant weight gain, and a sense of "leaden paralysis" where the patient's arms and legs feel heavy and unable to move, usually in the morning hours?

Numerous studies have suggested different types of depression respond differently to various types of medications, therefore, the type of depression present will significantly affect the physician's choice of medication.[lvii] [lviii] [lix]

Because depression rarely occurs alone, the physician must also consider the presence of comorbid psychiatric disorders. Does the patient exhibit any symptoms of obsessive-compulsive disorder, anxiety disorders, or impulse disorders? Does the patient have a comorbid substance abuse disorder? Studies have shown that it is possible to aggravate certain comorbid disorders with certain antidepressants and it is also possible to use one medication to successfully treat more than one disorder, if the medication is carefully chosen.[lx] The presence of any comorbid psychiatric disorder will potentially affect the physician's choice of medication.

The physician must consider every patient's complete medical history in order to appropriately and safely choose an initial antidepressant medication. Does the patient have any other neurological disease, such as epilepsy, or Parkinson's disease? Does an elderly patient also have dementia or Alzheimer's disease? Does the patient have any significant heart disease, liver or kidney disorder, blood disorder, or diabetes? Studies[lxi] [lxii] have increasingly documented that each of these factors will potentially affect the physician's choice of medication.

In addition, the physician must take into account the patient's prior psychiatric history. Has the patient had a depressive episode in the past, and if so, what medications (if any) has the patient responded to in the past? Similarly, has a family member had a depressive episode for which they have received pharmacotherapy in the past? A significant evidence base has suggested that prior response of the patient or a close family member to a specific pharmacotherapy increases the chance that a patient will respond to that same medication again.

Numerous studies [lxiii] [lxiv] [lxv] have documented that among the most important aspects of choosing an initial or subsequent medication for the treatment of major depression is management of the patient's acceptability or tolerability of potential side effects. Carefully considering and executing this match, all the while involving the patient in the decision, builds a strong therapeutic alliance between the physician and the patient with the patient assured that the best possible medication therapy is being prescribed. A strong therapeutic alliance can be pivotal in promoting high rates of patient compliance and adherence to their treatment plan.

Unfortunately, however, studies have shown that 25 percent to 35 percent of all patients prescribed an antidepressant by a primary care physician stop taking the medication within one month, solely due to side effects. More than 40 percent stop their antidepressant medication within four months. Nearly 60 percent of patients never build up enough of the medication in their blood to reach a therapeutic level. Studies have also documented that adherence does improve when a psychiatrist is involved along with a primary care physician or prescribes the antidepressant. If pharmacotherapy of major depression is to have any chance of success, physicians must be able to understand the binding profiles and side-effect profiles of each of the different medications and match them appropriately to what each individual patient will accept and tolerate. Restricting physicians' and patients' ability to choose from the full array of available treatment options completely negates this valuable and vital matching of medication to individual patient.

The Unique Characteristics of Antidepressants

Every medication licensed for marketing in the U. S. today as an antidepressant has a unique chemical structure, even though many are "classed" together because they share a presumed mechanism of action (e.g. MAOIs, SSRIs, NRI, SNRIs or the "atypicals") or specific chemical structure (e.g. TCAs). Regardless of the class of medication to which an antidepressant belongs, each medication's unique chemical structure causes that medication to have a binding profile that is unique to itself.
All existing antidepressants share the ability to increase norepinephrine, serotonin or both. However, which neurotransmitter is affected by a specific medication varies widely, as does the potency of the blockade. Blocking reuptake of serotonin is associated with antidepressant effects as well as antianxiety and anti-compulsion effects. However, it also is associated with initial weight loss early in treatment with weight gain likely later. Sexual function is frequently impaired by serotonin blockade, including decreased libido.

Paroxetine is the most potent inhibitor of serotonin reuptake, followed by duloxetine, clomipramine and sertraline. Medications such as fluoxetine, citalopram, imipramine and fluvoxamine are moderate inhibitors of serotonin reuptake while amitriptyline, venlafaxine, and desipramine show only low potency inhibition. The atypical antidepressants nefazodone, bupropion, and mirtazapine do not block serotonin reuptake.

Blocking of norepinephrine reuptake is also associated with an antidepressant effect, but can lead to tremor, increased heart rates and blood pressure. The most potent inhibitor of norepinephrine reuptake is desipramine. Duloxetine is a moderate potency inhibitor, while the remaining TCAs, SSRIs, and atypicals have little or no ability to inhibit norepinephrine reuptake.
Uniquely, sertraline is a potent inhibitor of dopamine reuptake, which is associated with enhanced motivation and ability to concentrate and focus. However, dopamine blockade can lead to agitation and potentially psychosis. Nearly all of the other antidepressants have little or no effect on dopamine.
Of the SSRIs, the selectivity of the medication also varies greatly among the group. Citalopram is the most selective, blocking the reuptake of serotonin over norepinephrine by a ratio of 3,600 to one. Sertraline favors serotonin by 1,400 to one, while paroxetine and fluoxetine favor serotonin by about 300 to one.

Antidepressants which bind to the histamine-1 receptor (H_1), like amitriptyline, clomipramine and imipramine, will also have antihistamine effects, and cause sedation as well as increased appetite that may lead to weight gain. Most SSRIs bind only weakly to the H_1 receptor, and so are not usually associated with sedation. Mirtazapine and nefazodone, however, have high binding affinity for the H_1 receptor, and are associated with significant sedation.

Antidepressants which bind to the muscarinic acetylcholine receptor (Musc) are likely to cause dry mouth, blurry vision, constipation, increased heart rate, and memory impairment. Amitriptyline and clomipramine have the highest affinity for binding Musc.

Antidepressants which bind to the alpha-1 and alpha-2 adrenergic receptors, such as nefazodone, amitriptyline, clomipramine, and desipramine, lead to postural changes in blood pressure and heart rate which could result in dizziness and falls.

Antidepressants and Pharmacogenetics

In addition to determining which binding profile is most appropriate for a patient's needs, physicians must consider the race and ethnic background of the patient in order to prescribe the best possible antidepressant.

Pharmacogenetic research – the study of the interactions of medications with specific genes in particular individuals – has in the last two decades revealed that there are significant differences among population groups in the metabolism, clinical effectiveness, and side effect profiles of many medications.[lxvi]

Many psychiatric medications have now been shown to have different profiles in different population groups, particularly in persons of African, Asian and Hispanic heritage.[lxvii] [lxviii] Specific genetic variations have now been correlated with "antidepressant intolerance," a syndrome marked by significantly more severe side effects in individuals who carry specific copies of certain genes controlling drug metabolism.[lxix] In addition, researchers have identified gender differences in both the presentation of depression and its response to treatment.[lxx] Side effect differences have also been identified between men and women being treated with antidepressant medications, indicating that women are at much higher risk for sexual dysfunction.[lxxi]

To date, most of the differences in clinical effectiveness and side effect profiles of antidepressants seen in persons of different racial or ethnic background or gender have been associated with genetic differences in drug metabolism. In humans, each antidepressant is metabolized in the body through several possible pathways. Nearly all psychotropic medications, including the antidepressants, undergo what is termed "first pass metabolism." This process occurs in the liver, after a medication is absorbed through the stomach. Within the liver, medications interact with a group of enzymes called cytochromes. Most antidepressants are metabolized specifically by a family of enzymes known as cytochrome P-450. The liver metabolizes the medication from the form that is absorbed into the bloodstream into a chemical form that is more easily eliminated from the body – either by being excreted in bile through feces or by the kidneys in urine.

Some antidepressants have very potent interactions with the cytochrome enzymes in the liver. The SSRIs fluoxetine and fluvoxamine in particular, are potent inhibitors of a large number of the cytochrome enzymes that are responsible for metabolism of medications. Paroxetine is a potent inhibitor of a specific cytochrome, as are some TCAs and some atypicals, notably nefazodone and bupropion. Metabolism of other medications is slowed by the presence of these antidepressants, leading to potentially significant drug to drug interactions, known as DDIs. DDIs may be relatively benign, simply requiring a reduction or increase in dosing of particular medications, or could be serious, leading to significant side effects and adverse events, including organ failure and death. Specific genetically induced differences in certain cytochromes have led to some patients being described as "rapid metabolizers," or "poor metabolizers." In addition, genetic differences effect another form of metabolism, known as acetylation, and certain individuals are classified as "slow acetylators." All of the research to date has come together to reveal that while the individual medications within each class of antidepressant, as well as the different classes may be comparable, they are absolutely not interchangeable. It is vitally essential that physicians have available all possible antidepressants from which to choose in order to prescribe the best medication for each patient.

Efficacy vs. Effectiveness: Two Different Concepts

One of the most significant factors affecting the ability to compare one medication to another is that research to date was never designed to produce a real world comparison. In fact, many researchers now believe that data from clinical trials of medications, and especially antidepressants, is meaningless in answering the question of how well a particular medication is likely to work for the average patient seen in the clinical setting.[lxxii] [lxxiii]

The difficulty lies in the stark difference between to pharmacological concepts – efficacy, which is a medication's ability to cause a physiological effect, and effectiveness, which is a medication's ability to cause measurable improvement in a patient's clinical condition. The difference between the two concepts is subtle, yet critical.

Clinical trials in the United States have traditionally been designed to measure the efficacy of the study medication, documented by some type of objective measurement tool or scale, compared to a placebo treatment. In the case of antidepressants, the FDA's standard has been to require a drug company to show that its medication causes a statistically significantly more improvement in a patient's score on the Hamilton Depression Rating Scale (the "Ham-D") compared to patients taking placebo. The FDA traditionally has used "a 50 percent reduction in Ham-D scores" as its benchmark for a medication causing a "response."

Most researchers believe this to be an arbitrary and relatively meaningless definition that focuses on simple symptom counts and lacks any measurement of the patients' sense of "wellness" and ability to return to normal function in their daily life.[lxxiv] [lxxv] Simply put, a patient who starts out with severe symptoms and experiences a "response" equating to half of their symptoms going away is still quite ill and likely remains functionally impaired on a daily basis.

FDA generally requires two studies – usually with several hundred patients each – that compare the efficacy, as well as the safety and tolerability of a medication directly to placebo. The study must be conducted using what is known as a "double blind," that is, randomly assigning each patient to either the medication being studied or the placebo, such that neither the researchers, nor the patient, know which pill the patient is receiving. The FDA requires a confidence level of at least 95 percent ($p= 0.5$), meaning that from a statistical standpoint, the researchers are 95 percent certain that the effect they measured is not due to random chance. Historically, on average, pharmaceutical manufacturers have had to conduct eight clinical trials in order to have two meet the FDA's minimum threshold for approval of a medication.

One key factor causing clinical trial data to be suspect is that all clinical trials are conducted including what are known as "pure patients." A pure patient in an antidepressant trial is one who meets very strict criteria for major depression but does not have any other psychiatric or medical disorder. In addition, they usually may not have been treated for depression for a given period of time prior to entering the study, or if they have been, they are required to stop any previous medications for at least a short period of time to "wash out" the previous medications' effects.

Recent studies have compared characteristics of real world patients with depression to those typically included according to the "pure patient" model in clinical trials. Astoundingly, researchers have found that as high as 86 percent of patients in real-world treatment for depression would have been excluded from a clinical trial for an antidepressant, mostly due to the presence of a comorbid disorder.[lxxvi] A second similar study again found that nearly 85 percent of patients with real world depression would not qualify to participate in a clinical trial, again because of comorbid psychiatric and medical conditions.[lxxvii]

A second critical factor making it difficult to translate clinical trial efficacy into real world effectiveness is the fact that standard medication clinical trials are short-term – lasting between six and 12 weeks. Practice guidelines have long recommended that antidepressant treatment continue for a minimum of 16 to 20 weeks following remission of symptoms – that is the absence of symptoms of depression, not simply cutting those symptoms in half. Following this "continuation phase," the Guidelines further recommend that maintenance treatment be strongly considered in order to prevent relapse. Recent research has indicated that continued antidepressant therapy for at least one year and as long as three years can significantly reduce the risk of relapse.[lxxviii]

Treating Depression to Remission

No clinical trials designed to meet FDA requirements for approval are capable of measuring a medication's real world, long-term effectiveness. However there is a growing body of evidence to suggest that it is possible to adequately and accurately study a medication's ability to help patients reach and maintain remission of their depression, including symptomatic and functional recovery. Recent studies have, for example, documented that antidepressant medications which have an effect on both serotonin and norepinephrine may be more effective at establishing and maintaining remission.[lxxix] The dual reuptake inhibitor venlafaxine has been shown [lxxx] to have more powerful antidepressant

effects than other SSRIs or NRIs. There is also a growing evidence base to suggest that two dual reuptake inhibitors currently in development by pharmaceutical companies, duloxetine and milnacipran, also yield significantly greater response and remission rates than SSRIs and venlafaxine.[lxxxi] [lxxxii]

Conclusion

If physicians are to achieve the best possible outcomes in the treatment of depression, they must aim optimal treatment toward remission -- the complete absence of symptoms and a full return to normal function for the patient.

Restricting access to the wide array of medications, proven to differentially provide the best chance of remission to highly variable populations of patients, results in remission being nearly impossible to achieve.

Many concerns regarding the high cost of antidepressant medications will be addressed by pending patent expirations of several popular antidepressants in the next three years. The antidepressants fluoxetine (Prozac), fluvoxamine (Luvox) and bupropion (Wellbutrin) are already available in more cost-effective generic formulations. In mid - 2003, a generic formulation of paroxetine mesylate, a "chemical cousin" of paroxetine hydrochloride, the active ingredient in Paxil, was made available in addition to generic formulations of nefazodone (Serzone). In 2004, patent protection is expected to end for citalopram (Celexa) followed in 2005 by paroxetine hydrochloride (Paxil) and in 2006 by sertraline (Zoloft). As these generics enter the marketplace, the cost of antidepressant therapy will significantly decrease.

If PBMs insist on utilizing formulary restrictions, it is critical that they be employed in a manner which preserves a physician's best clinical judgment for first line antidepressant therapy. As such, switching of medications (often referred to as “therapeutic substitution" as differentiated from generic substitution) without the approval of the treating physician, is contrary to medical practice guidelines and essentially voids the physician's clinical judgment. This, of course, is not true of generic substitution.

Fail-first policies, requiring physicians to prescribe one -- or even two -- formulary drugs, and document that the patient did not respond, before the physician is permitted to prescribe from outside the formulary are contrary to medical practice guidelines, and negate a physician's clinical judgment. In addition, these polices potentially delay a patient from receiving appropriate treatment, worsening outcomes, in addition to exposing them to medications which may actually aggravate their depression.

Finally, it is absolutely essential that psychiatrists be included as members of formulary review boards that are reviewing psychotropic agents. Inclusion of a Pharm.D. with certification in psychopharmacology does not sufficiently meet this need. Psychiatrists are uniquely qualified to recognize and manage the intricate and idiosyncratic presentation and course of psychiatric diseases, including depression. This vital knowledge and experience base cannot be filled by non-psychiatric

physicians, a psychiatric physician assistants or nurse practitioners, nor a Pharm.D., certified in psychopharmacology.

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