



Office of Healthcare Systems & Financing
1000 Wilson Boulevard, MS 1825
Arlington VA 22209
800 343 4671 • HSF@psych.org
Irvin Muszynski, JD, Director

MAXIMIZING PHARMACOTHERAPY IN THE TREATMENT OF SEVERE AND PERSISTENT MENTAL ILLNESS: The Case for Maintaining Open Access to Medically Indicated Medications for Schizophrenia¹

Prepared for:

The Office of Healthcare Systems and Financing
American Psychiatric Association
March 2004

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EXECUTIVE SUMMARY

It is well established that the cost of prescription medications has risen dramatically over the last decade, presenting a significant fiscal challenge to both private and government mediated health insurance plans (e.g. state Medicaid programs) that offer medication coverage. Recent efforts by pharmacy benefit managers to contain these increasing costs have focused on decreasing total pharmaceutical expenditures by limiting coverage to the most cost-effective medications within given therapeutic classes of drugs.

Because of the relatively high cost of newer-generation antipsychotic medications, pharmacy benefit managers have focused cost containment efforts on this increasingly utilized class of drugs. Two primary methods of cost containment have been utilized, "incentive formularies", and "restricted or closed formularies". Evidence now indicates that both methods ultimately result in the opposite of their intended effect: they reduce physician and patient choice, potentially resulting in decreased quality of care, which over time, results in increased utilization and rising costs.

Many pharmacy benefit plans, especially state supported Medicaid programs, use preferred drug lists to define their restricted formularies. 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.

This is extremely concerning for patients who take antipsychotic medications, as these medications are most commonly prescribed to persons with severe and persistent mental illness. These patients are some of society's most highly disadvantaged and marginalized citizens. They are significantly disabled, often unemployed, uninsured, and commonly homeless. It is extremely unlikely that they would be able to pay for their own medications.

In many cases, closed formularies have severely limited physicians' ability to choose the most effective treatment plan available for each individual patient. In restricted formularies, physicians are frequently required to prescribe medications that they consider to be "second line" – clinically less effective than the physician's first choice – simply because of cost concerns. In some formularies, patients are required to "fail first" on less expensive medications, before their physicians are allowed to prescribe more costly medications that are often more effective as well as safer.

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 were interchangeable, it might be logical to choose the least expensive medication within the class, administering that medication to a wide variety of patients with relatively equal effect at the lowest possible cost to the pharmacy benefit program.

However, nothing could be farther from the truth with regard to the medications that make up the class of "antipsychotics", so named for their initial use in treating the classical psychotic delusions and hallucinations associated with schizophrenia. Today these medications are increasingly prescribed to treat many severe and persistent mental illnesses, among them bipolar disorder, psychotic depression, and aggressive conduct disorders. Here, for simplicity, we concentrate our discussion on the use of antipsychotic medications in the treatment of schizophrenia, although the pharmacologic principles contributing to the non-interchangeability of these medications apply to their use in other disorders as well.

All antipsychotic medications are thought to act primarily on the brain's dopamine system, blocking dopamine activity and thereby reducing symptoms of psychosis, mania, and aggression. A vast body of research has confirmed that each of the three generations of antipsychotic medications affects dopamine activity in different ways. In addition, newer-generation medications also act on the brain's serotonin system, helping to alleviate the significantly debilitating mood and cognitive symptoms of schizophrenia, significantly reducing long-term disability and dysfunction.

Because each medication acts through its own individual mechanisms – referred to as a binding profile – each individual medication has slightly different clinically desirable effects as well as side effects. While these differences may be subtle, they are clinically significant. In fact, it is the side effect profiles of the antipsychotic medications which make each medication markedly unique.

Just as the effects of different antipsychotic medications are known to be highly variable, the signs and symptoms of schizophrenia are also highly variable between individuals and subpopulations of patients. As a result of this high degree of variability in the disease itself, it is critical that an experienced physician specializing in the treatment of mental illness closely match a medication's clinical effect, side effect, and adverse effect profiles to each specific patient's needs. In choosing which antipsychotic 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 policies directly negate the physician's ability to accomplish this delicate yet vitally important match, resulting in decreased quality of care. Formularies that restrict access to a subset of the full range of antipsychotic medications currently available result in significantly increased burden and suffering for patients with schizophrenia. For these patients, restrictions in access to the full array of medications proven to be safe and effective in treating this severely disabling disease results in prolonged illness, decreased patient compliance due to intolerable side effects, 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.

Indeed, for patients with schizophrenia, limitations on access to the most effective and appropriate medications available results not only in incomplete recovery and potential relapse, but carries significant risk of death as persons with schizophrenia are at significantly higher risk of suicide compared with the general population.

Cost-containment measures involving antipsychotic medications must be employed in a manner which preserves a physician's best clinical judgment for each individual patient. PMBs that employ highly restrictive formularies, allow open therapeutic substitution, and enforce fail-first policies, operate contrary to best practice guidelines and disavow physicians' highly developed clinical judgment, resulting in severe potentially fatal consequences for patients. In contrast,

evidence is now emerging that strategies that are aimed at prescriber education and disease management are both clinically and cost-effective.

INTRODUCTION

In the last two decades, the costs of insurance coverage for mental health claims has risen for patients of all ages. A significant proportion of these increases has been attributed to escalating utilization of medications, resulting in higher expenditures. This is especially true for patients with severe and persistent mental illnesses, such as schizophrenia, schizoaffective disorder, psychotic depression, and bipolar disorder.

These illnesses, by their very nature, commonly require ongoing, often long-term administration of antipsychotic and other medications, resulting in high utilization of pharmacy services and high expenditures, largely due to the high cost of many antipsychotic medications. Because of the highly debilitating effects of these disorders, patients often are unemployed and, as a result, uninsured. Therefore, access to mental health services for the severely and persistently mentally ill is often confined to the Medicaid system.

The U.S. Department of Health and Human Services in 2003 recognized that four of the top ten leading causes of disability in the United States were indeed psychiatric in origin: major depression, bipolar depression, schizophrenia, and obsessive-compulsive disorder.ⁱ In particular, a recent 14-country study estimated that in 1991, schizophrenia ranked as the third most disabling disorder.ⁱⁱ Patients with schizophrenia make up roughly 10 percent of the totally and permanently disabled population, consuming around 2.5 percent of total annual health care expendituresⁱⁱⁱ. In 1990, direct costs of the disease in the U.S. were pegged at \$17.3 billion, and indirect costs, including lost productivity, amounted to an additional \$15.2 billion.^{iv}

An analysis by the federal Centers for Medicare and Medicaid Services (CMS) confirmed that during the 11 year period from 1993 to 2003, absolute total expenditures in the United States for prescription drugs rose by nearly 200 percent.^v ^{vi} However, CMS determined that prescription costs comprised only 12 percent of the total health care costs during that time frame.

In spite of the relatively low proportion of expenditures dedicated to prescription medications, state Medicaid directors have focused cost containment efforts on reducing costs of those medications. Pharmacy benefit managers (PBMs) have in part targeted their efforts on limiting patients' access to psychiatric medications, particularly newer generation antipsychotics, because of their high relative costs.

PBMs have promoted 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, allowing only those 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, known as 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, while having its cost covered by the PBM. For patients with severe and persistent mental illness, such as schizophrenia, this is particularly troublesome, as they are highly likely to be economically disadvantaged and marginalized. Without coverage by

Medicaid for their prescriptions, patients with schizophrenia cannot afford to pay for the medication themselves, and simply stop taking it. The result is a disastrously reduced quality of care and negative outcomes, including potential relapse and re-hospitalization.^{vii viii ix} Similarly, if a patient has been stable on a particular antipsychotic medication and is required by the PBM to switch to a different drug, in order to have the medication covered, the result is often destabilization with significantly negative consequences.

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, again, many patients choose to simply stop taking medically necessary medications, rather than accept the increased out of pocket expense.^x

Indeed, for many patients with schizophrenia and other persistent and severe mental illnesses, it is inherently difficult for them to take their medications to begin with. Some estimates say as high as 70 percent to 80 percent of patients with schizophrenia do not take their medications as directed by their physicians. The reasons are numerous and complex, including patients' poor insight, cognitive deficits and mood symptoms that are part of the disease process. Also high on the list of significant barriers to patients consistently taking their medications are the often significant side effects associated with antipsychotic medications.

Recently many state Medicaid programs have attempted to engage policy reforms that limit access to the newer-generation, and more costly, antipsychotics. Commonly, only certain, competitively priced newer-generation drugs are included on the PDL, in addition to the older antipsychotic medications, all of which are available in inexpensive generic formulations.

These policies restricting access are based upon the flawed assumption that the various members of the antipsychotic class of medications are therapeutically equivalent and that substitution of less expensive medications within the class is clinically possible and appropriate. In reality, the opposite is true. The first-generation antipsychotics are pharmacologically significantly different from second and third-generation antipsychotics. In addition, members of the second-generation are individually unique, with differential effectiveness and side effect profiles. The recently introduced first of the third-generation of antipsychotics is unique unto itself.

A vast body of scientific research shows that therapeutic substitution of antipsychotic medications, based on cost considerations, is not only medically inappropriate, but potentially harmful, and may lead to higher services utilization and costs.

DEFINING SCHIZOPHRENIA

The most debilitating of all mental illnesses, schizophrenia is a disorder which is commonly misunderstood by the public. Contrary to everyday usage, schizophrenia does not involve "split" or multiple personalities. Rather, schizophrenia is defined by the *Diagnostic and Statistical Manual of Mental Disorders – Forth Edition – Text Revision (DSM-IV-TR)* as a primary psychotic disorder.^{xi} The term "psychotic" refers to the presence of specific symptoms: delusions, hallucinations, disorganized speech, and/or disorganized or catatonic behavior.

Schizophrenia is found in every country across the globe in which mental illness has been studied. Incidence rates for schizophrenia vary somewhat with the particular population studied, however range between 1 and 4 cases per 10,000 persons per year.^{xii}

Currently, the National Institute of Mental Health (NIMH) estimates that approximately one percent of the U.S. population develops schizophrenia during its lifetime,^{xiii} equating to over 2 million Americans suffering from the illness in a given year. The disease affects men and women equally, however, men usually manifest the disease in their late teens or early twenties, while women are generally affected in their twenties to early thirties.

Schizophrenia is a global brain disorder, affecting many different aspects of thinking processes, emotion, and behavior. Dysfunctions commonly exist in patients' perception of their world, inferential thinking, language and communication, ability to monitor their own behavior, emotional state and consistency, productivity and fluency of thought and speech, volition and drive, and attention. No single symptom is definitive of schizophrenia, rather the disease is marked by a constellation of symptoms that significantly and often severely impair the patient's ability to function in social, educational and occupational settings.

The hallucinations experienced by patients involve perceptions that occur without any connection to an appropriate, real source. They may be auditory, hearing voices that no one else hears; visual, seeing sights that are not real; or tactile, feeling sensations that have no source. In contrast, delusions are personal beliefs that have no grounding in reality, and commonly take on different themes. Delusions of grandeur or paranoia are common.

While hallucinations and delusions are the most common outward symptoms of the disorder, internally patients with schizophrenia suffer from disordered thinking – or an inability "to think straight." Thoughts may come and go rapidly, may not be relevant to the situation at hand, are often illogical, disorganized, or fragmented.

In addition, most patients with schizophrenia have a "flat affect" – that is, they have significantly reduced emotions and expressions. They are socially withdrawn, and often have low motivation and may disregard efforts to maintain personal hygiene.

While patients may often become anxious or agitated, there is no predisposition to violence inherent within schizophrenia, another common public misconception. Coexisting problems with substance abuse may increase the likelihood of violence, as can a history of violence or criminal activity prior to becoming ill.

The causes of schizophrenia have not been clearly illuminated, however, it has been known for many years that the disorder runs in families. A recent report analyzed results from 12 different studies of twins to determine a pooled risk of inheriting the disorder.^{xiv} The analysis determined that approximately 81 percent of the risk of developing schizophrenia is genetic, confirming a wide body of previous evidence. However, researchers also confirmed that at least some risk is due to a patient's environment, pegging the environmental influence at approximately 11 percent.

To date, no specific genes have been linked to the development of schizophrenia, however, researchers are actively studying associations between a number of genes and increased risk of developing the disorder. It is clear that the disorder is a complex trait – that is, there is no single, magical, "schizophrenia gene," rather numerous genes most likely combine to create the disorder when influenced by specific environmental triggers.

Several developmental conditions have been associated with the disorder^{xv}: significant illness (malnutrition or viral infections) of a pregnant women carrying a child that later develops schizophrenia; complications during pregnancy (mother-child blood type incompatibilities); birth complications/injuries (lack of oxygen or head trauma during birth.) However, no particular risk factors have been consistently demonstrated as being critical to the development of schizophrenia.

Brain studies of adults with schizophrenia have shown that abnormalities – both structural and functional – exist at many levels of neurobehavioral and neurophysiological processing as well as within several different brain systems. Most experts currently hypothesize that these widespread abnormalities – which they believe are clearly indicative of developmental abnormalities – are not fully expressed as a recognizable disorder until the brain is in the final processes of completing its maturation during late adolescence and early adulthood.^{xvi} Most agree, however, that invariably, some symptoms are present much earlier, often years before a patient's first psychotic episode.

As noted above, schizophrenia is severely disabling. It is estimated by NIMH that as many as two thirds of all homeless persons in the United States have schizophrenia^{xvii} and approximately 10 percent of all persons determined to be permanently disabled have schizophrenia.^{xviii} Patients are likely to be unemployed, unmarried or divorced, and commonly become involved with the criminal justice system.

In addition, the societal costs of schizophrenia are severe. Morbidity and mortality in patients with schizophrenia is unusually high, with death rates estimated by NIMH and WHO at least twice that of persons with no mental illness. The increased death rate is related to very poor levels of self care; homelessness; unemployment; a lack of consistent quality health care due to being uninsured; consequent higher rates of medical illness, including diabetes and cardiovascular disease; prolonged institutionalization; high rates of communicable diseases – including tuberculosis, HIV and hepatitis; high rates of comorbid substance abuse; and finally, critically high rates of suicide. Numerous studies have documented rates of attempted suicide at nearly 50 percent and completed suicide around 10 percent, nearly 12 times the rate in the general population.^{xix xx xxi}

Schizophrenia is listed by the WHO as the third leading cause of global disability in persons aged 15 to 44 years, as measured by the total number of years lived with disability. In the year 2000, schizophrenia accounted for 4.9 percent of total global disability burden in this age group.^{xxii} In persons of all ages, schizophrenia ranked seventh, at 2.8 percent of global burden of disability.

DIAGNOSING SCHIZOPHRENIA

Psychotic disorders are diagnosed using the criteria specified in the *DSM-IV-TR*.^{xxiii} The symptoms of schizophrenia are divided into three broad groups: positive symptoms, negative symptoms, and cognitive deficits. Positive symptoms are those that appear to be an excess or distortion of normal functions – such as delusions or hallucinations – while negative symptoms reflect a deficit in normal functions – such as a lack of emotional response or slowed movements, loss of goal directed behavior and decreased thought and speech production, as well as social withdrawal. Cognitive deficits include disorder thinking, decreased ability to concentrate or hold attention, difficulties with working memory, and executive function.

The diagnostic criteria require two (or more) characteristic symptoms to be present "for a significant portion of time during a 1-month period." The five characteristic symptoms listed by *DSM-IV-TR* are: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms such as affective flattening, lack of motivation, or decreased thought and speech production.

In addition, a significant portion of the time since the onset of symptoms must be spent experiencing marked dysfunction, at work or school, in interpersonal relationships, or self care.

Signs of the disorder must persist for at least six months, including the one month period of overt characteristic symptoms described above.

The characteristic symptoms observed cannot occur along with major depressive, manic or mixed periods, or the patient may have schizoaffective disorder or mood disorder with psychotic features, rather than schizophrenia. While mood symptoms can and do occur in schizophrenia, they are brief and less severe compared with active characteristic symptoms.

The patient's symptoms may not be due to the effects of a drug of abuse, a medication, or a general medical or neurological condition and must be carefully differentiated from pervasive developmental disorder or autism.

Schizophrenia may be classified as paranoid type if prominent delusions or auditory hallucinations occur with minimal dysfunction in cognition and emotion. The delusions are typically persecutory or grandiose, or both, and may take multiple forms, organized around a central theme. The disorganized type of schizophrenia, in contrast, presents with more prominent disorganization in speech and behavior as well as a flat or inappropriate affect. Catatonic schizophrenia is marked by an inability to move, or excessive motor activity, and extreme negativism, complete lack of speech, or echolalia (a parrot-like repeating of apparently senseless words or phrase fragments spoken by someone else.)

A complete and thorough psychiatric and general medical history and physical examination of any patient presenting with psychotic symptoms must be completed by a psychiatrist. Examination must include a complete mental status exam, a neurological exam, and laboratory tests. Assessment for medical causes of a patient's symptoms of psychosis is especially important because numerous medical conditions may present with psychosis, including Cushing's syndrome, epilepsy, brain tumors, traumatic brain injury, and metabolic disorders, among others. Substance abuse must be also be ruled out as a cause of psychotic symptoms as many illicit substances (amphetamines, cocaine, PCP, LSD) may cause delusions and/or hallucinations as well as disorganization of thought, speech, and behavior.

Lastly, it is vitally important for the psychiatrist to ascertain the presence of comorbid mental illness in order to establish a primary diagnosis of schizophrenia, differentiating it from schizoaffective disorder, or a mood disorder with psychotic features.

Treating Severe & Persistent Mental Illness

The goal of acute treatment for schizophrenia is the rapid reduction of positive symptoms of psychosis.^{xxiv} As positive symptoms decrease, the risk of self-harming behaviors (including suicide risk) decreases and disturbed behaviors are controlled. Some evidence exists to suggest that rapid acute treatment results in a return to the highest possible level of function for the patient, while delayed or ineffective treatment is associated with worsened prognosis and outcomes.

Because of the severity and persistence of disorders like schizophrenia, chronic treatment aims to prevent relapse of psychotic symptoms while addressing ongoing negative symptoms and cognitive deficits. Most importantly, research ^{xxv} has shown that if patients are to regain lost functionality at home, at school, or in the workplace, negative symptoms and cognitive deficits must be addressed and successfully treated. Studies have shown that it is the negative symptoms and cognitive deficits that drive the long-term disability of patients with schizophrenia.^{xxvi xxvii}

PHARMACOLOGIC INTERVENTIONS IN SCHIZOPHRENIA

Antipsychotic medications are the foundation of treatment for psychotic or positive symptoms. Today, antipsychotics are grouped into three sub-classes, according to the chronology of their development and subsequently, their putative mechanisms of action. The earliest medications to treat psychosis, introduced in the early 1950s, are now known as first-generation antipsychotics. For decades they were referred to as "conventional" or "typical" neuroleptics. These were followed some forty years later by the second-generation antipsychotics, introduced between 1990 and 2001. They are more commonly referred to as "atypicals". The first of the third-generation of antipsychotic medications was approved in the U.S. in late 2002.

First used in 1952 as a sedative by surgeons, chlorpromazine (Thorazine) was observed to produce a relaxed, indifferent attitude in surgical patients, without making them lose consciousness – an effect referred to by the surgeons of the day as "a chemical lobotomy." Chlorpromazine became the first antipsychotic medication as psychiatrists quickly started using the drug in patients with psychosis and reported significant improvements in their symptoms.

Unfortunately, those same psychiatrists also quickly began noting that many patients treated with chlorpromazine were exhibiting side effects similar to Parkinson's disease – muscle twitching, tremor and an unsteady, halting, gait. These effects would later become known as extrapyramidal side effects (EPS).

By 1961, an estimated 40 percent of patients taking a first generation antipsychotic were reported to have medication-induced EPS.^{xxviii} Today, EPS is known to occur in 75 percent to 90 percent of patients taking first-generation medications.^{xxix} Especially concerning for patients as they took antipsychotic medications for longer periods of time were persistent involuntary contractions of muscles surrounding the mouth and out into the cheeks, causing nearly constant and alarming facial contortions and twitching that clinicians' labeled tardive dyskinesia (TD). The annual incidence of TD in young, otherwise healthy patients with schizophrenia taking first-generation medications is 4 percent to 5 percent ^{xxx}. The incidence of TD increases as the age of the patient increases, or as patients take the drug long-term.^{xxxi}

Through the late 1950s and on into the 1970s, driven by the burden of EPS, nearly 40 first-generation antipsychotics were introduced in an effort to find an equally effective, but safer drug. They included thioridazine (Mellaril), fluphenazine (Prolixin), perphenazine (Trilafon) and trifluoperazine (Stelazine), to name but a few. These were followed by haloperidol (Haldol), arguably the most successful of all the first-generation medications. The final first-generation antipsychotic, molindone (Moban), was approved in 1975.

The quest for equally effective but safer antipsychotic medications continued onward into the second generation drugs. The first second-generation medication, clozapine (Clozaril) was synthesized in 1958 in Switzerland, however, was not approved in the U.S. until 1990. Risperidone (Risperdal) followed in 1994, olanzapine (Zyprexa) in 1996, quetiapine (Seroquel) in 1997, and ziprasidone (Geodon) in 2001.

With the introduction of aripiprazole (Abilify) late in 2002, the third generation of antipsychotics was born.

THE UNIQUE CHARACTERISTICS OF ANTIPSYCHOTICS

Each of the first-generation medications is chemically closely related to the others within the sub-class, and shares a common mechanism of action: the ability to block the effects of the neurotransmitter dopamine^{xxxii xxxiii xxxiv}. The newer first-generation antipsychotics were not more (or less) effective than those already available, they simply varied in potency^{xxxv}. Chlorpromazine and thioridazine are relatively low potency antipsychotics, while fluphenazine and haloperidol are the highest potency first-generation medications.

Nearly all of the first generation antipsychotics shared similar, very significant, side effects in varying degrees^{xxxvi xxxvii} – sedation, cognitive slowing, memory impairment and confusion (often referred to as “cognitive parkinsonism”), as well as frequent EPS, including parkinsonism, akathisia (an intense feeling of restlessness, often described as “wanting to jump out of my skin”) and TD. Other side effects include weight gain, blood pressure and heart-rate changes, and disturbances in heart rhythm that are potentially fatal.

A medication’s effects are directly correlated with what is pharmacologically known as its “binding profile” – those receptors, proteins, and cellular components in the body with which the drug physiologically interacts. A significant body of evidence now suggests that all antipsychotics reduce the positive symptoms of psychosis by blocking the actions of the neurotransmitter dopamine in specific areas of the brain. In particular, antagonism (or blockade) of dopamine type 2, or “D₂”, and D₂-like receptors, is responsible for the primary antipsychotic actions of both the first and second-generation medications.^{xxxviii xxxix xl}

The single third-generation drug works through a significantly different mechanism: partial agonism at D₂ receptors.^{xli} As a partial agonist, when levels of dopamine are high, aripiprazole blocks dopamine receptors, reducing dopaminergic activity. When levels of dopamine are low, the drug boosts the sensitivity of the receptors to the dopamine that is available. The same relationship is true for aripiprazole’s interaction with specific types of serotonin receptors. As a result, some refer to the drug as a dopamine/serotonin system stabilizer.

While most of the first-generation medications were chemically similar to each other, only two of the newer-generation medications are chemically related: olanzapine is a chemical derivative of clozapine. Each of the other four newer-generation medications available today is chemically unique, and therefore, has unique clinically desirable effects as well as side effects, based upon its own unique binding profile.

An emerging theory proposes that blockade of dopaminergic activity at D₂ receptors specifically within the meso-limbic area of the brain – known as the A10 dopaminergic tracts – is related to antipsychotic action.^{xlii} Binding to D₂ receptors in other areas of the brain is related to side effects, such as EPS and increased levels of the hormone prolactin.

An extensive amount of research has been completed comparing various members of the antipsychotic class. Studies now directly compare the efficacy and side effects of first-generation medications to those of second-generation medications. A large body of evidence now shows that there are also significant differences between individual members of the second-generation as well.

Efficacy vs. Effectiveness: Two Different Concepts

A series of recent meta-analyses has attempted to combine all published clinical trial data on each of the available second-generation antipsychotics, and compare the combined results to a first-generation medication, most usually haloperidol or chlorpromazine. Each of the studies has noted difficulty in attempting to make such comparisons because of a great deal of variability within the data for each of the medications – that is, different clinical trials have produced different results with the same drug. However, most researchers believe the differences are attributable to differences in methodology of individual studies.

A large British meta-analysis^{xliii} in 2000 concluded that as a group, the evidence was not clear that second-generation medications were more effective, compared to low doses of the high-potency first-generation medication, haloperidol. It was clear that compared to higher doses of haloperidol, second-generation medications had significant advantages – lower incidence of EPS, better cognitive function, and less sedation. In fact, the study conclusively noted that the newer medications caused fewer EPS – even when compared to low-dose haloperidol – a clinically significant advantage over first-generation medications.

A subsequent study determined that second-generation medications are a major advancement over the older drugs^{xliv}, providing benefits to patients that have a history of sub-optimal response to first-generation medications. The researchers noted that both olanzapine and risperidone appear to be superior to haloperidol on cognitive measures, and clozapine is superior with aggressive or suicidal patients. In addition, they again note that newer-generation antipsychotics show less burden of EPS, including a lower risk of TD. They also cite improved efficacy for negative symptoms and cognitive dysfunction.

In 2003, the most in-depth meta-analysis of the efficacy of the second-generation antipsychotics^{xlv} determined that in comparison to first-generation medications (both haloperidol and chlorpromazine) at any dose, clozapine, risperidone and olanzapine were clinically significantly more effective. The other second-generation medications were found to be equally effective haloperidol and/or chlorpromazine, emphasizing that the individual second-generation medications as a group are not equivalent or interchangeable.

In a 2003 meta-analysis of clinical trial results that measured rates of relapse^{xlvi} second-generation medications were determined to have modest but clinically significant advantages over older drugs in both rates of relapse and treatment failure.

A 2003 systematic review and meta-analysis^{xlvii} compared newer-generation medications with low-potency first-generation medications (mostly chlorpromazine). The low-potency older drugs have been shown to have less risk of significant side effects, in particular, lowered potential for EPS. However, this analysis found that second-generation medications were moderately more efficacious than low-potency older antipsychotics, regardless of the dose of the older drug used.

Lastly, clozapine has been shown to be superior to both the first-generation medications, and the other second-generation medications in treating positive symptoms^{xlviii xlix} as well as for the treatment of treatment resistant patients^l and patients who are suicidal.^{li} In fact, in 2003, the U.S. FDA approved a formal indication for clozapine for the treatment and prevention of suicidal ideation and behaviors.

While all of the studies cited above have looked at data from clinical trials, which are concerned with measuring a drug's efficacy under tightly controlled conditions, a large multi-center study is currently underway to measure the comparative effectiveness of antipsychotic medications in the real-world clinical setting. The \$47 million National Institute of Mental Health funded "Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia" trial ("CATIE") has recently completed the enrollment of 1,600 patients nationwide who are being treated with one of the six newer-generation medications, or perphenazine or fluphenazine decanoate, a long-acting injectable first-generation medication. Results from the real-world comparative study are not expected until 2007.

Differential Side Effects

A large body of evidence also confirms that not only do the individual antipsychotic medications differ in efficacy, they differ in their risk of certain side effects. These differences are directly linked to the different binding profiles of the individual medications.

A series of studies^{lii liii liv} have noted that while all of the newer-generation medications have lower risk of EPS compared with first-generation medications, the newer drugs differ among themselves as well in their association with EPS. In general, risperidone appears to have the highest liability for EPS (although still significantly lower than older drugs), followed by olanzapine and clozapine having moderate risk for EPS. Quetiapine, ziprasidone, and aripiprazole have little or no associated risk of EPS.

Numerous studies^{lv lvi lvii lviii} have documented the risk of weight-gain associated with antipsychotic medications, and the potential development of dysfunction in the patient's ability to regulate glucose, cholesterol and lipids. This dysfunction is clinically significant because of the risk of developing insulin resistance, which may lead to diabetes, heart disease, and kidney and liver problems. Of note, weight gain appears to be the greatest with clozapine, risperidone and olanzapine and only slight with quetiapine. Weight gain has not been associated with ziprasidone or aripiprazole. Differing incidence of diabetes and diabetes-like dysfunction in glucose regulation also vary significantly from one drug to the next.

The secretion of the hormone prolactin by the anterior pituitary in the brain is controlled by dopamine, and as a consequence of generalized dopamine blockade by older antipsychotics, levels of prolactin often are elevated during antipsychotic treatment. This is also true with the second-generation drug, risperidone, however is not associated with any of the other newer drugs.

Prolonged increases in prolactin levels leads to breast enlargement and sexual and reproductive dysfunction in both males and females.^{lix lx}

The Physician's Decision Tree

When a physician prescribes an antipsychotic, 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 the specific symptoms of schizophrenia are so highly variable from one patient to another – a phenomenon referred to as heterogeneity – and because each of the antipsychotics 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 and the freedom to choose the best medication for each patient.

Many efforts have been focused on assisting physicians in this critical matching of specific medication to individual patient. Significant efforts have been focused on prescriber education, beginning with the American Society of Clinical Psychopharmacology's Model Curriculum^{lxix} for psychiatric residency programs, training directors and teachers of psychopharmacology. The modules in the curriculum are evidence based and aimed at providing the foundation for good clinical decisions.

In addition, the now well known Texas Medication Algorithm Project has published medication flowcharts to guide physicians in their clinical decisions regarding schizophrenia and the use of antipsychotic medications.^{lxii lxiii} Additional programs and research are available, addressing the utility and cost-effectiveness of polypharmacy with antipsychotics, versus optimum dosing of single medications.

Conclusion

If physicians are to achieve the best possible outcomes in the treatment of severe and persistent mental illness, they must aim optimal treatment toward remission -- the complete absence of symptoms and a full return to normal function for the patient. Once remission is obtained, the focus of maintenance treatment must be the prevention of relapse as well as ongoing, sub-syndromal symptoms.

A substantial body of research now indicates that each of the available second-generation antipsychotic medications, as well as the first of the third-generation medications, has been proven to possess clinically significant differences from the other medications within the therapeutic class. Individual patients' response to different medications is variable, as is the risk of side effects. Therefore, it is absolutely critical that physician's closely match a specific medication to each individual patient's needs.

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. This invariably leads to worsened outcomes, increased utilization and higher expenditures.

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 antipsychotic 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 policies potentially delay a patient from receiving appropriate treatment, worsening outcomes, in addition to exposing them to medications which may actually aggravate their illness.

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, especially severe and persistent mental illnesses such as schizophrenia. 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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