to oral therapy, and the treatment of adverse effects. In addition, relapse costs may be less if patients who received i.m. olanzapine or ziprasidone in the hospital did not experience uncomfortable dystonic reactions and are therefore more likely to adhere to therapy as outpatients.

Quality-of-life issues become important when choosing maintenance therapy for patients with schizophrenia. The last article reviews potential adverse effects of antipsychotic therapy that should be considered, such as weight gain, diabetes mellitus, extrapyramidal symptoms, sexual dysfunction, cognitive dysfunction, and cardiac effects. Although the newer antipsychotic agents are not devoid of adverse effects, those that do occur, such as weight gain, can be managed. Because the newer antipsychotics are equally effective in improving the positive symptoms and more effective in improving negative symptoms and cognitive deficits associated with schizophrenia, patients now have the hope of being reintegrated into society. Having patients with fewer negative symptoms and improved cognitive functioning has revealed a host of new challenges in this patient population, such as improving long-term adherence to therapy, ensuring continuity of care, and providing life-skills rehabilitation.

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**Comprehensive understanding of schizophrenia and its treatment**

**Gerald A. Maguire**

**Abstract:** An overview of schizophrenia is presented, including diagnostic criteria, etiology, neurologic findings, pharmacotherapy options, quality-of-life issues, and the financial impact of the disease.

Schizophrenia is a chronic disease characterized by positive symptoms, negative symptoms, mood symptoms, and cognitive deficits. Often comorbid substance abuse is present. Schizophrenia accounts for 20% of all hospital bed-days and over 50% of all psychiatric beds in the United States. There is a strong genetic component to schizophrenia, and other possible contributing factors are explored. The diagnostic workup should include a detailed longitudinal history, mental status exam, physical and neurologic exams, and laboratory tests. A magnetic resonance imaging scan can rule out structural causes of psychosis and should be considered at the time of diagnosis. Treatment is based on a biopsychosocial model including pharmacotherapy in combination with individual, group, and family therapies. Rather than classifying antipsychotics as typical or atypical, a new classification scheme has been proposed based on risk of causing extrapyramidal symptoms and tardive dyskinesia (TD), effect on prolactin level, and efficacy profile: first-generation or traditional agents (e.g., chlorpromazine and haloperidol); second-generation agents (e.g., risperidone and ziprasidone); and third-generation agents (e.g., clozapine, olanzapine, and quetiapine). The binding affinities of antipsychotics in the brain help explain the mechanisms by which different antipsychotics alleviate specific symptoms of schizophrenia, as well as cause specific adverse effects.

Improved cognition, fewer depressive and mood symptoms, and decreased risk of TD associated with third-generation antipsychotics have improved the quality of life for patients with schizophrenia.

**Index terms:** Antipsychotic agents; Diagnosis; Economics; Quality of life; Schizophrenia

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hospitals. He probably would not have finished college, and only a few patients like Jason adapted well enough to be able to develop relationships or hold a job.

That is not what these parents wanted to hear about their son. And fortunately, today we can predict a different course. Even though there is no cure, we can provide hope. Yes, he can finish school. No, most likely he will not live in an institution. The newer antipsychotics and early intervention increase the odds of achieving positive results.

In this article, I will present an overview of schizophrenia, including its diagnosis, etiology, and neurologic findings. In addition, I will discuss pharmacotherapy options, adverse effects, and quality-of-life issues. I will use Jason’s experiences, as well as those of another patient named Mr. E., to illustrate points related to schizophrenia and its treatment.

Mr. E. is a 43-year-old man with a 23-year history of chronic schizophrenia of the paranoid type. His symptoms began during his second year of college. He had auditory hallucinations urging him to hurt himself and severe paranoid delusions of people plotting to kill him. He was found in the median of an interstate highway, where he believed he was safe from those trying to get him. The course of Mr. E.’s illness, treated with a traditional antipsychotic agent, will be contrasted with Jason’s course on a newer antipsychotic.

Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) defines schizophrenia as two or more of the following symptoms, each present for a substantial amount of time during a one-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms like affective flattening, alogia, or avolition.\(^1\) Other diagnostic criteria are social and occupational dysfunction for a duration of at least six months.

The DSM-IV description ignores many aspects of the disorder, however. Drive down any main street in America, and you can point to people who have schizophrenia. How can you tell? Perhaps the woman just sits on the park bench smoking cigarettes and drinking coffee. Or the man does not shave or wears the same clothes every day. I asked one of my patients, David, why he showers only every other week. He replied, “That way you really appreciate it, Doc.”

Historically, schizophrenia was characterized as a multifaceted disorder that goes beyond delusions, hallucinations, or decreased drive and motivation.\(^2\) In the late 1800s, Emil Kraepelin identified the cognitive impairment of schizophrenia, calling the disorder “dementia praecox.”\(^3\) Also, Eugen Bleuler identified the “four As” of schizophrenia: disturbances in affect, autism, ambivalence, and associations. Kurt Schneider talked about first-rank and second-rank symptoms, which included some positive symptoms, negative symptoms, and cognitive deficits. All of these go beyond the DSM-IV definition.

Figure 1 shows the current understanding of the features of schizophrenia. Positive symptoms are the “extra” aspects that people with schizophrenia have, such as delusions and hallucinations. Negative symptoms represent aspects that are lacking in people with schizophrenia, such as drive, motivation, and heightened affect. Cognitive impairment, mood symptoms, and comorbid substance abuse are other elements to be considered. All of these features can have an impact on patients’ ability to work, maintain jobs, and lead more independent lives, so treatment should address all of them.

If I were to focus treatment for Jason on just the positive symptoms, I would do a disservice to him and his family. Yes, his family wants fewer delusions, but they also want their son to improve his cognition and have the energy and drive to go back to school. In fact, Jason plans to start school again part time this quarter at a school closer to home. In contrast, about six months after his first episode in 1978, Mr. E. dropped out of the local community college as a part-time student because he could not function. Although chlorpromazine controlled his auditory hallucinations and reduced his paranoid thoughts, it did not improve his impaired cognition. He com-
plained about the inability to focus and read.

**Demographics and comorbid conditions**

Schizophrenia affects 1% of the general population, and its prevalence is equal in men and women. The peak age of onset is usually 15–25 years for men and 25–35 years for women. It is more common for babies carried in the womb in the winter months (and born in winter and spring) to have schizophrenia. To explain this latter finding, some theories suggest that the mother may be infected with a virus that affects the cortical development in the child in the second trimester.

Patients with schizophrenia tend to be in lower socioeconomic classes. Previous theories postulated that poverty caused this disorder. A "downward drift" hypothesis is more likely correct. Take my patient David, who receives about $625 per month in Supplemental Social Security Income. He lives in a poor area of Anaheim, California, because that is where he can afford to live. He and other patients drift downward such places.

There are several comorbid conditions that tend to be more prevalent in patients with schizophrenia. For example, substance abuse is quite common among people with schizophrenia. More than 75% are addicted to nicotine, 30–50% to alcohol, 15–25% to cannabis, and 5–10% to cocaine or amphetamine. It is not known why patients seek substances of abuse. Many patients with schizophrenia have impairments in cognition, especially impairments in attention, and these substances may improve attention. For example, in a classroom situation, a patient with schizophrenia can have problems with gating; the person focuses on competing stimuli—like a fan buzzing, people talking, and people walking in and out of the room—just as much as on the speaker's voice. If nicotine, caffeine, and cocaine improve attention, then patients with schizophrenia may use these substances to self-medicate.

In addition, diabetes mellitus is two to four times higher in patients with schizophrenia than in the general population. As Guthrie notes, some of the newer antipsychotics have been associated with diabetes mellitus, but, rather than the diabetes being a direct result of the medication, this may be because practitioners are more vigilant about detecting diabetes.

**Financial impact of schizophrenia**

Schizophrenia accounts for 20% of all hospital bed-days and over 50% of all psychiatric beds in the United States. One percent of the U.S. gross domestic product goes toward treatment of schizophrenia. Counting the loss of work productivity, schizophrenia costs up to $35 billion per year.

Of this, a very small percentage is for medications. The newer antipsychotics definitely cost more than traditional ones like haloperidol or fluphenazine hydrochloride, but the increased cost is minuscule in comparison with the total cost of this disorder. Furthermore, the benefits of the newer antipsychotics may enable a patient like Jason to attend school and hold a job, resulting in increased productivity and quality of life.

**Etiology**

There is a strong genetic component to schizophrenia as demonstrated by a 50% concordance rate in monozygotic twins, whether they are raised together or apart. If genetics were the sole cause, one would expect the concordance rate to be 100%. Among dizygotic twins, the concordance rate is 12%. There is a 40% risk of developing schizophrenia if both parents have it.

But genetics does not totally explain the etiology of schizophrenia, and other causes have been explored. The stress-diathesis model suggests that something in the environment may tip a person toward developing the disorder if the person is genetically predisposed. The dopamine hypothesis suggests that schizophrenia is associated with an increased dopamine level in the brain. All FDA-approved antipsychotics block dopamine type 2 (D₂) receptors. Agents that selectively block serotonin reuptake and those that block D₁ receptors alone have not shown efficacy in the treatment of this disorder. Also, psychosis (delusions and hallucinations) can be induced in patients taking levodopa for Parkinson's disease. Cocaine and amphetamine, which are dopaminergic compounds, can increase psychosis as well.

According to another hypothesis, lysergic acid diethylamide (LSD) can cause or increase hallucinations through its effects on the serotonin system. Maybe by blocking dopamine and serotonin, one may achieve a synergistic therapeutic effect with the newer generation antipsychotics.

New focus on the mechanisms by which antipsychotic agents work shows that increased activity of dopamine in the brain explains only the positive symptoms of schizophrenia, while increased serotonin activity explains some of the negative systems. It has been suggested that impairment in the N-methyl-D-aspartate (NMDA) or glutamate system explains more of the problems in cognition, delusions, and possibly even the negative symptoms associated with schizophrenia. Newer agents such as olanzapine and clozapine that act in the NMDA system have been shown in animal studies to reduce the delusions and hallucinations. This may be potentially valuable in treating patients who are high on phencyclidine hydrochloride (PCP) or ketamine; haloperidol and agents like risperidone do not help in this situation.

Schizophrenia may have viral influences as well. A mother's exposure to a virus may affect fetal develop-
ment. This theory would help explain why some siblings have schizophrenia and others do not.

From a neurologic standpoint, ventricular enlargement is seen in schizophrenia. Olanzapine has been shown to reduce and prevent the ventricular enlargement, while the older antipsychotics do not.7

Neurologic findings may support the theory that the disorder is present at birth but symptoms do not develop until the late teens and early 20s. Functional imaging of the brains of patients with schizophrenia shows low frontal lobe function. A problem with migration of cortical cells also exists. Normally, during the second trimester of fetal development, nerve cells build connections with each other. In patients with schizophrenia, for unclear reasons, the cortical cells fail to migrate to their proper locations and make the right connections, which leads to symptoms of schizophrenia.

Differential diagnosis

In making the differential diagnosis of schizophrenia, the following other psychiatric disorders must be ruled out:

- Brief psychotic disorder (less than one month’s duration);
- Schizophreniform disorder (one to six months’ duration);
- Schizoaffective disorder (chronic psychosis with intervening manias or depressions);
- Delusional disorder (fixed set or typically just one delusion);
- Mood disorders, such as bipolar disorder, with psychotic features;
- Substance-induced psychotic disorder;
- Personality disorders, especially borderline personality disorder; and
- Psychotic disorder caused by medical condition.

The diagnostic workup for schizophrenia requires obtaining a detailed longitudinal history because, for example, at a single point in time it is difficult to tell if a patient has schizophrenia or bipolar mania with psychotic features. One should gather information from the patient, as well as from collateral sources like the family, previous clinicians, medical records, friends, and the school system. Look for precipitating factors that may have tipped things over the edge. The workup should also include a mental status exam, physical and neurologic exams, and laboratory tests like blood chemistries and a complete blood count to rule out other medical causes of psychosis. I routinely do a magnetic resonance imaging (MRI) scan at the time of diagnosis to rule out structural causes of psychosis.

Functional imaging is still in the research stage, but eventually the results of a functional MRI, positron emission tomography, or single photon emission computed-tomography scan may help determine which agent will work best for that specific patient. Pharmacogenetic studies, as well, may eventually guide the clinician.

Treatment of schizophrenia

The treatment of schizophrenia is based on a biopsychosocial model. It includes behavioral and social skills training, family-oriented therapies, group therapy, and individual supportive therapy. The primary biological intervention consists of pharmacotherapy. Electroconvulsive therapy still has a role in treating patients with the catatonic type of schizophrenia and patients with an affective component for whom medications have failed.

Figure 2 illustrates the continuum of care for patients with schizophrenia. At different stages of therapy, efficacy focuses on different aspects of the disorder. For instance, in the beginning the emphasis is on controlling behavior and agitation. Then the focus switches to relief of positive symptoms. After about two weeks of therapy, care focuses on cognitive improvement, negative symptom relief, and improvement in mood and depressive symptoms. After that, relapse prevention is key. For each of these stages, specific adverse effects of therapy must be evaluated.

Classification of antipsychotics.

The current nomenclature classifying antipsychotics as typical and atypical can be misleading. The term atypical implies an agent that is not first-line treatment. For example, as a member of a pharmacy and therapeutics committee a few years ago, I

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**Figure 2.** The continuum of care for patients with schizophrenia. IM = intramuscular, PO = orally, EPS = extrapyramidal symptoms, TD = tardive dyskinesia.

**Efficacy**

- Positive symptom relief
- Hostility, aggression
- Smooth I.M. to P.O. transition
- Alleviation of comorbid depressive/manic symptoms

- Negative symptom relief
- Improvement of mood and depressive symptoms
- Cognitive improvement
- Suicide prevention

**Safety**

- Acute dystonia
- Sedation
- Orthostasis
- QTc prolongation

**Control Behavior (agitation)**

- 1–3 days
  - EPS
  - Drug-drug interactions
  - QTc prolongation

- 7–14 days
  - TD
  - Hyperprolactinemia
  - Weight gain
  - Hyperglycemia
  - QTc prolongation

- 6+ months
  - Relapse Prevention
requested coverage for specific atypical antipsychotics. The orthopedic
physician who chaired the committee questioned my liking of atypical,
unusual things. He said, "The typical drugs cost a lot less, and everyone
else likes them."

The atypical antipsychotics are the current standard of care, and they
are not all equal. When clozapine was first marketed, it was defined
as atypical because it had a low risk of extrapyramidal symptoms and
tardive dyskinesia (TD), did not elevate prolactin, and had a broader
efficacy profile than haloperidol and chlorpromazine. Table 1 shows a re-
vised nomenclature system that categorizes agents according to these
same characteristics.6

Psychiatry is an empirical science. So often one hears that psychia-
try is a group of treatments in search of science. Not unlike many
physicians, psychiatrists find treatments that work, and then they try
to figure out why they work. Here are some theories, based on the
binding affinities of the different compounds, that help illustrate the
differences we see clinically.

To be an antipsychotic, the agent must block D2 receptors. Every
agent achieves D2-receptor blockade. To be a third-generation agent
with a lower risk of extrapyramidal symptoms, it must block serotonin
type 2A and serotonin type 2C receptors. Blocking these serotonin rece-
ptors causes release of dopamine in the nigrostriatal pathway, which
can combat some of the extrapyra-
midal symptoms and can improve
negative symptoms as well. Halo-
peridol lacks this property.

Serotonin type 2C and perhaps
histamine may have a potential role
in appetite increase and weight gain.
Blockade of serotonin type 2C rece-
tors is greatest with clozapine and
olanzapine, and greater appetite
increase is seen with these agents.
But ranking agents on improvement
in negative symptoms, cognition, and
mood symptoms shows that the agents with greater appetite increase
possess greater efficacy. The his-
tamine blockade with quetiapine and
to some degree with olanzapine may
be the source of the sedating prop-
eties of these agents. Because queti-
apine has α1-adrenergic blocking activ-
ity, the dosage must be adjusted slow-
ly to avoid orthostatic hypotension.

Some people mistakenly ask why
an anticholinergic agent like olanzapine is used in patients with dementia.
Olanzapine is antimuscarinic, not anticholinergic. It blocks muscarinic M1
receptors greater, which are autoreceptors, which causes a release of
acetylcholine. Later I will discuss how olanzapine can improve cognition.
Clozapine's antimuscarinic activity includes M1 blockade but particularly
M2 and M3 blockade. The release of
acetylcholine in the salivary glands
may explain why some patients drool
when taking this agent.

Blockade of serotonin type 2A rece-
tors may result in mitigation of
extrapyramidal symptoms and im-
provement in negative symptoms.
Similarly, blockade of serotonin type
2C receptors may be responsible for
the improvement in negative and de-
pressive symptoms; the increase in
appetite may be related to this.

Different dopamine pathways ex-
ist in the brain, and where dopa-
mine is blocked is very important.
Blockade in the nigrostriatal path-
way can lead to extrapyramidal
symptoms of parkinsonism, such as
stiffness, rigidity, and tremors.
Long-term blockade can lead to an
upregulation of receptors resulting in
TD. Blockade of the tuberoinfundibular pathway can lead to prolactin el-
levation and its sequelae. Blockade of
the mesolimbic pathway produces
the antipsychotic effect. First- and
second-generation antipsychotics,
especially first-generation antipsy-
chotics, are nonselective. They block
all three of the major dopamine
pathways. The third-generation
agents are relatively selective for the
mesolimbic pathway.

This selectivity for the mesolim-
bic pathway was the stimulus for my
clinician to switch me from risperi-
done to olanzapine for my stuttering
when olanzapine was marketed four
years ago. Although I have a greater
risk of increased appetite, I can
manage that through diet and exer-
cise. On risperidone, however, one
cannot easily control the risks of
prolactin elevation and the possible
development of TD.

The specificity of an agent for the
mesolimbic pathway is demonstrat-

Table 1.
Revised Nomenclature of Antipsychotic Agents

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Risk of EPS</th>
<th>Risk of TD</th>
<th>Effect on Prolactin</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation, such as haloperidol and chlorpromazine</td>
<td>High</td>
<td>High</td>
<td>Elevation</td>
<td>Positive symptoms</td>
</tr>
<tr>
<td>Second-generation, such as risperidone and ziprasidone</td>
<td>Dose-dependent</td>
<td>Possibly dose-dependent</td>
<td>Elevation</td>
<td>Positive and negative symptoms</td>
</tr>
<tr>
<td>Third-generation, such as clozapine, olanzapine, and quetiapine</td>
<td>Low</td>
<td>Low</td>
<td>Sparing</td>
<td>Positive, negative, cognitive, and mood symptoms</td>
</tr>
</tbody>
</table>

EPS = extrapyramidal symptoms.
TD = tardive dyskinesia.
ed through neurophysiologic studies measuring the activity of the neurons. Olanzapine, quetiapine, and clozapine have been shown to be selective for the A10 neurolimbic pathway, as well as for the NMDA system, where they influence glutamate. Similarly, studies have demonstrated that these agents increase acetylcholine and thus improve cognition and that they block oral dyskinesias and improve TD. The newer agents that work in the frontal lobe, as measured by c-fos gene expression, result in improved cognition and less depression.

**Depression and suicide risk.** Mr. E. has had depressive episodes, and Jason is at risk for developing depression. The lifetime risk of major depressive disorder is approximately 60% in patients with schizophrenia. This is greater than the 8–26% lifetime risk of major depression in the general population.

First-generation and second-generation antipsychotics can cause or precipitate depression. Haloperidol and risperidone have both been shown to cause depression in patients not prone to developing depression. Studies of people with stuttering and Tourette’s syndrome have shown that treatment with such agents is worse than the disorder itself, and long-term compliance is poor. Worsening of depression with first-generation antipsychotic agents should be considered as a possible toxic drug effect.

The prolactin-sparing third-generation agents have been shown to have beneficial effects in improving depressive symptoms. Compared with haloperidol, olanzapine was significantly more effective in reducing depressive signs and symptoms in schizophrenia and related disorders. Clozapine showed a similar pattern. In an open-label study, quetiapine was also better than risperidone. Similarly, a long-term study showed that olanzapine was better than risperidone in improving depression subscores. Although the binding profile of ziprasidone suggests that it would have a positive effect on depressive symptoms, it has no better effect than haloperidol.

Further evidence that prolactin-elevating agents may be associated with depression comes from the postpartum literature. Prolactin elevation is associated with hostility and depression. Tumors producing prolactin are also associated with depression.

Depression potentially induced by antipsychotic therapy, as well as the depressive effects of schizophrenia alone, translates into suicide risk. Jason is especially at risk for suicide, and Mr. E. has made several suicide attempts during his lifetime. The risk of suicide in patients with schizophrenia is 10–25%, and an average of 15% of all patients will complete suicide. This 15% mortality rate, which often includes patients whose schizophrenia is first diagnosed during the late teens and early 20s, is a major public health concern.

Suicidal behavior in depressed patients with schizophrenia can be impulsive and unpredictable. These patients often choose very violent means. One of my patients swallowed battery acid; another jumped off an overpass onto a busy highway; another stepped in front of a train. These actions may constitute psychotic behavior by patients who are out of touch with reality.

Olanzapine and olanzapine have been shown to reduce suicidal behavior in patients with schizophrenia. In one study, patients taking olanzapine had 2.5 times fewer suicide attempts than patients taking haloperidol. A long-term study of olanzapine in 339 patients compared with risperidone showed seven times fewer suicide attempts with olanzapine after six months.

**Cognitive symptoms.** Jason wants to go back to school next quarter. How can he function? How will he be able to think and learn? In a one-year, multicenter study, 65 stable outpatients with schizophrenia or schizoaffective disorder who were taking olanzapine and were within five years of their first antipsychotic exposure performed better on cognitive measures than patients taking risperidone; risperidone was somewhat better than haloperidol. Use of a third-generation compound will give Jason the best chance to function in his life and in his school.

Cognitive deficits predict patient functioning better than positive symptoms. The vast majority (80%) of patients with schizophrenia are unemployed. The third-generation agents show promise for improving cognition. For example, compared with patients taking haloperidol, a greater percentage of clozapine-treated patients participate in psychosocial therapy, which is a foundation for reintegration into society. Twice as many patients taking olanzapine went back to work at one year, compared with patients taking haloperidol. While 80% of patients still were not working, at least we are beginning to build a foundation for patients to go back to work.

**Endocrine and sexual disturbances.** Prolactin elevation seems to be the “don’t ask, don’t tell” adverse effect of antipsychotics. If clinicians don’t ask about it, most patients are unlikely to report it. In women, however, the prolactin-elevating antipsychotic agents can produce menstrual disturbances, galactorrhea, breast engorgement, sexual dysfunction, infertility, and decreased bone density. For men, the elevated prolactin levels of first- and second-generation antipsychotics may result in loss of libido, erectile dysfunction, ejaculatory dysfunction, reduced spermatogenesis, and decreased bone density. For women the decreased bone density is mediated by relative or absolute deficien-
cy of estrogen; for men, it is mediated by testosterone.

TD. The incidence of TD is approximately 5% per patient per year for patients receiving first-generation agents. The risk is one seventh of this for patients taking second-generation agents like risperidone, and it is further reduced (one-twelfth) with third-generation agent olanzapine. This may be close to zero or the basal rate seen in patients with schizophrenia long before antipsychotics were marketed. Therefore, to prevent the development of TD, third-generation antipsychotic agents should be used as first-line therapy.

TD is believed to arise from long-term blockade of dopamine receptors in the nigrostriatal pathway, leading to an upregulation of receptors and a relative dopamine excess. Risk factors for TD are treatment with an antipsychotic agent that causes extrapyramidal symptoms, mood disorder, being elderly, being female, and concurrent medical illness. Among elderly patients taking a first-generation agent, 25% will develop TD within the first year; by year three, the percentage increases to 68%.

Case reports indicate that clozapine improves TD, but now the results of a blinded study show that olanzapine improves TD as well. It is not clear whether the improvement is a direct treatment effect or a result of allowing the brain to downregulate the receptors and "heal itself." According to Kinon et al., the longer patients were treated with olanzapine, the greater the improvement in TD. Also, to illustrate that olanzapine was not simply masking the TD, the symptoms did not worsen during a blinded dose reduction.

When acute extrapyramidal symptoms occur, consider treating them with anticholinergic medications like benztrapine, trihexyphenidyl, or diphenhydramine. Beta-blockers or benzodiazepines can be used for the treatment of akathisia. However, the best treatment is to avoid the development of extrapyramidal symptoms by using third-generation agents.

Weight gain. As Guthrie will discuss in greater depth, the exact mechanism of weight gain associated with antipsychotic therapy is not clear. It may arise from blockade of histamine type 1 and serotonin type 2C receptors. The weight gain appears to be associated with an appetite increase. Agents that have a greater weight gain potential may also have greater efficacy potential. A meta-analysis of weight gain associated with antipsychotic agents after 10 weeks of therapy showed that weight gain potential is greatest for clozapine and olanzapine. Ziprasidone and molindone were associated with little weight gain.

Relapse issues

It is important to keep Jason out of the hospital and support him for the long term. Relapse may be part of the natural course of schizophrenia. It can also result from a lack of insight, such as denial of illness or poor compliance with treatment recommendations. Relapse also can have psychosocial origins, such as lack of family support or inability to cope with the complex mental health system.

Pharmacologically, relapse may be related to dopamine-binding affinity. "Tightened-bound" agents like the first- and second-generation antipsychotics may work well initially, but upregulation of dopamine receptors in the long term may lead to greater potential for relapse. More moderately or loosely bound agents, such as olanzapine and clozapine, maintain response well. Quetiapine, however, may be so loosely bound that, while it is not associated with concerns about extrapyramidal symptoms or long-term prevention relapse data, it may not be as effective as the other third-generation agents, having shown efficacy only equal to that of haloperidol.

Patients on first-generation agents show a steady rate of decline in response, compared with placebo; after one year, these agents do not offer much benefit. Ziprasidone, which is tightly bound, has a rate of decline that is better than placebo but is still fairly rapid. Compared with placebo, haloperidol, and risperidone, olanzapine did much better in maintaining response. The savings achieved by keeping patients out of the hospital have made clozapine and olanzapine the two most cost-effective antipsychotic medications.

Conclusion

Antipsychotic medications are not "me-too" compounds. Substantial differences exist in their respective efficacy and adverse-effect profiles. With advancements in such medications, patients with schizophrenia no longer need to lead a life totally dictated by this disorder. Improvement in the multiple features of schizophrenia, including positive, negative, mood, and cognitive symptoms, enables patients like Jason and Mr. E. to lead their lives more fully in spite of this disorder.

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