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EFFECTIVE TREATMENT FOR SCHIZOPHRENIA

- *Schizophrenia affects 1% of the US population, or more than 2 million Americans.¹*
- *The annual cost of treating schizophrenia exceeds \$30 billion nationwide.*
- *While there are effective pharmacologic treatments for schizophrenia, almost 50% of patients in the US with this disorder do not remain in treatment over time.*
- *Veterans with schizophrenia occupy more hospital beds at any given time than veterans with any other illness, and the most severely ill may comprise at least 10% of homeless veterans receiving VA healthcare.*
- *Moderate doses of antipsychotic medications are required to treat acute schizophrenia and prevent relapse in stabilized patients.*
- *Research indicates that clozapine may be the most effective antipsychotic for the treatment of refractory patients.*
- *Research suggests the need for improving adherence to evidence-based guidelines for treating schizophrenia in VA.*

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BACKGROUND

Schizophrenia is a severe psychiatric disorder that is characterized by psychotic symptoms such as hallucinations and delusions, and impairments in social and vocational adjustment. It affects more than 2 million people in the United States and with 25% of hospital bed days devoted to patients with schizophrenia, the yearly cost of this disorder exceeds \$30 billion.^{1,2,3}

In 2001, the VA provided care to more than 98,000 veterans with schizophrenia at a cost of \$1.7 billion.⁴ Veterans with schizophrenia occupy more hospital beds at any given time than veterans with any other illness. In addition, even when stabilized in the community, many veterans with chronic schizophrenia function poorly. Many are chronically or periodically unemployed, some are isolated in the community, and the most severely ill may comprise at least 10% of homeless veterans receiving VA health care. Even those patients who have been stabilized may have persistent psychotic symptoms that can interfere with their community adjustment.

While there are effective pharmacologic therapies for schizophrenia, studies show that almost 50% of patients with schizophrenia who are discharged from hospitals do not remain in treatment over time.

TREATMENT AND AVAILABLE THERAPIES

Treatment Recommendations

During the past decade, research has contributed to substantial improvements in the pharmacological and psychosocial treatments of schizophrenia. The Schizophrenia Patient Outcomes Research Team, or PORT,⁵ examined the research evidence for a variety of treatments and found that there was sufficient evidence to make a series of treatment recommendations that include:

- the use of antipsychotic medications for the treatment of acute schizophrenia and the prevention of relapse in stabilized patients;
- the use of moderate antipsychotic doses;
- clozapine for the treatment of refractory patients;

- the use of adjunctive medications for depression and anxiety;
- family psychosocial treatment for patients who have ongoing contact with their families or non-family caregivers;
- supportive individual and group psychotherapies;
- assertive community treatment for patients who are high utilizers of service; and
- vocational rehabilitation.

Consensus on Prescribing Antipsychotics

A number of groups including VA, PORT, the American Psychiatric Association, the New York Office of Mental Health, and the Texas Department of Mental Health and Mental Retardation have reviewed the evidence and made recommendations for treating schizophrenia with antipsychotic medication. The recommendations from these groups are similar, but not always the same. The Mental Health QUERI and representatives from three Mental Illness Research Education and Clinical Centers (MIRECCs) recently participated in a consensus meeting that included experts who were working to revise the recommendations of all of the above groups. The goal of the meeting was to determine whether they could reach a consensus on a number of controversial issues using the available evidence.

The results of the meeting were summarized in a special issue of the *Schizophrenia Bulletin* that was published in Spring 2002.⁶ Following are a number of selected issues on which the group was able to reach a consensus based on the current evidence.

- Second-generation antipsychotics (SGAs) — with the exception of clozapine and ziprasidone — should be selected before first-generation (conventional) agents for patients experiencing a first episode of schizophrenia, or for those patients where there is no available history concerning response to antipsychotics.
- Conventional antipsychotics may be appropriate selections for: 1) Individuals who have a history of responding well to a conventional antipsychotic without experiencing extrapyramidal side effects; 2) Individuals who have a history of a better response to conventional agents than to second-generation

antipsychotics; and 3) Patients who have responded better to a long-acting injectable antipsychotic when compared to an oral antipsychotic.

- Clozapine appears to be the most effective antipsychotic for treatment-refractory patients. For this reason, patients should not be considered partial responders or non-responders until they have had an adequate trial with clozapine. However, clinicians should assess a patient's response to at least one second-generation antipsychotic before beginning clozapine.

There is sufficient evidence to conclude that SGAs are less likely to cause tardive dyskinesia (abnormal involuntary movements) than conventional agents. Other recommendations focused on the appropriate monitoring of patients receiving different antipsychotic medications, the duration of an adequate drug trial, and the selection of an antipsychotic for different populations.

Treating Refractory Patients

There is a substantial body of evidence indicating that patients with schizophrenia should not be considered treatment refractory until they have received a trial of clozapine. This finding is reinforced by a VA Cooperative study, which found that clozapine was more effective than haloperidol in veterans with treatment refractory schizophrenia.⁷ Although treatment refractory illness is relatively common in schizophrenia, only 2.9% of veterans with schizophrenia received clozapine in FY 2001.⁴ There was also wide variability in clozapine prescribing among facilities and VISNs, with one network prescribing clozapine to only 0.8% of veterans with schizophrenia. Moreover, this lack of access to clozapine existed in sites that treated substantial populations of patients with schizophrenia. Since nearly all treatment guidelines recommend the use of clozapine for patients who are treatment refractory, it is clear that many clinicians are failing to adhere to recommended evidence-based practices.

Many factors probably contribute to the underutilization of clozapine. Because clozapine is associated with a risk of agranulocytosis (pronounced reduction in white blood cells), patients who receive it require weekly neutrophil

counts for the first six months, followed by counts every two weeks. In addition, clozapine is associated with other undesirable side effects such as weight gain, seizures, orthostatic hypotension, and sedation. The VA also requires that – in order to use the drug – each facility develop a Clozapine Treatment Team, and new prescriptions for clozapine must be approved by the Clozapine Treatment Team and the National Clozaril Coordinating Center. It is also possible that clinicians are inexperienced with prescribing clozapine and, thus, are uncomfortable prescribing it. Because of these factors, clinicians may find it easier to prescribe alternative drugs.

Advances in Clinical Research

The Program for Assertive Community Treatment (or PACT model treatment) has been found to be cost effective for patients who are heavy users of clinical services.⁸ PACT programs usually include a high staff-to-patient ratio, a multidisciplinary team that provides a broad range of services in community settings, and the availability of services around the clock. The implementation of these programs has permitted severely ill patients, who were frequently hospitalized for long periods, to remain in the community. The VA implemented its own form of the PACT model treatment (originally Intensive Psychiatric Community Care), currently termed

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CLINICAL OPINION

Mental Health Intensive Community Management (MHICM).

Gaps in Current Practice

Despite the wealth of research supporting the above mentioned treatment modalities, multiple studies indicate that a substantial proportion of patients with schizophrenia — including veterans — are not benefiting from these advances. For example, even though, as mentioned earlier, clozapine appears to be the most effective antipsychotic for the treatment of refractory patients, there is wide variability in clozapine prescribing among VISNs. There is also evidence that veterans are not benefiting from advances in clinical research, such as the PACT model of treatment. Further, PORT investigators surveyed actual practice in a number of settings and found that there was reasonable compliance with most of the recommendations that focused on pharmacotherapy, but poor compliance with recommendations for psychosocial treatments.⁵ A recent survey by the VA's Committee on Care of Severely Chronically Mentally Ill also found that only a small fraction of veterans who were candidates for MHICM had access to these programs.

In a study from the Mental Health QUERI, Owen et al. looked at prescribing practices in a population that included veterans with schizophrenia.⁹ Findings show that only 52% were treated with antipsychotic doses within the range recommended by the Schizophrenia PORT. Moreover, Leslie and Rosenheck examined prescribing practices at all VA facilities and found that 13% of patients were prescribed antipsychotic doses greater than the PORT recommended range, with substantial variation among facilities.¹⁰

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The treatment of schizophrenia has become more complicated, but has also improved. Until 1990, the prescribing of antipsychotics was relatively straightforward: all of the antipsychotics were equally effective, and side effect concerns focused on neurological adverse effects such as Parkinsonism and tardive dyskinesia. Neurological side effects are a minor concern with the second generation of antipsychotics that include clozapine, risperidone, olanzapine, quetiapine, and ziprasidone. However, these newer agents are associated with new concerns about side effects that include weight gain, vulnerability to diabetes, hyperlipidemia, and cardiac arrhythmias. Moreover, these newer antipsychotics may differ in their effectiveness. Clozapine appears to be more effective for severely ill, treatment refractory patients than other antipsychotics, and there are indications that other second-generation agents are more effective for the neurocognitive impairments associated with schizophrenia. As a result, clinicians who manage schizophrenia have switched most patients to the second generation of antipsychotics. In 2001, more than 77.4% of veterans with schizophrenia were prescribed a second-generation antipsychotic, reflecting an upward trend in recent years.⁴ This change is reinforced by treatment guidelines, including those being developed by the VA, as well as the Texas Medication Algorithm Project.¹¹

This change in antipsychotic prescribing should also be associated with changes in the monitoring of patients. At a time when neurological side effects were the most serious concern, the VA selected tardive dyskinesia (TD) monitoring with the Abnormal Involuntary Movement Scale (AIMS) as a performance measure. Although yearly monitoring for TD is still an appropriate practice, TD is probably less of a problem than other side effects. For example, weight gain is a very serious concern for patients with schizophrenia. A meta-analysis of controlled trials found that during a 10-week period, patients receiving clozapine gained an average of 4.45 kg and patients receiving olanzapine gained 4.15 kg.¹² Both quetiapine and risperidone were also associated with some weight gain. Other

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reports have suggested that newer antipsychotics may also be associated with an increased risk for Type 2 diabetes and hyperlipidemias.¹³ Since individuals with schizophrenia have a greater likelihood of both obesity and diabetes, monitoring for these adverse consequences of drug treatment should probably be performed.^{14, 15}

Clinicians – and clinical managers in large health care organizations such as the VA – should consider focusing on weight and glucose monitoring for all patients with schizophrenia. The level of monitoring was recently considered by a consensus conference organized by the Mental Health QUERI and others, which recommended that patients have their weight monitored at every visit and that patients have their blood glucose monitored prior to starting an antipsychotic, as well as yearly.⁶ More careful monitoring may be appropriate if patients are receiving olanzapine or clozapine – which have been associated with new cases of diabetes, or if patients are obese or have a family history of diabetes.

The issue of monitoring is an important concern since there is evidence that psychiatrists in public mental health settings, such as the VA and community mental health centers, often fail to monitor side effects in patients with schizophrenia.¹⁶ Moreover, in settings like the VA, clinicians carry high caseloads – often more than 500 patients – which can result in very brief sessions with individual patients. Given this clinical reality, the VA and other health care organizations should assure that patients with schizophrenia are seen by a primary care provider at least yearly. New approaches, including collaborative care models with care coordinators, have been proposed to address the tendency of some specialists to fail to perform important routine monitoring.

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RECOMMENDATIONS

- Individuals with schizophrenia should be treated with antipsychotics that are prescribed within the recommended dose range for an adequate length of time.
- Second-generation antipsychotics (SGAs) should be selected before first-generation (conventional) agents for patients experiencing a first episode of schizophrenia.
- All patients with schizophrenia should have their weight monitored at every visit and their blood glucose monitored before starting an antipsychotic, and then yearly.
- Clozapine should be considered for patients who continue to be symptomatic on their current antipsychotic medication. However, clinicians should assess a patient's response to at least one second-generation antipsychotic before beginning clozapine.
- There should be increased availability and access to Mental Health Intensive Community Management (MHICM) programs for veterans who are heavy users of clinical services.

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