



Note: This letter has been recreated electronically from guidance previously issued in paper form.

FEB 12 1998

Dear State Medicaid Director:

The purpose of this letter is to provide information about recent advances in the treatment of schizophrenia. New medications have been approved which are called atypical antipsychotic drugs, and include risperidone, olanzapine (Zyprexa) and quetiapine (Seroquel). Several additional “atypicals” are in clinical trials and/or pending FDA approval. Current knowledge indicates side effects from these new antipsychotic drugs are much less severe than those of the older generation of drugs.

All of the older standard antipsychotic medications are associated with a considerable number of side effects, some of which are severe and can become permanent. Due to at least in part to these side effects, many people with schizophrenia stop taking standard antipsychotic medications within a year or two. In fact, a common reason for psychiatric hospital readmissions is that patients stop taking these medications after leaving the hospital. The costs of “revolving door” readmissions are obviously substantial. Short term saving achieved in formulary budgets by not including the new medications may be more than offset by spending on inpatient care.

I am enclosing a letter from the Director of the National Institute of Mental Health that includes more detailed information on this subject and summarizes the data indicating the clinical advantages of the newly available treatments for schizophrenia.

Although many States and managed care organizations have already adjusted their formularies to recognize these new medications, we realize that the price of change is uneven and we are providing this information to ensure that all States are aware of the progress that has been made in treating this devastating illness. For States that choose to require prior authorization, we include a reminder that Federal statute requires that any prior authorization request must be responded to within 24 hours, and in emergency situations the State must provide for pharmacy dispensing of at least a 72 hour supply of the requested drug.

We hope that this information proves useful in updating formularies that do not currently reflect the improvements that have taken place in the treatment of schizophrenia.

Sincerely,

/s/

Sally K. Richardson
Director
Center for Medicaid and State Operations

Enclosure

cc:

**All HCFA Regional Administrators
All HCFA Associate Regional Administrators
Division of Medicaid and State Operations
Lee Partridge
Joy Wilson
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January 16, 1998

Ms. Sally K. Richardson
Director, Center for Medicaid and
State Operations
Health Care Financing Administration
Baltimore, MD 21244

Dear Ms. Richardson:

Over the past decade, the serotonin re-uptake, inhibitor (SRI) Class of antidepressants has largely replaced the older and more problematic tricyclic anti-depressants, based in large part on safety, and side effect considerations. There is now clear evidence that a similar shift in the “state of the science” regarding treatment of schizophrenia is taking place, and we are concerned that despite recent medical advances in atypical antipsychotic treatments, the response of various health care delivery systems may not have kept up with the clinical research findings. Of course, formulary differences and prescribing practices may vary from state to state and from one delivery system to another. With the rapid pace of developments in psychopharmacology, some systems have been slower to change than others. We will attempt to summarize below some of the relevant data indicating that the newly available treatments for schizophrenia offer substantial clinical advantages.

The history of atypical antipsychotic medications is not itself a new phenomenon. The first drug of this class, clozapine, has been in use around the world for many years, but only in 1990 was it approved in the United States specifically for treatment-resistant schizophrenia. Unfortunately, clozapine has severe side effects, which require weekly blood testing and often limit its use to a treatment of nearly last resort. Thus, please note that our comment below about the new atypicals do not apply to clozapine.

The first of the new atypical antipsychotic medications, risperidone, was approved for use and marketed in the United States in 1994. Its efficacy is superior to placebo and at least equal to haloperidol, the standard antipsychotic medication, but risperidone has a more favorable side effect profile. In September 1996, the FDA approved another new atypical antipsychotic, olanzapine (Zyprexa), for use schizophrenia. Quetiapine (Seroquel) was approved on September 29, 1997, and is now available as well. Several additional atypicals are currently in large-scale clinical trials and/or pending FDA approval. The pharmacologic profiles of these newer antipsychotic medications tend to resemble that of clozapine but are not associated with clozapine’s severe side effects. Thus it appears that these atypical medications will be effective

for a broad range of symptoms of schizophrenia, with substantial improvements in side effect profiles.

All of the standard antipsychotic medications (many in use since the 1950s) are associated with a considerable number of side effects, including prominent extrapyramidal symptoms (EPS): acute dystonia, pseudoparkinsonism, akathisia, and even persistent (sometimes permanent) tardive dyskinesia (TD). The rate of development of TD among patients treated with standard antipsychotics has been found by Kane et al. (1995) to be approximately 5 percent per year. All off EPS movement disorders can be extremely troublesome to patients. In fact, virtually every psychiatrist whose practice includes individuals with schizophrenia know that, due at least in part to such side effects, most people with schizophrenia will discontinue the standard antipsychotic medications within a year or two, often without any medical supervision. One of the most common reasons for psychiatric readmissions, which may number in the dozens for many individuals, is the repeated discontinuation of medication after leaving the hospital. The need for frequent re hospitalization has obvious implications for employment, school, and social functioning as well as substantial costs involved for inpatient treatment via what has been referred to as a “revolving door”.

In some parts of the country, we understand that health care systems will not routinely allow new patients to be started on atypical antipsychotic medications until they have failed a course of the standard (less expensive generic) antipsychotic medications. We see no scientific justification for such a practice and consider it particularly ill-advised since, for many people with schizophrenia, their first exposure to antipsychotic medication may have life-long implications for compliance with treatment.

Given that these medications have been available for only a short time, there is relatively little scientific literature on the subject, but a recent issue of *Schizophrenia Bulletin* (Vol. 23, No.4, 1997), which is a peer-reviewed NIMH publication that does not accept drug or other advertisements, contains several important papers. One by Sheitman, Lee, Strauss, and Libermann (1997) seems particularly relevant to this issue. These authors note that “consistent with enhanced efficacy in refusing psychotic symptoms, first episode patients also appear more vulnerable to side effects than chronic multi-episode patients.” They further state: “in our soon to be marketed...should be seriously considered as a first line therapy for a first episode of psychosis. Enhanced efficacy in the treatment of negative symptoms, and a more favorable side effect profile, particular less EPS, have been demonstrated in chronic patient samples (Marder and Meiback 1995; Beasley et al. 1996) and might be expected to improve medication compliance, allowing longer periods of maintenance treatment in patients at the beginning of their illness (Lieberman 1993).”

Please note that the NIMH is not currently advocating taking patients who are doing well on standard antipsychotic medication of such treatments. Some patients do reasonable well on these older antipsychotic medications and may suffer relatively few troublesome side effects. For a great many individuals with schizophrenia, however the standard medications are largely ineffective and/or produce intolerable side effects, and there is a significant long-term risk of developing persistent TD. There are also a number of “partial responder” patients who may have been tried on a variety of standard antipsychotic medications without substantial clinical

improvement. Such patients may show a better overall response when given a trial on new atypical antipsychotic medications.

In addition to new patients with schizophrenia, we strongly believe that chronic patients who have relapsed while on standard antipsychotic medications should be candidates for the new atypical medications. As Conley and Buchannan (1997) note, “novel antipsychotics should be the first consideration after the failure of conventional drug therapy. With the exception of clozapine (because of its serious side effects) these drugs are also indicated as a first line therapy. “These authors of on to summarize the evidence for safety and efficacy of the new atypical antipsychotic medications, and one of their summary recommendations is to “aggressively prevent EPS through appropriate choice of primary therapy. With the availability of antipsychotic agents that are clearly effective at doses that do not produce EPS in the vast majority of patients, it should be possible to almost eliminate persistent side effects as a reason for therapeutic failure.” We believe those patients with a history of prior treatment failure on standard antipsychotics should be offered a trial on the new atypical medications.

Certain fairly recent publications, including the *American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia* and the *Expert Consensus Guidelines Series: Treatment of Schizophrenia*, have appeared during the past year or so but do not include such detailed consideration of the newest available medications, there will be an additional impetus to update optimal practice guidelines for 1998 and beyond.

While the evidence is clear and convincing regarding the superior safety profile of the new atypical antipsychotic medications, there are also pharmacoeconomic factors to be considered, as recently summarized by Glazer and Johnstone in the *Journal of Clinical Psychiatry* (1997). They note that “medications comprise a minor portion of the cost of schizophrenia, but may have a major impact on the likelihood of the successful outcome of the care. Novel antipsychotic medications which demonstrate superior symptom control and improved safety profile, and benefits to quality of life, may also reduce patients’ need for medical services and the associated cost of these treatments.” They compared the use of medical services and treatment costs for over eight hundred schizophrenic patients in the United States treated with either olanzapine or haloperidol, and report that “in comprehensive health care cost comparisons that incorporate the expenditures for study medications, the total cost of health care of olanzapine-treated patients was reduced by an average of \$431 per month in comparison with the haloperidol-treated patients during the initial six weeks of treatment. Amount treatment responders receiving double blind therapy for a maximum of one year, the total cost of care among olanzapine responders was reduced by an average of \$345 per month in comparison with haloperidol responders.”

There is one other financial issue that should be considered in this regard, and that is the potential cost of lawsuits that may result when patients now are started on standard antipsychotic medication (rather than new atypicals) and later develop persistent tardive dyskinesia. It would presumably take only one or two lawsuits of this sort to make up the difference between the cost of generic standard antipsychotics and the atypical antipsychotic medications currently available. Of course, the new atypicals do have some side effects, and such as sedation, weight gain, mild transient abnormalities of liver function tests, and a few anticholinergic and orthstatic side effects. Nevertheless, according to Dan Casey in the *Journal of Clinical Psychiatry* (1997),

“overall, the adverse effects profiles of the newest antipsychotics represent a major improvement over those of the older neuroleptics. Olanzapine, sertindole, and quetiapine produce minimal or no EPS across the effective dose range and probably will have low rates of TD.”

I should apologize for the excessive length of this letter but felt it necessary to document some of these serious public health implications. I believe this is a situation in which HCFA and the NIH institutes working in concert can have a substantial beneficial effect on the health care of the American people. I encourage you to contact me should you have any questions about the issues raised above and look forward to hearing from you.

Sincerely yours,

/s/

Steven E. Hyman, M.D.
Director

Enclosure:

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