DRUGS OF THE PSYCHOPHARMACOLOGICAL REVOLUTION IN CLINICAL PSYCHIATRY

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Editor's Note: **In the commentary below, Jeffrey A. Lieberman, M.D., and his colleagues discuss changes in pharmacological treatment that have occurred since 1993, when the article reprinted on page 1249 was published. That article reported one-year outcomes for patients treated with clozapine, an atypical antipsychotic approved for use in 1990. Dr. Lieberman and his colleagues describe events leading to the introduction of atypical antipsychotic drugs like clozapine and of the selective serotonin reuptake inhibitor antidepressants—second-generation drugs of the psychopharmacological revolution that began at midcentury. They review evidence of the effectiveness of these drugs and discuss the benefits of both types of medication, such as more favorable side effect profiles, as well as the drawbacks, such as greater costs for both kinds of drugs and weight gain among patients taking atypical antipsychotics. The authors point out that the second-generation drugs represent a valuable payoff from earlier investments in basic neuroscience research. (*Psychiatric Services* 51:1254–1258, 2000)**

When *Psychiatric Services* began publication a half-century ago, as *Mental Hospitals,* the paradigms of clinical psychiatry were already in flux. The first psychotropic agents capable of treating psychotic and mood disorders had been introduced, general hospitals were developing units for patients with mental illnesses rather than sending them to large remote institutions, and the biomedical research enterprise had been launched at the National Institutes of Health and at academic medical centers.

Psychiatrists and other mental health professionals began to use the first generation of psychotropic drugs almost immediately after they were introduced, and the nature of clinical practice entered a phase of inexorable transition. This transition precipitated a number of tensions and conflicts, most notably between the psychodynamic and pharmacologic paradigms of psychiatric medicine.

Over the past 50 years, as chronicled in the pages of this journal, the transition has continued rather than abated, largely fueled, on one hand, by the innovations that have occurred in drug development and, on the other, by pervasive changes in mental health care delivery systems and health care financing. No longer is treatment predominantly inpatient based and fee for service. A broader array of health care professionals are involved in treating patients with psychiatric disorders, and the role of psychiatrists has changed. Although certain psychotropic agents are now widely used, there are many more, of differing biochemical and pharmacologic types, to choose from.

The pervasive effects of these developments are forcing the field of clinical psychiatry—as well as the rest of clinical medicine—to adapt at a pace that it is hard pressed to maintain. Many of the elements of this transition in the field of mental health care were reflected in the paper on clozapine treatment by Breier and his colleagues (1) published in this journal in December 1993 at a pivotal point in the process of change.

The study they reported foreshadowed many of the issues that have crystallized in the past decade in clinical research and mental health care. The study examined the effects of clozapine, the prototype of the second-generation antipsychotic drugs; it focused on outpatients rather than inpatients; it was a long-term study of 12 months rather than a six-week acute treatment study, as most previous studies had been; and it used outcome measures reflecting general clinical status and health service utilization in addition to traditional ratings of patients' psychopathology.

These design features were not common at the time, but they have become increasingly so as research addresses

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questions of treatment and cost-effectiveness rather than simply efficacy and safety. Moreover, the study was supported by the National Institute of Mental Health (NIMH) rather than the pharmaceutical industry, reflecting the important role in treatment research that NIMH has played. That role began with the Early Clinical Drug Evaluation Units and extended to the recent ambitious initiatives in intervention research, including the research programs of the Systematic Treatment and Evaluation Program in Bipolar Disorder, Systematic Treatment of Affective Disorders, Clinical Antipsychotic Trials of Intervention Effectiveness, and Treatment of Adolescent Depression.

Two of the most important pharmacologic developments of this transition period were the advent of the atypical antipsychotic drugs and the introduction of the selective serotonin reuptake inhibitor antidepressants (SSRIs). This article briefly describes the significance of these developments and their contributions to the field's evolution.

Atypical or second-generation antipsychotic drugs

The development of antipsychotic drugs in the 1950s heralded the golden age of psychopharmacology. Their discovery was comparable to the discovery of antibiotics for infectious diseases, anticonvulsants for epilepsy, and antihypertensive drugs for cardiovascular disease. The antipsychotic drugs soon became the cornerstone in the pharmacopoeia for the treatment of psychiatric illnesses, and enthusiasm for their potential pervaded the mental health field. However, optimism gradually faded as these drugs—typified by chlorpromazine, a low-potency medication; perphenazine, a drug of intermediate potency; and haloperidol, a high-potency agent—proved to have substantial limitations despite their efficacy in the treatment of schizophrenia.

These medications were most effective against psychotic symptoms of the illness and in its early stages. Moreover, the rates of side effects, including extrapyramidal symptoms, tardive dyskinesia, hyperprolactinemia, and neuroleptic malignant syndrome, were extremely high and troubling (2). These side effects contributed significantly to noncompliance, which led to relapse and rehospitalization. The conventional antipsychotics also did not alleviate all of the symptoms and disability caused by the illness, and at least 20 percent of patients relapsed despite taking adequate doses of medication (3,4).

Thus, despite several decades of effort to effectively treat severely mentally ill patients in community-based treatment programs, a substantial proportion of these patients continued to be severely disabled and relapsed frequently, requiring hospitalization (5,6). This hospital recidivism produced substantial human costs in suffering and demoralization, in addition to a significant financial burden to public and private mental health systems laboring under fierce demands for cost-containment (7–9).

The introduction of clozapine (Clozaril) in 1990 and the subsequent development of other atypical antipsychotic drugs with the potential for enhanced efficacy and safety changed the risk-benefit profile of this drug class for multiple indications (10). Atypical agents became available after a long fallow period in the development of antipsychotic drugs. Although more than 20 antipsychotic agents were introduced after chlorpromazine, none were introduced for schizophrenia in the 14 years before 1990. The new drugs differ pharmacologically from typical antipsychotics. Principally, they have a lower affinity for the dopamine 2 (D_2) receptor and relatively greater affinities for other neuroreceptors, including those for serotonin ($5HT_{1a}$, $5HT_{2a}$, $5HT_{2c}$, $5HT_3$, $5HT_6$, and $5HT_7$) and norepinephrine ($alpha_1$ and $alpha_2$), and they can modulate glutamate receptor-mediated functions and behaviors (11).

A pharmacologic property that has been emphasized as critical for conferring atypical activity is the ratio between D_2 and $5HT_{2a}$ receptor antagonism; a low ratio is characteristic of the atypical agents (12). In addition, they appear to exhibit some degree of regional anatomic specificity, altering neurochemical activity in the limbic and frontal cortical regions while having very little effect on the corpus striatum (13). Unfortunately, the prototypical atypical drug, clozapine, was found to produce a selective hematologic toxicity against polymorphonuclear white blood cells in 1 percent of patients exposed to the drug for at least six months (14). This potential for adverse effects, as well as the need to monitor white blood cell counts, has limited the use of clozapine to patients who are unresponsive to or markedly intolerant of other first-line antipsychotic drugs.

Despite its limitations, clozapine has had a seminal effect on antipsychotic drug development and on our understanding of schizophrenia. The result has been an accelerated search for novel compounds and a rapid rate of antipsychotic drug development. Risperidone (Risperdal) was approved by the Food and Drug Administration (FDA) and introduced by Janssen in 1994, olanzapine (Zyprexa) by Lilly in 1996, and quetiapine (Seroquel) by Zeneca (now Astra-Zeneca) in 1997. A fourth drug, sertindole (Serlect), was approved by the FDA in 1998, but it requires electrocardiogram monitoring because of a concern for cardiac arrhythmia (torsade de pointes). The pharmaceutical company, Abbott, chose not to market the drug in the United States. A fifth drug, ziprasidone (Zeldox), introduced by Pfizer, is expected to be approved by the FDA by the time this article is published.

Other putative atypical compounds are in early stages of development. Among them are aripripazole (Abilitat), by Otsuka and Bristol-Myers Squibb, and iloperidone (Zomaril), by Novartis, which are in phase III trials. Thus several new compounds have come into clinical use since clozapine, with the promise of more to follow.

Recent research has provided strong evidence of the efficacy of atypical antipsychotics for schizophrenia and has demonstrated that they greatly reduce the risk of extrapyramidal symptoms and tardive dyskinesia (15). There is a growing sense that they are becoming or should become first-line treatments for schizophrenia (16). Moreover, their better safety profile is increasing the number of indications for which they are being prescribed. Besides schizophrenia, the indications include dementia with psychosis and psychotic mood disorders.

However, the exact nature and extent of the clinical advantages of the atypical drugs are not known. It also appears that the atypical drugs as a class produce substantial weight gain compared with conventional drugs (17), although the effect varies among individual drugs. Clinical trials of the efficacy and safety of atypical antipsychotics show weight gain for 50 to 80 percent of study subjects (18). To date, little is known about the natural history of the weight gain, and the physiologic mechanism of weight gain is wholly unknown. There is no known treatment. Also unknown are the medical consequences, which could range from solely cosmetic consequences to increased rates of cardiovascular disease, such as hypertension and coronary artery disease, and diabetes.

Atypical antipsychotic drugs have also been associated with alterations in glucose metabolism. There are two published case series reports of ten patients on atypical antipsychotics who either developed diabetes or had a significant exacerbation of existing disease (19,20). The etiology of atypical-antipsychotic-induced diabetes is unknown. In addition, the atypical drugs have been associated with elevations of blood cholesterol and lipids (17). The relationships between the drug effects on weight gain and the effects on glucose, cholesterol, and lipids are not known.

It is not inconceivable that the nutritional and metabolic effects of the atypical antipsychotics could be found to be their most serious safety problem and as onerous to patients treated with them as tardive dyskinesia is to patients treated with conventional antipsychotics.

Although a variety of claims for the efficacy and safety of the atypical antipsychotic drugs have been made, the evidence for these claims is highly variable and in many cases inadequate. Some questions can be answered from the available literature and from data presented at scientific meetings, but many more cannot. It is reasonably clear that these drugs are at least as effective as the conventional agents in reducing positive symptoms among patients with schizophrenia. However, claims that they are superior in reducing positive symptoms remain to be proved (15). They appear to be more effective than conventional antipsychotics in reducing negative symptoms, but it is not clear whether the reduction is due to a direct therapeutic effect or to the absence of extrapyramidal symptoms or other secondary causes of negative symptoms such as depression (15).

Long-term trials of the effectiveness of atypical antipsychotics in reducing negative symptoms are needed (4). Despite some claims, studies of effects on cognitive function are inconclusive, as are studies of the effects on mood symptoms. Exploration of the effects of these drugs on long-term outcome, relapse prevention, social and vocational functioning, quality of life, and family and caregiver burden has just begun.

Despite incomplete evidence, the use of the new atypical agents has grown steadily. Since the introduction of risperidone in 1994, olanzapine in 1996, and quetiapine in 1997, these three atypical antipsychotics have come to account for slightly more than half of the new antipsychotic prescriptions in the United States (21,22). Patients who had inadequate therapeutic responses to conventional antipsychotics or who suffered problematic side effects were the first to be switched to the atypicals. Now, however, these newer agents are initially prescribed for many newly diagnosed or first-break patients with the hope—not yet backed by evidence—of giving them every early advantage (16). At the same time, many patients with schizophrenia continue treatment with the conventional drugs. Because long-acting preparations of atypicals are available, conventional agents in long-acting injectable form retain an important role for patients who cannot adhere to oral regimens.

Atypical antipsychotic medications cost 15 to 20 times more than conventional medications, averaging $5,000 per patient per year. Although their high cost might serve to discourage their use, they have the potential to generate substantial savings in health care and non-health-care resources if they are more effective than other available treatments. And even if the net cost of a particular drug and related services is greater than the cost of other drugs, its use may be warranted by its greater effectiveness. This is a serious question because expenditures of large sums of money on treatments that are less cost-effective than available alternatives may result in needless waste of scarce resources and deprive some patients of clinical benefits that they could otherwise obtain. The concern about increased drug cost and cost-effectiveness has resulted in formulary restrictions in many health care systems and has promulgated the development of treatment guidelines from many organizations, including the American Psychiatric Association (23).

Empirical evidence does not address these issues fully and comprehensively. The studies to date, which were for the most part sponsored by pharmaceutical companies and designed to achieve FDA approval on the basis of evidence of efficacy and safety, have been largely short term (six to eight weeks), involving initially hospitalized patients, and focusing mainly on the core psychopathology of schizophrenia and well-known side effects such as extrapyramidal symptoms. Although informative, these studies do not definitively demonstrate the extent of the real-world benefits of the newer agents and their cost-effectiveness. Thus a clinical and public policy decision to replace conventional with atypical antipsychotic agents, although appealing, requires more empirical evidence.

The SSRIs: changing the face of depression

A precedent for the broad changes in treatment that clozapine and the other second-generation antipsychotics produced was established earlier for depression by the introduction of fluoxetine (Prozac) and the other selective serotonin reuptake inhibitors. The advent of Prozac and other SSRIs led to far-reaching changes not only in the clinical treatment of depression but also in the public perception of mood disorders and, by extension, in the entire field of psychiatry.

In 1988 fluoxetine became available for clinical use in the United States, and it quickly became one of the most

widely prescribed medications in the country. Several other SSRIs were introduced in fairly rapid succession: sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and, most recently, citalopram (Celexa). Prozac, possibly because it was the first to reach the market, became more of a cultural icon than the others, and it continued to enjoy the largest market share even after its competitors had been introduced.

The enormous success of Prozac was probably due to a combination of its clinical pharmacological properties and other, more pragmatic factors. The SSRIs clearly are superior to the tricyclic antidepressants and the monoamine oxidase inhibitors (MAOIs) in terms of toxicity (24). Their side effect profiles are relatively more benign, and the therapeutic margin—the ratio of a lethal dose to a therapeutic dose—is substantially greater, even in comparison to some of the earlier second-generation antidepressants, such as maprotiline and amoxapine (26). Thus, even though the SSRIs offered no advantage in efficacy or lag time to clinical response, physicians embraced their greater safety, and patients found their side effects to be much more acceptable.

From a practical perspective, fluoxetine was also remarkably easy to prescribe. When it was originally introduced, there was a common perception that "one size fits all," and most patients received a single daily dose of 20 mg—the only dose strength that was initially available. From the perspective of a busy primary care clinician, this dosing schedule was much easier than the careful titration that tricyclic antidepressants and some of the other second-generation antidepressants required. In fact, the prescription of fluoxetine appeared to be very uncomplicated: a single daily pill and no dietary restrictions.

Of course, over time, it has become clear that in many instances its optimal use is not quite so simple; some patients require different doses. The medication is now available, as are the other SSRIs, in more than one dose strength. Also, the potential for pharmacokinetic drug interactions must be considered. Still, the explosive initial success of Prozac was due, at least in part, to the apparent ease with which doctors prescribed it and patients consumed it, compared with the tricyclics and MAOIs.

Like no other psychotropic medication, Prozac captured the public's attention and became a cultural icon. Peter Kramer's thoughtful and articulate book, *Listening to Prozac* (26), published in 1993, enjoyed a remarkably long run on the bestseller lists, as it introduced a broad audience to the excitement of recent developments in the neurosciences and clinical psychiatry. "Prozac" and, by extension, "depression," became household words, appearing everywhere from *New Yorker* cartoons to the covers of national news magazines, afternoon talk shows, and comedians' monologues on late-night television.

These cultural phenomena probably helped destigmatize depression and made it easier for patients and their families to seek help for what was now clearly defined as a common and treatable illness. The change that had already begun in the public perception of psychiatry was accelerated, with the stereotyped image of the analytic couch replaced by the symbol of a medication capsule or tablet.

Although this intensive public focus on Prozac and the other SSRIs produced many beneficial effects, as with any medication, it also generated some untoward side effects. A few overly enthusiastic proponents made reckless claims that "everyone should be on Prozac." The flip side to the advantages afforded by the relative safety and tolerability of the SSRIs was the unfortunate tendency for these medications to be overprescribed and misprescribed in some settings. The great strides that had been made in educating primary care physicians about well-defined, validated psychiatric syndromes and the need to carefully apply specific diagnostic criteria as a requisite for treatment planning began to unravel.

Because prescribing Prozac seemed much easier and safer than prescribing MAOIs, tricyclics, or electroconvulsive therapy, some physicians misprescribed the drug for patients who did not have a specific mood disorder but were simply unhappy because of difficult circumstances. Not surprisingly, the SSRIs did not relieve the sadness that people felt in these situations, and some disappointed physicians and their patients began to talk about the ineffectiveness of antidepressant pharmacotherapy.

However, the overall impact of the SSRIs was to increase the availability of effective antidepressant treatment for patients who needed it. Today, although many people still suffer with untreated—and in many cases undiagnosed—depression, their numbers are much smaller than they would be if the pharmacological treatment options were still limited to the tricyclic medications and the MAOIs. In addition, the superior cardiovascular side effect profile of the SSRIs, compared with those of the earlier antidepressants, has greatly expanded the field of "psychocardiology"; studies have begun to demonstrate the life-saving impact that these medications can have for patients with comorbid cardiac and mood disorders, such as patients who are depressed after suffering a myocardial infarction (27).

The SSRIs, like the atypical antipsychotic medications, cost more than their predecessors, many of which were available in generic formulations when the newer compounds were introduced. A daily dose of an SSRI can cost a patient a dollar or more, while a daily dose of lithium carbonate costs pennies. Coincidentally, the introduction of these higher-priced new medications overlapped with the revolution in American health care financing, and managed care companies began to view the seemingly high price of pharmacotherapy as an easy target for cost cutting. Some patients found that their choice of antidepressant was dictated not by the side effect profile but by their managed care carrier's formulary and policies. In some settings, patients had first to "prove" that a generic tricyclic was not tolerable before they could receive approval for treatment with an SSRI. Over time, however, pharmacoeconomic studies have demonstrated that there are clear savings in cost, not to mention human suffering, to be gained by offering the best available treatment for a given patient.

The SSRIs share another important feature with the

atypical antipsychotic medications: they represent an enormously valuable payoff from earlier investments in basic neuroscience research. The original antidepressants were discovered by serendipity (28,29). Years of increasingly sophisticated basic and translational research demonstrated the role that enhanced synaptic availability of serotonin plays in the mechanism of action of many of the initial antidepressant compounds. Further research led to the recognition of the potential advantages that might be afforded by a molecule that specifically blocked the serotonin reuptake site without affecting other neurotransmitter receptors responsible for unwanted side effects.

Each of the SSRIs represents a deliberate, prospective, hypothesis-driven effort to target a specific pharmacological action. Thus, just as we entered "the decade of the brain" in 1990, the wisdom and value of earlier commitments to neuroscience research became evident through the dramatic impact of the new antidepressant and antipsychotic medications on clinical practice and outcomes.

Conclusions

As we move into the 21st century, the field of clinical psychiatry continues to evolve. In one sense that is good: the field is dynamically responding to the economic, scientific, and academic pressures that have an impact on it. However, in another sense it is perhaps lamentable that the field has not been more proactive in defining itself and its vision for change instead of being reactive as it is swept along by the scientific revolution occurring in medicine and neuroscience and the reform in health care financing (30). The effects of both are rapidly reconfiguring the health care delivery system and the roles and practice of clinical psychiatry. ♦

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