Review of Antipsychotic Medication Administration: A Proposal of Intermittent Dosing

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Abstract

Despite advances in the treatment of schizophrenia, there are substantial gaps in systematically established knowledge concerning the application of antipsychotic agents. We still do not know how antipsychotic drugs work, where they work, how much to prescribe, or how often to prescribe. No consensus exists on the definition of relapse or recovery. Based on new knowledge of delayed onset and offset of pharmacological response in schizophrenia, of signal transduction, of time-delayed effects at the neuronal level, and of the complexities of etiologic and clinical heterogeneity in these disorders, we propose an alternative dosing strategy. Fixed intermittent dosing for initiation and maintenance of remission of clinical symptoms holds promise for improving response to medication, reducing side effects, increasing compliance, and limiting cost. It may help clarify the taxonomic conundrum of schizophrenia by providing a probe for identifying discrete pathophysiologic substrates in these disorders.

Keywords: Schizophrenia, antipsychotic medication, medication administration, intermittent dosing.


The epistemological basis of pharmacotherapy is meaningful measurement of outcome. Outcome measures must be valid and reliable indicators of the intended result. Evaluation of antihypertensive agents is straightforward because the outcome measure—reduced blood pressure—is both the anticipated goal of the treatment (validity criterion) as well as a reproducible measure (reliability criterion). When nitrogen mustards were initially utilized for the treatment of children with leukemia (Gilman and Philips 1946), outcome measures were equally clear: the number of malignant cells killed by the treatment, and the survival of the patient. The initial strategy, maintaining a steady state level of antitumor agent, employed a standard daily dosing schedule. However, when the number of tumor cells killed—the efficacy—quickly diminished, pediatric oncologists scheduled intermittent administration of higher doses of the same agents. This strategy killed more tumor cells, provided time for the patient's bone marrow to recover, and increased the patient's chance for survival (Vietti et al. 1977).

In contrast to these straightforward examples from medicine, evaluation of pharmacological treatment of schizophrenia has been constrained by myriad dilemmas. All physicians and all oncologists agree on criteria of treatment outcome in leukemia. This has not been the case with schizophrenia. Kraepelin first described dementia praecox as a disease entity in 1896. Since that time, the definition of schizophrenia has fluctuated widely, with the result that studies from different time periods have sampled disparate populations of patients.

Compounding this sampling conundrum are the changing ethical standards for clinical research. Patients who were enrolled in early clinical studies were merely observed. Those who have participated in more recent clinical studies have been required to provide informed consent and often perform complex tasks. Many schizophrenia patients living in institutions or supervised settings have not participated in such studies because they cannot or will not give consent or because they are not able to cooperate with the investigators. Are research subjects a representative sample of the total population of all schizophrenia patients, or is there bias of ascertainment based on recruiting difficulties? Finally, a review of the literature demonstrates a mélange of outcomes (Hegarty et al. 1994). Does the elimination of auditory hallucinations and delusions define remission of schizophrenia? Are positive symptoms, those most frequently measured, the most disabling symptoms of this most disabling disorder? As we have learned more about the protean nature of schizophrenia, positive symptoms have ceased to be the sine qua non of the condition.

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Kraepelin's definition of schizophrenia as a "series of states, the common characteristic of which is a peculiar destruction of the internal connections of psychic personality" (1919, p. 3) remains an accurate description of one essential manifestation of this multidimensional condition. However, it does not translate into the empirical outcome criteria required for scientific inquiry. Over the last century, we have collected a massive amount of information, including descriptions of diverse clinical symptoms (Bleuler 1924; Stevens 1973; Crow 1980; Andreasen et al. 1995) and identification of motor and sensory abnormalities (Stevens 1973; Manschreck 1983; Seidman 1983; Rogers 1985; Ismail et al. 1998) and neuropsychological (Gray et al. 1991), cognitive, and psychiatric deficits (Maher et al. 1995; Manschreck et al. 1996). Anatomical studies have revealed both macroscopic (Jacobi and Winkler 1927; Johnstone et al. 1976; Weinberger et al. 1979) and microscopic abnormalities (Stevens 1982; Benes 1991; Benes et al. 1991; Bogerts and Falkai 1991; Waddington 1993; Raijowska et al. 1998) in the brains of some, but not all, schizophrenia patients.

While the body of empirical knowledge has expanded, we have yet to identify the locus or set of loci of pathology that defines schizophrenia. One way of resolving this dilemma has been to regard schizophrenia not as a single disease but rather as a spectrum disorder or a family of disorders that have discrete neurological lesions but share a common clinical presentation (McCarley et al. 1993a). Attempts have been made to identify clusters of abnormalities, but this approach has not yielded an improved nosology (Garver et al. 1998).

In spite of incomplete understanding of the pathophysiology of schizophrenia, we have made substantial progress in treating schizophrenia patients with antipsychotic medication. Indeed, nearly all patients receiving medication experience some improvement in their behavior, perception, delusions, and disorganized thinking. But the many dimensions of pathology—psychiatric symptoms, cognition, behavior, and social functioning—make the concept of remission more complicated than resolution of psychotic features. Only recently have we begun to examine inter- and intraneuronal function in sufficient detail to appreciate how medications might work. These advances have contributed to a new generation of drugs for schizophrenia but have had no impact on the way that we determine appropriate dosage or the way we schedule its administration.

A central intent of this article is to review the epistemological basis of the current practice of administering antipsychotic medication, thereby demonstrating that it is primarily grounded on the subjective clinical experience of practitioners and not on scientifically derived data. This uncontrolled, empirical approach dates from initial reports by Delay et al. (1953) concerning their clinical experience with chlorpromazine. There have been studies testing alternative dosing schedules, but they have been rejected for diverse reasons that we shall address. There have been virtually no studies establishing, in a rigorous manner, the point in time when antipsychotic agents begin to ameliorate bizarre behavior and psychotic symptoms or when effectiveness of medication ceases after discontinuation. Outcome studies, a rich source of information about clinical response over the last 50 years, have not yielded consistent results because they define schizophrenia, remission, and recovery in varying ways.

Many questions remain unanswered in clinical psychopharmacology. How do antipsychotic agents affect thought, emotion, and behavior? When do these effects begin, and how often do medications need to be given? How do we know what is the minimum appropriate dose if we are not certain of the onset of action of the drug? Are our outcome criteria valid descriptors of the multiple dimensions of schizophrenia? Why do we persist in dosing patients on a daily schedule in spite of data that suggest that this may not be necessary or even desirable? Why has the Food and Drug Administration failed to question currently unproven dosing schedules while requiring Phase III clinical trials for dose finding and efficacy? Is it possible that some if not all patients might benefit from differing schedules and that this differential response may, in fact, inform us of differences in underlying neuropathology, thus leading to a more operational nosology for schizophrenia?

With increasing awareness of these problems as well as increasing knowledge of neurophysiology at the molecular level, it is appropriate to generate and test hypotheses consistent with an expanded understanding of schizophrenia. To do so requires that we (1) consider the historical development of patterns of dosing; (2) review the history of pharmacological treatment of schizophrenia as well as critically examine the concept of remission; (3) evaluate studies proposing a time course for neuroleptic onset and offset of action; (4) critically examine our knowledge and definition of relapse; and, finally, (5) review previous efforts at modifying dosing strategies in order to minimize exposure to neuroleptics. Integrating these historical perspectives with emerging knowledge from neuroscience—signal transduction and time-dependent sensitization—has led to the conclusion that alternative dosing strategies deserve a trial. Evidence, both clinical and experimental, supports the idea that antipsychotic medication should be equally effective given on a fixed intermittent schedule, thereby reducing side effects, morbidity, and costs.
Determining which schedule of intermittent dosing best suits individual patients may provide a probe for identifying subtypes of schizophrenia based on pharmacology rather than clinical symptomatology.

**Historical Origins of Neuroleptic Dosing**

The discovery that chlorpromazine has antipsychotic properties provides a superb example of Louis Pasteur's maxim: "In the field of research, Nature favors the prepared mind" (Stryer 1995). In 1950, ether was the principal available anesthetic. Surgeons sought a preanesthetic sedative to make ether administration less traumatic. Chlorpromazine had been synthesized not long before and was known to have antihistaminic properties that made it a good candidate for such a sedative. Henri Laborit, a French surgeon, included chlorpromazine in a cocktail administered before surgery. He recognized that in addition to sedating patients, chlorpromazine produced a postoperative psychological effect that he described as "artificial hibernation." Recovering patients seemed calmer in contrast to other patients who had undergone similar procedures; in fact, they were described as strikingly indifferent to their surroundings (Baldessarini 1996). Laborit reported his observations to French psychiatrists, and they began using chlorpromazine to sedate agitated or manic patients. After treating some patients with chlorpromazine, Jean Delay and Pierre Deniker undertook a more systematic study and confirmed Laborit's observations. They reported efficacy in treating "psychosomatic conditions" such as duodenal ulcers and colitis (perhaps because of anticholinergic side effects) and eczema with 200 or 250 mg of chlorpromazine daily. They also discovered that sustained use of chlorpromazine ameliorated agitation, delusions, and hallucinations and produced extrapyramidal system effects. Dosage for the treatment of dementia praecox ranged from 250 mg per day to 200 mg four times per day. The authors did not mention how the limitations of the DA hypothesis of schizophrenia, burgeoning knowledge about other neurotransmitter systems, and increasing appreciation of anatomical abnormalities (both macro- and microscopic) have contributed to more comprehensive theories of the etiology of schizophrenia. Feinberg (1982) hypothesized a developmental model: abnormal apoptosis during adolescence. Weinberger (1987) also proposed a neurodevelopmental hypothesis with greater specificity: perinatal insults to the dorsolateral prefrontal cortex (DLPFC) expressed in late adolescence, when this region of the brain is myelinated. Data supporting the latter model include cytoarchitectural abnormalities observed in the DLPFC and the observation that late adolescence is the time when schizophrenia most frequently presents. These newer models accounted for more of the observed phenomena of the disease than did preceding ones. Olney and Farber (1995) and others (Akbarian et al. 1995) suggested that reduced activity of mesocortical dopaminergic neurons that normally inhibit glutamatergic neuronal activity could result in overactivation via N-methyl-D-aspartate (NMDA) receptors, one of the new developments.
the family of glutamate receptors. Their hypothesis, based on multiple lines of evidence, explained how disinhibited glutamatergic neurons could lead to cytotoxicity, producing the observed anatomical abnormalities, cognitive deterioration, negative symptoms, and erratic response to D2 receptor blockers (Shapiro 1993; Benes 1995). None of these manifestations of schizophrenia had been accounted for by the DA hypothesis. The DA deficit-NMDA receptor hypothesis (or glutamate hypothesis) is also consistent with observed delayed onset of action of antipsychotic agents (Coyle 1996).

A Review of the Pharmacology of Schizophrenia, Including the Question/Definition of Remission

Conventional antipsychotic agents have been used for nearly 50 years by millions of patients worldwide and have been the subject of numerous research studies. When these studies are reviewed, no consensus emerges on how to dose psychotic patients appropriately, either to achieve or to maintain remission.

A meta-analysis conducted by Davis and Andriukaitis (1986) examined the results of 35 controlled studies that followed 3,500 patients to determine the efficacy of neuroleptic treatment over periods as long as 2 years. Clinical rating instruments were not utilized in most of the earlier studies. Rather, patients were described as much improved, minimally improved, unchanged, or worsened. Relapse was defined as recurrence of psychotic symptoms. These studies showed that neuroleptics maintained remission in 85 percent of patients, while the relapse rate for a comparable population of schizophrenia patients treated with placebo but receiving other treatments such as milieu therapy was 58 percent. Furthermore, the data suggested that neuroleptic treatment during the initial phase of the illness produced a consistently better long-term outcome. Finally, the authors examined dose-response relationships and found that high doses (1,000 chlorpromazine-unit-equivalent doses [CUD] or more) were not significantly more effective than low doses (300 CUD or less).

Wyatt (1991) reviewed 22 studies to assess how neuroleptic treatment affects the natural course of schizophrenia. The earliest cohort of untreated patients was from 1931 to 1933. A second cohort of patients from 1935 to 1945 received somatic therapies, including insulin-induced coma, electroconvulsive therapy, or psychosurgery. The majority of studies followed patients from the 1950s through the 1980s. Earlier studies among this latter group had compared drug-free treatment regimens with neuroleptic treatment. In all studies reviewed by Wyatt, relapse was defined as rehospitalization. This meta-analysis highlights the methodological difficulties of comparing patients who may have received electroconvulsive therapy, insulin-induced coma, or psychosurgery followed by neuroleptics with patients who have been treated only with medication. In addition, Wyatt acknowledges variations in diagnostic criteria that limit the comparability of the findings. In none of the studies reviewed did the authors explain how dosing ranges were derived or define remission or recovery. In spite of these limitations, the few studies that did address dosing ranges (300–900 CUD) concluded that patients receiving higher doses had similar numbers of rehospitalizations as did those receiving lower doses.

Baldessarini and others (1995) compared hospital use of neuroleptics from 1989 to 1993 to see whether shorter lengths of inpatient treatment were accompanied by more aggressive (larger) doses of antipsychotic drug. They also examined doses of antipsychotic medication (all converted to CUD) in several Boston hospitals and compared the pooled Boston data with data from comparable facilities across the continent. An earlier study had established a weighted mean dose of neuroleptics to be 760 CUD and one for the more potent neuroleptics, haloperidol and fluphenazine, to average 1,416 CUD (Baldessarini et al. 1984). By the late 1980s, patterns of dosing had changed; a weighted-pooled median dose of all neuroleptics had decreased to 240 CUD. By 1993, the mean length of hospitalization of patients receiving neuroleptics had also decreased from 73 to 18 days. In spite of fewer days of hospitalization, in 1993 the median dose of neuroleptic had been decreased to 227 CUD (mean dose equaling 305 CUD). It should be noted that most of these patients were also receiving adjunctive medications, which may have contributed to overall reduction in the use of antipsychotic agents. The authors emphasized that the pattern of lower dosages of neuroleptics in Boston teaching hospitals may not have reflected a national trend. They noted a study that examined patterns of drug administration in several New York facilities between 1973 and 1982 that contradicted the results from Boston. In a New York State mental hospital in 1973, the average dose was 1,590 CUD; in a general hospital, the average dose was 1,370 CUD; and in a community mental health center inpatient unit, patients received 800 CUD. By 1982, average doses of drugs in the three sites had doubled (mean = 197%), with an average reduction in the length of inpatient stays of 31 percent. The same authors reviewed another study out of Canada that set an upper limit of administration of medication. At a university medical center in 1991, the average daily dose of neuroleptic was 3,000 CUD on the first hospital day (Baldessarini et al. 1984).

Finally, in a study of first break schizophrenia, Lieberman and coworkers (1992) reported that 74 percent of patients achieved full remission and 12 percent achieved partial remission. The mean fluphenazine dose
for remitted patients was 24 mg/day, which is equivalent to 1,200 CUD. Remission or recovery (used interchangeably) was defined as "no rating > 3 on any of the SAD S-C + PD positive psychotic symptom item [Schedule for Affective Disorders and Schizophrenia—change and positive psychotic symptoms, Spitzer and Endicott 1978], a CGI severity item rating of < 3 (mild), a CGI [Clinical Global Impression, Guy 1976] improvement item rating of 2 (much improved) or better, and the maintenance of this level of improvement for 8 weeks" (p. 355). The mean time required to reach remission was 36 weeks, with the median time being 11 weeks.

As these examples demonstrate, outcome studies are difficult to compare, owing to multiple methodological variables. First, the definition of schizophrenia has been in flux since Kraepelin proposed dementia praecox. Criteria used in the United States for diagnosing schizophrenia were generally broadened through the first half of the 20th century until schizophrenia became a catchall for chronic severe psychotic conditions. *DSM-I* (1952) was published in order to standardize diagnostic criteria, but by the time of its publication, criteria for schizophrenia in the United States were distinctly non-Kraepelinian. As was fashionable, schizophrenia was defined as a "reactive psychosis" rather than in terms of specific symptomatology. By 1980, *DSM-III* had modified criteria to be more consistent with the new ICD-9-CM (1979), the World Health Organization classification of disease, which narrowed the definition of schizophrenia. Since that time, criteria have been progressively modified so that the 1994 *DSM-IV* definition closely conforms to those of Kraepelin.

The outcome literature reveals no consensus regarding the definition of outcome. "Remission" and "recovery" are frequently used interchangeably, in spite of the fact that remission as the absence of psychotic symptoms is not the same as recovery of premorbid level of function. The chronically institutionalized, "burned out" schizophrenia patient may no longer hear voices or be frankly delusional and may speak clearly and coherently, albeit only when spoken to, but he or she has not recovered. We better appreciate those newly reemphasized domains of symptomatology, including motor activity, cognition, social awareness, and behavior, that remain impaired long after the disappearance of psychotic symptoms and bizarre behavior. Remission of psychotic symptoms is a necessary but not sufficient condition for recovery.

An additional confound in the studies we have referenced is bias of ascertainment. Most of the studies that have been reviewed (excluding Lieberman et al. 1992) have examined hospitalized patients and have described relapse in terms of rehospitalization. A seminal study by Engelhardt and colleagues (1982) followed 646 schizophrenia outpatients for up to 20 years. All patients were treated with neuroleptics. The best predictor of future hospitalization was hospitalization prior to the start of the study. Of the 21 percent of patients who had never been hospitalized when the study began, only 39 percent required hospitalization over 20 years. Among the previously hospitalized patients, 68 percent required subsequent hospitalization. All these patients were followed in a clinic providing pharmacotherapy as well as counseling. While diagnostic criteria and patterns of neuroleptic administration were not described, the authors concluded that patients who were more severely ill initially (patients requiring hospitalization) had a worse prognosis than those less severely affected.

The review of Davis and Andriukaitis and that of Wyatt assessed outcomes of hospitalized patients carrying the diagnosis of schizophrenia. Both acknowledged the importance of early intervention as the best predictor of better outcome. The results of the study of Engelhardt and others may reflect the same phenomenon in that their nonhospitalized cohort's members may have received earlier intervention owing to the fact that their disease was recognized earlier. Alternatively, Engelhardt may have followed a population with a less severe illness.

The most comprehensive meta-analysis (Hegarty et al. 1994) reviewed virtually all 20th-century literature on the impact of pharmacotherapy on the long-term outcome of schizophrenia patients. In their analysis, the authors included how patients had been diagnosed. They then separated studies on the basis of diagnostic criteria into a broader non-Kraepeliane group and a narrower Kraepeliane group, the latter conforming more closely to criteria in *DSM-IV*. The authors then compared each set of pooled data. They demonstrated that less than half of all schizophrenia patients as defined by contemporary criteria showed any significant improvement after 6 years. Taking into account all dimensions of premorbid function—including motor activity, cognition, and social function—yields an even bleaker outcome. Schizophrenia patients today are no more likely to recover than schizophrenia patients 100 years ago and may carry an iatrogenic burden. Broader diagnostic criteria account for more (apparent) improvement than pharmacotherapy. Finally, all patients in so-called remission continued to deteriorate in comparison with premorbid levels of function. This last point underlines the importance of the distinction between remission and recovery.

**Studies of Neuroleptic Onset and Offset of Action**

In a review of the extensive literature on antipsychotic drugs, Cohen (1988) concluded that the time course for
Ameliorating hallucinations, delusions, and illogical thinking requires weeks or even months (Angrist et al. 1981; Baldessarini et al. 1987, 1988; Cohen et al. 1992).

Meltzer and coworkers (1990) studied the timing of onset of action of clozapine in previously unresponsive schizophrenia patients using the Quality of Life Scale (QLS, Heinrichs et al. 1984) and the Brief Psychiatric Rating Scale (BPRS, Overall and Gorman 1962) as outcome measures. By 6 weeks, 37 percent of the patients showed a decrease of greater than 20 percent on the BPRS score. By 6 months, the percentage of patients showing this degree of improvement had increased to 61 percent. Changes in QLS ratings were comparable. Initial mean level of impairment was in the moderate to severe range. After 6 months of treatment with clozapine, the mean score had increased by 60 percent. An improvement of total QLS score of greater than 50 percent was achieved by 58 percent of the patients, and an improvement of more than 100 percent was achieved by 42 percent of the patients. The authors concluded that clozapine continues to ameliorate symptomatology for at least 6 months.

Previous studies had reported onset of action of clozapine ranging from 8 to 12 weeks to 6 to 12 months (Owen et al. 1989). Conley and coworkers (1997) designed a standardized dosing protocol in which all patients would initially receive a minimum dose of 400 mg/day of clozapine. Clinical response was determined by use of the BPRS as well as the Clinical Global Impression (CGI, ECDEU 1976). Response was defined as a 20 percent or greater reduction in BPRS score from baseline and either a CGI score of 3 (mild) or less or a total BPRS score of 35 or less at the time of response. Clinical response was assessed for 6 weeks, after which the dose was raised to 600 mg and assessed for another 6 weeks. Patients who had not responded were then increased to a dose of 700 mg/day for up to 6 weeks and finally to a maximum dose of 900 mg/day. In this study, 68 percent of the patients enrolled improved at some dose of clozapine. More important, no patient’s response changed after week 8 at any dose increase. Some patients reached their maximum response sooner because their optimal response was achieved at a lower dose. Others required a longer time because their optimal response required a higher dosage. The time varied according to the amount of drug required to achieve maximum remission of symptoms. This clinical trial addresses many of the methodological problems in evaluating studies of onset of action of antipsychotic agents. In addition, its findings suggest that the onset of antipsychotic action of clozapine is similar to that of typical as well as other atypical antipsychotic agents.

Finally, Rosenheck and others (1999) examined the time period required to obtain a response to either clozapine or haloperidol in schizophrenia patients refractory to conventional antipsychotics. After 12 weeks, 37 percent of patients receiving clozapine had at least a 20 percent global improvement over baseline on the Positive and Negative Syndrome Scale (Kay et al. 1987), while only 26 percent of patients given haloperidol achieved this degree of improvement. After 52 weeks, percentage improvement for patients on clozapine had increased by only another 4 percent, while those on haloperidol also increased by 4 percent. These results suggest that both groups of patients achieved almost all of their response within 12 weeks. However, because these patients were judged treatment refractory, this outcome may not be generalizable to all schizophrenia patients. As noted above, Meltzer and colleagues (1990) had reported that patients on clozapine continued to improve after 6 months. Multiple clinical trials on the other atypical agents have demonstrated delayed onsets of action comparable to that of clozapine.

More germane to our questioning of conventional dosing schedules for schizophrenia patients is the vast body of information concerning the offset of action (the time after which the medication ceases to have any effect) of neuroleptic drugs. The most compelling observation consistent with residual medication effects is demonstrated by relapse studies. Davis and Andriukaitis (1986) published a meta-analysis of 35 relapse studies summarizing data on more than 3,000 patients. Historically, the presentation of such studies had supported the necessity for continuous medication for the treatment of schizophrenia patients. What is remarkable, especially for those convinced of the imperative for continuing pharmacological intervention, is that after 6 months, approximately 50 percent of patients off all chemotherapy remained in remission.

A recent study, authored by Viguera and colleagues (1997), compared clinical risk following either abrupt or gradual discontinuation of antipsychotic medication for both outpatients and inpatients. Their data both confirm and extend the conclusions drawn by Davis and Andriukaitis in their earlier reviews (figure 1a, Viguera et al. 1997). Looking at relapse rates among the several populations they studied, these authors saw that by approximately 6 months, relapses had leveled off, with no significant subsequent occurrences. Many of these patients have
Figure 1a. Computed “survival” functions based on findings from studies that discontinued maintenance oral neuroleptic drugs in patients with schizophrenia. Data are the percentage of patients whose conditions remained stable vs. the weeks after the abrupt stoppage of treatment ($n = 1,006$). Dashed lines indicate 95% confidence intervals. Data from Viguera et al. 1997.

been followed for as long as 4 years and remained clinically stable without medication. Inspection of figure 1b reveals that there is no immediate relapse among any patients after abrupt discontinuation of all antipsychotic agents; there is delay in offset of action of these drugs.

These findings, standing in stark contrast to current clinical practice, affirm the experiences of many who treat severely ill schizophrenia patients: Response to medication varies. The several iterations of $DSM$, based exclusively on clinical symptomatology, contribute nothing to our understanding of this heterogeneity of drug response among schizophrenia patients or our ability to predict it. These data are consistent with the hypothetical models of schizophrenia that have been debated since Bleuler and Kraepelin: the subtype model and the spectrum model. The subtype model describes the data in terms of one or more subtypes requiring medication for a sufficient period of time to achieve a permanent remission of symptoms, while other subtypes require chronic treatment. The spectrum model can equally be fitted to these data: a continuum of illness ranging from a milder form that can be stabilized without further treatment for years to a more severe form, with presumably more neurological impairment, that requires constant treatment. What is apparent is that medication offset time varies widely and may provide a probe for identifying patients who share a common or at least similar neuropathology.

Observations of extended therapeutic as well as adverse effects of these agents cannot be readily explained
on the basis of ordinary pharmacokinetic parameters. Plasma elimination half-lives for traditional neuroleptics are estimated at between 20 and 40 hours. For butyrophenones, the half-life may exceed a week (Baldessarini 1985). Atypical antipsychotics are similar to phenothiazines, with the exception of quetiapine (Seroquel), whose plasma elimination half-life is given as approximately 6 hours. However, these values may not reflect true terminal elimination, owing to many factors, including enterohepatic recirculation, sequestration in fatty tissue, or both, as well as the central nervous system within the blood-brain barrier (Sandaresan and Rivera-Calimilin 1975; Baldessarini 1985). Clinical studies also suggest that neuroleptics remain in tissues in measurable concentrations for far longer times than had been previously suspected from plasma elimination data.

Sampath and coworkers (1992) addressed the question of the correlation of serum level of medication with relapse in a stable population of inpatients receiving fluphenazine decanoate. Nine of twelve patients whose decanoate injections were stopped experienced relapse after a 12-month period, while only 3 of 12 controls relapsed. The authors concluded that chronic patients need to continue receiving active medication. A closer inspection of their results suggests that this conclusion, albeit correct, may not be the whole story. Among those receiving sham injections (no fluphenazine), two relapsed after a 10 percent reduction in serum fluphenazine, two relapsed after a 50 percent reduction, and the remainder relapsed after a 90 percent reduction. To quote the authors: "There was no direct correlation between the time of occurrence of relapse and the actual serum neu-
roleptic level" (p. 261). Furthermore, three of the control patients, who had been clinically stable for years, also relapsed. The authors questioned whether increased contact with the people conducting the study had perturbed the patients, who were not used to such frequent and intense interactions. Werner Heisenberg's uncertainty principle may apply to phenomena beyond the realm of subatomic physics; it may be relevant in the evaluation of psychopharmacology studies. It is fair to conclude that the relationship between relapse and serum drug concentration is not strictly correlated or even obvious. Then why do we administer medication on a daily or even twice or thrice daily schedule? Or, put differently, do current dosing strategies make sense in the light of onset and offset of action as well as relapse data?

We persist in our scheduling of medication in spite of the fact that clinicians and research psychopharmacologists have inferential evidence that daily administration of medication may not be necessary. Depot neuroleptics have been used for nearly 20 years. The conventional wisdom dictates that medication is uniformly metered out from a reservoir of injected neuroleptic over several days or weeks (Forsman and Ohman 1977). Daily serum concentrations belie the conventional wisdom. What is observed is a typical pattern of drug absorption with a peak in concentration at the time of injection, followed by a first order decay curve and finally a small but consistent upturn as drug absorbed in tissue begins to reequilibrate with the plasma (figure 2, Ershesky et al. 1984). By just over 24 hours, 50 percent of the injected dose is in circulation; by less than 2.5 days (60 hours), more than 75 percent of the reservoir of drug is in circulation. Injection of "depot" neuroleptic may be thought of as a form of intermittent dosing.

Figure 2. Fluphenazine plasma levels following the injection of a single dose of 25 mg fluphenazine decanoate. Data from Ershesky et al. 1984.
After the initial increase in concentration, which lasts for 30 hours, reduction in drug concentration follows an approximation of first order decay kinetics. The final phase appears at around 104 hours with a rebound of drug concentration in the plasma. The plasma concentration of drug is nearly undetectable after 2 weeks (Ershesfsky et al. 1986), but patients may remain in remission for months (Sampath et al. 1992; Chang et al. 1993). Furthermore, Hogarty and coworkers (1979) demonstrated that patients receiving intermittent injections of fluphenazine decanoate may do better than controls receiving oral fluphenazine-HCl. Both populations received doses thought to be adequate to maintain remission. This double-blind prospective study, lasting 2 years, concluded that decanoate was slightly more effective than oral medication—even for apparently compliant patients (Hogarty et al. 1979). The authors surmised that the superior outcome among those receiving decanoate injections, particularly in the second year, could be attributed to a subtle decrease in compliance among those patients receiving the oral form of the drug. A more parsimonious interpretation of the difference between the two groups attributes the improvement to the pulse effect of the injected fluphenazine, the intermittent peak concentration rather than the maintenance of a constant concentration of drug being the variable that increases efficacy.

Nyberg and others (1997) have reported that postsynaptic D2 receptors remained blocked up to 6 months following the last injection of haloperidol decanoate. Their data suggest that current schedules of monthly injections of decanoate might be excessive. A recent study by Carpenter and colleagues (1999) compared the effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks and found no difference in relapse of symptoms. In this study, the average serum level of the injections every 6 weeks was presumably lower than that of the injections every 2 weeks. These data are most consistent with the paradigm that “tonic” serum concentration is not the variable that accounts for decanoate’s superiority to oral fluphenazine.

A recent PET study from the University of Toronto, discussed below, taken together with the report from Nyberg’s group (1997), challenges current hypotheses about antipsychotic activity at the molecular level as well as how we assess it. In brief, the hypothesis states that receptor blockade is a necessary condition for antipsychotic medication to function. If haloperidol decanoate binds to D2 receptors for 6 months, then patients receiving this medication should not require injections more than two or three times per year. But the consensus of clinical experience is that patients receiving haloperidol decanoate require more frequent injections—perhaps not every 4 weeks but certainly not every 20 or 26 weeks.

The PET studies of Kapur and others (2000) demonstrated that both clozapine and quetiapine dissociate more rapidly from D2 receptors than do any of the other antipsychotic agents. Two to three hours after administration of a dose of quetiapine (following 3 weeks of treatment with quetiapine), 58 percent to 64 percent of D2 receptors were occupied by quetiapine. Two hours later, occupancy of D2 receptors had fallen to 0 percent to 27 percent. In spite of rapid dissociation, quetiapine has characteristics of delayed onset of action similar to those of other typical and atypical antipsychotic agents. The two sides of the conundrum are that Nyberg’s data imply that therapeutic efficacy decays in spite of D2 binding by haloperidol, while Kapur’s data demonstrate ongoing therapeutic efficacy in the absence of D2 binding by quetiapine. We shall return to this important issue in the Discussion and Proposal section.

Data from other than decanoate studies also support the proposition that antipsychotic (and other psychotrophic) agents have a delayed offset of action. Neuroleptic malignant syndrome can occur weeks after discontinuation of medication, when the drug is undetectable (Hubbard et al. 1987). A single injection of butyrophenone, administered to a rat, produced central dopaminergic blockade up to 6 weeks in spite of the fact that the plasma elimination half-life for rats is similar to that of humans—approximately 7 days (Campbell et al. 1985). Human subjects given a single oral dose of 5 mg of haloperidol reported side effects lasting several weeks (Hubbard et al. 1987). All these findings suggest that plasma and urinary elimination half-lives may not bear a meaningful relationship to levels of drug activity in the central nervous system and that estimates of drug elimination kinetics based on traditional pharmacological methodology may be misleading.

Problem of Compliance and Alternative Dosing Solutions

Since antipsychotic agents have been available, symptom relapse and gradual deterioration of social and cognitive function have been primarily attributed to noncompliance with medication (Zusky 1984). Patients have always objected to side effects, including weight gain, stiffness, and sexual dysfunction. In addition, noncompliance may be attributed to specific extrapyramidal system, antimuscarnic, and antihistaminic side effects producing a generalized blurring of consciousness and forgetfulness (Baldessarini 1985). Studies evaluating the effects of typical antipsychotic medication on specific neuropsychological functions have produced mixed conclusions because of wide-ranging doses of neuroleptics (Cassens et al.
1990). Deterioration in cognitive and motor abilities as measured by these tests may reflect a previously unrecognized manifestation of schizophrenia or a delayed side effect of medications (Baldessarini 1985; Kolakowska et al. 1985). Comparable studies on atypical antipsychotic medications show possible improvement in a variety of neuropsychological functions (Manschreck et al. 1999).

Finally, noncompliance may result from the cognitive lacuna common to many schizophrenia patients that prevents them from understanding that they function better when they take their medication. Many patients in remission insist that they do not need medication. Olfson and colleagues (2000) recently reported on noncompliance among patients discharged from the hospital. They corroborated earlier studies concerning noncompliance and added substance abuse and poor treatment alliance with hospital caretakers as additional factors for noncompliance.

Practitioners have sought to minimize exposure to neuroleptic medication because they want to improve compliance and because they believe that chronic administration of neuroleptics causes movement disorders (Baldessarini and Tarsy 1979). The possibility of tardive dyskinesia (TD) has been a major rationale for reducing dosage of medication or discontinuing it altogether. On the other hand, Crow and others (1982) have argued that TD may not be a medication effect but rather a motor manifestation of schizophrenia. They note that Kraepelin described identical involuntary movements in schizophrenia patients who had never received medication (1919). Manschreck (1983) reported that increased motor disturbance correlates more closely with severe psychopathology than with exposure to high doses of neuroleptics. The more severe forms of schizophrenia (including motor manifestations) may therefore receive more aggressive treatment, leading to the false conclusion that a causal relationship exists between amount of medication and motor abnormalities. However, almost all researchers agree that long-term treatment and high doses of medication exacerbate the dyskinesias (Saltz et al. 1991; Kane et al. 1992; Glick et al. 1995). Whether schizophrenia is a progressive neurodegenerative disease with the development of more symptomatology (such as TD) or whether it is a static encephalopathy has not been resolved (Arnold et al. 1998).

The atypical antipsychotics that are replacing the older neuroleptics as first line agents for the treatment of schizophrenia are believed to produce less TD than the first generation of drugs did (Kane et al. 1993). While the question has not been definitively answered, reports of TD with atypical antipsychotics are sufficiently rare to warrant publication (Gelber and Belmaker 1999; Herran and Vasquez-Barquero 1999; Hong 1999). The observed reduction in incidence of TD associated with the newer agents provides evidence that the first generation of neuroleptics, in fact, either caused movement disorders or at least exacerbated them.

Reduced frequency of TD has been one of many benefits of the second generation of antipsychotics, but the unanticipated metabolic side effects of the newer agents may, in the long run, lead to greater morbidity and mortality than TD or other side effects associated with the older drugs. Weight gain is not unique to atypical antipsychotics; many patients, particularly children, treated with the older neuroleptics gained weight. Reduced activity secondary to sedation and extrapyramidal system side effects as well as lack of motivation, characteristic of many schizophrenia patients, confounded interpretation of weight gain and tended to minimize its significance. In the past decade, people have attended to “wellness” for chronic schizophrenia patients, which includes better nutrition and more exercise. Current data are unambiguous; clozapine, risperidone, olanzapine, and quetiapine are all associated with substantial weight gain, hyperglycemia, hyperlipidemia, and hypercholesterolemia. Many cases of new-onset insulin-dependent diabetes mellitus have been reported, raising the possibility that these agents cause insulin resistance in some patients (Masand and Gupta 2000).

A final “side effect” of the newer agents is the substantial increase in the cost of treating schizophrenia patients. Reduction in rehospitalizations obviously decreases the financial burden of a chronic disease like schizophrenia, but the direct costs of newer pharmaceutical products is a hot-button issue in discussions of medical economics and national health policy. All of the atypical antipsychotics are very expensive in comparison with the first generation agents.

Noncompliance as well as the known and suspected risks of chronic medication have been the major factors motivating psychopharmacologists to examine alternative dosing schedules over the past quarter-century. An entire issue of Archives of General Psychiatry (volume 52, March 1995) was devoted to reviewing the extensive literature on the subject of reducing or discontinuing medication, accompanied by commentaries from luminaries in the field. Many of the studies could not be compared owing to widely differing levels and durations of dosing as well as discontinuation strategies. Multiple methodological problems limited any definitive conclusions. But the editors seemed to agree that the risks of reducing medications or discontinuing them altogether outweighed the potential benefits. Too little is known about rates or degrees of reduction of doses, although everyone agrees that there is a substantial effect on outcome (Gilbert et al. 1995; Jeste et al. 1995; Viguer et al. 1997). While discussing the confounds of alternative dosing strategies,
some authors have acknowledged that drug response is not uniform and may reflect the variability associated with heterogeneous populations of patients grouped under the clinical tent of schizophrenia (Schooler 1991; Schooler et al. 1997). Over the years, there have been published several comprehensive articles that review multiple studies and highlight all aspects of this prolix topic (Prien et al. 1968; Carpenter and Heinrichs 1983; Carpenter et al. 1987; Herz et al. 1991; Schooler 1991; Kane and Marder 1993; Dixon et al. 1995; Gilbert et al. 1995; Schooler et al. 1997).

In spite of skepticism about the feasibility of reducing the total amount of antipsychotic medication, there is evidence that supports the concept. Carpenter and his coworkers have been advocating this approach for years and have recently stated, “It has been demonstrated that dose reduction during maintenance therapy is feasible. Cumulative medication reduction has been achieved either by lowering the dose while maintaining a standard frequency of administration or by targeting standard dose administration to early signs of exacerbation” (2000, p. 412). It is beyond the scope of this endeavor to discuss and evaluate all of Carpenter’s references. Other investigators reviewing this topic do not agree with this conclusion (see editorial comments in Archives of General Psychiatry as well as the other reviews alluded to above). Moreover, it is indisputable that the dosing strategies advocated by Carpenter have not achieved wide acceptance in routine clinical practice. It is our belief that other arguments (Vigueria et al. 1997) as well as delayed offset of action of antipsychotic agents provide more compelling reasons for studying alternative dosing strategies.

**Signal Transduction**

By the 1980s, delayed onset and offset of the effects of many psychotropic agents were recognized but not understood. Since then, neuroscientists have incorporated newly acquired information about eukaryotic cellular physiology to elucidate precise mechanisms of action of neurotransmitters and receptors as well as subsequent events that affect postsynaptic neurons following the release of neurotransmitters. What has emerged is a model of neurotransmitter function that describes the transfer of information from the membrane-bound receptor to the nucleus wherein individual genes or batteries of genes can be either activated or repressed. Membrane-bound receptor activity along with genetic reprogramming account for both short-term effects on the individual cell as well as long-term effects on the brain and behavior. Excellent reviews elaborating the molecular biology of signal transduction include those of Civelli (1995) and Nestler and Duman (1995).

The emerging model is consistent with the time course of changes observed with antipsychotic agents as well as the delayed offset of action of antipsychotic agents (also antidepressants and mood-stabilizing agents). Because all of the described molecular processes are reversible, modification of neuronal activity by means of antipsychotic medication is not durable. Discontinuation of medication may eventually result in the remodification of the neuron to its original physiological state, with an attendant clinical relapse. Furthermore, this process is consistent with the observed symmetrical delayed offset of action of these drugs because relapse also entails reprogramming of genomic activity (Hyman and Nestler 1996).

Clinical data demonstrate that relapse rates off medication are strikingly low: Nearly 50 percent of patients off medication are still in remission after 6 months (figures 1a and 1b) and may remain in remission for years (Viguera et al. 1997). Patients requiring medication for infections, hypertension, or cardiac disease would relapse within hours or days after discontinuation of medication. We now understand that antipsychotic medication acts differently from antibiotics, antipyretics, antihypertensives, or ionotropic/chronotropic agents. Membrane-bound psychotropics, acting through second and third messenger systems, cause genetic reprogramming of neuronal structures and ultimately neuronal function. These processes take a substantial period of time to achieve or reverse (Duman and Nestler 1996). The model of neuronal plasticity (Hyman and Nestler 1996) would predict that following discontinuation of an antipsychotic agent, we would expect a 3- to 8-week period of clinical stability followed by rapid deterioration. What we observe is one curve that approximates first order kinetics (Curry 1981). What we also observe is a cohort of approximately 50 percent of patients in remission who remain stable up to 4 years. Our understanding of neuronal plasticity does not provide a sufficient explanation for either the observed first order decay constant of one cohort or the 4-year remission of the other cohort.

**Time-Dependent Sensitization**

Almost 20 years ago, Antelman and others described time-dependent sensitization (TDS; 1986, 1987; Lace and Antelman 1983). In a series of animal experiments utilizing several classes of psychotropic agents, his group observed enhanced biological response to repeated administration of drugs even with dosing intervals far exceeding the necessary time for complete clearance of the substance. Neuroleptics (Antelman et al. 1987), tricyclic antidepressants, benzodiazepines, psychostimulants, antimanic agents, and even electroconvulsive therapy (Chiodo and Antelman 1980) have all been shown to elicit
an exaggerated response (sensitization) to a second dose after the animal has been primed with an initial dose (Muller and Seeman 1978; Post 1980). TDS is similar to the "kindling" hypothesized by Post (1980), who argues that repeatedly stimulated neural pathways respond to progressively diminished stimuli as they become "facilitated" (Post et al. 1984).

Glantz and Lewis (2000) demonstrated anatomical evidence for time-delayed effects of antipsychotic agents. These researchers found that schizophrenia patients who had never received medication had reduced dendritic spine densities in the pyramidal neurons of the DLPFC—an area long suspected as a possible locus of the "schizophrenic lesion." Brains of schizophrenia patients treated with antipsychotic agents had dendritic spine density comparable to that of control specimens' brains. These data provide an anatomical example of "remodeling" (Hyman and Duman 1996). Furthermore, the time required for the resynthesizing of dendritic spines seems consistent with Antelman's parameters of time-delayed sensitization.

Stevens and coworkers (1997) have demonstrated what may be a molecular mechanism that dovetails with the data reported by Glantz and Lewis (2000), further substantiating the model of TDS. It also buttresses the argument for scheduled intermittent dosing. Stevens' study was predicated on the now largely ignored observation that led Meduna to develop convulsive therapy (1934). At that time it was believed that epilepsy and psychosis were mutually exclusive. Stevens and colleagues note that all antipsychotic agents, typical and atypical, are capable of eliciting generalized seizures. Clozapine is the most proconvulsant antipsychotic as well as the most powerful antipsychotic drug. It induces electroencephalographic changes similar to those seen in epilepsy in 10 percent to 20 percent of patients who are not experiencing generalized seizures as a side effect. Stevens and colleagues propose that the therapeutic effect of neuroleptics may include more than blocking DA receptors in subcortical regions. Neuroleptics may also activate or kindle cortical neurons or neuronal tracts either damaged, deficient, or previously inactivated by some unknown pathological process. They tested this hypothesis in rats using myoclonic jerks as a measure of cortical excitation. Not only did the results support their proposal, but they found that intermittently administered clozapine was more efficacious in producing myoclonic jerks than daily administered clozapine (Stevens et al. 1997). They pursued the hypothesis that kindling/sensitization was associated with neuronal adaptation by measuring levels of mRNA for the c-fos gene. This early transcription gene, c-fos, encodes a transcription factor that activates a battery of so-called early genes essential for modifying portions of the genetic program of a differentiated cell. Stevens' group reported that levels of newly synthesized "c-fos mRNA were significantly higher in the anterior thalamic nucleus and the ventral tegmental area in clozapine-sensitized rats than in vehicle-treated controls" (Stevens et al. 1997, p. 775).

Earlier, Robert Post had proposed that intermittent stimulation was more effective than continuous stimulation for the modification of neuronal activity—the development of tolerance (Post 1980). The arguments of Post, Stevens et al., and Hyman and Nestler are all consistent with a model of neuronal adaptation or learning that is enhanced by intermittent stimulation or dosing.

This study is central to several aspects of our argument. First, it suggests an additional hypothesis for the mechanism of action of neuroleptics: excitation of previously inactivated pathways. Second, it demonstrates that intermittent dosing may be more efficacious than daily dosing in producing that excitation. Third, it demonstrates the activation of a gene known to be essential for the modification of cellular activity through genetic reprogramming. The question remains whether this mechanism can account for the observed rate of long-term remissions, which is the core of this proposal. Could the kindling/sensitization activation last from a few weeks in some schizophrenia patients to beyond 6 months in other patients before dissipating?

Discussion and Proposal

A review of the history of the pharmacological treatment of schizophrenia emerges as a murky landscape of shifting definitions, conclusions based on inadequate and/or incomplete information, and apparently comparable studies coming to different conclusions. The serendipitous discovery of antipsychotic medication focused attention on those symptoms that were treatable and weighted the definition of schizophrenia in terms of the positive symptoms that were amenable to pharmacological treatment. Perforce, the motor and cognitive symptoms described by Kraepelin and Bleuler were deemphasized. These pitfalls make it difficult to evaluate earlier treatment research, let alone build on it.

Nonetheless, several important pharmacological conclusions have emerged. Early, aggressive intervention results in improved outcome. There is no benefit in high-dose treatment in comparison with low-dose treatment. In fact, there may be health costs in addition to financial ones associated with higher doses. Routine side effects, tardive dyskinesia, neuroleptic malignant syndrome, and noncompliance are all associated with higher doses of the earlier antipsychotic medications. Weight gain is associated with the newer atypical antipsychotics, and hyperlipidemia, hypercholesterolemia, and insulin-dependent diabetes mellitus are associated in a dose-dependent relationship with many of these agents.
The history of the treatment of schizophrenia highlights its multiple dimensions as a pan-neurological disorder involving motor, sensory, and cognitive systems in addition to its behavioral and psychotic manifestations. It is now recognized that the core deficit of schizophrenia, standing in the way of return to premorbid function for the majority of patients, no longer suffering from positive symptoms, is in the cognitive domain (Harvey and Keefe 1997). Manschreck et al. (1999) demonstrated, among chronically institutionalized schizophrenia patients, that baseline cognitive performance and not baseline psychiatric symptomatology is a better predictor of outcome in a clozapine trial—outcome being defined as discharge from hospital. These authors subsequently reported that certain neurological abnormalities were associated with specific cognitive deterioration (Manschreck et al. 2000). Poor hygiene, bizarre appearance, inappropriate and frightening behavior, and noncompliance with medication can all be understood as deficits of self-awareness, interpersonal awareness, empathy, and insight—all domains of cognition (Gardner 1983). Failure to adjust in the community or to achieve employment and function socially all may be related to deficits in working memory, attention, and executive function (Green 1996; Harvey and Keefe 1997; Manschreck et al. 1999).

While we have made advances in the neurobiology of schizophrenia, these exciting observations are still isolated phenomena: the “first principles” of schizophrenia continue to elude us. We have a substantial model for the mechanism of action of antipsychotic agents on individual neurons. But we have no idea why some patients do better on medication than others, while still other patients seem to experience no benefit at all. Finally, there is no experimental basis for daily administration of medication. We all have treated patients who seem to decompensate within days of discontinuing medication, but a compelling argument can be made that intermittent dosing may be beneficial for most patients. As we have already reported, intermittently administered clozapine produces more cortical activation than daily administered clozapine; and fluphenazine decanoate, administered monthly, is more effective than oral fluphenazine, administered daily.

We must attend to the data: Daily administration of medication is not optimal for a multitude of reasons. Animal studies, clinical studies, an enhanced understanding of the molecular biology of neural transmission and activation, and relapse data all support an alternative strategy for initiation and maintenance treatment of schizophrenia. Specifically, we suggest that scheduled intermittent dosing may benefit some patients. To substantiate this hypothesis, we must address all of the issues: Recovery, relapse, heterogeneity of response, and heterogeneity of the pharmacokinetics of relapse.

Finally, one of the cornerstones of psychopharmacological doctrine may require modification or even rejection: That is, that psychotropic drugs remain bound to their receptors in order to function. The reports of Nyberg and others (1997) and of Kapur and others (2000) support alternative interpretations and provide a logical starting point for testing the intermittent dosing hypothesis. D2 receptor association has been thought to be essential for antipsychotic activity. But Kapur’s study of quetiapine’s pharmacodynamics suggests that transient blockade of D2 receptors—binding followed by rapid dissociation (not strong vs. weak binding) is sufficient for clinical efficacy. More striking is the fact that clozapine, the most powerful agent in the antipsychotic armamentarium, has binding characteristics similar to those of quetiapine. And clozapine demonstrates a pattern of delayed onset and offset of action similar to that of the rest of the family of antipsychotic agents. If patients receiving clozapine or quetiapine on an intermittent schedule (see below) were to maintain clinical remission, it would imply that continuous blockade of D2 receptors by DA antagonists is not essential for therapeutic effect. Such an outcome would rationalize the conundrum implicit in the data of Nyberg and others (1997) that binding does not necessarily correlate with therapeutic effect. A speculation consistent with a paradigm of intermittent dosing would predict that the initial association of ligand (drug) and receptor at the cell membrane triggers a chain of intracellular events. One might hypothesize that if the ligand remains bound for a prolonged period of time, some heretofore unknown homeostatic mechanism is activated to disarm the cascade of second and third messengers, thereby undoing the effect of the initial reaction. Hyman and Nestler (1996) refer to this reversal as re-remodeling. By contrast, if the ligand associates and dissociates from the receptor, as would be the case with intermittent dosing, the intracellular cascade would be continuously reactivated. The natural decay time of this cascade would define the gap in scheduled dosing. Intermittent dosing may elucidate important aspects of neuronal physiology.

Initial studies should examine clinically stabilized patients to establish whether intermittent dosing maintains remission to the same degree as traditional schedules of dosing. At this point in our understanding, we know of no rational basis for predicting which patients on which drugs will benefit from a specific dosing interval. Empirical evidence must provide the basis for specific hypothesis formation. Schedules of intermittent dosing in a double-blind paradigm must be compared with daily dosing schedules, with the dose of medication given on intermittent days identical to the dose given previously on a daily basis. This strategy will certainly reduce the aggregate amount of prescribed medication, resulting in fewer
side effects as well as lower costs. The accumulated evidence makes it difficult to believe that at least some, if not all, patients would benefit from less total medication.

Finally, intermittent dosing strategies could contribute to an improved nosology. Numerous attempts have been made to subdivide schizophrenia patients based on the multidimensional manifestations of this disease. All have failed (Lieberman et al. 1992). Garver and others (1988) have proposed that drug response may provide an alternative taxonomic probe for identifying biologically homogeneous subtypes of schizophrenia. There is a distribution of clinical responses among schizophrenia patients, including those taking atypical antipsychotics, from almost complete remission of symptoms to no apparent response. Patients present with myriad behavioral and neurological abnormalities, including anatomical, motor, neuropsychological, and cognitive deficits. Patients have an equally varied pattern of long-term outcomes—not only with regard to clinical symptoms but also with regard to cognitive and neurological symptoms. While no taxonomic principle has emerged to divide this conglomeration into homogeneous subtypes, differential responses to intermittent dosing schedules might provide the basis of an improved nosology, particularly in conjunction with other signs and symptoms (Garver 1997). For example, do cognitive and neuropsychological abnormalities remit in parallel with routine clinical symptoms? The time-to-relapse variable might be a significant predictor of shared pathophysiology. Intermittent dosing schedules that differentiate subgroups of patients might elucidate a shared pathological process underlying that mysterious rate constant. Stevens and colleagues' hypothesis (1997) of kindling/sensitization could be tested by monitoring changes in electroencephalographic tracings among patients receiving different schedules of neuroleptic agents to observe duration of the kindling effect. Post's (1980) hypothesis of intermittent stimulation to enhance kindling might apply to pharmacotherapy.

Conclusion

In spite of our ability to provide improved treatments to schizophrenia patients, patterns of pharmacological practice are not based on scientifically based data. There is no proof that the way we medicate patients is the optimal way. The precise point in time when medication begins to manifest specific antipsychotic effects remains unidentified. Since it is increasingly apparent that schizophrenia may not be a single entity, we cannot know whether current scheduling of treatment is optimal for all schizophrenia patients. Controlled, blinded, prospective studies comparing stabilized patients in conventional patterns of drug administration with stable patients receiving their predetermined daily dose on an intermittent schedule is a modest first step in testing the feasibility of intermittent dosing.

We are proposing a fundamentally different strategy for medicating schizophrenia patients. Moreover, we encourage empirical studies to rationalize dosing and optimize antipsychotic treatment practice. Relapse studies, improved understanding of cellular mechanisms, and historic observations all support scheduled intermittent dosing.

Differential rates and degrees of response to medication may enhance our recognition of subtypes of schizophrenia. A meaningful taxonomy—one that will identify pathophysiological homogeneity—may clarify our understanding of a diathesis that has been recognized for more than a century.

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