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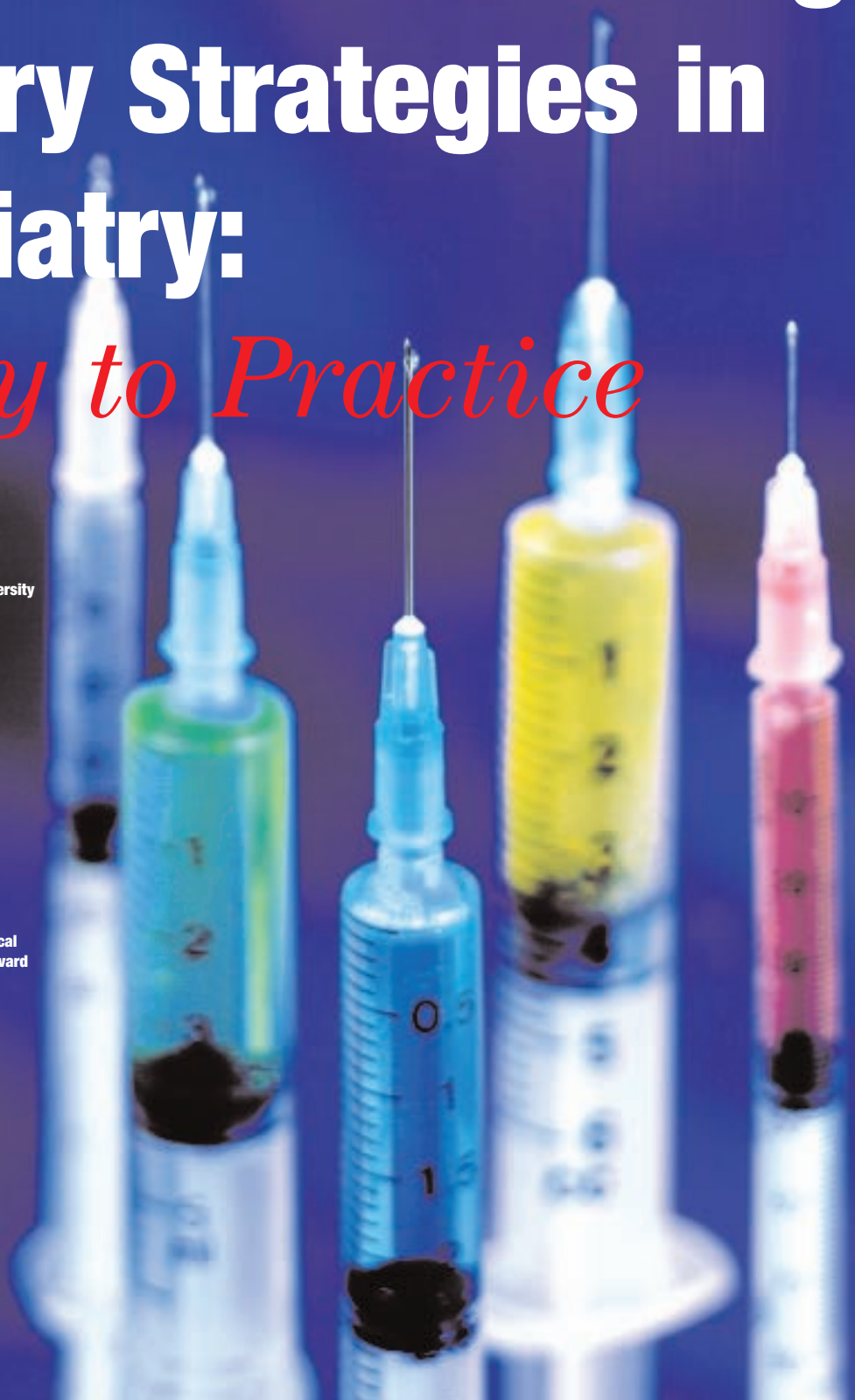
Extended Release Drug Delivery Strategies in Psychiatry:

Theory to Practice



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ACKNOWLEDGMENT:
This work was supported by the Stanley Medical Research Institute.

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ABSTRACT

Objective: **An overview of the emerging field of long-term delivery strategies for improved convenience and adherence with psychiatric medications is provided. This review is motivated by the hypothesis that adherence to treatment is an important determinant of clinical outcomes in a wide range of settings and is particularly important in psychiatry practice where patients require treatment for months or years and premature discontinuation can have serious consequences for patient health and quality of life.**

Design: **The author reviews the relevant literature and highlights several approaches to providing improved access to continuous medication through new and innovative delivery strategies ranging from days to annual intervals.**

Benefits and Disadvantages: **Several solutions to the problem of discontinuous access to pharmacotherapy are being developed in the form of new, long-acting drug-delivery systems, which gradually release medication over a period of several days or weeks with a single application. Long-acting formulations of psychiatric medications offer a number of potential benefits in comparison with conventional immediate-release agents, including improved safety and effectiveness. Potential limitations to using long-acting formulations may include pain and discomfort at the injection site, perceived inconvenience of a new treatment method, preference for oral medications, and length of time to titrate down to the lowest effective dose.**

Conclusions: **The introduction of new, long-acting drug formulations could provide significant improvements in clinical outcomes and patient satisfaction for many patients, including those with affective disorders, schizophrenia, and alcohol dependence. Switching from oral administration to these new agents requires careful monitoring to reach the optimal dose, and patient concerns regarding the use of new delivery methods must be addressed. Long-acting formulations are not intended to be a sole form of treatment, and the use of psychotherapy as an adjunct form of treatment is still required. Controlled clinical trials of these new formulations have only recently been completed, offering clinicians a new option in their treatment regimens; however, as technologies improve, several new formulations are likely to enter clinical trials during the next few years. Psychiatrists will need to become acquainted with these technologies and educate their patients about them so they may work together to determine the most effective treatment option.**

Adherence to treatment is an important determinant of clinical outcomes for patients in a wide range of clinical settings. Adherence is particularly important in psychiatry practice in which patients often require treatment for months or years and premature discontinuation of treatment can have serious consequences for patient health and quality of life. Patients fail to take medication as directed for many different reasons: they may feel better and may decide that treatment is no longer necessary; they may experience disagreeable side effects; they may find medication schedules inconvenient; they may be unable to afford to fill their prescriptions; they may simply forget to take their medication; or they may be concerned that taking pills may betray desired confidentiality about being ill and needing treatment, as opposed to an injection, which takes place in the privacy of the doctor's office. Regardless of the specific reason for treatment nonadherence, the failure of patients to continue to take medication as prescribed contributes to high rates of relapse, hospitalization, and in some patients (e.g., patients with major depressive disorder, bipolar disorder, or schizophrenia) an increased risk of death.[1–3]

Across a wide variety of disease states, recent advances in drug delivery technologies have led to the development of innovative delivery systems designed to improve therapeutic outcomes. Emerging drug delivery platforms, which include extended-release oral, injectable, and implantable formulations; transdermal patches and transmucosal technologies; inhalation compounds for pulmonary delivery; parenteral delivery systems; target-specific drug technologies; and liposome and polymer/polymeric micelles delivery systems, may offer superiority over conventional products by improving safety and efficacy through prolonged duration of action and reducing adherence issues, such as frequent dosing, side effects, and tolerability.

LONG-TERM DELIVERY

During the last several years, a number of new "extended release" or "sustained release" medication formulations have entered psychiatry practice. Many medications that once required two or three daily doses are now available in once-daily formulations. For example, stimulant medications used for the treatment of attention-deficit/hyperactivity disorder (ADHD) have recently become available in extended-release formulations that are designed to provide more stable drug delivery throughout the day and eliminate the need for mid-day dosing. These formulations use either a

DRUG KEY

Bupropion (Wellbutrin®, GlaxoSmithKline)
Citalopram (Celexa®, Forest Laboratories)
Divalproex (Depakote®, Abbott Laboratories)
Haloperidol (Haldol®, Ortho-McNeil Pharmaceuticals)
Naltrexone (Long-Acting Injectable) (Vivitrex®, Alkermes)
Paroxetine (Paxil®, SmithKline Beecham)
Risperidone (Risperdal®, Janssen Pharmaceutica
Venlafaxine (Effexor®, Wyeth-Ayerst)

combination of immediate-release and delayed-release beads in a single-dose capsule to deliver medication throughout the day[4,5] or an osmotic delivery system that gradually expels methylphenidate from a perforated capsule.[6] Other examples of extended-release agents in psychiatry practice include several recently introduced once-daily antidepressant formulations (venlafaxine,[7] bupropion,[8] citalopram,[9] and paroxetine,[10]), extended-release divalproex,[11] and extended-release benzodiazepines.[12] Although these new formulations offer patients greater convenience and privacy, many controlled clinical trials have also shown that extended-release agents are associated with improved tolerability, greater patient adherence to treatment, reduced total treatment costs, and better long-term clinical outcomes.

Despite these improvements in drug formulation, very few medications in psychiatry practice are currently available in forms that permit dosing less often than once per day. An enteric-coated, extended-release formulation of fluoxetine may be administered on a weekly basis, although this is largely due to the long half-life of fluoxetine.[13] Although several antipsychotic drugs are available in long-acting injectable "depot" forms, including haloperidol, fluphenazine, flupenthixol, perphenazine, and fluspirilene, only the first two are available in the United States.[14] Few other psychiatric medications are currently available in truly long-acting formulations, although a number of novel drug delivery technologies are in clinical development and may soon begin to enter clinical practice. These medication delivery systems are designed to provide relatively constant drug delivery over long periods of time, making it easier for patients to remain adherent to treatment and possibly reducing the risk of side effects. Recent clinical trials demonstrate that these new technologies have the potential to improve outcomes for difficult-to-treat patients in clinical settings that typically require long-term treatment, and notably schizophrenia. Currently, other debilitating conditions like substance abuse and alcohol dependence are also being treated with long-acting preparations; this recent indication is discussed in greater detail later in this paper.[15,16] Similarly, efforts to introduce surgically implantable, long-term delivery systems for psychiatric medication hold the promise of extending these benefits for periods of time up to one year.[17,18]

PATIENT ADHERENCE TO PHARMACOLOGIC THERAPY

Numerous studies have shown that treatment adherence is one of the strongest predictors of clinical outcome. The relationship between treatment adherence and clinical outcome has been noted in disorders as diverse as asthma,[19] ulcerative colitis,[20] myocardial infarction,[21] and in HIV infection.[22] Even in behavioral training programs, the success of the intervention is strongly related to patient adherence to the training regimen.[23]

Despite the clear relationship between adherence and clinical outcome, studies of patients across a broad range of clinical settings consistently report low rates of adherence to treatment, especially with long-term treatment. Although many approaches have been developed to evaluate adherence, from questionnaires to microchip-equipped bottles, studies generally report that medication nonadherence occurs in about 20 to 30 percent of patients who are undergoing short-term curative treatments, increasing to about 50 percent of patients with chronic illnesses requiring long-term pharmacotherapy.[22] Even patients with potentially life-threatening disorders have high rates of medication nonadherence in long-term treatment. For example, among patients with type II diabetes, adherence to treatment gradually declined during the two years following initiation of treatment.[24] Analysis of prescription refills in this study found that patients lacked medication on 21 percent of study days and that, depending on the medication prescribed, only 31 to 60 percent of patients had medication continuously available throughout the follow-up period. Similarly, 40 to 60 percent of patients either with HIV or receiving tamoxifen for breast cancer exhibit some degree of nonadherence, with many patients taking "drug holidays" of days or weeks.[22,25]

ADHERENCE IN PSYCHIATRIC ILLNESS

Poor treatment adherence can be especially difficult in patients with mental illness. Psychotic disorders may profoundly affect patient insight into the severity of the condition or the effects of treatment, and nonadherence to treatment has been described as the single most common cause of

relapse and rehospitalization in patients with schizophrenia.[26] Patients with depression often experience significant medication side effects well before the beneficial treatment effects begin to emerge, and patients with bipolar disorder may find their manic episodes rewarding. Many studies have found that large numbers of mentally ill patients often go days or weeks with unfilled prescriptions.[27] However, even when patients have adequate supplies of medication, they may not take their medications as needed. In a study of patients with depression, Demyttenaere and colleagues found that although the average use of medication over time may approximate the correct number of pills per day, many patients take their medication irregularly, alternating between taking too many pills on some days and too few pills on other days.[2] Using a computerized system to evaluate pill-taking behavior, these investigators found that 31 percent of patients had at least one three-day drug holiday over a nine-week study period.

EXTENDED-RELEASE TECHNOLOGIES IN PSYCHIATRY PRACTICE

One possible solution to the problem of poor adherence to pharmacotherapy is the development of new, long-acting drug-delivery systems, which gradually release medication over a period of several days or weeks with a single application. Long-acting formulations of psychiatry medications offer a number of potential benefits in comparison with conventional immediate-release agents, including improved safety and effectiveness. An important limitation of many immediate-release agents is that they produce marked variability in plasma drug concentration during the course of the day. This variability in peak-to-trough drug concentration creates the opportunity for drug levels that are higher than desirable shortly after ingestion (contributing to a high risk of adverse effects) and lower than desirable later in the day as the drug is eliminated (contributing to waning effectiveness). If long-acting formulations are able to deliver a more predictable and continuous quantity of medication over an extended period of time, they may improve both the effectiveness and the tolerability of pharmacotherapy. In this way, long-acting formulations of psychiatry medications augment and facilitate psychotherapy by relieving acute illness and preparing patients for a more meaningful engagement in psychotherapy. No long-acting preparation is intended or able to replace face-to-face interaction of a patient with a psychotherapist or physician, and this point should be discussed at the outset with the patient. Indeed, these long-acting preparations may facilitate less time being spent counseling the patient regarding medication adherence and more time being spent in addressing other therapeutic aspects. The importance of an integrated approach is discussed later.

Long-acting extended-release preparations could also help to improve one of the most difficult problems in psychiatry practice: the relatively poor relationship that is often observed between how well drugs perform in controlled clinical trials and how they perform in actual clinical practice. To some extent, the gap between clinical trials and clinical practice may reflect characteristics of the patients enrolled in clinical trials, who may be more highly motivated and less severely ill than patients in routine clinical practice, or otherwise not representative of the general clinical population.[28] However, it has also been noted that randomized, controlled clinical trials are typically highly structured and heavily supervised, while patients in actual clinical practice are more likely to be prescribed medication doses that are too low, to skip doses, or to fail to stay on treatment for the required length of time.[27] By removing some of the variability in how patients take their medication, long-acting, extended-release compounds may help to achieve results in clinical practice that more closely resemble the results obtained in carefully controlled clinical trials. Additionally, by eliminating the need for daily self-dosing, a single injection of extended-release medication administered once every few weeks may offer an added degree of patient confidentiality and privacy.

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Considerable evidence suggests that extended-release drug formulations can improve a number of clinical outcomes. Cramer and Saks conducted an extensive review of sustained-release formulations (primarily once-daily oral medications and transdermal patches) in cardiovascular therapy, pain management, and hormone replacement.[29] Even with an older generation of sustained-release products available a decade ago or more, these authors described the results of a large number of studies demonstrating that extended-release agents reduced the incidence of side effects and improved medication adherence, symptoms (e.g., angina attacks, severity of cancer pain, osteoporosis, or bone fractures), and patient ratings of quality of life. Although initial drug acquisition costs were generally higher with the sustained-release preparations than with conventional immediate-release formulations, several economic analyses found that total treatment costs were often lower with sustained-release products as a result of savings in physician, hospital, or laboratory costs. Finally, some studies found that patients preferred long-acting drug forms to conventional short-acting oral agents.

ANTIPSYCHOTIC DEPOT FORMULATIONS

Depot antipsychotic agents are perhaps the best characterized of the extended-release agents used in psychiatry practice. Depot formulations of conventional antipsychotics, in which an esterified drug is injected in an oil suspension, have been shown to significantly reduce rehospitalization in comparison with oral antipsychotics in patients with schizophrenia. Most studies have also found that depot antipsychotics produce better adherence to treatment and reduce rates of relapse.[30,31] Reaching the optimal depot dose may take a longer time period than what is needed with conventional antipsychotics, and requires monitoring of patients to prevent relapse. Once a full treatment response has been established, the depot agent may then be titrated down to the lowest effective dose.

Survey data indicate that many patients have a favorable attitude toward long-acting psychiatry medicines.[32,33] In a recent review of studies examining patients' attitudes toward depot antipsychotic medication, 5 out of 6 studies comparing oral and depot routes of administration found that the majority of study participants preferred depot administration over oral administration.[32] The reasons given for favoring long-term treatment were desire to avoid the adverse consequences of missing oral doses and to stay well, avoidance of the need for daily oral medications, avoidance of the tendency to forget to take medication on time, and decreased family burden.

Although favorable attitudes are expressed by a number of patients, some negative attitudes do exist, such as not wanting to try something new, the perceived inconvenience of a different treatment method, preference for oral medication, concern about feeling controlled, and general dislike of injections.[32–35] Pain and discomfort at the injection site may deter some patients from accepting depot antipsychotic treatment; however, pain at the injection site varies with the drug used,[35] location and technique of the injection,[35] injection volume,[14,15] and patients' perception of injection site pain, which often decreases with repeated injection.[1]

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Side effects are a significant problem with all conventional antipsychotics, including depot agents. Although some studies have found that the incidence of extrapyramidal symptoms (EPS) is similar for oral and depot antipsychotics, other studies suggest that the incidence of EPS may actually be greater when conventional antipsychotics are administered in depot form.[14] However, the occurrence of EPS appears to be dose-related; therefore, greater drug exposure due to better adherence with depot preparations, compared with lower drug exposure due to poorer adherence with oral prepara-

tions, may account for reported differences in incidence of EPS.[36] Many authors have presented data indicating that depot and conventional oral antipsychotic formulations carry a similar risk of tardive dyskinesia.[36,37] The relationship between risk of tardive dyskinesia and the amount of drug exposure, which relates to treatment adherence, has not been clearly established, although a positive relationship would be logical. The lowest effective antipsychotic dose should be used to minimize the severity of tardive dyskinesia should it occur.[36,38]

PSYCHOSIS

In an attempt to reduce the burden of side effects in patients undergoing treatment for schizophrenia, Conlon and colleagues switched patients from depot antipsychotics to treatment with the newer atypical antipsychotic risperidone.[34] A total of 33 patients who consented to the treatment change discontinued their depot antipsychotics and began treatment with open-label risperidone at a maximum daily dose of 8mg (mean dose, 4mg). The acute study period was six months, with additional follow-up for as long as two years. Compared with baseline, risperidone treatment was associated with small but statistically significant improvements in psychotic symptoms and quality of life during the six-month treatment phase. However, the rate of treatment discontinuation by the patients was very high during long-term follow-up; 40 percent of risperidone-treated patients discontinued treatment over two years, whereas none of the patients who continued on depot antipsychotics discontinued treatment. At two years, 58 percent (19 of 33) of patients who switched to oral risperidone had experienced clinically detrimental events, including relapse of illness (13 patients), unacceptable side effects (3 patients), and unsatisfactory response (3 patients). These findings suggest that even though risperidone may be more effective and more tolerable for patients than older antipsychotics, the benefits of the superior medication were outweighed in long-term treatment by the disadvantages of a less convenient dosing regimen. In addition, the high incidence of relapse (39%) observed in patients who switched to oral risperidone underscores the generally held belief that the consequences (i.e., relapse) of reducing or discontinuing treatment in patients with debilitating psychiatric conditions far outweigh the risks of long-term treatment. Risk/benefit studies generally support the use of depot antipsychotic medications,[14] and surveys of patient attitudes toward long-term psychiatric pharmacotherapy indicate that the majority of patients recognize that the benefits of medication outweigh the risk.[33]

More recent research suggests that it may be possible to combine the more favorable efficacy and tolerability profile of risperidone with a more convenient long-lasting dosing formulation. A new formulation of risperidone was recently introduced for biweekly administration. This extended-release risperidone formulation uses biodegradable drug-containing microspheres that are manufactured from a medical polymer similar to those used in disposable sutures, bone fixation devices, and other medical applications. The polymer microspheres are suspended in an aqueous suspension for intramuscular injection. Pharmacokinetic studies have found that extended-release risperidone produces total drug exposure (the area under the time-plasma concentration curve) that is similar to that of oral

The reasons patients gave for favoring long-term treatment were as follows:

- Desire to avoid the adverse consequences of missing oral doses and to stay well
- Avoidance of the need for daily oral medications
- Avoidance of tendency to forget to take medication on time
- Decreased family burden.

The reasons patients gave for NOT favoring long-term treatment were as follows:

- Not wanting to try something new
- Perceived inconvenience of a different method
- Preference for oral medication
- Concern about feeling controlled
- General dislike of injections

risperidone, but with lower peak plasma concentration and less peak-to-trough variability in plasma drug concentration.[30] The efficacy and safety of extended-release risperidone were recently examined in a large, randomized, double-blind, placebo-controlled clinical trial. A total of 400 patients with schizophrenia were randomized to biweekly injections of either placebo or one of three doses of long-acting risperidone (25-, 50-, or 75mg). Placebo-treated patients exhibited a slight worsening from baseline (an increase of 2.6 points) on the Positive and Negative Symptom Scale (PANSS), the primary study endpoint. In contrast, patients in the three risperidone groups improved from baseline by an average of 6.2, 8.5, and 7.4 points for the 25-, 50-, and 75mg dose groups, respectively. Treatment with long-acting risperidone was well tolerated by the patients, and local injection-site reactions were rarely rated as painful. Extrapyramidal symptoms were no more common in the low-dose risperidone group (10%) of patients than with placebo (13%). The incidence of EPS was greater in the two higher-dose risperidone groups.[1,39,40] Thus, as with all treatments, the decision to use long-term depot preparations for schizophrenia is made on the basis of a risk/benefit assessment.

SUBSTANCE ABUSE

Polymer microsphere technology is also being evaluated in the long-term pharmacologic treatment of substance abuse. The treatment of patients with alcohol dependence, opiate dependence, or other forms of substance abuse often presents a number of difficult challenges. The opiate antagonist naltrexone is approved as an adjunct to psychosocial therapy for the treatment of alcohol dependence. However, it is important to recognize that treatment with conventional oral naltrexone tablets is associated with significant limitations. Naltrexone produces side effects that are disagreeable, although not hazardous, including nausea, headache, and vomiting, all occurring more often in patients who received naltrexone than in those who received placebo.[41] These side effects likely contributed to the observation that, on average, patients receiving pharmacologic therapy for alcohol dependence took only 65 percent of the total number of pills prescribed.[42] A second study reported that 80-percent adherence to treatment was noted for only 78 percent of patients in a randomized, clinical trial comparing oral naltrexone with placebo.[43] Naltrexone is effective only for the prevention of relapse when treatment adherence is high. In a randomized, placebo-controlled clinical trial of naltrexone for alcohol dependence, Volpicelli and colleagues found that patients who remained adherent to their naltrexone treatment improved significantly on several measures of alcohol consumption compared with placebo-treated patients, whereas patients who were randomized to naltrexone but who did not remain adherent to therapy exhibited no more improvement than the placebo group.[44] In addition, even patients who strongly desire to remain adherent to their treatment may encounter cues that increase their likelihood of treatment discontinuation or relapse.

Treatment adherence problems in people with substance abuse disorders are part of a widespread problem across all aspects of medical care, occurring with an overall prevalence rate of 25 percent among patients undergoing treatment for nonpsychiatric conditions.[45] As mentioned earlier, even though highly adverse clinical outcomes are prevented by good adherence with medications, high percentages of patients

with chronic medical conditions do not adhere to treatment regimens.[46] For example, 30 to 50 percent of patients with hypertension,[47] 40 percent of patients with asthma, 60 percent of adult patients with type 1 diabetes mellitus, 19 percent of patients with arthritis, and 23 percent of patients with cardiovascular disease do not fully adhere to their medication regimens.[45,48] The homeless population represents a unique situation in terms of adherence to treatment, especially for substance abuse, which was reported to be present in 55 percent of a group of homeless adults in Philadelphia.[49] In their studies of homeless schizophrenic adults, Opler and colleagues found a complex pattern of substance abuse and nonadherence with neuroleptic medications, with 21 percent of the study population being less than moderately adherent with prescribed neuroleptics.[49] They also found that symptom severity in this population was associated with substance abuse and neuroleptic nonadherence.[49] It should be noted that patients with psychotic and/or substance abuse disorders often have comorbid medical conditions for which they require medication. One study in this patient population found nonadherence to psychiatric and nonpsychiatric medication to be problematic with mean adherent fill rates for antipsychotic, antihypertensive, antihyperlipidemic, and antidiabetic medications ranging from 52 to 64 percent.[50] Thus, for all patient populations and for all medical treatments, simplification of treatment is an important measure for improving adherence.[51] This concept has been demonstrated in the management of hypertension, where the problem of treatment nonadherence is effectively alleviated by reducing the number of daily doses.[47]

IMPLANTS

All of the factors listed above indicate that the introduction of long-acting medications to prevent relapse could significantly improve the pharmacologic treatment of substance abuse. These agents are less dependent on patient participation to maintain efficacy and would therefore help to ensure that patients continued to receive their medication even when confronted by cues that increased their risk of relapse. Additionally, evidence suggests that a more gradual delivery of naltrexone could improve substance abuse treatment. A pilot study conducted in the United Kingdom found that naltrexone implants reduced the reinforcing properties of opiate drugs and reduced the incidence of early relapse in a supervised opiate detoxification program.[16] In this study, at 12 weeks after initial implantation, only 21 percent and 26 percent of the two groups studied, respectively, had relapsed, and none of the patients reported any opiate effects at less than five weeks after implantation (the time during which a naltrexone implant provides blockade). For comparison, a follow-up study of 50 opiate addicts found that 62 percent relapsed within five weeks after completion of an inpatient opiate detoxification program.[52]

ALCOHOL DEPENDENCE

The biodegradable polymer technology that has been used to develop a long-acting injectable formulation of risperidone has also been used to develop an extended-release naltrexone formulation for the treatment of alcohol dependence. Vivitrex®, a polymeric, extended-release, injectable formulation of naltrexone, was designed to facilitate adherence to treatment by providing extended duration of therapeutic levels of naltrexone with an intramuscular injection regimen of every four weeks, eliminating the need for daily adherence. Moreover, monthly administration is designed to avoid both the daily peaks of naltrexone and extensive first-pass metabolism associated with oral administration, which may result in enhanced tolerability. The naltrexone long-acting drug delivery technology uses injectable, biodegradable, polymeric microspheres as the delivery medium. The microspheres are composed of naltrexone incorporated into a matrix of polylactide-co-glycolide (PLG), a common biodegradable medical polymer with a history of safe human use in sutures, bone plates, abdominal mesh, and extended-release pharmaceuticals. Once injected into the body, the polymer erodes over time, thereby releasing naltrexone.

In preliminary pharmacokinetic and safety studies, long-acting, injectable naltrexone was safe and well tolerated and demonstrated favorable pharmacokinetic results compared with daily oral naltrexone.[53] In a six-month, phase III, multicenter, randomized, double-blind, placebo-controlled study, alcohol-dependent patients receiving this extended-release naltrexone formulation at a dose of 380 mg plus psychosocial therapy experienced a statistically significant 25-percent reduction in the rate of heavy drinking days, and a 48-percent median reduction in the percentage of days of heavy drinking, compared with patients treated with placebo and psychosocial therapy.[15] The most common adverse events were nausea, headache, and fatigue, but the majority of these events occurred only during the first month of treatment.

INTEGRATING PSYCHOSOCIAL SUPPORT

Even the most effective new medication technologies will not replace a comprehensive treat-

When a patient is not improving as expected, it is often difficult to distinguish between the effects of poor treatment adherence, lack of response to treatment, or progression of illness.

ment program that includes psychosocial support in the treatment of substance abuse. The importance of combining pharmacologic and behavioral approaches was recently demonstrated in a clinical trial that examined the use of naltrexone for the treatment of substance abuse. Balldin and colleagues examined a combination of naltrexone and behavior therapy in outpatient treatment of alcohol dependence.[43] In this six-month, multicenter, parallel-group clinical trial of 118 patients, cognitive behavior therapy (CBT) significantly increased the mean time to a first episode of heavy drinking when compared with "treatment as usual." However, the difference between CBT and usual care was even greater for patients who had also received naltrexone (50mg/day) than for those who were randomized to treatment with placebo. These findings illustrate that greatest improvements in control of drinking are obtained when behavioral and pharmacological approaches are used together. Oral naltrexone is currently approved for the treatment of alcoholism in the United States as an adjunct to behavioral intervention, and long-acting, injectable delivery systems, such as one using naltrexone, are likely to enhance the synergy between psychotherapy and pharmacotherapy.

SUMMARY AND CONCLUSIONS

Adherence to treatment is clearly associated with better clinical outcomes in many clinical settings, yet long-term patient adherence to pharmacotherapy is often poor. The introduction of new, long-acting drug formulations, which permit drug dosing once every few weeks, could provide significant improvements in clinical outcomes and patient satisfaction for many difficult-to-treat patients in psychiatric practice, including patients with schizophrenia, bipolar illness, and substance abuse. These formulations may also offer benefits for the treating physician. When a patient is not improving as expected, it is often difficult to distinguish between the effects of poor treatment adherence, lack of response to treatment, or progression of illness. By reducing the impact of nonadherence to treatment, long-acting medications may make it easier to identify why a patient is not improving as expected. Controlled clinical trials of these new formulations have only recently begun, but several of these new formulations may enter clinical practice during the next few years.

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By reducing the impact of nonadherence to treatment, long-acting medications may make it easier to identify why a patient is not improving as expected.