Medication Adherence Failure in Schizophrenia: A Forensic Review of Rates, Reasons, Treatments, and Prospects

John L. Young, MD, Reuben T. Spitz, PhD, Marc Hillbrand, PhD, and George Daneri, MSN

Forensic patients with schizophrenia who fail to adhere to prescribed antipsychotic medication risk recidivism, which continues to be a serious concern. It affects all stages of trial proceedings and impacts on the treaters' liability. Although much remains unchanged since the authors reviewed the subject in 1986, significant advances have occurred. A patient's insight can be assessed with greater precision. Risks posed by past noncompliance, substance abuse, and a dysphoric response to medication are more clearly documented. Clinical and laboratory methods for assessing compliance have improved. Major advances in the effective amelioration of adverse effects can be applied to promote adherence. New augmentation strategies enable adequate treatment at lower doses. The development of atypical antipsychotic agents makes compliance easier to achieve and maintain. Other advances apply to the containment of relapse when it does occur. This review organizes the literature documenting these trends for use in both treatment and consultation.

Recent advances in the treatment of schizophrenia have so far not improved adherence to treatment nor have they decreased the public's concern about the violence of some patients with this disorder. In fact, the reported risk of medication noncompliance with its potential for relapse and recidivism has not changed over the 12 years since this subject was updated under a forensic codification. At the same time, notable progress in the understanding and treatment of schizophrenia has produced developments highly relevant to the problems of noncompliance and relapse. The purpose of this update is to organize and present this information for the use of those who treat forensic patients with schizophrenia and consult on the issue of potential dangerousness arising from relapse following nonadherence to prescribed medication.
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This review provides information that applies to both criminal and civil proceedings. Medication compliance influences the handling of pretrial matters such as diversion programs, bail negotiations, restorations of competency to stand trial, plea bargains, and applications for accelerated rehabilitation. After trial, medication compliance is salient to discussions of alternatives to incarceration, sentence modification, parole application, and the management of insanity acquittees. Deliberations about the prospect of noncompliance leading to dangerousness or grave disability dominate civil commitment proceedings. The issue continues to be of concern in connection with efforts to assure patients’ rights and their informed consent to proposed medication regimens.

Most applications for the information presented here are not new. Liability for alleged negligent release is the major exception. This trend is especially worrisome because of the decreasing length of inpatient stays and its correlation with early relapse, along with significant erosion of protections from such liability. Also new is a trend favoring prearraignment diversion programs. These programs offer courts the option of an immediate referral to treatment for patients recognized to be in relapse and have been shown to expedite proceedings. To respond to some cases, prosecutors will need expert opinion on the prognosis for compliance.

Definition and Extent of Noncompliance

The basic landmarks remain unchanged since our 1986 review: general compliance rates for all of medicine continue to be approximately 50 percent; the usual methods for measuring compliance are interviews, pill counts, and assays based on the drug or a marker; and clinicians persist in blaming the patient for default. Treaters also remain poor predictors of their own patients’ default rates. The many forms of compliance failure continue to include the following: inadequate engagement in the treatment relationship after accepting a referral, repeated missed appointments, ignoring or misinterpreting instructions or adjusting the medication regimen independently, and abrupt termination of treatment.

Since failure to comply with depot (long-acting injectable) medications is readily recognizable, noncompliance with oral medications retains the primary focus. In accordance with continuing concern about undue blaming of the patient, there is a growing consensus on the value of reformulating the usage of compliance in terms of adherence, thereby acknowledging that compliance includes participation in an alliance with shared responsibility for effective collaboration.

Most authors, continuing to report medication default across a broad spectrum, use a definition based on clinical significance. The present review, based on targeted reading of refereed journals supplemented by literature searches covering the years 1986 through 1997, generated a total of 34 reports. Table 1 summarizes the results for oral medication; 35 default measurements in 29 reports show a median default rate of 46 percent, ranging from 5 to 85 percent. Table 2 shows the same information for
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<td>Casper and Regani</td>
<td>85 (354/416)</td>
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<td>Fernando et al.</td>
<td>81 (47/58)</td>
<td>Discharged patients</td>
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<td>Drake et al.</td>
<td>74 (14/19)</td>
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<td>Razali and Yahya</td>
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<td>Casper</td>
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<td>Hicks</td>
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<td>Frank and Gunderson</td>
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<td>Kelly et al.</td>
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<td>Discharged veterans</td>
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<td>Awad and Hogan</td>
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<td>Clinic outpatients</td>
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<td>Weiden and Glazer</td>
<td>50 (25/50)</td>
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<td>Single point</td>
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<td>McEvoy et al.</td>
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<td>Discharged prior noncompliers</td>
<td>Four to 42 months</td>
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<td>Nageotte et al.</td>
<td>47 (91/195)</td>
<td>Readmitted patients</td>
<td>Three years</td>
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<td>Scottish Schizophrenia</td>
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<td>Jenkins et al.</td>
<td>44 (19/43)</td>
<td>Discharged patients</td>
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<td>Eckman et al.</td>
<td>40 (64/160)</td>
<td>Outpatient study volunteers</td>
<td>Single point</td>
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<td>Kapur et al.</td>
<td>40 (8/20)</td>
<td>Day hospital patients</td>
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<td>Riboflavin urine marker</td>
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<td>Opler et al.</td>
<td>37 (37/100)</td>
<td>Homeless indigent men</td>
<td>Single point</td>
<td>Self-report</td>
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<td>Davidhizar et al.</td>
<td>36 (18/50)</td>
<td>Newly admitted patients</td>
<td>Single point</td>
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<td>Eckman et al.</td>
<td>33 (53/160)</td>
<td>Outpatient study volunteers</td>
<td>Single point</td>
<td>Psychiatrist rating</td>
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Table 1
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<table>
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<th>Reference</th>
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<tr>
<td>Buchanan et al.33</td>
<td>32 (19/59)</td>
<td>Patients two years after discharge</td>
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<td>McFarland et al.34</td>
<td>27 (59/215)</td>
<td>Outpatients</td>
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<td>26 (14/53)</td>
<td>Discharged patients</td>
<td>One month</td>
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<tr>
<td>Buchanan et al.33</td>
<td>25 (15/61)</td>
<td>Patients one year after discharge</td>
<td>Single point</td>
<td>Records, urine tests</td>
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<td>McEvoy et al.26</td>
<td>25 (9/36)</td>
<td>Discharged prior noncompliers</td>
<td>One month</td>
<td>Records, clinician interviews</td>
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<td>Drake et al.14</td>
<td>23 (13/56)</td>
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<td>Patient interview, clinician rating</td>
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<tr>
<td>Opler et al.31</td>
<td>18 (18/100)</td>
<td>Never homeless indigent men</td>
<td>Single point</td>
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<td>Sellwood and Tarrier26</td>
<td>17 (43/256)</td>
<td>Discharged patients</td>
<td>Up to three years</td>
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<td>Pablo et al.37</td>
<td>15 (23/150)</td>
<td>Readmitted patients</td>
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<td>Owen et al.38</td>
<td>15 (20/130)</td>
<td>Inpatients</td>
<td>Two one-month</td>
<td>Self-report, informants</td>
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<tr>
<td>Hazel et al.39</td>
<td>5 (100/1,992)</td>
<td>Clinic outpatients</td>
<td>Single point</td>
<td>Clinician assessment</td>
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Table 2
Results Reported from Investigations of Outpatient Depot Medication Compliance

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<thead>
<tr>
<th>Reference</th>
<th>Default Rate % (N)</th>
<th>Subjects</th>
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<td>Soni et al.41</td>
<td>48 (42/88)</td>
<td>Medication clinic patients</td>
<td>Up to five years</td>
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<td>Tunnicliffe et al.42</td>
<td>21 (18/84)</td>
<td>Medication clinic patients</td>
<td>One year</td>
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<tr>
<td>Hogarty et al.43</td>
<td>17 (12/70)</td>
<td>Consecutive admissions</td>
<td>Two years</td>
<td>Record study</td>
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<tr>
<td>Pan and Tantam44</td>
<td>11 (47/415)</td>
<td>Medication clinic patients</td>
<td>One year</td>
<td>Record review</td>
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<tr>
<td>Weiden et al.35</td>
<td>8 (3/40)</td>
<td>Discharged patients</td>
<td>One month</td>
<td>Multiple interviews, records</td>
</tr>
<tr>
<td>Fernando et al.13</td>
<td>0 (0/12)</td>
<td>Discharged patients</td>
<td>Up to one year</td>
<td>Patient interview</td>
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</table>
reports concerning default with depot medication, producing a median rate of 17 percent, ranging from 0 to 54 percent.

Factors Affecting Risk of Noncompliance

Data reported during the past dozen years confirm the basic set of interacting risk factors for nonadherence described in our 1986 report. A recent clinically oriented review organizes these risk factors usefully under four headings according to their origins: the patient, the medication, the environment, and the clinician. The authors rightly place responsibility for therapeutic alliance with the clinician. They list such patient-related risk factors as symptom severity, lack of insight, and substance abuse. Side effects and dosage issues fall under their medication heading, and the environmental factors accrue from poor personal and material support.

From a forensic point of view, some notable shifts in emphasis have occurred. Recent literature strikingly supports the importance of a strong therapeutic alliance in increasing the rate of compliance. There is also an increasing emphasis on the power of insight for improving compliance. Definitions of insight have come into clearer focus. For example, one study proposes that insight includes three factors: a stated intention to take medication, a belief that it had been helpful, and an optimistic stance toward the future. Each of these factors correlated positively with compliance one year after discharge. In contrast, merely acknowledging one’s illness and need for medication did not correlate with compliance, and it is made less likely by grandiosity and similar symptoms that interfere with insight. A thoughtful description of insight has been prepared, and a practical questionnaire proposed for measuring it. Still appearing occasionally in the compliance literature is the negative effect of so-called high expressed emotion; but interest in this concept has turned to its part in the overall impact of family environment on relapse despite compliance.

Authors have identified three compliance hazards since our 1986 report: a history of previous noncompliance, substance abuse, and education. Paradoxically, the more educated patients tend to be less compliant with prescribed medication. In addition, the uncertainty regarding the impact of having an initial unpleasant or dysphoric response to medication has been resolved; this unpleasant experience does add to the risk of later noncompliance.

Our 1986 update described various medication side effects in detail as leading factors that increase the risk of noncompliance. The intervening years have seen such dramatic improvements in the treatment of side effects that rather than discussing them here, we cover them through direct discussions of their remedies under the heading “Promoting Compliance.”

Measuring Compliance

Interviews During the last decade, there have been continuing efforts to organize what is known about factors that influence compliance behavior into interview schedules or other instruments that can be predictively applied in clinical sit-
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These instruments tend to be focused on patients’ perceptions of how medication affects their lives. Weiden and colleagues have developed a brief and practical interview schedule that improves considerably on previous subjective measures, with little additional effort. Another group have shared the results of their careful thinking about how to combine good interviewing with pill counts to assess compliance. In this context, it should be noted that devices continue to be developed to mark the times and dates when a pill container has been opened.

**Blood Levels** Continuing study has led to increased sophistication in the clinical application of blood levels of antipsychotic medications, especially to avoid toxicity and minimize needless suffering from side effects. Despite this progress, frustrating limitations remain with respect to both drugs and patients. However, the process of establishing a dose that is therapeutic without undue adverse effects and of determining the corresponding blood level can, for some patients, provide an ideal means to both evaluate and promote compliance.

We select some details among recently reported progress in the application of antipsychotic medication blood levels because of their particular relevance to monitoring compliance. Levels of perphenazine and one of its active metabolites were successfully applied to reduce side effects while maintaining therapeutic response. Success has been achieved in correlating serum levels with the clinical response for molindone but not for fluphenazine. Similar work with trifluoperazine has begun to identify a therapeutic window. Ideally, this information eliminates both inadequate and excessive doses, both of which inhibit long-term compliance. Most studies of haloperidol levels show a clear therapeutic window for this drug as well.

Advantages continue to be noted for alternatives to monitoring blood levels of antipsychotic medications; for example, prolactin levels may be followed. One can also resort to measuring levels in alternative fluids, particularly saliva. Urine presents another alternative, where uric acid has been used to monitor chlorprothixene and markers added to the medication can be assayed. In general, however, improvements in the direct monitoring of blood levels have decreased interest in the alternatives.

**Promoting Compliance**

**Dynamic Factors** Explorations of schizophrenic patients’ beliefs and feelings about illness and medication indicate that respectful consideration from clinicians promotes compliance with medication. In particular, the value of making certain that patients understand the benefits of prescribed medication in their own terms is clear. Similarly, a clinician who pays specific attention to how the patient adjusts to becoming a person who takes medication for mental illness is promoting compliance. A moderate but vocal consumer provides detailed applications of this principle. Prescribers often overlook the demonstrated value of keeping the medication regimen simple. Some patients may be helped by a variety of user-friendly de-
ervices, which have been summarized recently. These include blister packs with calendars and small medication containers marked for days of the week and divided for times of the day.

**Treatment of Side Effects** Reflecting the recent trend of advances in treatments for adverse effects of antipsychotic medications, a comprehensive review has appeared, with useful attention to compliance issues. Most serious of all the adverse effects is akathisia, an intensely unpleasant feeling of restlessness, which is both common and difficult to predict. Akathisia can worsen symptoms of psychosis, and treating it successfully tends to reduce these symptoms. The past dozen years have brought an improved understanding of akathisia, including practical objective ways to measure it. The often dissatisfying results when using anticholinergic agents, the standard treatment, are now being surmounted with beta blockers, benzodiazepines, and other agents. These advances should prove helpful in encouraging medication adherence. Further, it is now recognized that akathisia can appear long after antipsychotic medication has been started. Since akathisia is a particularly disturbing experience for patients, it must be recognized and skillfully processed in order to avoid a serious threat to compliance.

The impact of medications on sexual function remains an ill-defined problem, but some progress has been made. Impotence, loss of libido, and anorgasmia remain problematic for some patients, but promising treatment possibilities are increasing. Priapism is a newly recognized adverse effect that needs to be acknowledged. Gynecomastia and galactorrhea can now be readily addressed by medication change or by the cautious use of bromocriptine.

The vexing problem of weight gain from antipsychotic medication may impair compliance to an increased extent due to growing social pressure toward slimness. Fortunately, significant strides have occurred in understanding and managing this problem. In particular, a medication change to molindone, which sometimes causes weight loss, can be considered.

Tremor and dystonia are notorious for discouraging adherence. Recent case reports show success in treating tremor with metaprolol and with primidone. Dystonia, or stiffness, especially affects younger male patients and may be either acute or, more rarely, chronic. The usual treatment is benzotropine and when it fails or cannot be used, other similar agents can be tried. There has also been some success with substituting pimozide or chlorprothixene for the offending antipsychotic. Finally, although the practice has lately fallen from favor, in some circumstances it may be advisable to give anticholinergics prophylactically in order to promote compliance. Often these circumstances can be identified with considerable confidence.

**Dose Reduction** The past dozen years have seen successful dose reduction studies, demonstrating that this can be an effective means of improving the treatment course as well as compliance. Most of the few relapses observed in one study took place early in the course of
dose reduction; most patients without a relapse in the first year had none in the next two. An interesting study of 49 newly diagnosed schizophrenic patients found no difference in course for one year between patients given depot medication and those receiving an oral medication only once a week. Careful studies have increased the precision with which the appropriate candidates for dosage reduction are identified. For example, traditional predictors of good outcome (including benign premorbid history and ability to acquire skills) correlated with long, relapse-free periods on no medication. One large study suggested the dose of antipsychotic medication required for effective treatment could be used to identify patients likely to relapse following withdrawal of the medication. Another report summarized studies illustrating that handwriting tests instead of plasma drug levels may be used to identify individual patients’ minimum effective doses.

Caution is in order when contemplating this strategy. What we know about relapse despite compliance serves as a reminder that low doses are not appropriate for all patients. A British consensus statement detailing guidelines for safe and effective use of high dose antipsychotic medication is useful for identifying and treating patients for whom low dose strategies are not appropriate.

A study quoted in the previous review showing no difference between two doses in a year was extended, and regrettably in the second year patients on the lower dose fared much worse. A review of 66 studies of withdrawal of antipsychotic medication published since 1960 underscored the value of tapering off slowly, over several months, as a means of reducing the risk of relapse. A more recent large quantitative study demonstrated the same point. Increasing the dose in response to symptom emergence significantly reduced the risk of relapse. But the extreme of restricting medication entirely to periods of symptom exacerbation (sometimes called “targeting”) was usually inferior to continuous medication administration.

**Depot Medication** Significant advances have taken place recently in the use of depot administration of antipsychotic medication, most notably the introduction of haloperidol decanoate. A recent five-year study shows that haloperidol has fewer side effects and a lower relapse rate than other neuroleptics. Nonetheless, depot antipsychotics remain underutilized. A European source laments the apparent trend of marketing forces away from the development of new depot formulations and the promotion of existing ones. Depot medication remains a uniquely powerful tool for compliance promotion, because when it fails the alert clinician always knows.

Great care must be taken in order to utilize the depot route of administration. It is important to be mindful that half-life is measured in months, requiring a long period to reach steady-state concentration. Therefore, a loading strategy, either oral or intramuscular, is often used for beginning depot injections and changes of depot dose must be very gradual. There is general agreement that the goal of finding the lowest effec-
tive dose applies to depot medications and that plasma levels are helpful in this determination. Injection site reactions have been reported; these reactions can sometimes be helped by using a lower concentration of drug for the injection and by exercising care in the injection technique. Finally, the depot route of administration alone is not sufficient to maintain compliance over extended periods of time; careful monitoring and supportive therapy are needed to minimize default leading to relapse.

**Augmentation** The practice of adding a second drug to an antipsychotic has begun to emerge strongly as a strategy to promote compliance by improving therapeutic response while potentially moderating side effects. Among the more familiar agents, both lithium and valproate continue to be found useful. This is also true for benzodiazepines, especially lorazepam and alprazolam. Clonidine has also been suggested, and paradoxically, idazoxan, which has opposite effects on neurotransmission but presumably in different parts of the brain. In addition, other agents have been found helpful: fluoxetine, buspirone, and d-cycloserine. The search for more and better augmenting agents likely bears watching for continued progress.

**New Medications** The introduction of the atypical antipsychotic agents is a major advance in the promotion of compliance. It is well known that the first of these, clozapine, was approved in large part because it proved effective for patients who had repeatedly relapsed despite medication compliance. The other atypical antipsychotic agents, which to date include risperidone, olanzapine, and quetiapine, are especially notable for their favorable side effect profiles. Full details are beyond the scope of this paper, except to note an early description of clozapine use with forensic patients, two recent forensic trials of risperidone, one study each on olanzapine and quetiapine, and a recent comprehensive review describing how these agents are being used for patients who are aggressive and difficult to treat.

**Containing Relapse**

Relapse containment requires a multifaceted strategy, with adherence promotion as one of its central components. Unfortunately, schizophrenic patients may experience relapses of their illness despite their compliance with prescribed medication. A recent literature review covering 66 medication discontinuation studies found a relapse rate of 53 percent among study patients who were withdrawn from medication, and 16 percent for those kept on medication over an average period of only 9.7 months. Similarly, a recent meta-analysis showed twice as many schizophrenic patients readmitted to the hospital as a result of medication failure as from noncompliance during the first year after discharge, and equal readmission rates for both reasons during the second year. However, physicians still tend to mistake noncompliance for medication failure and respond by prescribing increasing doses of antipsychotic medication. In contrast, alleged histories of noncompliance with medication taken on multiple readmis-
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sions may merely reflect a staff preconception.\textsuperscript{153}

Enhanced Monitoring The study of relapse despite medication compliance over the past dozen years has demonstrated a strong association with stressful life events such as a move or the death or retirement of a close relative.\textsuperscript{154} Other patients at risk for relapse while taking their medication are those with poor remission of psychotic symptoms, particularly negative symptoms such as isolation and apathy, and those who develop extrapyramidal side effects.\textsuperscript{155} Relapse, sometimes involving noncompliance, may be triggered by family conflict, especially with discouragement of expressing feelings,\textsuperscript{156,157} missed therapy appointments,\textsuperscript{158} and substance abuse.\textsuperscript{55} Regular monitoring for these situations will help contain relapse, since ordinarily three to six months elapse after stopping medication before relapse occurs.\textsuperscript{159} A small study shows that pharmacists can be effective at performing this task.\textsuperscript{160}

Prodromal Signs During the past dozen years much has been learned about how to recognize prodromal signs. These indicators include changes in mood, appearance, or behavior associated with a first episode that often herald the onset of a schizophrenic relapse.\textsuperscript{161} Marder and colleagues\textsuperscript{122} found that 50 percent of symptom exacerbations were not preceded by a prodrome, while 53 percent of untreated prodromal episodes did not lead to exacerbations. Despite this discrepancy, intervention in response to prodromes greatly reduces the relapse risk.\textsuperscript{162} Prompt improvement is usual when the dosage of antipsychotic medication is increased or treatment is restarted.\textsuperscript{163} Prodromal signs can\textsuperscript{164} but usually do not\textsuperscript{165} appear to be psychotic. According to one group of clinicians, schizophrenic patients themselves can learn to recognize nonpsychotic changes as indicators that they are getting worse.\textsuperscript{166} It remains evident that prodromal signs are unique for each patient and must be identified individually by history, rather than in general by type of change.\textsuperscript{167} Practical strategies are available for clinicians to apply,\textsuperscript{168,169} including use of the fact that family members often see the changes first.\textsuperscript{170}

Early Relapse Prediction Although some relapses occur without warning, their proportion definitely tends to decrease over time, especially when the patients and their clinicians are working well together.\textsuperscript{122} The most successful study was that of Birchwood and colleagues\textsuperscript{171} who reported that their checklist, done biweekly by the patient and an observer, predicted 79 percent of the relapses with almost no false positives and with favorable responses when medication dosage was increased. Another study\textsuperscript{172} showed how to predict at least 70 percent (and potentially more among patients known to be subject to relapse), again with very few false positives, between two and four weeks prior to decompensation. There have been recent advances in the form of biologically based potential predictors of relapse,\textsuperscript{173,174} but they are not yet sufficiently practical for general use in the containment of relapse.

Environmental Support Strategies A stable living situation of good quality fa-
cilitates medication adherence$^{14, 26}$ and retards recidivism.$^{175}$ It can be difficult to apply this relationship to the forensic patient population,$^{176}$ but the value of assertive community treatment for maintaining adherence and preventing relapse is well established.$^{177}$ A model for tailoring environmental support to the needs of forensic patients has been suggested.$^{178}$ In a few jurisdictions environmental support has been legally formalized under Psychiatric Security Review Boards. These extensions of the criminal court deal effectively with noncompliance and provide containment of relapse.$^{179, 180}$ Further, outpatient commitment has been gaining acceptance as an effective way to buttress environmental support with legal force.$^{181}$

 Patients' knowledge about their medications tends to be overestimated, especially among those with schizophrenia.$^{182}$ Although patients receiving a few lessons about medications will have no measurable impact on compliance,$^{183, 184}$ a more serious effort at patient education clearly improves the rate of compliance.$^{23, 30}$ In this vein, a voluntary program of carefully structured teaching for inpatients significantly reduced the time they spent in hospital during the succeeding year,$^{185}$ as did a cognitive-behavioral therapy program.$^{186}$ Group therapists have recently reported similar results,$^{187}$ particularly for patients with substance abuse problems.$^{188}$ There is evidence that patients can learn to associate relief of their symptoms with medication and that this association results in better compliance.$^{19}$

 Finally, during the past 12 years, the use of family psychoeducation has been shown to promote medication compliance and thereby reduce relapses in schizophrenia.$^{8, 15, 189}$ In fact, multifamily groups are particularly efficacious in promoting medication compliance.$^{190}$ A recent review$^{191}$ provides detailed information on how to structure these family-based interventions for the best results. Patients' adherence to medication correlates with their recognition of encouragement and support from those around them.$^{26}$

**Conclusion**

Forensic experts concerned with minimizing the problem of relapse among schizophrenic patients as a result of medication noncompliance may view the past dozen years as a time of highly encouraging progress. Whereas our previous review emphasized risk factors, this one has much more to report concerning interventions. It has become easier to deal effectively with the legal concerns regarding schizophrenic patients' tendencies toward medication noncompliance and subsequent relapse. Experts can now offer more precise information about this issue. The fact that reported default rates nonetheless remain essentially unchanged indicates that much challenging and interesting work remains to be done. Glazer$^{192}$ has gone so far as to state that we are now in a position to "eliminate most of the cases of schizophrenic relapse."

Significant advances in the area of medication adherence, in addition to those reported here, are likely to continue. For example, a recent review has opened the area of randomized trials of interventions to promote medication compli-
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The small number of rigorous studies in several areas of medicine include two for schizophrenia. However, both of these studies were done in China, where cultural differences hamper generalizing the applications to western countries. Further progress in the scientific study of compliance can be expected. Another example is a guarded optimism regarding long-term prognosis for some patients with schizophrenia deriving from extended follow-up studies.194

The near future will doubtless prove as interesting and productive as the recent past. Refinements in the subtyping of schizophrenia according to symptom patterns are moving forward quickly195 and will enable experts to provide more reliable opinions regarding the prognosis for compliance. Similar gains in sophistication increasingly mark the current studies of relapse and its prevention, with medication default as but one among a host of interrelating factors. The challenge of applying an ever more vast and diverse clinical literature to legal questions, while remaining vigilant to ethical concerns, is likely to increase in coming years. Meanwhile, we expect that this review will provide significant assistance toward making effective use of recent and current progress in the study of medication adherence among patients diagnosed with schizophrenia.

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