

# 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.<sup>1</sup> 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.

---

The authors are affiliated with the Whiting Forensic Division of Connecticut Valley Hospital, Middletown, CT. Drs. Young and Hillbrand are also affiliated with the Yale University School of Medicine, New Haven, CT. Dr. Spitz is affiliated with the Albert Einstein College of Medicine, Bronx, NY. An earlier version of this paper was presented at the 27th annual meeting of the American Academy of Psychiatry and the Law, October, 1996, San Juan, PR. Address correspondence to: John L. Young, MD, Box 70, Middletown, CT 06457. E-mail address: jlyoung@pol.net

## Medication Adherence Failure

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.<sup>2</sup> This trend is especially worrisome because of the decreasing length of inpatient stays and its correlation with early relapse,<sup>3</sup> along with significant erosion of protections from such liability.<sup>4</sup> Also new is a trend favoring prearrest diversion programs. These programs offer courts the option of an immediate referral to treatment for patients recognized to be in relapse<sup>5</sup> and have been shown to expedite proceedings.<sup>6</sup> To respond to some cases, prosecutors will need expert opinion on the prognosis for compliance.<sup>7</sup>

### 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.<sup>8,9</sup> 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.<sup>10</sup> 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.<sup>11</sup>

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.<sup>8, 12-44</sup> 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

**Table 1**  
**Results Reported from Investigations of Outpatient Oral Medication Compliance**

Reference	% Default Rate (N)	Subjects	Observation Period	Method of Detection
Casper and Regan <sup>12</sup>	85 (354/416)	Newly admitted recidivists	Single point	Nurse rating
Fernando et al. <sup>13</sup>	81 (47/58)	Discharged patients	Up to one year	Patient interview
Drake et al. <sup>14</sup>	74 (14/19)	Rural outpatients, unstable housing	One year	Patient interview, clinician rating
Razali and Yahya <sup>15</sup>	73 (165/225)	Readmitted patients	Two weeks	Questionnaires
Casper <sup>16</sup>	72 (53/74)	Patients admitted three or more times within 18 months	Three years	Patient interview, record review
Kashner et al. <sup>17</sup>	66 (80/121)	Random Veterans Affairs-admitted patients	Single point	Record review
Girón and Gomez-Beneyto <sup>18</sup>	66 (49/74)	Discharged patients	Two years	Self- and relatives' reports
Adams and Howe <sup>19</sup>	62 (26/42)	Newly admitted patients	One month	Interview of patient
Casper <sup>16</sup>	61 (74/121)	Patients admitted fewer than three times within 18 months	Three years	Patient interview, record review
Hicks <sup>20</sup>	60 (18/30)	Readmitted patients	Up to one year	Patient interview
Frank and Gunderson <sup>21</sup>	58 (42/72)	Psychotherapy patients	Six months	Patient and therapist reports; record review
Smoot et al. <sup>22</sup>	58 (14/24)	Readmitted patients	Single point	Patient interview
Kelly et al. <sup>23</sup>	57 (240/418)	Discharged veterans	Available past history	Record review
Awad and Hogan <sup>24</sup>	54 (81/150)	Clinic outpatients	Single point	Therapist rating
Weiden and Glazer <sup>25</sup>	50 (25/50)	Newly readmitted high utilizers	Single point	Assessment by admitting team
McEvoy et al. <sup>26</sup>	47 (22/46)	Discharged prior noncompliers	Four to 42 months	Records, clinician interviews
Nageotte et al. <sup>27</sup>	47 (91/195)	Readmitted patients	Three years	Self- and relatives' reports
Scottish Schizophrenia Research Group <sup>28</sup>	46 (10/22)	First episode inpatients	Five weeks	Radioimmunoassay of serum
Jenkins et al. <sup>29</sup>	44 (19/43)	Discharged patients	Nine months	Record review
Eckman et al. <sup>30</sup>	40 (64/160)	Outpatient study volunteers	Single point	Caregiver rating
Kapur et al. <sup>8</sup>	40 (8/20)	Day hospital patients	Three months	Riboflavin urine marker
Opler et al. <sup>31</sup>	37 (37/100)	Homeless indigent men	Single point	Self-report
Davidhizar et al. <sup>32</sup>	36 (18/50)	Newly admitted patients	Single point	Record review
Eckman et al. <sup>30</sup>	33 (53/160)	Outpatient study volunteers	Single point	Psychiatrist rating

Table 1  
Continued

Reference	% Default Rate (N)	Subjects	Observation Period	Method of Detection
Buchanan <sup>33</sup>	32 (19/59)	Patients two years after discharge	Single point	Records, urine tests
McFarland <i>et al.</i> <sup>34</sup>	27 (59/215)	Outpatients	Single point	Questionnaire mailed to relatives
Weiden <i>et al.</i> <sup>35</sup>	26 (14/53)	Discharged patients	One month	Multiple interviews, records
Buchanan <sup>33</sup>	25 (15/61)	Patients one year after discharge	Single point	Records, urine tests
McEvoy <i>et al.</i> <sup>26</sup>	25 (9/36)	Discharged prior noncompliers	One month	Records, clinician interviews
Drake <i>et al.</i> <sup>14</sup>	23 (13/56)	Rural outpatients, stable housing	One year	Patient interview, clinician rating
Opler <i>et al.</i> <sup>31</sup>	18 (18/100)	Never homeless indigent men	Single point	Self-report
Sellwood and Tarrier <sup>36</sup>	17 (43/256)	Discharged patients	Up to three years	Psychiatrist interview
Pablo <i>et al.</i> <sup>37</sup>	15 (23/150)	Readmitted patients	Single point	Record review
Owen <i>et al.</i> <sup>38</sup>	15 (20/130)	Inpatients	Two one-month periods six months apart	Self-report, informants
Hazel <i>et al.</i> <sup>39</sup>	5 (100/1,992)	Clinic outpatients	Single point	Clinician assessment

Table 2  
Results Reported from Investigations of Outpatient Depot Medication Compliance

Reference	Default Rate % (N)	Subjects	Observation Period	Method of Detection
Bartó <i>et al.</i> <sup>40</sup>	54 (30/56)	Discharged patients	One year	Appointment record
Soni <i>et al.</i> <sup>41</sup>	48 (42/88)	Medication clinic patients	Up to five years	Observation
Tunncliffe <i>et al.</i> <sup>42</sup>	21 (18/84)	Medication clinic patients	One year	Record review
Hogarty <i>et al.</i> <sup>43</sup>	17 (12/70)	Consecutive admissions	Two years	Record study
Pan and Tantam <sup>44</sup>	11 (47/415)	Medication clinic patients	One year	Record review
Weiden <i>et al.</i> <sup>35</sup>	8 (3/40)	Discharged patients	One month	Multiple interviews, records
Fernando <i>et al.</i> <sup>13</sup>	0 (0/12)	Discharged patients	Up to one year	Patient interview

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.<sup>45</sup> 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.<sup>21, 46</sup> There is also an increasing emphasis on the power of insight for improving compliance.<sup>26, 27, 47, 48</sup> 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.<sup>33</sup> In contrast, merely acknowledging one's illness and need for medication did not correlate with compliance,<sup>49</sup> and it is made less

likely by grandiosity and similar symptoms that interfere with insight.<sup>40, 50</sup> A thoughtful description of insight has been prepared,<sup>51</sup> and a practical questionnaire proposed for measuring it.<sup>52</sup> Still appearing occasionally in the compliance literature is the negative effect of so-called high expressed emotion,<sup>18, 43</sup> but interest in this concept has turned to its part in the overall impact of family environment on relapse despite compliance.<sup>53</sup>

Authors have identified three compliance hazards since our 1986 report: a history of previous noncompliance,<sup>33, 54</sup> substance abuse,<sup>12, 34, 55, 56</sup> and education. Paradoxically, the more educated patients tend to be less compliant with prescribed medication.<sup>54</sup> 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.<sup>57, 58</sup>

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-

## Medication Adherence Failure

uations.<sup>19, 24, 32</sup> These instruments tend to be focused on patients' perceptions of how medication affects their lives. Weiden and colleagues<sup>59</sup> have developed a brief and practical interview schedule that improves considerably on previous subjective measures, with little additional effort. Another group<sup>60</sup> 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.<sup>9, 61, 62</sup>

**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.<sup>63</sup> Despite this progress, frustrating limitations remain with respect to both drugs and patients.<sup>64</sup> 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.<sup>65</sup> Success has been achieved in correlating serum levels with the clinical response for molindone<sup>66</sup> but not for fluphenazine.<sup>67</sup> Similar work with trifluoperazine

has begun to identify a therapeutic window.<sup>68</sup> 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.<sup>69-71</sup>

Advantages continue to be noted for alternatives to monitoring blood levels of antipsychotic medications; for example, prolactin levels may be followed.<sup>66</sup> One can also resort to measuring levels in alternative fluids, particularly saliva.<sup>72</sup> Urine presents another alternative,<sup>33</sup> where uric acid has been used to monitor chlorprothixene,<sup>73</sup> and markers added to the medication can be assayed.<sup>8</sup> 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.<sup>58, 74, 75</sup> In particular, the value of making certain that patients understand the benefits of prescribed medication in their own terms is clear.<sup>19</sup> 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.<sup>76</sup> A moderate but vocal consumer provides detailed applications of this principle.<sup>77</sup> Prescribers often overlook the demonstrated value of keeping the medication regimen simple. Some patients may be helped by a variety of user-friendly de-

vices, which have been summarized recently.<sup>9</sup> 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.<sup>78</sup> Most serious of all the adverse effects is akathisia, an intensely unpleasant feeling of restlessness, which is both common and difficult to predict.<sup>79</sup> Akathisia can worsen symptoms of psychosis, and treating it successfully tends to reduce these symptoms.<sup>80</sup> The past dozen years have brought an improved understanding of akathisia,<sup>81</sup> including practical objective ways to measure it.<sup>82, 83</sup> The often dissatisfying results when using anticholinergic agents, the standard treatment, are now being surmounted with beta blockers,<sup>84, 85</sup> benzodiazepines,<sup>86</sup> and other agents.<sup>87</sup> 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.<sup>88</sup> 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.<sup>89</sup> Priapism is a newly recognized

adverse effect that needs to be acknowledged.<sup>90</sup> Gynecomastia and galactorrhea can now be readily addressed by medication change<sup>91</sup> or by the cautious use of bromocriptine.<sup>92</sup>

The vexing problem of weight gain from antipsychotic medication may impair compliance to an increased extent due to growing social pressure toward slimness.<sup>93</sup> Fortunately, significant strides have occurred in understanding and managing this problem.<sup>94</sup> In particular, a medication change to molindone, which sometimes causes weight loss, can be considered.<sup>95, 96</sup>

Tremor and dystonia are notorious for discouraging adherence. Recent case reports show success in treating tremor with metoprolol<sup>97</sup> and with primidone.<sup>98</sup> Dystonia, or stiffness, especially affects younger male patients and may be either acute<sup>99</sup> or, more rarely, chronic.<sup>100</sup> The usual treatment is bztropine,<sup>101</sup> and when it fails or cannot be used, other similar agents can be tried.<sup>102</sup> There has also been some success with substituting pimozide<sup>103</sup> or chlorprothixene<sup>104</sup> 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.<sup>105, 106</sup> Often these circumstances can be identified with considerable confidence.<sup>107</sup>

**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.<sup>108</sup> Most of the few relapses observed in one study took place early in the course of

## Medication Adherence Failure

dose reduction; most patients without a relapse in the first year had none in the next two.<sup>109</sup> 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.<sup>110</sup> Careful studies have increased the precision with which the appropriate candidates for dosage reduction are identified.<sup>111, 112</sup> 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.<sup>113</sup> One large study<sup>114</sup> 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<sup>115</sup> 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.<sup>116</sup> 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.<sup>117</sup> A study quoted in the previous review<sup>118</sup> 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.<sup>119</sup> 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.<sup>120</sup> A more recent large quantitative study demonstrated the same point.<sup>121</sup> Increasing the dose in response to symptom emergence significantly reduced the risk of relapse.<sup>122</sup> But the extreme of restricting medication entirely to periods of symptom exacerbation (sometimes called "targeting") was usually inferior to continuous medication administration.<sup>123</sup>

**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<sup>124</sup> shows that haloperidol has fewer side effects and a lower relapse rate than other neuroleptics. Nonetheless, depot antipsychotics remain underutilized.<sup>125</sup> A European source<sup>126</sup> 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.<sup>127</sup> Therefore, a loading strategy, either oral or intramuscular, is often used for beginning depot injections,<sup>128, 129</sup> and changes of depot dose must be very gradual.<sup>130, 131</sup> 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.<sup>132</sup> 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.<sup>133</sup> 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.<sup>35</sup>

**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<sup>134</sup> and valproate<sup>135</sup> continue to be found useful. This is also true for benzodiazepines, especially lorazepam<sup>136</sup> and alprazolam.<sup>137</sup> Clonidine has also been suggested,<sup>138</sup> and paradoxically, idazoxan,<sup>139</sup> which has opposite effects on neurotransmission but presumably in different parts of the brain. In addition, other agents have been found helpful: fluoxetine,<sup>140</sup> buspirone,<sup>141</sup> and D-cycloserine.<sup>142</sup> 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.<sup>143</sup> 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,<sup>144</sup> two recent forensic trials of risperidone,<sup>145, 146</sup> one study each on olanzapine<sup>147</sup> and quetiapine,<sup>148</sup> and a recent comprehensive review describing how these agents are being used for patients who are aggressive and difficult to treat.<sup>149</sup>

### Containing Relapse

Relapse containment requires a multifaceted strategy, with adherence promotion as one of its central components.<sup>16</sup> Unfortunately, schizophrenic patients may experience relapses of their illness despite their compliance with prescribed medication.<sup>150</sup> 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.<sup>120</sup> Similarly, a recent meta-analysis<sup>151</sup> 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.<sup>152</sup> In contrast, alleged histories of noncompliance with medication taken on multiple readmis-

## Medication Adherence Failure

sions may merely reflect a staff preconception.<sup>153</sup>

**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.<sup>154</sup> 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.<sup>155</sup> Relapse, sometimes involving noncompliance, may be triggered by family conflict, especially with discouragement of expressing feelings,<sup>156, 157</sup> missed therapy appointments,<sup>158</sup> and substance abuse.<sup>55</sup> Regular monitoring for these situations will help contain relapse, since ordinarily three to six months elapse after stopping medication before relapse occurs.<sup>159</sup> A small study shows that pharmacists can be effective at performing this task.<sup>160</sup>

**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.<sup>161</sup> Marder and colleagues<sup>122</sup> 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.<sup>162</sup> Prompt improvement is usual when the dosage of antipsychotic medi-

ation is increased or treatment is restarted.<sup>163</sup> Prodromal signs can<sup>164</sup> but usually do not<sup>165</sup> 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.<sup>166</sup> 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.<sup>167</sup> Practical strategies are available for clinicians to apply,<sup>168, 169</sup> including use of the fact that family members often see the changes first.<sup>170</sup>

**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.<sup>122</sup> The most successful study was that of Birchwood and colleagues<sup>171</sup> 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<sup>172</sup> 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,<sup>173, 174</sup> 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<sup>14, 26</sup> and retards recidivism.<sup>175</sup> It can be difficult to apply this relationship to the forensic patient population,<sup>176</sup> but the value of assertive community treatment for maintaining adherence and preventing relapse is well established.<sup>177</sup> A model for tailoring environmental support to the needs of forensic patients has been suggested.<sup>178</sup> 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.<sup>179, 180</sup> Further, outpatient commitment has been gaining acceptance as an effective way to buttress environmental support with legal force.<sup>181</sup>

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

Finally, during the past 12 years, the use of family psychoeducation has been

shown to promote medication compliance and thereby reduce relapses in schizophrenia.<sup>8, 15, 189</sup> In fact, multifamily groups are particularly efficacious in promoting medication compliance.<sup>190</sup> A recent review<sup>191</sup> 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.<sup>26</sup>

## 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<sup>192</sup> 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-

## Medication Adherence Failure

ance.<sup>193</sup> 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.<sup>194</sup>

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 quickly<sup>195</sup> 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.

### Acknowledgments

We gratefully acknowledge the literature search assistance of Pauline A. Kruk, MS, and Stephen H. Curtin, MS, of Hallock Medical Library, Connecticut Valley Hospital, and the scholarly impetus of Howard V. Zonana, MD, of Yale University.

## References

1. Young JL, Zonana HV, Shepler L: Medication noncompliance in schizophrenia: codification and update. *Bull Am Acad Psychiatry Law* 14:105–22, 1986
2. Miller RD, Doren DM, Van Rybroek G, *et al*: Emerging problems for staff associated with the release of potentially dangerous forensic patients. *Bull Am Acad Psychiatry Law* 16:309–20, 1988
3. Appleby L, Desai PN, Luchins DJ, *et al*: Length of stay and recidivism in schizophrenia: a study of public psychiatric hospital patients. *Am J Psychiatry* 150:72–6, 1993
4. Felthous AR: Liability of treaters for injuries to others: erosion of three immunities. *Bull Am Acad Psychiatry Law* 15:115–25, 1987
5. Steadman HJ, Morris SM, Dennis DL: The diversion of mentally ill persons from jails to community-based services: a profile of programs. *Am J Public Health* 85:1630–5, 1995
6. Exworthy T, Parrott J: Comparative evaluation of a diversion from custody scheme. *J Forensic Psychiatry* 8:406–16, 1997
7. Davis S: Factors associated with the diversion of mentally disordered offenders. *Bull Am Acad Psychiatry Law* 22:389–97, 1994
8. Kapur S, Ganguli R, Ulrich R, *et al*: Use of random-sequence riboflavin as a marker of medication compliance in chronic schizophrenics. *Schizophr Res* 6:49–53, 1992
9. Wright EC: Non-compliance—or how many aunts has Matilda? *Lancet* 342:909–13, 1993
10. Chen A: Noncompliance in community psychiatry: a review of clinical interventions. *Hosp Community Psychiatry* 42:282–7, 1991
11. Corrigan PW, Liberman RP, Engel JD: From noncompliance to collaboration in the treatment of schizophrenia. *Hosp Community Psychiatry* 41:1203–11, 1990
12. Casper ES, Regan JR: Reasons for admission among six profile subgroups of recidivists of inpatient services. *Can J Psychiatry* 38:657–61, 1993
13. Fernando MLD, Velamoor VR, Cooper AJ, *et al*: Some factors relating to satisfactory post-discharge community maintenance of chronic psychotic patients. *Can J Psychiatry* 35:71–3, 1990
14. Drake RE, Wallach MA, Teague GB, *et al*: Housing instability and homelessness among rural schizophrenic patients. *Am J Psychiatry* 148:330–6, 1991
15. Razali MS, Yahya H: Compliance with treatment in schizophrenia: a drug intervention

- program in a developing country. *Acta Psychiatr Scand* 91:331-5, 1995
16. Casper ES: Identifying multiple recidivists in a state hospital population. *Psychiatr Serv* 46:1074-5, 1995
  17. Kashner TM, Rader LE, Rodell DE, *et al*: Family characteristics, substance abuse, and hospitalization patterns of patients with schizophrenia. *Hosp Community Psychiatry* 42:195-7, 1991
  18. Girón M, Gomez-Beneyto M: Relationship between family attitudes measured by the semantic differential and relapse in schizophrenia: a 2-year follow-up prospective study. *Psychol Med* 25:365-71, 1995
  19. Adams SG, Howe JT: Predicting medication compliance in a psychotic population. *J Nerv Ment Dis* 181:558-60, 1993
  20. Hicks MB: A community sojourn from the perspective of one who relapsed. *Issues Ment Health Nurs* 10:137-47, 1989
  21. Frank AF, Gunderson JG: The role of the therapeutic alliance in the treatment of schizophrenia. *Arch Gen Psychiatry* 47:228-36, 1990
  22. Smoot SL, Vandiver RM, Fields RA: Homeless persons readmitted to an urban state hospital. *Hosp Community Psychiatry* 43:1028-30, 1992
  23. Kelly GR, Scott JE, Mamon J: Medication compliance and health education among outpatients with chronic mental disorders. *Med Care* 28:1181-97, 1990
  24. Awad AG, Hogan TP: Subjective response to neuroleptics and the quality of life: implications for treatment outcome. *Acta Psychiatr Scand* 89(Suppl 380):27-32, 1994
  25. Weiden P, Glazer W: Assessment and treatment selection for "revolving door" inpatients with schizophrenia. *Psychiatr Q* 68:377-93, 1997
  26. McEvoy JP, Freter S, Everett G, *et al*: Insight and the clinical outcome of schizophrenic patients. *J Nerv Ment Dis* 177:48-51, 1989
  27. Nageotte C, Sullivan G, Duan N, *et al*: Medication compliance among the seriously mentally ill in a public mental health system. *Soc Psychiatry Psychiatr Epidemiol* 32:49-56, 1997
  28. Scottish Schizophrenia Research Group: The Scottish first episode schizophrenia study II. treatment: pimozide versus flupenthixol. *Br J Psychiatry* 150:334-8, 1987
  29. Jenkins JH, Karno M, de la Selva A, *et al*: Expressed emotion of relatives, maintenance drug treatment, and relapse in schizophrenia and mania. *Psychopharmacol Bull* 22:621-7, 1986
  30. Eckman TA, Liberman RP, Phipps CC, *et al*: Teaching medication management skills to schizophrenic patients. *J Clin Psychopharmacol* 10:33-8, 1990
  31. Opler LA, Caton CLM, Shrout P, *et al*: Symptom profiles and homelessness in schizophrenia. *J Nerv Ment Dis* 182:174-8, 1994
  32. Davidhizar RE, Austin JK, McBride AB: Attitudes of patients with schizophrenia toward taking medication. *Res Nurs Health* 9:139-46, 1986
  33. Buchanan A: A two-year prospective study of treatment compliance in patients with schizophrenia. *Psychol Med* 22:787-97, 1992
  34. McFarland BH, Faulkner LR, Bloom JD, *et al*: Chronic mental illness and the criminal justice system. *Hosp Community Psychiatry* 40:718-23, 1989
  35. Weiden P, Rapkin B, Zygmunt A, *et al*: Postdischarge medication compliance of inpatients converted from an oral to a depot neuroleptic regimen. *Psychiatr Serv* 46:1049-54, 1995
  36. Sellwood W, Tarrier N: Demographic factors associated with extreme non-compliance in schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 29:172-7, 1994
  37. Pablo RY, Kadlec KE, Arboleda-Florez J: The readmission of psychotic patients to a general hospital psychiatry unit. *Gen Hosp Psychiatry* 8:190-7, 1986
  38. Owen RR, Fischer EP, Booth BM, *et al*: Medication noncompliance and substance abuse among patients with schizophrenia. *Psychiatr Serv* 47:853-8, 1996
  39. Hazel KL, Herman SE, Mowbray CT: Characteristics of seriously mentally ill adults in a public mental health system. *Hosp Community Psychiatry* 42:518-25, 1991
  40. Bartkó G, Herczeg I, Zádor G: Clinical symptomatology and drug compliance in schizophrenic patients. *Acta Psychiatr Scand* 77:74-6, 1988
  41. Soni SD, Gaskell K, Reed P: Factors affecting rehospitalisation rates of chronic schizophrenic patients living in the community. *Schizophr Res* 12:169-77, 1994
  42. Tunnicliffe S, Harrison G, Standen PJ: Factors affecting compliance with depot injection treatment in the community. *Soc Psychiatry Psychiatr Epidemiol* 27:230-3, 1992
  43. Hogarty GE, McEvoy JP, Munetz M, *et al*: Dose of fluphenazine, familial expressed

## Medication Adherence Failure

- emotion, and outcome in schizophrenia. *Arch Gen Psychiatry* 45:797–805, 1988
44. Pan P-C, Tantam D: Clinical characteristics, health beliefs and compliance with maintenance treatment: a comparison between regular and irregular attenders at a depot clinic. *Acta Psychiatr Scand* 79:564–70, 1989
  45. Fenton WS, Blyler CR, Heinssen RK: Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull* 23:637–51, 1997
  46. Axelrod S, Palgi E: Developing an alliance with schizophrenic patients in day hospital treatment. *Bull Menninger Clin* 54:340–52, 1990
  47. Walker EF, Rossiter J: Schizophrenic patients' self-perceptions: legal and clinical implications. *J Psychiatry Law* 17:55–73, 1989
  48. Smith CM, Barzman D, Pristach CA: Effect of patient and family insight on compliance of schizophrenic patients. *J Clin Pharmacol* 37:147–54, 1997
  49. Cuffel BJ, Aford J, Fischer EP, *et al*: Awareness of illness in schizophrenia and outpatient treatment adherence. *J Nerv Ment Dis* 184:653–9, 1996
  50. White L, Parella M, McCrystal-Simon J, *et al*: Characteristics of elderly psychiatric patients retained in a state hospital during downsizing. *Int J Geriatr Psychiatry* 12:474–80, 1997
  51. Amador XF, Strauss DH, Yale SA, *et al*: Awareness of illness in schizophrenia. *Schizophr Bull* 17:113–32, 1991
  52. Amador XF, Strauss DH, Yale SA, *et al*: Assessment of insight in psychosis. *Am J Psychiatry* 150:873–9, 1993
  53. Nuechterlein KH, Snyder KS, Dawson ME, *et al*: Expressed emotion, fixed-dose fluphenazine decanoate maintenance, and relapse in recent-onset schizophrenia. *Psychopharmacol Bull* 22:633–9, 1986
  54. Ruscher SM, De Wit R, Mazmanian D: Psychiatric patients' attitudes about medication and factors affecting noncompliance. *Psychiatr Serv* 48:82–5, 1997
  55. Drake RE, Osher FC, Wallach MA: Alcohol use and abuse in schizophrenia: a prospective community study. *J Nerv Ment Dis* 177:408–14, 1989
  56. Pristach CA, Smith CM: Medication compliance and substance abuse among schizophrenic patients. *Hosp Community Psychiatry* 41:1345–50, 1990
  57. Weiden PJ, Mann JJ, Dixon L, *et al*: Is neuroleptic dysphoria a healthy response? *Compr Psychiatry* 30:546–52, 1989
  58. Awad AG: Subjective response to neuroleptics in schizophrenia. *Schizophr Bull* 19:609–18, 1993
  59. Weiden P, Rapkin B, Mott T, *et al*: Rating of medication influences (ROMI) scale in schizophrenia. *Schizophr Bull* 20:297–310, 1994
  60. Stephenson BJ, Rowe BH, Haynes RB, *et al*: Is this patient taking the treatment as prescribed? *JAMA* 269:2779–81, 1993
  61. Eisen SA, Hanpeter JA, Kreuger LW, *et al*: Monitoring medication compliance: description of a new device. *J Compliance Health Care* 2:131–42, 1987
  62. Bond WS, Hussar DA: Detection methods and strategies for improving medication compliance. *Am J Hosp Pharm* 48:1978–88, 1991
  63. Preskorn SH, Burke MJ, Fast GA: Therapeutic drug monitoring. *Psychiatr Clin North Am* 16:611–41, 1993
  64. Markowitz JS, Morton WA, Gaulin BD: Antipsychotic blood concentrations: nonstandardization of reference ranges. *J Clin Psychopharmacol* 17:121–4, 1997
  65. Mazure CM, Nelson JC, Jatlow PI, *et al*: The relationship between blood perphenazine levels, early resolution of psychotic symptoms, and side effects. *J Clin Psychiatry* 51:330–4, 1990
  66. Pandurangi AK, Narasimhachari N, Blackard WG, *et al*: Relation of serum molindone levels to serum prolactin levels and antipsychotic response. *J Clin Psychiatry* 50:379–81, 1988
  67. Koren AR, Lieberman J, Alvir J, *et al*: Relation of plasma fluphenazine levels to treatment response and extrapyramidal side effects in first-episode schizophrenic patients. *Am J Psychiatry* 151:35–9, 1994
  68. Janicak PG, Javaid JI, Sharma RP, *et al*: Trifluoperazine plasma levels and clinical response. *J Clin Psychopharmacol* 9:340–6, 1989
  69. Van Putten T, Marder SR, Mintz J, *et al*: Haloperidol plasma levels and clinical response: a therapeutic window relationship. *Am J Psychiatry* 149:500–5, 1992
  70. Palao DJ, Arauxo A, Brunet M, *et al*: Haloperidol: therapeutic window in schizophrenia. *J Clin Psychopharmacol* 14:303–10, 1994
  71. Volavka J, Cooper TB, Czobor P, *et al*: Plasma haloperidol levels and clinical effects

- in schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 52:837-45, 1995
72. Dysken MW, Johnson SB, Holden L, *et al*: Haloperidol and reduced haloperidol in saliva and blood. *J Clin Psychopharmacol* 12: 186-90, 1992
  73. Shalev A, Hermesh H, Munitz H, *et al*: Chlorprothixene-induced hypouricemia: a biologic indicator of drug compliance. *J Clin Psychiatry* 50:424-7, 1989
  74. Kelly G, Mamon JA, Scott JE: Utility of the health belief model in examining medication compliance among psychiatric outpatients. *Soc Sci Med* 25:1205-11, 1987
  75. Budd RJ, Hughes ICT, Smith JA: Health beliefs and compliance with antipsychotic medication. *Br J Clin Psychol* 35:393-7, 1996
  76. Nevins DB: Psychoanalytic perspectives on the use of medication for mental illness. *Bull Menninger Clin* 54:323-39, 1990
  77. Blaska B: The myriad medication mistakes in psychiatry: a consumer's view. *Hosp Community Psychiatry* 41:993-8, 1990
  78. Hansen TE, Casey DE, Hoffman WF: Neuroleptic intolerance. *Schizophr Bull* 23:567-82, 1997
  79. Sachdev P, Kruk J: Clinical characteristics and predisposing factors in acute drug-induced akathisia. *Arch Gen Psychiatry* 51: 963-74, 1994
  80. Lipinski JF, Keck PE, McElroy S:  $\beta$ -adrenergic antagonists in psychosis: is improvement due to treatment of neuroleptic-induced akathisia? *J Clin Psychopharmacol* 8:409-16, 1988
  81. Sachdev P: The epidemiology of drug-induced akathisia: Part I. Acute akathisia. *Schizophr Bull* 21:431-49, 1995
  82. Barnes TRE: A rating scale for drug-induced akathisia. *Br J Psychiatry* 154:672-6, 1989
  83. Rapoport A, Stein D, Grinshpoon A, *et al*: Akathisia and pseudoakathisia: clinical observations and accelerometric recordings. *J Clin Psychiatry* 55:473-7, 1994
  84. Dupuis B, Cateau J, Dumon J-P, *et al*: Comparison of propranolol, sotalol, and betaxolol in the treatment of neuroleptic-induced akathisia. *Am J Psychiatry* 144:802-5, 1987
  85. Kim A, Adler L, Angrist B, *et al*: Efficacy of low-dose metoprolol in neuroleptic-induced akathisia. *J Clin Psychopharmacol* 9:294-6, 1989
  86. Kutcher S, Williamson P, MacKenzie S: Successful clonazepam treatment of neuroleptic-induced akathisia in older adolescents and young adults: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 9:403-6, 1989
  87. Fleischhacker WW, Roth SD, Kane JM: The pharmacologic treatment of neuroleptic-induced akathisia. *J Clin Psychopharmacol* 10: 12-21, 1990
  88. Sachdev P: The epidemiology of drug-induced akathisia: Part II. Chronic, tardive and withdrawal akathisias. *Schizophr Bull* 21: 451-61, 1995
  89. Correa N, Opler LA, Kay SR, *et al*: Amantadine in the treatment of neuroendocrine side effects of neuroleptics. *J Clin Psychopharmacol* 7:91-5, 1987
  90. Thompson JW, Ware MR, Blashfield RK: Psychotropic medication and priapism: a comprehensive review. *J Clin Psychiatry* 51: 430-3, 1990
  91. Uehlinger C, Baumann P: Clozapine as an alternative treatment for neuroleptic-induced gynecomastia. *Am J Psychiatry* 148:392-3, 1991
  92. Perovich RM, Lieberman JA, Fleischhacker WW, *et al*: The behavioral toxicity of bromocriptine in patients with psychiatric illness. *J Clin Psychopharmacol* 9:417-22, 1989
  93. Silverstone T, Smith G, Goodall E: Prevalence of obesity in patients receiving depot antipsychotics. *Br J Psychiatry* 153:214-7, 1988
  94. Stanton JM: Weight gain associated with neuroleptic medication: a review. *Schizophr Bull* 21:463-72, 1995
  95. Owen RR, Cole JO: Molindone hydrochloride: a review of laboratory and clinical findings. *J Clin Psychopharmacol* 9:268-76, 1989
  96. Dufresne RL, Valentino D, Kass DJ: Thioridazine improves affective symptoms in schizophrenic patients. *Psychopharmacol Bull* 29:249-55, 1993
  97. Chaturvedi SK: Metoprolol in the treatment of neuroleptic-induced tremor: case report. *J Clin Psychiatry* 48:378, 1987
  98. Goumentouk AD, Hurwitz TA, Zis AP: Primidone in drug-induced tremor. *J Clin Psychopharmacol* 9:451, 1989
  99. Singh H, Levinson DF, Simpson GM, *et al*: Acute dystonia during fixed-dose neuroleptic treatment. *J Clin Psychopharmacol* 10: 389-96, 1990
  100. Wojcik JD, Falk WE, Fink JS, *et al*: A review of 32 cases of tardive dystonia. *Am J Psychiatry* 148:1055-9, 1991
  101. Goff DC, Arana GW, Greenblatt DJ, *et al*: The effect of benzotropine on haloperidol-

## Medication Adherence Failure

- induced dystonia, clinical efficacy and pharmacokinetics: a prospective, double-blind trial. *J Clin Psychopharmacol* 11:106–12, 1991
102. de Leon J, Canuso C, White AO, *et al*: A pilot effort to determine bentspines equivalents of anticholinergic medications. *Hosp Community Psychiatry* 45:606–7, 1994
  103. Suzuki E, Kanba S, Nibuya M, *et al*: Use of pimozide in the Pisa syndrome. *Am J Psychiatry* 149:1114–5, 1992
  104. Gardos G, Cole JO: A forgotten antipsychotic. *Hosp Community Psychiatry* 41:1261–2, 1990
  105. Lake CR, Casey DE, McEvoy JP, *et al*: Anticholinergic prophylaxis in young adults treated with neuroleptic drugs. *Psychopharmacol Bull* 22:981–4, 1986
  106. Frances A, Weiden P: Promoting compliance with outpatient drug treatment. *Hosp Community Psychiatry* 38:1158–60, 1987
  107. Keepers G, Casey DE: Prediction of neuroleptic-induced dystonia. *J Clin Psychopharmacol* 7:342–5, 1987
  108. Kane JM, Marder SR: Psychopharmacologic treatment of schizophrenia. *Schizophr Bull* 19:287–302, 1993
  109. Faraone SV, Cirelli V, Curran JP, *et al*: Neuroleptic dose reduction for schizophrenic outpatients: a three-year follow-up study. *Hosp Community Psychiatry* 39:1207–8, 1988
  110. Scottish Schizophrenia Research Group: The Scottish first episode schizophrenia study: V. One-year follow-up. *Br J Psychiatry* 152:470–6, 1988
  111. Lieberman JA, Kane JM, Sarantakos S, *et al*: Prediction of relapse in schizophrenia. *Arch Gen Psychiatry* 44:597–603, 1987
  112. van Kammen DP, Agren H, Yao JK, *et al*: Noradrenergic activity and prediction of psychotic relapse following haloperidol withdrawal in schizophrenia. *Am J Psychiatry* 151:379–84, 1994
  113. Fenton WS, McGlashan TH: Sustained remission in drug-free schizophrenic patients. *Am J Psychiatry* 144:1306–9, 1987
  114. Buchanan RW, Kirkpatrick B, Summerfelt A: Clinical predictors of relapse following neuroleptic withdrawal. *Biol Psychiatry* 32:72–8, 1992
  115. Bitter I, Volavka J, Scheurer J: The concept of the neuroleptic threshold: an update. *J Clin Psychopharmacol* 11:28–33, 1991
  116. Brotman AW, McCormick S: A role for high-dose antipsychotics. *J Clin Psychiatry* 51:164–6, 1990
  117. Thompson C: The use of high-dose antipsychotic medication. *Br J Psychiatry* 164:448–58, 1994
  118. Marder SR, Van Putten T, Mintz J, *et al*: Costs and benefits of two doses of fluphenazine. *Arch Gen Psychiatry* 41:1025–9, 1984
  119. Marder SR, Van Putten T, Mintz J, *et al*: Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. *Arch Gen Psychiatry* 44:518–21, 1987
  120. Gilbert PL, Harris MJ, McAdams LA, *et al*: Neuroleptic withdrawal in schizophrenic patients: a review of the literature. *Arch Gen Psychiatry* 52:173–88, 1995
  121. Viguera AC, Baldessarini RJ, Hegarty JD, *et al*: Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. *Arch Gen Psychiatry* 54:49–55, 1997
  122. Marder SR, Wirshing WC, Van Putten T, *et al*: Fluphenazine vs placebo supplementation for prodromal signs of relapse in schizophrenia. *Arch Gen Psychiatry* 51:280–7, 1994
  123. Carpenter WT, Hanlon TE, Heinrichs DW: Continuous versus targeted medication in schizophrenic outpatients: outcome results. *Am J Psychiatry* 147:1138–48, 1990
  124. Youssef HA: A five-year study of chronic schizophrenics and other psychotics treated in the community: depot haloperidol decanoate versus other neuroleptics. *Adv Ther* 6:186–95, 1989
  125. Glazer WM, Kane JM: Depot neuroleptic therapy: an underutilized treatment option. *J Clin Psychiatry* 53:426–33, 1992
  126. Hale T: Will the new antipsychotics improve the treatment of schizophrenia? *Br Med J* 307:749–50, 1993
  127. Simpson GM, Yadalam KG, Levinson DF, *et al*: Single-dose pharmacokinetics of fluphenazine after fluphenazine decanoate administration. *J Clin Psychopharmacol* 10:417–21, 1990
  128. Ereshefsky L, Toney G, Saklad SR, *et al*: A loading-dose strategy for converting from oral to depot haloperidol. *Hosp Community Psychiatry* 44:1155–61, 1993
  129. Wei F-C, Jann MW, Lin H-N, *et al*: A practical loading dose method for converting schizophrenic patients from oral to depot haloperidol therapy. *J Clin Psychiatry* 57:298–302, 1996
  130. Marder SR, Hubbard JW, Van Putten T, *et al*: Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications. *Psychopharmacology* 98:433–9, 1989
  131. Inderbitzin LB, Lewine RRR, Scheller-



- Gilkey G, *et al*: A double-blind dose-reduction trial of fluphenazine for chronic unstable schizophrenic patients. *Am J Psychiatry* 151: 1753-9, 1994
132. Yadalam KG, Simpson GM: Changing from oral to depot fluphenazine. *J Clin Psychiatry* 49:346-8, 1988
  133. Hamann GL, Egan TM, Wells BG, *et al*: Injection site reactions after intramuscular administration of haloperidol decanoate 100 mg/ml. *J Clin Psychiatry* 51:502-4, 1990
  134. Goldney RD, Spence ND: Safety of the combination of lithium and neuroleptic drugs. *Am J Psychiatry* 143:882-4, 1986
  135. Wassef A, Watson DJ, Morrison P, *et al*: Neuroleptic-valproic acid combination in treatment of psychotic symptoms: a three-case report. *J Clin Psychopharmacol* 9:45-8, 1989
  136. Gracia RI, Gutierrez JM, Faraone SV, *et al*: Use of lorazepam for increased anxiety after neuroleptic dose reduction. *Hosp Community Psychiatry* 41:197-8, 1990
  137. Douyon R, Angrist B, Peselow E, *et al*: Neuroleptic augmentation with alprazolam: clinical effects and pharmacokinetic correlates. *Am J Psychiatry* 146:231-4, 1989
  138. Maas JW, Miller AL, Tekell JL, *et al*: Clonidine plus haloperidol in the treatment of schizophrenia/psychosis. *J Clin Psychopharmacol* 15:361-4, 1995
  139. Litman RE, Hong WW, Weissman EM, *et al*: Idazoxan, an  $\alpha_2$  antagonist, augments fluphenazine in schizophrenic patients: a pilot study. *J Clin Psychopharmacol* 13:264-7, 1993
  140. Goff DC, Brotman AW, Waites M, *et al*: Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. *Am J Psychiatry* 147:492-4, 1990
  141. Goff DC, Midha KK, Brotman AW, *et al*: An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* 11:193-7, 1991
  142. Goff DC, Tsai G, Manoach DS, *et al*: Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. *Am J Psychiatry* 152:1213-5, 1995
  143. Kane J, Honigfeld G, Singer J, *et al*: Clozapine for the treatment-resistant schizophrenic. *Arch Gen Psychiatry* 45:789-96, 1988
  144. Maier GJ: The impact of clozapine on 25 forensic patients. *Bull Am Acad Psychiatry Law* 20:297-307, 1992
  145. Buckley PF, Ibrahim ZY, Singer B, *et al*: Aggression and schizophrenia: efficacy of risperidone. *J Am Acad Psychiatry Law* 25: 173-81, 1997
  146. Beck NC, Greenfield SR, Gotham H, *et al*: Risperidone in the management of violent, treatment-resistant schizophrenics hospitalized in a maximum security forensic facility. *J Am Acad Psychiatry Law* 25:461-8, 1997
  147. Tollefson GD, Beasley CM, Tran PV, *et al*: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 154:457-65, 1997
  148. Arvanitis LA, Miller BG, Borison RL, *et al*: Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 42:233-46, 1997
  149. Conley RR, Buchanan RW: Evaluation of treatment-resistant schizophrenia. *Schizophr Bull* 23:663-74, 1997
  150. Steingard S, Allen M, Schooler NR: A study of the pharmacologic treatment of medication-compliant schizophrenics who relapse. *J Clin Psychiatry* 55:470-2, 1994
  151. Weiden PJ, Olfson M: Cost of relapse in schizophrenia. *Schizophr Bull* 21:419-29, 1995
  152. Krakowski MI, Kunz M, Czobor P, *et al*: Long-term high-dose neuroleptic treatment: who gets it and why? *Hosp Community Psychiatry* 44:640-4, 1993
  153. Geller JL: In again, out again: preliminary evaluation of a state hospital's worst recidivists. *Hosp Community Psychiatry* 37:386-90, 1986
  154. Bartkó G, Mayláth E, Herczeg I: Comparative study of schizophrenic patients relapsed on and off medication. *Psychiatry Res* 22: 221-7, 1987
  155. Kinon BJ, Kane JM, Chakos M, *et al*: Possible predictors of neuroleptic-resistant schizophrenic relapse: influence of negative symptoms and acute extrapyramidal side effects. *Psychopharmacol Bull* 29:365-9, 1993
  156. Schnur DB, Friedman S, Dorman M, *et al*: Assessing the family environment of schizophrenic patients with multiple hospital admissions. *Hosp Community Psychiatry* 37: 249-52, 1986
  157. Postrado LT, Lehman AF: Quality of life and clinical predictors of rehospitalization of persons with severe mental illness. *Psychiatr Serv* 46:1161-5, 1995
  158. Goodpastor WA, Hare BK: Factors associated with multiple readmissions to an urban

## Medication Adherence Failure

- public psychiatric hospital. *Hosp Community Psychiatry* 42:85-7, 1991
159. Dencker SJ, Maim U, Lepp M: Schizophrenic relapse after drug withdrawal is predictable. *Acta Psychiatr Scand* 73:181-5, 1986
  160. Dorevitch A, Aronzon R, Zilberman L: Medication maintenance of chronic schizophrenic out-patients by a psychiatric clinical pharmacist: 10-year follow-up study. *J Clin Pharm Ther* 18:183-6, 1993
  161. Yung AR, McGorry PD: The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull* 22:353-70, 1996
  162. Herz MI, Lambert J: Prodromal symptoms and relapse prevention in schizophrenia. *Schizophr Bull* 21:541-51, 1995
  163. Glovinsky D, Kirch DG, Wyatt RJ: Early antipsychotic response to resumption of neuroleptics in drug-free chronic schizophrenic patients. *Biol Psychiatry* 31:968-70, 1992
  164. Falloon IRH, Kydd RK, Coverdale JH, *et al*: Early detection and intervention for initial episodes of schizophrenia. *Schizophr Bull* 22:271-82, 1996
  165. Herz MI, Simon JC: Prodromal signs of schizophrenic relapse. *Am J Psychiatry* 143:115-6, 1986
  166. McCandless-Glimcher L, McKnight S, Hamera E, *et al*: Use of symptoms by schizophrenics to monitor and regulate their illness. *Hosp Community Psychiatry* 37:929-33, 1986
  167. Norman RMG, Malla AK: Prodromal symptoms of relapse in schizophrenia: a review. *Schizophr Bull* 21:527-39, 1995
  168. Marder SR, Mintz J, Van Putten T, *et al*: Early prediction of relapse in schizophrenia: an application of receiver operating characteristic (ROC) methods. *Psychopharmacol Bull* 27:79-82, 1991
  169. Cohen K, Edstrom K, Smith-Papke L: Identifying early dropouts from a rehabilitation program for psychiatric outpatients. *Psychiatr Serv* 46:1076-8, 1995
  170. Ruskin PE, Nyman G: Discontinuation of neuroleptic medication in older, outpatient schizophrenics. *J Nerv Ment Dis* 179:212-4, 1991
  171. Birchwood M, Smith J, MacMillan F, *et al*: Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. *Psychol Med* 19:649-56, 1989
  172. Subotnik KL, Nuechterlein KH: Prodromal signs and symptoms of schizophrenic relapse. *J Abnorm Psychol* 97:405-12, 1988
  173. van Kammen DP, Kelley ME, Gurklis JA, *et al*: Behavioral vs biochemical prediction of clinical stability following haloperidol withdrawal in schizophrenia. *Arch Gen Psychiatry* 52:673-78, 1995
  174. Glazer WH, Bowers MB, Charney DS, *et al*: The effect of neuroleptic discontinuation on psychopathology, involuntary movements, and biochemical measures in patients with persistent tardive dyskinesia. *Biol Psychiatry* 26:224-33, 1989
  175. Brown DL, Felthous AR, Barratt ES, *et al*: The incompetent defendant: support systems help avoid future legal problems. *J Forensic Sci* 39:1057-68, 1994
  176. Solomon P, Draine J, Meyerson A: Jail recidivism and receipt of community mental health services. *Hosp Community Psychiatry* 45:793-7, 1994
  177. Herinckx HA, Kinney RF, Clarke GN, *et al*: Assertive community treatment versus usual care in engaging and retaining clients with severe mental illness. *Psychiatr Serv* 48:1297-1306, 1997
  178. Heilbrun K, Lawson K, Spier S, *et al*: Community placement for insanity acquittees: a preliminary study of residential programs and person-situation fit. *Bull Am Acad Psychiatry Law* 22:551-60, 1994
  179. Scott DC, Zonana HV, Getz MA: Monitoring insanity acquittees: Connecticut's psychiatric security review board. *Hosp Community Psychiatry* 41:980-4, 1990
  180. Bloom JD, Williams MH, Bigelow DA: Monitored conditional release of persons found not guilty by reason of insanity. *Am J Psychiatry* 148:444-8, 1991
  181. Lamb HR, Weinberger LE, Gross BH: Court-mandated community outpatient treatment for persons found not guilty by reason of insanity: a five-year follow-up. *Am J Psychiatry* 145:450-6, 1988
  182. Clary C, Dever A, Schweizer E: Psychiatric inpatients' knowledge of medication at hospital discharge. *Hosp Community Psychiatry* 43:140-4, 1992
  183. Brown CS, Wright RG, Christensen DB: Association between type of medication instruction and patients' knowledge, side effects, and compliance. *Hosp Community Psychiatry* 38:55-60, 1987
  184. Macpherson R, Jerrom B, Hughes A: A controlled study of education about drug treatment in schizophrenia. *Br J Psychiatry* 168:709-17, 1996

185. DeProspero T, Riffle WA: Improving patients' drug compliance. *Psychiatr Serv* 48:1468, 1997
186. Lecompte D, Pelc I: A cognitive-behavioral program to improve compliance with medication in patients with schizophrenia. *Int J Ment Health* 25:51-6, 1996
187. Guimón J: The use of group programs to improve medication compliance in patients with chronic diseases. *Patient Educ Counseling* 26:189-93, 1995
188. Nigam R, Schottenfeld R, Kosten TR: Treatment of dual diagnosis patients: a relapse prevention group approach. *J Subst Abuse Treat* 9:305-9, 1992
189. Mari JdJ, Streiner DL: An overview of family interventions and relapse on schizophrenia: meta-analysis of research findings. *Psychol Med* 24:565-78, 1994
190. McFarlane WR, Lukens E, Link B, *et al*: Multiple-family groups and psychoeducation in the treatment of schizophrenia. *Arch Gen Psychiatry* 52:679-87, 1995
191. Penn DL, Mueser KT: Research update on the psychosocial treatment of schizophrenia. *Am J Psychiatry* 153:607-17, 1996
192. Glazer WM: Psychotic relapse: a multisystems perspective. *J Clin Psychiatry* 54(Suppl 3):3-4, 1993
193. Haynes RB, McKibbin KA, Kanani R: Systematic review of randomized trials of interventions to assist patients to follow prescriptions for medications. *Lancet* 348:383-6, 1996
194. McGlashan TH: A selective review of recent North American long-term followup studies of schizophrenia. *Schizophr Bull* 14:515-42, 1988
195. Arndt S, Andreasen NC, Flaum M, *et al*: A longitudinal study of symptom dimensions in schizophrenia. *Arch Gen Psychiatry* 52:352-60, 1995