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Predicting Duration of Clinical Stability Following Haloperidol Withdrawal in Schizophrenic Patients

Daniel P. van Kammen, Mary E. Kelley, John A. Gurklis, Mark W. Gilbertson, Jeffrey K. Yao, Ruth Condray, and Jeffrey L. Peters

Although chronic maintenance antipsychotic drug treatment is the most effective way of preventing relapse in schizophrenic patients, it is not very successful. A considerable number of patients relapse on medication, and many others do not take their medications as prescribed after leaving the hospital. Unfortunately, clinicians are not able to identify how long patients will remain clinically stable after drug discontinuation. To develop a model consisting of behavioral and monoaminergic variables to identify the risk of symptom exacerbation, we obtained in the week prior to haloperidol discontinuation global behavioral ratings and cerebrospinal fluid (CSF) values for monoamine metabolites in a sample of 109 DSM-III-R schizophrenic patients. Patients were followed until specific criteria for increases in psychosis were met for up to 1 year and then returned to antipsychotic drug treatment. Cox regression analysis identified predictors of the survival function, or the probability of relapse at a given time drug free. The best model indicated that increased psychosis, decreased anxiety, an increased CSF homovanillic acid (HVA) to 5-hydroxyindoleacetic acid (5-HIAA) ratio, and decreased CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) prior to haloperidol withdrawal were associated with early increases in psychosis. Our study indicates that it is possible to identify those patients who are more likely to remain clinically stable without medication. When the model is validated, it will help clinicians assess the relapse risk over time, lower doses in treatment-resistant patients, and possibly determine the optimal time for aftercare visits following hospital discharge. ***[Neuropsychopharmacology 14:275–283, 1996]***

KEY WORDS: *Schizophrenia; Relapse prediction; Dopamine; Serotonin; Norepinephrine; CSF*

Schizophrenia is a chronic but episodic illness (Meyer 1922; Bleuler 1978; Strauss et al. 1985) that challenges clinicians and patients when they try to prevent episodic psychotic exacerbations. The risk of relapse is affected by medication status, dose of antipsychotic drug, increased stress or life events (Ventura et al. 1992), and changes in the internal biochemical milieu (van Kammen 1991). Many groups have shown that antipsychotics decrease relapse rates by 40% (Davis 1975; Kane 1987), but do not eliminate relapses completely (Kane et al. 1983; Kane and Lieberman 1987; Marder et al. 1987; Hogarty et al. 1991). Such studies have also shown that many drug-free patients can remain clinically stable for some time (Lieberman et al. 1994). Our previous studies identifying relapse risk established that behavioral and biochemical variables could be used as prodromes, identifying those patients likely to relapse or to remain stable 6 weeks after haloperidol withdrawal (van Kammen et al. 1989, 1994, 1995). However, those studies did not provide us with an idea of when these patients would relapse following haloperidol discontinuation.

From the Veterans Affairs Medical Center (DPvK, MEK, JAG, MWG, JKY, RC, JLP), Pittsburgh, PA; and Western Psychiatric Institute and Clinic (DPvK, JAG, MWG, JKY, RC, JLP), University of Pittsburgh, School of Medicine, Pittsburgh, PA.

Address correspondence to Dr. van Kammen, Professor of Psychiatry, Chief of Staff, VAMC, 7180 Highland Drive, Pittsburgh, PA 15206.

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The clinician's inability to identify when clinically stable patients enter a prerelapse state has led to the recommendations of continued neuroleptic treatment for up to 1 year following the first, up to 5 years after the second, and indefinitely after the third episode (Kissling 1991). Many patients refuse, however, to take medications as prescribed (Buchanan 1992; Weiden et al. 1991, 1994). Antipsychotic drugs have unpleasant side effects (e.g., akinesia, akathisia) that interfere with quality of life and social functioning (Kane et al. 1983; Cohen et al. 1989; Marder et al. 1987). Tardive dyskinesia has an incidence of 5% per year of neuroleptic exposure (Kane et al. 1985). Antipsychotic drug treatment decreases but does not eliminate the relapse risk because of stress responsiveness (Ventura et al. 1992; Schooler 1993). Some clinically stable patients function better when drug free (Marder et al. 1979; Cohen et al. 1989). Unfortunately, prodromal behaviors can only be identified retrospectively (Docherty et al. 1978; Szymanski et al. 1983) and do not exhibit prospective specificity or sensitivity (Johnson et al. 1983; Nuechterlein and Dawson 1984; Dencker et al. 1986; Buchanan et al. 1992). Fifty percent of patients relapse without clinical warning signs, by denying or not sharing with their therapists the emerging psychotic symptoms (Jolley et al. 1989; Carpenter et al. 1990; Hirsch et al. 1990; Herz et al. 1991; Gaebel et al. 1993). To be able to identify *how long* patients are likely to remain clinically stable is highly important in the treatment of the many patients who stop taking medication as soon as they leave the hospital.

Knowing the relapse risk of a given patient at discharge, outpatient visits or brief respite hospitalizations for stress reduction (van Kammen et al. 1993) can be scheduled in a timely manner and severe relapses may be prevented. Intermittent antipsychotic drug treatment may become feasible (Carpenter et al. 1990; Hirsch et al. 1990; Herz et al. 1991; Gaebel et al. 1994). Dose reductions in patients with incomplete responses but with unpleasant side effects (Kane et al. 1985; Marder et al. 1987) can be accomplished safely without increasing the risk of relapse. It will help in deciding whether fluctuations in symptomatology are real prodromes of relapse or inconsequential to the course. Furthermore, in periods of low relapse risk with or without drug treatment, rehabilitation efforts can be more successful (Hogarty et al. 1991). In the present article we assess potential markers prior to haloperidol withdrawal [e.g., behavioral measures and CSF monoamine metabolites (van Kammen et al. 1989, 1994, 1995)] to predict the probability of symptom exacerbation at any given time drug free. Based on our studies indicating that altered CSF measures of monoaminergic turnover precede psychotic symptom exacerbation, we hypothesized that increased catecholamine and decreased serotonin activity would identify the time to relapse. This builds on our previous finding of predictors of relapse *status* in that it provides a more realistic approach to the prediction of relapse, (i.e., that nonrelapsers are not a separate diagnostic subgroup, but will also become re-lapsers if followed long enough).

SAMPLE AND METHODS

Sample

The current sample consisted of 109 physically healthy male psychiatric patients with a diagnosis of chronic schizophrenia [DSM-III-R; APA 1987]. The patients were on antipsychotic maintenance treatment and participated in the study following admission to the Schizophrenia Research Unit at the Department of Veterans Affairs Medical Center in Pittsburgh. All lived in the community before admission to the hospital and gave written informed consent that was approved and monitored by the Institutional Review board. Clinical and demographic information on the present sample is provided in Table 1. Ninety-nine of the subjects were caucasian and 10 were African American, which reflects the community composition. All subjects were screened with a complete physical, neurological, and psychiatric evaluation conducted by board-certified psychiatrists. Trained staff obtained the diagnostic data from a structured interview using the Schedule for Affective Disorders and Schizophrenia-Lifetime version [SADS-L; Spitzer and Endicott 1979] and a DSM-III-R checklist. Patients who met DSM-III-R criteria for current alcohol or substance abuse or dependence were excluded at the time of the study but were included if they had been in remission for at least 6 months. Diagnostic, clinical, and demographic data, as well as the ability to understand the risks involved, were examined at a consensus conference. Patients with high risk of suicide or violent behavior associated with relapse were excluded. All subjects were put on a low-monoamine and caffeine- and alcohol-free diet on admission, and their medication was converted to haloperidol for at least 3 months if they were not already being treated with it. Following this, they were switched to haloperidol in unmarked capsules for at least 2 weeks prior to testing. Medications were administered in a double-blind fashion because the haloperidol was withdrawn between 1 and 7 days following the last procedure. If benztropine mesylate (1 to 4 mg/day) was given, this was discontinued at least 2 weeks prior to the lumbar puncture (LP). No other medications were given. Identical-looking placebo capsules replaced the haloperidol capsules overnight within 6 ± 4 days (range 0–16) of the LP. The drug-free period was a maximum of 6 weeks for the majority of patients, and some were followed for up to 1 year. Most patients remained in the hospital for the duration of the study. After completion of the study patients were returned to their clinical treatment regimens.

Table 1. Demographics (N = 109)

	Mean (SD)	Range
Age (years)	36.7 (8.1)	20–63
Age of onset (years)	23.3 (5.1)	13–35
Duration of illness (years)	13.4 (7.1)	0.5–30
Haloperidol dose (mg/day)	10.9 (7.3)	1–40
Weight (kg)	82.9 (16.2)	56.3–134
Height (cm)	174.5 (11.2)	85–196
CSF (pmol/ml)		
HVA	175.2 (94.8)	36–608
NE	0.65 (0.49)	0.02–2.9
MHPG	42.6 (16.8)	10–104.2
5-HIAA	92.6 (41.4)	24–247
Behavior (Bunney-Hamburg)		
Anxiety	5.0 (1.8)	1–9
Psychosis	5.6 (1.9)	2–10
Premorbid functioning	2.4 (1.1)	0.3–4.6

Age of onset = age of first psychotic symptoms; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol; 5-HIAA = 5-hydroxyindolacetic acid; NE = norepinephrine; Premorbid functioning = average of childhood, early and late adolescence subscales, 0–6 scale, Cannon-Spoor et al. 1982.

Behavioral Assessments

Patients were rated daily on a global psychosis scale (Bunney and Hamburg 1963) by the well-trained nursing staff who were blind to the medication status. In addition, other protocols that were going on at the same time kept the focus off the medication status for a given patient. The 15-point psychosis item of this scale is subdivided into 5 consecutive levels of intensity involving 3 points at each level. Relapse was considered to have taken place when an increase in 3 points in global psychosis ratings compared with the mean of those psychosis ratings of the last 7 days of haloperidol treatment determined by the nursing staff was sustained for at least 3 days. In addition, the increase was to a rating of 6 or higher, which ensured a clear presence of psychotic symptoms. These criteria have been previously validated (van Kammen et al. 1989, 1994). Of the 109 subjects, 74 were followed until relapse criteria were met. The remaining 35 patients were considered to be lost to follow-up and had not met relapse criteria by their last known day drug free; this ranged from 6 to 52 weeks.

The therapists, who were blind to medication status, independently rated patients weekly on the Bunney-Hamburg global scale for psychosis, mania, depression, and anxiety. Weekly meetings were conducted to ensure interrater reliability at greater than 85% for all behavioral measures. Only the ratings of the last week of haloperidol treatment were used in the model. The social worker obtained the premorbid functioning data (Cannon-Spoor et al. 1982) with assistance from the patient, his relatives, and previous charts.

Procedures

Lumbar Punctures. Lumbar punctures were obtained during the last week of haloperidol treatment, with the patient in the lateral decubitus position between 7:30 and 8:30 A.M. after overnight fasting and bed rest as previously described (van Kammen and Sternberg 1980). Cerebrospinal fluid (CSF) was collected on ice; 12 ml were well mixed and divided in 0.5- and 1-ml aliquots; the CSF was then stored at −80°C until assayed. The CSF measures included CSF homovanillic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA), norepinephrine (NE), and 3-methoxy-4-hydroxyphenylglycol (MHPG).

Assays for CSF HVA, MHPG, and 5-HIAA. We utilized the procedure of Scheinin et al. (1983) for the simultaneous determination of CSF MHPG, 5-HIAA, and HVA. The within-run coefficient of variation for MHPG was 6.33% at a concentration of 41 pmol/ml; 3.21% at a concentration of 64 pmol/ml for 5-HIAA and 3.32% for HVA, at a concentration of 147 pmol/ml. Between-run coefficients of variation for MHPG were 7.41% at a concentration of 41 pmol/ml; 6.81% for 5-HIAA at a concentration of 64 pmol/ml; and 4.41% for HVA at a concentration of 147 pmol/ml.

Assay for CSF NE. The procedure for the extraction of NE from CSF and plasma was a modified method of Lin et al. (1984). This method produced excellent within-run and between-run coefficients of variation for NE of

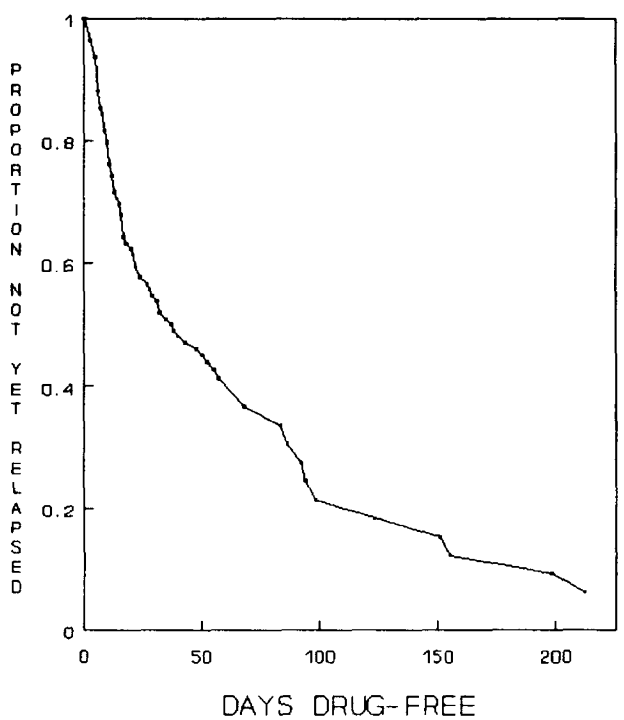

Figure 1. Kaplan-Meier survival curve of time to relapse (N = 109).

2.15% and 2.86%, respectively, at a concentration of 5.60 pmol/ml.

Statistical Analysis

The Kaplan-Meier product limit method (Kaplan and Meier 1958) was used to obtain a survival curve for time to relapse following haloperidol withdrawal. The survival curve is a plot of the time to relapse with the proportion of patients who have not yet relapsed at that time. In this adaptation of survival analysis, the "event" is relapse, and those who do not relapse are considered the censored group or "lost to follow-up." Thus, the curve plots specific points only for those who relapse (Figure 1), and the nonrelapsers contribute only to the "proportion of patients not yet relapsed" until they leave the study (i.e., the denominator of the proportion). The majority of the censored observations occur at 6 weeks, our original drug-free protocol length. In this relapse risk model, the dependent "variable" is the survival curve, which is defined by the parameters days drug free and the probability of relapse.

A Cox regression analysis (Cox 1972; Greenhouse et al. 1987) was used to determine which of our biochemical or behavioral variables were significant predictors of time to relapse. For model building we used CSF catecholamines, specifically dopaminergic (HVA), serotonergic (5-HIAA), and noradrenergic measures (MHPG and NE). In addition, we used those behaviors that have been consistently found to predict relapse in our previous studies, specifically anxiety and psychosis levels.

RESULTS

Cox Regression

All variables were entered into the model to predict time to relapse. Because of the high correlation between CSF HVA and 5-HIAA ($r = 0.77$), we chose to avoid multicollinearity in the model by using the ratio of HVA to 5-HIAA, which has been used as a measure of the interaction between the dopamine (DA) and 5-HT systems (Hsiao et al. 1993). Brief changes in this ratio following haloperidol treatment have correlated significantly with changes in Brief Psychiatric Rating Scale scores (Kahn et al. 1993). The final model indicated that increased psychosis, an increased HVA to 5-HIAA ratio, decreased CSF MHPG, and anxiety were significantly associated with earlier relapse (Table 2). The increased HVA to 5-HIAA ratio would indicate that higher HVA and lower 5-HIAA were associated with earlier relapse.

Interpretation of Relative Risk

Relative risk (RR) calculated by the Cox model represents the risk of relapse at a given point in time (i.e., the time must be specified to use the model to predict the risk of relapse). Thus relative risks are a multiplier of the baseline probability of relapse at any given point in time, raising or lowering the corresponding baseline curve for each individual (demonstration of effect in Figure 2). Interpretation of relative risk for continuous variables is an extension of this idea. The relative risk associated with a continuous variable is that associated with each unit of measure. For example, if CSF MHPG is 43 pmol/ml, then the computed probability of psychotic worsening at a given time point (using the model relative risk of 0.98 (Table 2)) would be multiplied by $(0.98)^{43} = 0.42$. Thus a higher MHPG value decreases the probability of relapse at any time point (i.e., the subject will remain clinically stable longer). This explains why relative risks that are apparently close to the null hypothesis of 1 can be significant in the model. The relative risks for the behavioral measures are also calculated per unit (e.g., if the Bunney-Hamburg psychosis value is 7, then the probability of relapse at a certain point in time is multiplied by 1.24^7, or 4.51; see Table 2).

DISCUSSION

The final model indicated that relatively lower levels of psychosis, a lower CSF HVA to 5-HIAA ratio, and higher

Table 2. Cox Regression Model

		Wald		
Variable	β Coefficient	χ^2	p	Relative Risk
Psychosis (BH)	0.2112	6.845	0.0089	1.24
Anxiety (BH)	−0.1387	3.151	0.0759	0.87
CSF HVA/5-HIAA	0.4002	5.645	0.0175	1.49
MHPG	−0.0174	4.800	0.0285	0.98
NE	0.3982	2.669	0.1023	1.49

Model log likelihood, $\chi^2 = 16.71$, df = 5, $p = .005$,
BH = Bunney-Hamburg; HVA = homovanillic acid; 5-HIAA = 5-hydroxyindolacetic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol; NE = norepinephrine.

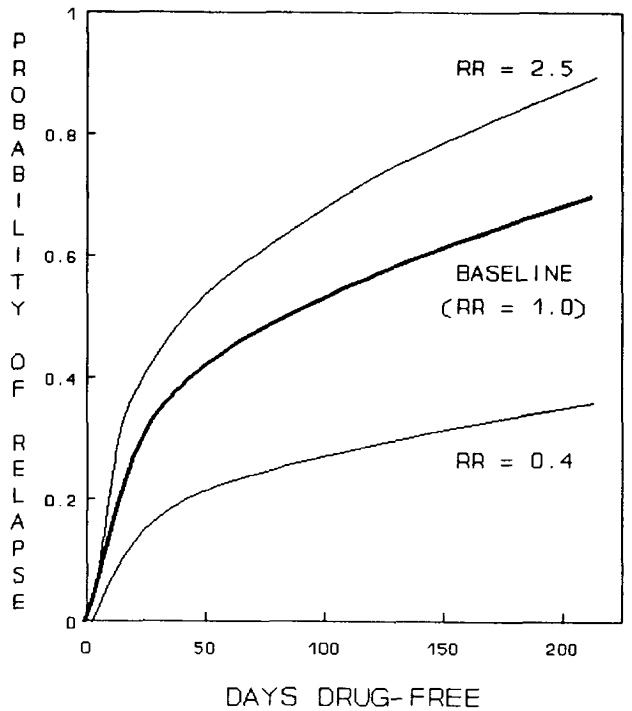

Figure 2. The effect of covariates on the probability of relapse (1 − survival). *RR* = relative risk. The covariates in the Cox regression are multipliers of the baseline risk (*RR* = 1 ; computed from the model) and thus either increase or decrease survival across all time points.

CSF MHPG and anxiety levels identified the male patients who remained clinically stable for a longer time after haloperidol withdrawal. Our data suggest that clinical stability is under control of all three monoaminergic systems, noradrenergic, serotonergic, and dopaminergic, when controlled for the two behavioral measures (psychosis and anxiety). Whether the anxiety rating represents a trait- or state-dependent measure is unknown.

Before discussing the implications for clinical practice, some methodological issues need to be addressed. Defining relapse criteria is a major problem in many studies of relapse in schizophrenia (Andrews et al. 1976; Falloon et al. 1983); Because there are several types of psychotic relapse, we decided to use a global behavioral scale of psychosis for our relapse criteria. We chose the sensitive Bunney-Hamburg (BH) 15-point global psychosis scale as rated *daily* by the nursing staff based on our experience with this scale (van Kammen et al. 1982). The present relapse rate appears higher than those reported in the literature (Hogarty et al. 1974; Davis 1975; Kane et al. 1983). In terms of clinical relevance we defined relapse with a predetermined moderate increase in psychosis rather than with the community practice of rehospitalization (e.g., dangerousness, severe decompensation). Such clinically defined relapse criteria may reflect more the severity of the patient's acute distress level, the dangerousness or suicidality, social inappropriateness, agitation of the patient and the tolerance of aberrant behavior of those close to the patient (Andrews et al. 1976) than actual recurrence or change in intensification of psychotic symptoms. In the beginning of the study we had an additional criterion for psychotic worsening defined by the BPRS psychosis subscale as used by Lieberman et al. (1987), which was less sensitive than the BH criteria.

The study only assessed relapse risk over time in male schizophrenic patients treated with a relatively specific D_2 receptor blocker (i.e., haloperidol) without the use of anticholinergics. Future studies need to determine whether the model would apply to other D_2 receptor blockers as well.

Increased Dopamine Turnover and Psychotic Worsening

The role of dopamine in relapse is not surprising. Amphetamine (Angrist et al. 1981; van Kammen et al. 1982), methylphenidate (Lieberman et al. 1994), l-DOPA (Davidson et al. 1987), and other indirect dopamine agonists have been reported to identify early relapsers. Indirect dopamine agonists also affect norepinephrine and serotonin release (Graham and Aghajanian 1971; Cheng and Long 1973; Groves et al., 1988). Levels of CSF HVA have been shown to correlate negatively with psychosis in drug-free patients, but not in haloperidol-treated patients (Beuger et al. in press). Lieberman et al. (1994) have shown in a similar drug withdrawal study that response to methylphenidate, which increases dopamine turnover, and tardive dyskinesia, presumably an indicator of increased dopamine activity, were associated with a greater risk of relapse. Although our data are consistent with their results, tardive dyskinesia was virtually absent in our sample.

Serotonin and Relapse Prevention

The association of a lower 5-HT turnover with earlier psychotic decompensation is intriguing. Low CSF 5-HIAA has been associated with increased aggression, violence (Åsberg et al. 1981; Brown et al. 1981; Linnoila et al. 1989), and violent suicide (Ninan et al. 1984). The relatively low levels could indicate increased risk of suicidality (Ninan et al. 1984; van Praag 1986), often seen within 6 months after hospitalization early in the illness. However, the reported relationship between relatively low CSF 5-HIAA values and decreased impulse control (Linnoila et al. 1989) may be more relevant for the association with earlier worsening in psychosis. The earlier relapse-prone patients may have been less able to control the thought intrusion and impulsiveness associated with psychotic exacerbation. Potentially, the decreased turnover may indicate increased 5-HT receptor activity in schizophrenia as well (Joyce 1993; Joyce et al.

1993) while patients with less 5-HT_2 receptor binding (Arora and Meltzer 1991; Mita et al. 1986; Laruelle et al. 1993) are more likely to remain clinically stable. Conceivably, blockade of 5-HT_2 receptors could lead to an upregulation of 5-HT_2 receptors or an increase of 5-HT turnover that stimulates other 5-HT receptors and decreases aggressiveness and poor impulse control. Haloperidol has a low 5-HT_2 receptor affinity relative to its D_2 receptor blockade, compared with serotonin-dopamine receptor antagonists (SDAs) (Meltzer 1989). The possibility exists that patients with low CSF 5-HIAA in the model also are at higher risk of relapse during chronic treatment with traditional antipsychotics.

The involvement of the ratio of HVA over 5-HIAA suggests that cortical, limbic, and striatal serotonin-dopamine interactions determine the behavioral shift into exacerbation. In all likelihood serotonin decreases dopamine release. This ratio has been shown to increase with haloperidol treatment relative to changes in BPRS scores (Kahn et al. 1993). Our data show the reverse: the higher the ratio the sooner the exacerbation of symptoms will occur. If serotonin turnover is higher, the patient will be more stable and will be better able to control abnormal thought patterns and behavior.

Noradrenergic Functioning and Time to Relapse

We have shown in earlier studies that noradrenergic measures were higher in relapsers prior to haloperidol withdrawal (van Kammen et al. 1989, 1994), except in the 6-week dichotomous model ($N = 88$), in which noradrenergic activity was included but did not add significantly to the model (van Kammen et al. 1995). In the present sample norepinephrine activity contributed more significantly when modeling time to relapse. The dissociation of CSF NE and MHPG suggests that relapse occurs sooner when phasic release of norepinephrine is increased and tonic release (as reflected by MHPG) is decreased. We have previously described other indirect evidence that the regulation of norepinephrine release is impaired in schizophrenia (Linnoila et al. 1983; van Kammen and Antelman 1984; van Kammen and Kelley 1991). We speculate that the increased stress sensitivity (e.g., being more likely to relapse quickly) may be the consequence of dysregulated monoamine activity.

Potential Benefits of the Model

Noncompliance rates for patients with schizophrenia are at least 50% in 1 year and 75% in 2 years (Weiden et al. 1994), which is not different from long-term medical patients with chronic illnesses. Drug-free schizophrenic patients as a group are vulnerable to psychotic exacerbation. Many patients dislike taking medication. They may experience temporary relief and sometimes a *decrease* of psychotic symptoms following drug withdrawal, when the unpleasant side effects of haloperidol recede (Marder et al. 1979; Cohen et al. 1989). Chronic patients are well aware of this, which may play an additional role in noncompliance. To be able to establish early in treatment what the probability of relapse will be at a certain time is critical information for the clinician. Because of the high noncompliance rate with all antipsychotics, including long-acting depot medication, as well as with the newer atypical antipsychotics, knowing the relapse risk at a given time has major clinical benefits. Although LPs are a safe procedure, they are presently not a part of psychiatric practice. If LPs are obtained with behavioral ratings prior to discharge from the hospital, the model can be applied, and the appropriate time for the next outpatient appointment can be determined. Timely scheduling of outpatient visits or brief respite admissions may prevent relapse in patients who are not compliant outside the hospital setting (van Kammen et al. 1993).

At a time when managed care and treatment costs of mental illness are at issue, it becomes increasingly important from an economic point of view to prevent relapse. Being able to identify relapse risk improves clinical management by allowing for timely assessments, medication reinstatements or changes, support, stress reduction, and other clinical interventions to prevent relapse. Ultimately, it will assist the patient in functioning optimally in the community. Our model also has implications for those patients who are chronically hospitalized (or are considered to be treatment resistant) but may be able to function better with lower doses if we knew the acceptable relapse risk. Finally, our model may have a place in relapse prevention studies of future antipsychotics (SDAs) that have strong serotonin-receptor blocking effects. The effectiveness of such agents could be assessed by comparing the actual relapse rate with the predicted relapse rate in high-risk patients.

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