Pupillary Constriction During Haloperidol Treatment as a Predictor of Relapse Following Drug Withdrawal in Schizophrenic Patients

Stuart R. Steinhauer, Daniel P. van Kammen, Kathleen Colbert, Jeffrey L. Peters, and Joseph Zubin

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Abstract. It has been proposed that the autonomic nervous system is dysregulated in schizophrenia. We hypothesized that measures of autonomic function, even during neuroleptic stabilization, might predict relapse following withdrawal of medication. Previously, shorter latencies to maximum pupillary constriction have been reported to differentiate acutely hospitalized schizophrenic patients from control subjects. Pupillary light reactions were recorded weekly from 19 chronic schizophrenic inpatients who were initially maintained on haloperidol and subsequently were withdrawn from medication under double-blind, placebo-controlled conditions. Patients were then classified as either relapsed or nonrelapsed (clinically stable) during the drug-free period. During the treatment phase, a shorter latency to maximum pupillary constriction significantly distinguished patients who were later to relapse from the nonrelapsers. The potential use of autonomic activity as an indicator of prodromal sensitivity was supported. In addition, these findings emphasize the need for classification of drug-free patients according to clinical status.

Key Words. Autonomic function, neuroleptic response, pupillometry.

Psychotic decompensation in schizophrenia (Docherty et al., 1978; Herz and Melville, 1980; Szymanski et al., 1983) is a process with biochemical and behavioral changes preceding the actual psychotic decompensation. This process implies that there are physiological and biochemical prodomes that may be present before the actual behavioral decompensation. Unfortunately, prodromal symptoms can only be defined after relapse has been observed. Several groups have attempted, through

Stuart R. Steinhauer, Ph.D., is Research Health Scientist, Biometrics Research Program, VA Medical Center, Highland Drive, Pittsburgh, and Research Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA. Daniel P. van Kammen, M.D., Ph.D., is Chief of Staff, VA Medical Center, Highland Drive, Pittsburgh, and Professor of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA. Kathleen Colbert, M.E.R., is Research Associate, Biometrics Research Program, VA Medical Center, Highland Drive, Pittsburgh, PA. Jeffrey L. Peters, M.D., is Chief of Psychiatry, VA Medical Center, Highland Drive, Pittsburgh, and Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA. Joseph Zubin, Ph.D., was Research Career Scientist, Biometrics Research Program, VA Medical Center, Highland Drive, Pittsburgh, and Distinguished Research Professor of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA. Dr. Zubin, who died on December 18, 1991, is remembered with great respect and affection by his colleagues, to whom he gave unstintingly of his knowledge, insight, and encouragement. (Reprint requests to Dr. S.R. Steinhauer, Biometrics Research, 151R, VA Medical Center, Highland Drive, Pittsburgh, PA 15206, USA).

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pharmacological challenge tests, to improve our ability to identify schizophrenic patients who would relapse soon after neuroleptic withdrawal. Behavioral and biochemical responses to stimulant tests (d-amphetamine or methylphenidate) have been used to identify those patients who would relapse soon after neuroleptic withdrawal (Angrist et al., 1981; van Kammen et al., 1982; Lieberman et al., 1987). Recently, we have demonstrated that levels of norepinephrine, measured in cerebrospinal fluid (CSF) during haloperidol treatment, are elevated before relapse (van Kammen et al., 1989). If monoamines are involved in this process, it may be hypothesized that the autonomic nervous system (ANS) is also affected. Zahn et al. (1987) reported that schizophrenia is associated with ANS dysregulation (see also Zahn, 1986; Zahn et al., 1991). In this study, we evaluated pupillary responses to light during neuroleptic treatment in two groups of patients: those who relapsed within 8 weeks following haloperidol withdrawal and those who did not.

The pupillary reaction to light is deviant in schizophrenic patients as compared with normal subjects (Hakerem et al., 1964; Lidsky et al., 1971; Patterson, 1976; Rubin, 1960, 1974; Steinhauer and Hakerem, 1992). Usually, there is less pupillary constriction in patients, although a subgroup of patients reportedly shows larger than normal constrictions (Rubin, 1974). Patients undergoing prolonged neuroleptic administration continue to show reduced light reactions (Okada et al., 1978; Oono and Ishikawa, 1976). Decreased pupillary constriction has been reported in both medicated and unmedicated groups of patients compared with control subjects (Ikushima and Matsunaga, 1975). Decreased pupillary responsiveness has been reported for schizophrenic patients even during periods of remission (Rubin and Barry, 1972; Ikushima and Matsunaga, 1975). This finding suggested that the decreased pupillary light reaction may be a long-term indicator of vulnerability to schizophrenia (trait marker), instead of being only a transient phenomenon (state marker) associated with an episode of psychosis (Zubin and Steinhauer, 1981).

There is limited information about the manner in which neuroleptics affect tonic or phasic pupillary activity. Single acute doses of chlorpromazine produce miotic pupils, which recover within a day (Jonas, 1959). Patterson and Venables (1981) examined the effects of single doses of neuroleptics or placebo given to the same normal subjects. They found (1) a minimal effect of haloperidol; (2) a large anticholinergic effect of scopalamine (increased initial diameter and decreased constriction); and (3) a somewhat complex effect of chlorpromazine, including smaller resting diameter (as also noted by Jonas, 1959), slightly decreased light reaction, and decreased redilation, providing signs of both anticholinergic and anticholaminergic effects on the pupil.

In most studies, measurement takes place on but a single occasion, so that the variation of pupillary response with chronic pharmacological treatment has not been examined. We sought to examine pupillary responses in patients during periods of treatment with haloperidol and during drug-free periods. Extreme changes in symptomatology could also be compared with changes in the physiological measures at different stages of the drug-free period.

**Methods**

**Subjects.** Data were collected weekly from 19 physically healthy male patients who met
Research Diagnostic Criteria (Spitzer et al., 1978) and DSM-III criteria (American Psychiatric Association, 1980) for chronic schizophrenia on the basis of a semistructured interview (Schedule for Affective Disorders and Schizophrenia-Lifetime Version; Endicott and Spitzer, 1978) and other available information. Patients ranged in age from 24 to 51 years, with a mean (± SD) of 35.2 ± 7.6 years. All subjects were inpatients on the Schizophrenia Research Unit at the Highland Drive VA Medical Center. Throughout their hospitalization, they received a low monoamine, caffeine-free diet. Subjects had all been receiving neuroleptic medication for at least 6 months. On entering the protocol, patients were maintained on haloperidol for at least a 6-week period, with dosage stabilized at a mean of 13.2 mg/day (range = 2.6-40 mg/day) at the time of testing. Seven patients who received benztropine had been withdrawn from the drug for at least 3 weeks. No other medications were administered at any time during the study. Subjects were then withdrawn from haloperidol under double-blind, placebo-controlled conditions (identical capsules contained the placebo) and maintained on placebo during a 2- to 8-week period. At the completion of the protocol, the blind was broken, so that it was possible to identify, for each patient, specific periods of neuroleptic or placebo treatment.

Patients were rated daily by the staff, who were unaware of the treatment condition, on the Bunney-Hamburg Global Psychosis scale (Bunney and Hamburg, 1963) and weekly by their therapist (who was also unaware of pharmacological treatment) on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). Relapse was defined as an increase of 3 points over a 3-day period on the Bunney-Hamburg Psychosis Scale (daily nursing ratings) or 8 points in the BPRS subscale while patients were receiving placebo, as compared with the baseline ratings obtained during the last week of haloperidol treatment. Subjects who relapsed during the drug-free period were subsequently placed on medication.

Two groups of patients were distinguished: those who, during the drug-free phase, remained clinically stable (nonrelapsers, n = 10), and those who met criteria (van Kammen et al., 1989) for relapse (n = 9). Relapse occurred after an average of 20.6 days (range 3-47 days). Patients in the nonrelapsed group were all clinically stable up to a minimum followup period of 8 weeks, after which time neuroleptic treatment was reinstated.

Data were also collected in a single session from 13 male control subjects, aged 31.2 ± 2.7 years (range 27-35), for comparison with the patient group. This control group consisted of five staff members with no history of psychiatric disorder and eight subjects recruited locally who met Feighner criteria for “no disease” (no history of disorder) on the basis of the Renard Diagnostic Interview (Helzer et al., 1981). There were no significant differences in age among the control subjects and patient groups.

Pupillographic Recording. Pupillary diameter was measured with a Gulf & Western Applied Sciences Laboratory Video Pupillometer. An infrared light source was used for illumination, permitting accurate recording even in complete darkness.

The analog output of the pupillometer, corresponding to pupil diameter in mm, was digitized every 20 msec during two resting periods of 10-second duration each, and during presentation of visual stimuli during the 200-second test period. Digitization was performed with a PDP-11/03 (MINC) laboratory computer; all data were stored on floppy disk for off-line analysis.

Stimuli. Visual stimulation was provided by a yellow, focused light-emitting diode (Monsanto #MV-5354), placed in the center of a diamond formed by four red light-emitting diodes (2.54 cm apart) which provided fixation. The 5-mm diameter yellow light-emitting diode was placed 80 mm from the subject’s eye (subtending a visual angle of 0.38°), with a luminance of 93 cd/m².

Procedure. Weekly testing was carried out in a light-proof, completely dark, sound-attenuating room adjacent to the laboratory apparatus room. The subject placed his head in a head rest; the pupillometer measured the left eye as the subject viewed the fixation lights. After
1 minute of dark adaptation, a 10-second prestimulus sample of resting pupil diameter was recorded. Next, for 50 trials, the light stimulus was presented for 1 second followed by 3 seconds of darkness (the study of repeated samples for assessment of pupillary light reactions, instead of only one or two samples, was suggested by the work of Lowenstein and Loewenfeld [1952]). One second after the termination of the 40th light stimulus, a single orientation tone (800 Hz, 90 dB, 250 msec) was presented; analyses of these auditory responses are not included in this report. Subjects were encouraged to minimize blinking but, if necessary, to blink just before a light was presented. It was sometimes necessary to remind subjects to hold their eyes open during the recording period. Following 50 trials of light, the subject was given a brief rest, and a poststimulus 10-second sample of resting pupillary diameter was obtained.

**Data Analysis.** The primary analysis of the data was performed by computer. The program detected blinks or prolonged eye closures. Other artifacts (such as partial closure of the eye) were first identified and coded by a technician who inspected a graphic display of each trial.

For the prestimulus and poststimulus samples of resting diameter, blink-free segments were used to compute average diameter, standard deviation, and a measure of pupilary motility (total deviation in mm/sec).

Light reaction data were analyzed by computer as follows: data from the first 3 seconds of each trial were examined for blink artifacts. From blink-free trials (mean = 24, range = 9-37), an average diameter and standard deviation were computed at each time point. Trial 1 was excluded from the average, because both the initial diameter and the extent of constriction were larger for the first trial (the longest period of dark adaptation had preceded trial 1). Trial 41, following the presentation of the auditory stimulus, was also excluded from the averaging procedure. There were no significant differences among subject groups in the number of trials included in each average.

A number of key variables representing pupillary diameter, maximum rates of change in diameter, and timing of specific events were computed from the average of the artifact-free trials (Fig. 1), including the following:

- Initial diameter (the average diameter from time 0 to 80 msec, representing the first 5 points sampled on each trial; since the minimum latency for the initiation of pupillary constriction is approximately 180 msec even for intense visual stimuli, this measurement occurs before the pupil has begun to respond to light onset).
- Constricted diameter (the absolute pupil diameter at the termination of the constriction process).
- Extent of constriction (the initial diameter minus the constricted diameter).
- Latency to the start of constriction.
- Latency to maximum constricted diameter.
- Maximum rates of constriction and redilation, and the times at which they occurred, as well as the times at which the pupil redilated to 50% and 75% of initial diameter, were also computed (see Fig. 1).

The objectives of data analysis were to compare the constriction responses of those patients who relapsed during the drug-free period to those patients who did not relapse during the same period. Pupillary data for the final week of haloperidol treatment, and for the initial drug-free period, were compared between groups. In addition, data were compared for the weeks preceding and during relapse among those patients whose condition worsened; the comparison used data for the stable patients based on the average duration of the drug-free period for the relapsed group. Differences between patient groups or among patients and control subjects were examined by analysis of variance (BMDP2V).

**Results**

**Haloperidol Phase.** During the final week of haloperidol stabilization, patients who would later relapse were observed to show a shorter latency to the end of the
constriction process than those who remained clinically stable (Fig. 2). In contrast, absolute measures of pupillary diameter and extent of constriction did not differ between the two groups. Table 1 presents characteristics of the two patient groups for this test period.

The maximum extent of constriction occurred significantly earlier \((F = 4.4; df = 1, 17; p < 0.05)\) in those patients who subsequently relapsed (889 msec) than in the nonrelapsers (1036 msec). The redilation of the pupil to 50% of initial diameter also occurred sooner in the relapsed group \((F = 5.6; df = 1, 17; p < 0.03)\). When the constriction latency was covaried from the redilation measure, no significant differences in redilation remained (Table 1). Thus, the redilation effect was attributed primarily to the earlier cessation of the constriction response.

It is also worthwhile to note that neither the maximum rate of pupillary constriction nor the maximum rate of redilation differed between the two groups. Haloperidol doses and psychosis ratings showed no significant differences between the groups, although relapsers were noted to have required a slightly higher mean dose than nonrelapsers (15.6 mg vs. 11.0 mg, respectively).

However, the constriction latency measure did not predict how soon relapse would occur. For those patients whose conditions deteriorated in the drug-free phase, no relationship was found between maximal constriction latency during haloperidol treatment and number of drug-free days before relapse.

The latency to the end of constriction was then examined with respect to several factors that could conceivably have been related to response latency. No significant correlations were found for latency of maximal constriction with age, haloperidol dose, or level of psychosis during the week recorded. Analysis of covariance using each measure indicated that both level of psychosis and dose reduced the significance of the latency of maximum constriction as a predictor.
Fig. 2. Distribution of the latency of maximal pupillary constriction for schizophrenic patients who relapsed vs. those who did not relapse during the drug-free period

Outcome When Drug-Free

Measurements were obtained during the final week of haloperidol treatment. Means ± 1 standard error are indicated for each group.

Table 1. Age, dose, psychosis rating, and pupillary measurements for patients during final week of haloperidol treatment before double-blind placebo period

<table>
<thead>
<tr>
<th>Outcome following haloperidol withdrawal</th>
<th>Relapsers (n = 9)</th>
<th>Nonrelapsers (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33.7</td>
<td>36.6</td>
<td>NS</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>15.6</td>
<td>11.0</td>
<td>NS</td>
</tr>
<tr>
<td>Psychosis rating</td>
<td>4.6</td>
<td>5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Resting diameter (mm)</td>
<td>6.68</td>
<td>5.97</td>
<td>NS</td>
</tr>
<tr>
<td>Initial diameter (mm)</td>
<td>6.24</td>
<td>5.94</td>
<td>NS</td>
</tr>
<tr>
<td>Constriction amplitude (mm)</td>
<td>0.83</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Constriction latency (msec)</td>
<td>888.89</td>
<td>1036.00</td>
<td>0.05</td>
</tr>
<tr>
<td>50% Reciliation (msec)</td>
<td>1716.33</td>
<td>1874.00</td>
<td>0.03</td>
</tr>
<tr>
<td>75% Reciliation (msec)</td>
<td>2246.67</td>
<td>2380.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

Significance of t tests is given between groups of patients who would later relapse compared with those who remained stable during the placebo period.
For comparison with findings reported previously by Patterson (1976), a separate series of analyses were conducted using only the data from trial 1, at which time the pupil was maximally dilated, and thus yielded the largest constriction response. No differences between groups were observed on any of the trial 1 measures, suggesting that the single trial estimate was not adequate as an estimate of pupillary motility.

**Drug-Free Phase.** Pupillary data were examined during different periods of the drug-free phase. No significant differences between the two subject groups were observed during the first week following double-blind placebo replacement. Maximal constriction latency had decreased to a mean of 990 msec for the nonrelapsers, and increased slightly to 935 msec for the relapsed group (n = 8; because one patient relapsed within the week after withdrawal of medication, no drug-free data were collected on this subject).

Data were also examined for the week before relapse (available for 7 of the relapsed patients). For comparison, data for the third week of the drug-free period (Table 2) were available for nine of the nonrelapsed patients (approximating the same average period drug-free as the relapsed group). Latency to maximal constriction did not differentiate the groups. In fact, the latency had decreased for the nonrelapsed population to that seen for the relapsed group. During the week of relapse, no differences between groups were observed on any measure.

**Table 2. Psychosis ratings and pupillary measurements of relapsed and nonrelapsed patients, measured during the drug-free period**

<table>
<thead>
<tr>
<th></th>
<th>Relapsers(^1)</th>
<th>Nonrelapsers(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 9)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Psychosis rating</td>
<td>5.86</td>
<td>1.57</td>
</tr>
<tr>
<td>Resting diameter (mm)</td>
<td>6.45</td>
<td>1.32</td>
</tr>
<tr>
<td>Initial diameter (mm)</td>
<td>6.29</td>
<td>1.34</td>
</tr>
<tr>
<td>Constriction amplitude (mm)</td>
<td>0.63</td>
<td>0.21</td>
</tr>
<tr>
<td>Constriction latency (msec)</td>
<td>908.57</td>
<td>116.53</td>
</tr>
<tr>
<td>50% Redilation (msec)</td>
<td>1725.71</td>
<td>194.50</td>
</tr>
<tr>
<td>75% Redilation (msec)</td>
<td>2171.43</td>
<td>191.78</td>
</tr>
</tbody>
</table>

1. Data collected in week before relapse.
2. Data collected during third week drug-free.

The data for the control subjects (see Table 3) were contrasted with those recorded from the patient groups. For patient data collected in the week before relapse (Table 2), only the measurement of resting pupillary diameter differentiated patients from control subjects (F = 6.0; df = 2, 26; p < 0.007). Post hoc Scheffé tests (p < 0.05) indicated that the control subjects had significantly larger pupils than the nonrelapsers. No differences in extent of constriction or latency to maximal constriction were observed, although control subjects showed a trend for larger constriction amplitude and longer latency. When control data were compared with patient data recorded during the haloperidol phase, both resting diameter (F = 8.1; df = 2, 29; p < 0.002) and initial diameter (F = 5.7; df = 2, 29; p < 0.008) were found
to differ among groups, with larger diameters among control subjects than patients. Post hoc Scheffé tests indicated that control subjects differed significantly only from the nonrelapsers on both measures.

| Table 3. Age and pupillary data for nonpatient control subjects (n = 13) |
|---------------------------------|-------|-------|
|                                 | Mean  | SD    |
| Age (yr)                        | 31.2  | 2.7   |
| Resting diameter (mm)           | 7.21  | 0.50  |
| Initial diameter (mm)           | 6.51  | 0.61  |
| Constriction amplitude (mm)     | 0.98  | 0.31  |
| Constriction latency (msec)      | 981.54| 157.58|
| 50% Reactivation (msec)         | 1831.54| 222.11|
| 75% Reactivation (msec)         | 2410.77| 338.00|

Discussion

The latency to the cessation of the pupillary constriction response of schizophrenic patients stabilized on haloperidol was found to distinguish subsequent change in clinical status following withdrawal of medication for up to 8 weeks. Those patients who relapsed during the drug-free period were characterized by a shorter latency to maximum constriction before haloperidol withdrawal.

Most previous research comparing schizophrenic and control populations has emphasized a more extensive amplitude of constriction in control subjects (e.g., Lidsky et al., 1971; Rubin, 1974; Hakerem and Lidsky, 1975). No differences in response amplitude were noted between the two patient groups in the present study. In addition, patients did not differ significantly from control subjects in the extent of the constriction response, as typically reported, although the trend for a larger constriction in control subjects was noted. Previously, Hakerem et al. (1964) also reported no significant difference in constriction amplitude between control subjects and drug-free schizophrenic patients.

In darkness, larger pupillary diameter has usually been reported in control subjects as compared with schizophrenic patients. Hakerem et al. (1964) observed a larger pupillary diameter in control subjects compared with that in acute schizophrenic patients, but not compared with that in chronic (hospitalized longer than 5 years) patients. Smaller diameters in patients have also been reported by Lidsky et al. (1971) and Rubin and Barry (1976), while no differences in diameter have been reported by Okada et al. (1978). No consistent differences in resting diameter between patients and control subjects have been reported for measurements obtained under light-adapted conditions (Rubin and Barry, 1972; Patterson, 1976).

Few studies have reported the temporal characteristics of the pupillary light reflex in patients. This omission is attributable primarily to the technical difficulties involved in obtaining accurate latency measurements with noncomputer-based technology. Hakerem et al. (1964), however, using a resolution of 0.1 second, observed that control subjects took longer to reach the end of constriction than either acutely admitted or chronically hospitalized schizophrenic patients who had been drug-free
for 2 weeks at the time of testing. The range of latencies for all subjects was from 800
to 1300 msec, with the patient data being similar to those observed in the present
study. Patterson (1976) noted that medicated schizophrenic patients who showed
fast recovery of skin conductance also showed a longer latency to reach maximal
constriction as compared with those patients who exhibited slow recovery. More
extensive constrictions were observed for those who also showed longer latencies to
maximal constriction, which are highly correlated in such conditions; thus, it should
be expected that a greater constriction should occur over a longer period of time.
(Patterson discussed shorter skin conductance recovery as indicative of greater
impairment on other experimental tasks, although no clinical data were available to
assess the psychopathological status of the patient groups tested.)

In the present study, constriction amplitude was similar for both patient groups
and therefore cannot explain the latency differences. Thus, the data for patients who
would later relapse indicate a beginning of the redilation process at an earlier stage
than for those patients who remained stable, the latter being more consistent with the
pattern seen for control subjects by Hakerem et al. (1964) and with the trend for
control subjects compared with unmedicated patients in the present data.

How can we interpret these findings? An attempt to understand the significance of
the shorter latency to maximal constriction among the subsequent relapers must
deal with two issues: possible physiological interactions and the positive response of
this group to medication (as indexed by relapse after withdrawal of medication).

Possible mechanisms for a shorter constriction latency include strong and earlier
sympathetic inhibition of constriction, or less extensive parasympathetic activation.
Both ascending reticular inputs and descending cortical inputs inhibit para-
sympathetic centers at the Edinger-Westphal complex of the third nerve nucleus
(Beatty, 1986), which is the source of efferent fibers to the ciliary ganglion, and
finally to the pupillary sphincter muscles. Tonic levels of sympathetic activity, at
least as measured by the resting diameter before and after all trials, and by the initial
diameter at the start of each trial, did not show significant differences between
groups (although the relapers did show a trend for larger diameters). Thus, there is
no clear indication of an active sympathetic inhibitory influence, much less a phasic
response correlated with stimulus initiation, that seems to account for the earlier
onset of redilation.

What remains is the probability of dysfunction in the maintenance of para-
sympathetic tone. The initiation and total extent (amplitude) of constriction do not
differ between groups, but the nonrelapers are able to maintain a prolonged
constriction until after the light has ceased. One approach to an examination of
maintained parasympathetic tone would be to examine responses to prolonged light
stimuli (i.e., > 1 sec), since after the initial constriction, normal subjects will show
some redilation to a larger diameter even while the light source is still present.

The question posed by these data requires the explanation of why a decreased
maximal constriction latency occurs in medicated patients who are likely to relapse.
One aspect that must be considered is that the time of treatment and data sampling
may interact with other ongoing changes in the patient's course of illness and
recovery. Thus, if we postulate that all patients go through various cycles of stability
and relapse, then we may have sampled patients who were at risk of relapse, perhaps
even if maintained on neuroleptics. In other words, if the nonrelapsed patients had been followed drug-free for longer than 8 weeks, some of them would have been likely to relapse.

There are significant clinical implications for such findings. One of the major problems in neuroleptic maintenance programs is deciding when pharmacological treatment can be decreased or even discontinued entirely. This is particularly crucial with patients who are urging that their medication be curtailed because they feel that their symptomatology is minimal, but are distressed by side effects of their medication. If the likelihood of relapse could be estimated, then an informed decision could be made by the treatment team. In the present data, for example, if a cutoff of approximately 1000 msec were chosen as a minimal latency to predict a stable outcome in the drug-free state, only one patient who subsequently relapsed would have been taken off medication; half of the stable population would also have been identified as unlikely to relapse by this criterion. Thus, it is a relatively conservative criterion: few drug-free patients would relapse, but several who might do well without medication would still be maintained on medication.

Signal averaging of repeated individual light reactions, which tends to minimize the effects of background activity, appeared to be a more useful approach than using only a single initial light reaction. Inspection of our data suggests that 15-20 trials provide an optimal data base for averaging these pupillary data.

These results emphasize the notion that in studies of drug-free patients, differences in clinical status (e.g., stable or relapsed) must be taken into consideration. Our initial hypothesis—that prodromal sensitivity may be reflected in autonomic activity—was supported. The findings encourage the continued investigation of easily monitored psychophysiological variables that may aid in deciding who would benefit from reduction or withdrawal of neuroleptics.

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