Neuroleptic Plasma Levels

by Theodore Van Putten, Stephen R. Marder, William C. Wirshing, Manickam Aravagiri, and Nicole Chabert

Abstract

There is enormous variation in plasma levels of most neuroleptics in patients on the same dose. Much of the past research on the relation between plasma levels of antipsychotic drugs and clinical change, however, has been difficult to interpret. It does appear that decreased bioavailability, at least in public institutions, is rarely the cause of treatment failure. Aberrantly low plasma levels are more likely due to surreptitious non-compliance or drug interactions with enzyme inducers such as carbamazepine. Therapeutic plasma level ranges, in which good antipsychotic effect occurs without undue side effects, have been tentatively identified for perphenazine, haloperidol, fluphenazine, and chlorpromazine. The extent to which aberrantly high plasma levels are associated with inferior antipsychotic response is unclear. Antipsychotic plasma levels may be most useful when the distinction between side effects and worsening psychosis is unclear. The utility of high neuroleptic plasma levels in the treatment-resistant patient is unclear.

Studies over the past two decades have indicated that there is enormous (up to a hundredfold) variation in plasma levels of most neuroleptics in patients on the same dose (Dahl 1986; Midha et al. 1988). This observation raised the hope that plasma levels of neuroleptics could standardize dosing practices and that aberrant plasma levels could explain some cases of treatment resistance. Pi and Simpson (1981) even suggested that plasma level determinations could provide laboratory evidence to extend and tighten the definition of refractory schizophrenia.

Much of the past research on the relationship between plasma levels of antipsychotic drug and clinical change, however, has been difficult to interpret because of shortcomings with the assays or design deficiencies such as lack of fixed-dose design, contamination with other treatments, and inclusion of treatment-resistant patients (Davis et al. 1978; May and Van Putten 1978). Nevertheless, one important question is whether the drug is bioavailable to the patient.

Bioavailability as a Cause of Treatment Failure

Although “hypermetabolism,” “decreased absorption,” and “decreased bioavailability” are terms used by clinicians to justify administering high doses of neuroleptics, there are few examples in the literature that support decreased bioavailability as the cause of treatment failure.

Cooper and co-workers (1975) described a patient who responded well initially to butaperazine. During the ensuing weeks of therapy, however, the patient’s clinical response to the same dose of butaperazine showed gradual deterioration, while steady-state levels of the drug fell until it was no longer detectable in his plasma. The authors suggested that the decline in butaperazine level might be attributable to enzyme autoinduction and subsequent enhancement of metabolism. Smith et al. (1984a) similarly noted two to seven times lower butaperazine plasma levels in chronic refractory inpatients than in patients who responded to...
butaperazine. Further, when the poor responders were given a test dose of butaperazine, peak plasma levels of butaperazine were again two to seven times lower than the peak butaperazine levels in the responding patients.

Smith et al. (1979) also noted a strong correlation between steady-state levels of thioridazine (TDZ) and steady-state levels of butaperazine in the same nonresponding patients ($r = 0.74$, $p < 0.05$): patients with the lowest plasma butaperazine levels also had the lowest plasma TDZ levels. In this same sample, 36 relative responders treated with oral haloperidol (HPL) (15 mg/day) had mean (± SEM) steady-state plasma HPL levels of 15.3 ± 2.0 ng/ml after 1 week of treatment. This contrasts with the much lower HPL levels measured in six chronic nonresponders (mean = 4.0 ng/ml, range = 0-9 ng/ml), in spite of the fact that these nonresponders were treated with much higher doses of HPL (20 to 60 mg/day).

Curry et al. (1970), in a nonsystematic survey, reported very low chlorpromazine (CPZ) plasma levels in chronically hospitalized schizophrenic patients who had showed a consistently poor response to neuroleptic drugs. One patient on CPZ, 600 mg daily, had a nondetectable plasma CPZ level, and this same patient showed very low CPZ plasma levels following a 300-mg oral CPZ test dose.

In a dramatic illustration of enzyme induction described by Hansen and Larsen (1982), the patient was responding well to oral perphenazine (PPZ) until he started concomitant therapy with disulfiram. His clinical condition then deteriorated markedly and his plasma level of PPZ fell to about one-third of the steady-state level before disulfiram. At the same time, plasma concentrations of inactive sulfoxide metabolite were markedly elevated. Doubling the oral dose of PPZ had little effect on either plasma concentrations or clinical condition. However, changing the route of administration to intramuscular resulted in a substantial clinical improvement and an increase in plasma PPZ concentrations to a therapeutic level. By contrast, PPZ sulfoxide concentrations fell sharply. The authors suggested that disulfiram induced the enzyme(s) responsible for the sulfoxidation of PPZ so much that most of the drug given by mouth was biotransformed to inactive metabolites. On the other hand, parenteral administration avoided the first pass effect in the liver.

Carbamazepine is also known to reduce plasma neuroleptic levels by 50 percent or more through microsomal enzyme induction (Ereshefsky et al. 1984a; Jann et al. 1985), and there is one reported case (Fast et al. 1986) of treatment failure secondary to this interaction.

Since most treatment-refractory patients, at least in public institutions, have been given a trial of treatment with fluphenazine decanoate (FD) (thereby avoiding the first pass metabolism), it is very unlikely that decreased bioavailability is an adequate explanation for treatment failure except in an occasional patient. To confirm this, we examined the plasma levels in 12 long-stay, treatment-refractory patients in a State hospital. Over the years, these patients had been on high doses of HPL (40-420 mg/day) on the prescribing clinician's assumption that they were "hypermetabolizers" or "poor absorbers." In only two cases was the plasma HPL level low relative to dose (but not so low as to explain their treatment resistance), and the regression line of the high-dose patients was merely an extension of the regression line of newly admitted patients treated with more conventional doses of HPL (Van Putten et al. 1985). Since then, we have consulted on at least 30 more treatment-refractory patients on high doses of HPL (> 30 mg/day) and in no case was the plasma level of HPL less than 15 ng/ml.

Although plasma levels of neuroleptics (at least in the case of HPL) in the treatment-resistant patient are usually adequate, there remains the possibility that the drug is not available to the central nervous system because of excessive protein binding. It is well known that drugs such as CPZ, trifluoperazine, TDZ, and HPL are extensively bound to plasma proteins (Cohen et al. 1976; Forssman and Ohman 1977; Nyberg et al. 1978; Verbeeck et al. 1983). Consequently, only a small portion of the total drug in the plasma remains free from binding, although it is this "free fraction" that is responsible for therapeutic activity. Once again, there is interindividual variation in protein binding such that a tenfold variation in plasma free fraction has been reported among individuals with identical total plasma concentrations of CPZ (Curry 1970). The reason for this variation is that the acute phase reactant alpha, acid glycoprotein (AGP) plays an important role in the binding of neuroleptic drugs (Piafsky 1980). The plasma concentration of AGP can show large fluctuations, even in the same individual, due to changes in normal physiological functions and pathological processes such as schizophrenia. Hence, the all-important free fraction of the drug in plasma will vary as the concentrations of the acute phase reactant proteins change. Therefore, it may be important to take steps to establish the protein binding status of
a refractory patient who appears to have adequate total plasma levels of neuroleptic. To date, this has not been investigated.

Identification of Behavioral Toxicity

Once it has been established that a drug is bioavailable to the refractory patient, the next question is whether neuroleptics may have led to the development of behavioral toxicity. If there is a "therapeutic-window" relationship between neuroleptic plasma levels and clinical response, then some patients, at least in theory, could be refractory (or exhibit behavioral toxicity) because of excessively high plasma levels.

Behavioral toxicity secondary to neuroleptics is well documented. For example, the administration of phenothiazines can lead to the development of a catatonic-like state (May 1959; Gelenberg 1976). Akathisia is often difficult to differentiate from psychotic excitement and can be associated with psychotic exacerbation (Van Putten and Marder 1987; Van Putten et al. 1987). Akinesia is very difficult (if not impossible) to differentiate from schizophrenic blunting, apathy, and withdrawal, and "akineti
depression" has been described (Van Putten and Marder 1987). What is not clear is whether behavioral toxicity is associated with unusually high plasma levels.

High Plasma Level and Behavioral Toxicity. A number of studies have described therapeutic-window relationships between neuroleptic plasma levels and clinical response (Dahl 1986). There are only a few reports, however, of patients with manifest psychotic symptoms and high plasma neuroleptic levels who have improved with dose reduction.

Rivera-Calimlim et al. (1973) reported that two patients who had plasma CPZ concentrations in the range of 750 to 1,000 ng/ml showed pronounced toxic symptoms (tremor, hypotension, and convulsions), and improved when the plasma concentrations were brought below 350 ng/ml. Van Putten et al. (1981) observed that four of six patients who became worse after a dose increase had CPZ plasma concentrations well above 95 ng/ml. Three of these patients developed an agitated excitement and became assaultive. When the plasma CPZ level was lowered, this behavior disappeared. Curry (1970) also reported on a patient with a high (605 ng/ml) plasma level of CPZ who remained "uncooperative, assaultive, fearful and hostile." Reduction of dosage by one-third to 600 mg/day resulted in a corresponding reduction in plasma level and in considerable and sustained improvement, characterized by reduction of fear and hostility and absence of assaultive behavior.

Extein et al. (1983) also reported a single patient in whom the initial antipsychotic effect of HPL was lost, then regained, as plasma levels went above (27.5 ng/ml) and then were brought back into the therapeutic window (10 ng/ml). Bjorndal et al. (1980) compared standard versus high dosage HPL therapy in 22 male, relatively treatment-resistant, chronic schizophrenic inpatients. Patients were randomly assigned to receive either 2- or 20-mg tablets of HPL. At the end of the trial, the dose of HPL in the standard dosage group was 12 to 36 mg/day (mean = 15); in the high dosage group it was 10 to 240 mg/day (mean = 103). Three of the high-dosage patients with plasma levels above 100 ng/ml exhibited attacks of violent aggression during which they struck fellow patients and staff and damaged furniture. These attacks disappeared after a 50 percent reduction in plasma level. Further, depression (somatic concern, anxiety, guilt, and depressive mood) increased significantly during high-dosage treatment in the nonresponders. Schulz et al. (1984) report a patient who improved on HPL 5 mg/day. On the 5-mg dosage, the patient had a surprisingly high plasma HPL level of 22 ng/ml. When the dose of HPL was increased to 15 mg/day, the patient had a plasma level of 64 ng/ml and developed increased psychotic symptomatology. When plasma level was again lowered, the psychotic symptomatology improved.

These cases indicate that, at least for some patients, behavioral toxicity exists at higher plasma levels. Further, these high plasma levels in some cases occurred at very ordinary dosages. Since treatment-refractory patients are usually on high doses of neuroleptics, it is likely that some would improve if dosage and plasma level were lowered. Clinically, one does encounter very treatment-resistant cases in which a reduction of dosage is associated with marked improvement. The extent of this phenomenon is unknown; systematic research in which high plasma levels in treatment-resistant patients are systematically lowered is just getting started.

Assays

High-performance liquid chromatography (HPLC) has been used increasingly, and HPLC methods for nearly all neuroleptics have been available since 1981 (Dahl 1986). Radioimmunoassays tend to be less precise but
more sensitive than HPLC methods and are available for HPL (Poland and Rubin 1981) and fluphenazine (FLU) (Midha et al. 1980). The radioreceptor assay (RRA) is a new biological technique in which a neuroleptic drug and its dopamine-blocking metabolites compete with tritiated spiroperidol (or tritiated HPL) for dopamine D₂ binding sites on preparations of membranes from rat striatum. Theoretically, RRA measures the total D₂ receptor-blocking activity of drug and metabolites in the plasma or serum. Although theoretically attractive, the utility of the RRA is unknown; it has only the promise of becoming useful to the practicing psychiatrist (Midha et al. 1987). At this time, the state of the art for measuring neuroleptic plasma levels is HPLC.

Fixed-Dose Plasma Level Studies With Neuroleptics

To detect a relationship between plasma levels of a neuroleptic and clinical response, patients need to be treated with a fixed dose(s) of neuroleptic. Preferably, patients are randomly assigned to low, average, or high doses so that both ends of the therapeutic window (if such exists) are represented. Variable dose studies tend to produce artifactual "therapeutic windows" (Van Putten and Marder 1986).

Haloperidol. Most of the work on the relation between plasma levels of neuroleptic and clinical response has been done with haloperidol (HPL). Table 1 summarizes the fixed-dose studies with HPL. Four fixed-dose studies with HPL suggest a therapeutic-window relationship between plasma HPL and clinical response. The suggested therapeutic ranges of these studies are 6.5-16 ng/ml (Smith et al. 1984a); 4-11 ng/ml (Mavroidis et al. 1983); 4-22 ng/ml (Potkin et al. 1985); and 12-55 ng/ml (Santos et al. 1989). The therapeutic range of 12-55 ng/ml suggested by Santos et al. (1989) is higher and out of line with the therapeutic ranges of the other three studies. Inspection of Santos et al.'s data indicates a positive linear relationship between about 2 and 20 ng/ml. Above 20 ng/ml there were five cases with plasma levels of about 22, 24, 25, 34, and 52 ng/ml. In these five cases there was a slight drop in response from about 62 percent improvement in the best responder at 20 ng/ml to about 54 percent in the poorest responder, but the data, in our opinion, were compatible with a plateau relationship starting at 20 ng/ml. (Recallulation of the Santos data using two sigmoidal dose-effect functions indicates a plateau relationship starting at ± 19 ng/ml, and logarithmic conversion of plasma HPL levels suggests a plateau relationship starting at ± 18 ng/ml.)

Six fixed-dose studies did not find a therapeutic-window relationship, but these studies were so designed that detection of such a relationship (if it exists) was unlikely. Three of the studies (Rimon et al. 1981; Itoh et al. 1984; Bigelow et al. 1985) used primarily poor neuroleptic responders. Three used such low doses (5 or 10 mg, Bleeke et al. 1984; 6 mg, Itoh et al. 1984; 0.2 mg/kg, Wistedt et al. 1984) that detection of an upper toxic limit was unlikely. In another three, the doses were too high (60 and 120 mg, Rimon et al. 1981; 0.4 mg/kg, Bigelow et al. 1985; 30 mg, Linkowski et al. 1984) to have plasma levels in the subtherapeutic range. To summarize, of the 10 fixed-dose studies with HPL, 4, in retrospect, were designed properly, and these 4 found a therapeutic-window relationship.

In the four studies (Mavroidis et al. 1983; Smith et al. 1984a; Potkin et al. 1985; Santos et al. 1989) that suggested a therapeutic range, there are only 25 cases that define the proposed toxic range; 17 of these cases were in Potkin and colleagues' investigation of Chinese schizophrenic patients, in which the curvilinear fit explained only 8 percent of the variance of clinical improvement. Further, these studies did not answer the obvious clinical question—what is the clinical state of patients with toxic HPL levels? Do such patients appear to be overmedicated to start with? And, perhaps more compelling, do patients with toxic plasma levels improve when their plasma levels are lowered, and is the reverse true? Only Mavroidis et al. (1983) mentioned that when they halved the dose in the patient with the highest plasma level (18.5 ng/ml) and little clinical improvement (11%), the patient improved "dramatically."

Volavka et al. (1990) randomly assigned 152 schizophrenic inpatients to three fixed HPL plasma level ranges: low (2-13 ng/ml), medium (13.1-24 ng/ml), and high (24.1-35 ng/ml). Raters were blind to plasma level, and patients were rated on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) and the Simpson–Angus Scale (Simpson and Angus 1970) for side effects. No significant differences were detected among any of the three HPL range assignment groups in side effects, dropout rate, BPRS raw score, or categorical improvement. A final version of this study has not been published. The study may also have a number of problems: the acutely exacerbated patients who usually respond to antipsychotic drug treatment during the first 2 weeks may...
Table 1. Haloperidol (HPL) fixed-dose studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>HPL daily dose</th>
<th>Duration of treatment (weeks)</th>
<th>Type of patient included</th>
<th>Proposed HPL window (ng/ml) or other relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleecker et al.</td>
<td>29</td>
<td>5 or 10 mg</td>
<td>2</td>
<td>Atypical &amp; brief reactive psychosis</td>
<td>None</td>
</tr>
<tr>
<td>(1984)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potkin et al.</td>
<td>43</td>
<td>0.40 or 0.15 kg</td>
<td>6</td>
<td>Chinese schizophrenics</td>
<td>4.0–26.0</td>
</tr>
<tr>
<td>(1985)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bigelow et al.</td>
<td>19</td>
<td>0.40 kg</td>
<td>6</td>
<td>Institutionalized poor responders</td>
<td>None</td>
</tr>
<tr>
<td>(1985)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rimon et al.</td>
<td>12</td>
<td>60 and 120 mg</td>
<td>8</td>
<td>Institutionalized poor responders</td>
<td>None</td>
</tr>
<tr>
<td>(1981)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al.</td>
<td>27</td>
<td>10, 20, or 25 mg</td>
<td>3</td>
<td>Newly admitted schizophrenics; poor responders excluded</td>
<td>7.0–17.0</td>
</tr>
<tr>
<td>(1984a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mavroidis et al.</td>
<td>14</td>
<td>6, 12, or 24 mg</td>
<td>2</td>
<td>Newly admitted DSM-III schizophrenics in psychotic exacerbation</td>
<td>4.7–11.0</td>
</tr>
<tr>
<td>(1983)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wistedt et al.</td>
<td>10</td>
<td>0.2 kg</td>
<td>4</td>
<td>Acute schizophrenic patients</td>
<td>Linear</td>
</tr>
<tr>
<td>(1984)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itoh et al.</td>
<td>11</td>
<td>6 mg</td>
<td>4</td>
<td>Institutionalized chronic schizophrenic patients</td>
<td>None</td>
</tr>
<tr>
<td>(1984)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linkowski et al.</td>
<td>20</td>
<td>30 mg</td>
<td>6</td>
<td>Newly admitted schizophrenics: 6 acute, 8 sub-acute, 6 sub-chronic</td>
<td>None</td>
</tr>
<tr>
<td>(1984)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Santos et al.</td>
<td>30</td>
<td>10, 15, or 30 mg</td>
<td>3</td>
<td>Nonresponders; schizophrenic, schizoaffective patients excluded</td>
<td>12–55</td>
</tr>
<tr>
<td>(1989)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

have been excluded, leaving a more chronic, neuroleptic-insensitive population; dropout rate was so high that only the first 2 weeks of the study were analyzed and it took 2 weeks to raise the plasma levels to the medium and high range.

On balance, there is evidence for a therapeutic-window-type relationship with HPL in the acutely exacerbated patient, but the evidence is not strong. Some chronic, neuroleptic-resistant patients seem to be able to tolerate high plasma levels, possibly without a deterioration of response. The use of the high plasma HPL levels (Van Putten et al. 1985) in neuroleptic-resistant patients is an unresearched area.

A new study with HPL. Sixty-nine newly admitted or readmitted,
drug-free (for at least 2 weeks, but usually several months), schizophrenic (by DSM-III [American Psychiatric Association 1980]) men were randomly assigned to receive HPL either 5, 10, or 20 mg/day for 4 weeks (Van Putten et al. 1990a). In cases of nonresponse, the doctor could use clinical judgment to increase or decrease the dose for another 4 weeks. Clinical response was measured at baseline, weekly for the first 4 weeks, and at week 8 after the flexible-dose period. Clinical ratings were blind to plasma levels.

On average, these patients were in their early thirties and had had four previous hospitalizations. All had served in the armed forces, had worked for 4.5 years at some time in their lives, were judged "markedly ill" on the Nurses Observation Scale for Inpatient Evaluation (NOSIE; Honigfeld et al. 1966), and had scored at least "moderate" on conceptual disorganization, unusual thought content, or hallucinatory behavior. In fact, their mean baseline BPRS-Schizophrenia factor score was 13 (normal = 3; maximum = 21), indicating they were quite psychotic at baseline. Those who were very excited or menacing and those who had a history of nonresponse to neuroleptics were not included in this study.

HPL plasma levels were averaged during fixed-dose treatment, and clinical change was measured by the change from baseline on the BPRS Psychosis cluster (Thought Disturbance + Hostile Suspiciousness clusters). These data were fit to a theoretical model that proposed the presence of two sigmoidal dose-effect functions, one resulting in a positive treatment response and the other in toxicity or other negative effects as suggested by Teicher and Baldessarini (1985). In this two-component model, the predicted BPRS change score is obtained by subtracting the negative or toxic component from the positive or therapeutic component.

Figure 1 shows this two-component model superimposed on the scatterplot of change in the BPRS Psychosis cluster versus mean plasma HPL (multiple $r = 0.46$, $p = 0.001$). By inspection, it appears reasonable to divide the data into the following ng/ml ranges: $< 2 = \text{ineffective}$, $2-5 = \text{threshold}$, $5.1-12 = \text{optimal}$, $> 12 = \text{toxic}$. Mean improvement on the BPRS Psychosis factor was significantly greater by $t$ test in the optimal than in the toxic range ($p = 0.004$) or the threshold range ($p = 0.004$) (table 2). Mean improvement in the optimal range was roughly twice that in the threshold and toxic ranges. The standardized effect sizes were both large (0.95 and 0.90, respectively).

**Figure 1. Curvilinear relationship between plasma concentration of haloperidol and change in Brief Psychiatric Rating Scale (BPRS) Psychosis factor**

![Figure 1](image_url)

<table>
<thead>
<tr>
<th>Range (ng/ml)</th>
<th>Ineffective $(n = 12)$</th>
<th>Threshold $(n = 14)$</th>
<th>Optimal $(n = 30)$</th>
<th>Toxic $(n = 13)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD)</td>
<td>2.4 ± 4.9</td>
<td>4.2 ± 4.4</td>
<td>8.8 ± 5.0$^1$</td>
<td>4.6 ± 3.7</td>
</tr>
</tbody>
</table>

Note.—BPRS = Brief Psychiatric Rating Scale.

$^1$Improvement better than at threshold or toxic levels, $p = 0.004$. 

![Table 2](image_url)

Table 2. Improvement in four haloperidol plasma level ranges
Reducing excessive (> 12 ng/ml) plasma levels. Thirteen patients had mean HPL plasma levels > 12 ng/ml at the end of the fixed-dose period. Three insisted on leaving the hospital before a dosage adjustment was possible; all had become more paranoid (BPRS-Paranoia = -3.5, SD = 2.5) and two had become extremely dysphoric. One patient with a mean HPL plasma level of 15.6 ng/ml insisted he needed more HPL and his plasma level eventually reached 90 ng/ml. Another patient with an HPL plasma level of 14.7 was mildly retarded (BPRS-Retardation = -2) but refused dosage reduction. The remaining eight patients, when their plasma level was reduced to < 12 ng/ml (range = 4.0-10.8 ng/ml, mean = 7.8 ng/ml), experienced fewer side effects (in particular a subjective sense of sedation and/or objective akinesia), became less psychotic (five of eight), less dysphoric (three of eight), or less retarded (eight of eight). No case deteriorated. Table 3 summarizes these changes.

Raising HPL plasma level above 12 ng/ml in relative nonresponders. In eight relative nonresponders (defined as a global improvement rating of “minimally improved” or less) with plasma levels in the 2-12 ng/ml range, the plasma level was raised above 12 ng/ml (range = 12.9-24 ng/ml, mean = 17.8 ng/ml). Six of eight cases became worse on the global improvement ratings. On balance, these six became more dysphoric. Table 4 summarizes the changes.

The lower therapeutic-window limit. If the lower limit of plasma HPL is 2 ng/ml, as figure 1 suggests, patients with plasma levels < 2 ng/ml at the end of the fixed-dose period should improve as the plasma level is gradually raised > 2 ng/ml. Patients with plasma levels of 1.8, 1.5, 1.6, 1.1, 1.1, and 1.4 ng/ml all improved (using the Clinical Global Impressions scale [CGI; Guy 1976] as criterion) as their plasma levels rose > 2.0 ng/ml. The respective plasma levels at which “improvement” occurred were 2.9, 2.6, 2.1, 2.2, 2.0, and 6.7 ng/ml. One man with a plasma level of 1.8 ng/ml made a complete recovery. The two patients with plasma levels of 1.9 and 1.4 did not improve at any plasma level, suggesting their illness was not sensitive to HPL.

A curvilinear relationship between plasma HPL and clinical response was found in these acutely exacerbated patients, most of whom had not taken a neuroleptic for 6 months or more. The upper and lower limits of this proposed therapeutic window were 12 ng/ml and 5 ng/ml, respectively. When plasma levels in relative nonresponders were pushed beyond 12 ng/ml (as in routine clinical practice), they, on balance, deteriorated. In particular, relative to their status at the therapeutic plasma level, they became more dysphoric (BPRS-Depression factor = -2.6, SD = 2.8, p < 0.07), more withdrawn (Withdrawal-Retardation factor = -1.3, SD = 2.6, NS), and did not improve in global psychosis ratings (Schizophrenia + Paranoid factors = -0.83, SD = 3.4, NS).

Similarly, when patients with plasma levels > 12 ng/ml had their plasma levels lowered, they, on bal-

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### Table 3. Effect of reducing plasma haloperidol (HPL) levels < 12 ng/ml (change scores relative to baseline, n = 8)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HPL (mean ± SD ng/ml)</th>
<th>BPRS-S</th>
<th>BPRS-D</th>
<th>BPRS-P</th>
<th>BPRS-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>15.0 ±2.1</td>
<td>5.1 ±1.6</td>
<td>1.0 ±4.3</td>
<td>2.4 ±2.9</td>
<td>-2.3 ±3.4</td>
</tr>
<tr>
<td>5-8</td>
<td>7.8 ±2.1</td>
<td>6.4 ±2.2</td>
<td>2.8 ±3.8</td>
<td>3.0 ±3.5</td>
<td>-0.1 ±3.8</td>
</tr>
<tr>
<td></td>
<td>t = 2.76</td>
<td>—</td>
<td>1.93</td>
<td>5.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = &lt; 0.05</td>
<td>—</td>
<td>&lt; 0.10</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 4. Increasing haloperidol (HPL) plasma levels in relative nonresponders (change scores relative to baseline, n = 8)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HPL (mean ± SD ng/ml)</th>
<th>BPRS-S</th>
<th>BPRS-R</th>
<th>BPRS-P</th>
<th>BPRS-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>7.0 ±4.0</td>
<td>1.7 ±2.2</td>
<td>0.3 ±1.2</td>
<td>1.5 ±2.3</td>
<td>-1.2 ±2.7</td>
</tr>
<tr>
<td>5-8</td>
<td>17.8 ±5.0</td>
<td>2.7 ±2.0</td>
<td>-1.0 ±2.2</td>
<td>-0.3 ±2.6</td>
<td>-3.8 ±4.1</td>
</tr>
<tr>
<td></td>
<td>t =</td>
<td>2.33</td>
<td>NS</td>
<td>NS</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>p = NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

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Note.—Ratings are on Brief Psychiatric Rating Scale (BPRS) Schizophrenia (S), Depression (D), Paranoia (P), and Retardation (R) factors. Higher change scores = improvement; negative scores = deterioration.

*Paired t test, two-tailed.
ance, improved (BPRS-Schizophrenia 1.25, p < 0.05; Withdrawal-Retardation = 2.1, p < 0.01). No case deteriorated. Some improved in the sense that they no longer appeared overmedicated or had a personal sense of sedation and/or objective akinesia. In these cases a plasma level would only have confirmed what was already clinically apparent. Three cases with plasma levels > 12 ng/ml had become globally worse, developed frantic agitation, and insisted on leaving the hospital before their plasma levels could be lowered. (Two of these cases had become profoundly depressed.) Finally, two cases had developed delusions of bodily destruction that disappeared as the plasma level was lowered into the therapeutic range. We, like Quitkin et al. (1975), believe that delusions of bodily destruction can be a psychotic interpretation of neuroleptic toxicity.

We do not mean to imply that patients with plasma levels above 12 ng/ml cannot improve relative to their baseline. After all, it is not unusual for schizophrenic patients in the United States to be treated with plasma levels > 12 ng/ml (table 5). Table 6 dichotomizes patients into either "much" or "very much improved" versus "minimally improved," "no change," or "worse." Five patients were rated improved at plasma levels > 12 ng/ml. Also, some patients tolerated very high plasma levels. One chronic patient in this sample requested more and more HPL, claiming that each dosage increase made him feel somewhat better. Finally, at a dose of 90 mg of HPL (plasma level of 90 ng/ml), he became slightly sedated and developed moderate akathisia and dyskinesia but remained much improved. When his plasma level was decreased to the therapeutic range, he remained improved and had fewer side effects (including less dyskinesia).

Since the correlation between dosage and plasma level is rather high (r = 0.76) in this and other studies, a plasma level usually does not provide much extra information. On a dose of 10-15 mg/day nearly all patients would be within the therapeutic window. Recent work from the Karolinska Institute (Llerena et al., submitted for publication), however, indicates that about 7 percent of Caucasians may be at risk of developing side effects from aberrantly high plasma HPL levels. (Seven percent of Caucasians have a decreased capacity to hydroxylate debrisoquine, and they eliminated a 4-mg HPL dose significantly more slowly than normal debrisoquine metabolizers. Further, the poor debrisoquine metabolizers developed severe extra-pyramidal side effects [EPS].) On balance, it would seem prudent to consider dosage reduction in any nonresponding patient with a plasma level > 12 ng/ml. Similarly, it may also be prudent to measure plasma HPL in responding patients who are on a high dosage. If the plasma HPL is > 12 ng/ml, a trial dosage reduction may be indicated. Finally, plasma HPL levels may be most informative with drug interactions. For example, carbamazepine is known to reduce plasma HPL levels by 50 percent or more through microsomal enzyme induction (Ereshefsky et al. 1984; Jann et al. 1985; Fast et al. 1986). Other drug interactions are likely to be discovered.

The reason patients tend not to do as well at plasma levels > 12 ng/ml is unknown. It is unclear whether efficacy is lost above a certain plasma level or whether adverse effects diminish therapeutic response. Our clinical sense is the latter, but there was no relationship in this sample between plasma HPL level and objectively rated akinesia or akathisia. However, when side effects were rated on the CGI scale, there was a powerful relationship between plasma HPL and what the patient experienced as "disabling side effects" (defined as "side effects that significantly interfered with patient's functioning" or "side effects that outweigh therapeutic effects"). Figure 2 shows the relationship between plasma HPL and disabling side effects significant at the p = 0.0002 level by logistic regression. This relationship between plasma HPL and a more global and subjective side-effect rating suggests that side effects—at least in acutely exacerbated patients—contribute to a poorer response at plasma levels > 12 ng/ml.
Table 6. Global improvement at the end of the haloperidol (HPL) fixed-dose period (n = 68)

<table>
<thead>
<tr>
<th>Range</th>
<th>HPL level (mean ± SD)</th>
<th>HPL level (ng/ml)</th>
<th>Improved¹</th>
<th>Not Improved¹</th>
<th>Ratio of improved to not improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineffective</td>
<td>1.3 ± 0.5</td>
<td>&lt; 2</td>
<td>1</td>
<td>9</td>
<td>0.10</td>
</tr>
<tr>
<td>Threshold</td>
<td>3.2 ± 0.7</td>
<td>2-5</td>
<td>6</td>
<td>43</td>
<td>0.75</td>
</tr>
<tr>
<td>Optimal</td>
<td>8.2 ± 1.6</td>
<td>5-12</td>
<td>22</td>
<td>73</td>
<td>2.75</td>
</tr>
<tr>
<td>Toxic</td>
<td>15.2 ± 2.7</td>
<td>&gt; 12</td>
<td>5</td>
<td>39</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Note. — $\chi^2 = 10.75; df = 3, p = 0.013.$  
¹Improved = very much or much improved on the Clinical Global Impressions scale; Not Improved = minimal improvement, no change, or minimally worse.

Figure 2. Disabling side effects and plasma haloperidol

Logistic regression model, N=68, Chi-square=13.5, p=.0002

Fluphenazine. Three fixed-dose studies examined the relationship between plasma fluphenazine (FLU) and clinical response in newly admitted schizophrenic patients. Dysken et al. (1981) assigned 29 schizophrenic and schizoaffective patients to receive 5 mg, 10 mg, or 20 mg of FLU hydrochloride daily. Outcome was measured on the New Haven Schizophrenic Index (NHSI; Astrachan et al. 1972) and, after 2 weeks of treatment, both an upper and lower end of the therapeutic window were suggested by three nonresponders whose plasma FLU levels were above 2.8 ng/ml and by two nonresponders and one partial responder whose plasma FLU levels were below 0.2 ng/ml. It was possible to fit a quadratic regression line (curvilinear relationship) at the $p = 0.02$ level. A fortyfold variability in steady-state plasma FLU levels (0.1 to 4.2 ng/ml) was found on the 20-mg dose. There was no relationship between plasma level and EPS. Mavroidis et al. (1984b) similarly assigned 19 schizophrenic patients to receive the same level. Further, the higher plasma levels in some treatment-refractory patients are really used for "chemical restraint" or result from our compulsion to "do something."

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Three doses of FLU (5, 10, or 20 mg/day). After 2 weeks of treatment, the best response (a mean reduction of 59% on the NHSI) occurred in the 0.13–0.7 ng/ml range. In the 0.8–2.3 ng/ml range (mean = 1.48, SEM = 0.17 ng/ml), improvement was more modest (34%) and this difference in improvement rates (59% vs. 34%) was significant (t = 3.22, p < 0.01, two-tailed test). A curvilinear correlation between plasma FLU and clinical improvement was significant (r = 0.47, p < 0.05). There was no mention of side effects. Levinson et al. (1988), in a preliminary report, assigned 22 schizophrenic patients to receive either 10 or 20 mg of oral FLU. After 24 days of treatment, there was a linear correlation (r = 0.43, p < 0.05) between plasma FLU and improvement on the BPRS Thinking Disturbance factor, and this improvement occurred in the 0.20–4.5 ng/ml range with no indication of decreased antipsychotic effect at the higher plasma FLU levels. There was no mention of side effects.

In sum, two studies suggest an optimal plasma FLU range for antipsychotic effect, but the evidence is not robust and the point at which antipsychotic response diminishes—if indeed it does—is unclear. Further, the aforementioned three studies analyzed only for antipsychotic effect. It is not unlikely that improved antipsychotic effect at higher plasma FLU levels might be counterbalanced by deterioration in emotional withdrawal, blunted affect, motor retardation, depression, anxiety, and, quite possibly, side effects, leading to a complex risk-benefit analysis as suggested by Van Putten et al. (1990a) in the case of HPL.

A new study with fluphenazine. Seventy-two newly admitted or readmitted drug-free men with a diagnosis of schizophrenia by DSM-III were assigned randomly to receive FLU hydrochloride either 5, 10, or 20 mg daily for 4 weeks. Patients with a history of nonresponse to neuroleptic drugs were excluded, as were those who had a history of intractable EPS with high-potency neuroleptics.

Briefly, these patients were in their thirties and, on average, had had five previous hospitalizations. All had served in the armed forces, had worked an average of 4.5 years at some time, were currently judged "markedly ill" on the NOSIE, and scored at least "moderate" on conceptual disorganization, unusual thought content, or hallucinatory behavior on the BPRS. In fact, their mean baseline BPRS-Schizophrenia factor score was 12.9 (normal = 3, maximum = 21), indicating they were quite psychotic at baseline.

Clinical status was assessed weekly in semistructured interviews with the senior author using the CGI scale, the BPRS, and the Involuntary Movement and Extrapyramidal Side Effects Scale (IMEPS; May and Van Putten, unpublished scale) which rates akathisia and akinesia on 7-point scales. Akinesia was broken down into decreased facial expression, decreased expressive gestures, decreased spontaneous movement, and slow speed of movement.

FLU, FLU sulfoxide, 7-hydroxy FLU, and FLU N-oxide were measured using previously described highly specific and sensitive RRAs (Midha et al. 1980, 1987, 1988; Aravagiri et al. 1990). Blood was drawn at 9 a.m., 12 hours after the bedtime dose.

Data were analyzed by logistic regression using "disabling side effects" and "global improvement" as the outcome measures with log of plasma FLU as the independent variable. Disabling side effects consisted of either "side effects that significantly interfered with patient's functioning" or "side effects that outweigh therapeutic effects" on the CGI scale. Global improvement consisted of either "marked" or "moderate" improvement on the CGI scale. We also analyzed by logistic regression the percentage of patients who improved without experiencing side effects using a quadratic function of plasma FLU.

Figure 3 shows the logistic regression for improvement, which is significant at the p = 0.015 level. Figure 4 shows the logistic regression for disabling side effects, which is significant at the p = 0.0008 level, and figure 5 combines figures 3 and 4. Figure 6 shows the percentage of patients who improved without experiencing disabling side effects. This figure indicates that the maximum percentage of patients rated improved without disabling side effects occurred at a plasma level of 0.67 ng/ml.

In this sample, higher plasma FLU levels (up to 4.23 ng/ml) were associated with a greater rate of global improvement. Our data indicate, however, that close to 90 percent of acute patients will have disabling side effects at a plasma level of 2.7 ng/ml. At least in the patient's view, these disabling side effects negated or compromised the improvement in psychosis.

Both Mavroidis et al. (1984b) and Dysken et al. (1981) claim a lower therapeutic limit of 0.13 and 0.2 ng/ml, respectively. At these plasma levels, our data suggest a global improvement rate of only 20 percent and 30 percent, respectively.

Disabling side-effect data were elicited by the senior investigator in semistructured interviews in which specific questions about side effects...
were asked. Thus, if a patient stated that a certain amount of drowsiness, restlessness, or jitteriness (akathisia), or a feeling of being "slowed down" were unbearable to him, the side effect would be listed as "outweighing therapeutic effects" even though objectively the patient may not have appeared drowsy, slowed down, or akathisic. If the patient indicated that he felt the side effects would interfere with functioning outside of the hospital, the side effect was listed as "significantly interferes with patient's functioning."

Because many of the patients who complained of disabling side effects did not objectively appear overmedicated or distressed by side effects, we would expect the side-effect/dose-response curve to shift markedly to the right when evaluated in other settings. In other words, in many settings the therapeutic index of FLU would appear much larger. From the patient's point of view, however, the therapeutic index of FLU is much narrower, reaching a ratio of therapeutic to unwanted effects of 1 at a plasma FLU level of approximately 3 ng/ml. Another reason for our narrow therapeutic index might be the large portion of patients with no exposure to a neuroleptic drug for 12 months or more.

Disabling side effects were highly correlated with the EPS ratings of akinesia (r = 0.44, p = 0.0001), akathisia (r = 0.60, p = 0.0001), and akathisia plus akinesia (r = 0.66, p = 0.0001). The objective EPS ratings of akathisia and akinesia were mild or less in 83 percent of cases, and these ratings would likely be dismissed in many other settings. Weiden et al. (1987) have shown that akathisia was markedly underdiagnosed in most clinical settings.

Figure 6 should not be construed as a therapeutic window. It shows
that at a plasma FLU level of 0.67 ng/ml, the maximum percentage (approximately 48%) improve without disabling side effects. Above this plasma level, an increasing percentage of patients improve vis-à-vis psychotic symptoms but with a progressive increase in disabling side effects. We believe that such a risk-benefit analysis is the most appropriate way of analyzing neuroleptic plasma level and clinical response data.

Fluphenazine decanoate. Long-acting injectable neuroleptics (LINS) such as fluphenazine decanoate (FD) are usually prescribed during the maintenance phase of treatment. At this stage, the goal of treatment is the prevention of relapse, rather than the management of a psychotic episode. In addition, the pharmacokinetics of LINS also require study designs that differ substantially from those used for studying oral neuroleptics. These constraints result in a number of complications in the design of studies that focus on the relationship between plasma level and relapse rates. First, patients treated with LINS require a much longer period of time to reach a steady state than patients treated with oral drugs. For FD, steady state is reached after 3 months (Marder et al. 1989). In addition, relapse occurs gradually over a prolonged period of time, necessitating that patients be followed for 1 year or more. Also, patients treated during the maintenance phase of therapy will usually receive substantially lower drug doses, which may result in plasma concentrations that are difficult to measure. For FD, FLU concentrations may be in the subnanogram range.

These problems may explain why there are few controlled studies that focus on the relationship between plasma levels and relapse rates for patients treated with depot FLU.
Wistedt et al. (1982) studied levels of FLU and a metabolite, 7-hydroxyfluphenazine, in patients who received FD (mean dose = 21.4 mg every 2 weeks). Patients who relapsed had lower plasma levels (mean = 0.92 ng/ml) than those who did not relapse (mean = 1.36 ng/ml). Ereshefsky et al. (1984b) found a therapeutic threshold of 0.2 to 0.4 ng/ml for a patient group treated with either oral FLU or FD.

We (Marder et al., in press) monitored plasma levels of FLU in patients randomly assigned to a double-blind comparison of 5 and 25 mg of FD administered every 2 weeks. We measured plasma levels at 3, 6, and 9 months (because of the time it takes to reach steady state with LINS) and evaluated the relationship between these levels and rates of psychotic exacerbation during the following year. Using both logistic regression and survival analysis we found statistically significant relationships at both 6 and 9 months, indicating that lower plasma concentrations were associated with a greater risk of relapse (using logistic regression, \( p = 0.04 \) at 6 months and \( p = 0.003 \) at 9 months; using survival analysis, \( p = 0.052 \) for 6 months and \( p = 0.0008 \) for 9 months; see figures 7 and 8).

Figure 7 indicates that rates of psychotic exacerbation were relatively low above FLU levels of 0.8 or 0.9 ng/ml, suggesting that this may be a reasonable plasma level for maintenance. On the other hand, very few patients with levels above 1.2 ng/ml experienced exacerbations, suggesting that if the clinician had given a priority to preventing relapse and was less concerned about side effects, then this higher level might be preferable. Our findings indicate that patients with FLU levels below 0.9 ng/ml may be on the linear part of
the curve and would benefit from a dosage increase. Patients who received 25 mg of FD every 2 weeks had mean levels of about 1.4 ng/ml and nearly all were on the flatter part of the curve. Patients receiving a 5-mg dose in our study had mean FLU levels of 0.6 to 0.7 ng/ml with SD of 0.5 to 0.6, indicating that this dose led to a substantial number of patients having levels that rendered them vulnerable to psychotic exacerbations.

These results, if confirmed, suggest a management strategy for clinicians who are attempting to treat patients with relatively low doses of FD. As doses are gradually reduced, FLU plasma levels would be monitored. Dosage reduction would stop when a level of less than 0.8 ng/ml was reached.

Perphenazine. Bolvig-Hansen et al. (1982) randomly assigned 34 schizophrenic patients to either a low (< 3 Nmol/l) or high (5-10 Nmol/l) plasma perphenazine (PPZ) level. Seven dropped out during the first week because of "lack of compliance" and one patient developed a confusional episode requiring parenteral therapy. Data on these eight dropouts were not analyzed. After 5 weeks of treatment at these respective plasma levels, plasma concentration above 2 Nmol/l resulted in a significantly better therapeutic outcome than concentrations below this value (p = 0.005). All patients received biperidine 2 mg t.i.d. which apparently successfully suppressed EPS. These authors also studied 32 newly admitted patients (6 dropped out because of poor compliance but these data were not analyzed) and treated them with a flexible dosage of PPZ (mean = 30.5 mg/day, range = 12-48 mg/day). The dosage was kept constant during the entire investigation and the purpose of the study was to examine relationships between EPS and PPZ levels. When a patient developed EPS, a plasma sample was taken and the patient was terminated from the study. Patients with no side effects had a plasma PPZ sample taken 4 weeks after PPZ treatment. PPZ levels in excess of 3 Nmol/l were associated with a highly increased risk of EPS (p < 0.02).

Plasma concentrations high enough to elicit EPS (greater than 3 Nmol/l) seemed to result in a slightly weaker therapeutic response, but this was not statistically significant. On the basis of these two studies, these authors suggested a plasma PPZ concentration between 2-3 Nmol/l for optimal antipsychotic effect.

In a survey to test the clinical utility of a plasma PPZ level, Bolvig-Hansen and Larsen (1985) measured plasma PPZ in 228 psychotic inpatients who were treated with individually determined doses of PPZ. Of these patients, 105 (46%) had plasma PPZ levels (mean PPZ level = 11.4 Nmol/l) above the "optimal" therapeutic range of 2-3 Nmol/l; 50 percent of these patients had EPS and 80 percent had a "definite" antipsychotic response. EPS was defined as "akathisia, akinesia, dystonia or parkinsonism of such degree that supplementary treatment with an antiparkinson agent was required" (p. 17). Plasma level was reduced to the 2-3 Nmol/l range in 24 of these patients, and EPS disappeared without alteration of antipsychotic effect. Of the 85 patients with plasma levels in the 2-3 Nmol/l range, 86 percent responded and only 8 percent had EPS. Of the 38 patients with PPZ levels < 2 Nmol/l, only 17 (45%) responded and 4 (11%) experienced EPS. Increasing the plasma PPZ level to the 2-3 Nmol/l range improved the antipsychotic effect without causing additional EPS (no figures given).

In their abstract, Bolvig-Hansen and Larsen (1985) recommend a range of 2-6 Nmol/l, although no data were shown to support this range. The relationship between dose and plasma level was such that a dosage range of 4-54 mg/day was required to achieve a plasma PPZ level between 2.0-2.9 Nmol/l, but no correlation was given. About 7 percent of Caucasians are poor metabolizers of debrisoquine and developed peak concentrations of PPZ more than three times higher than normal metabolizers when given a single oral dose of PPZ (Dahl-Puustinen et al. 1989). It is my understanding (personal communication, S.G. Dahl, 1990) that PPZ levels are frequently obtained in the Scandinavian countries and that the range of 2-6 Nmol/l appears clinically useful.

Mazure et al. (1990) treated 66 newly admitted patients (25 men, 41 women) with PPZ 0.5 mg/kg/day for 10 days. This was a mixed sample: manic psychosis (n = 32), major depression with psychotic features (n = 16), schizophrenia (n = 10), and schizophreniform disorder (n = 8). Benzotropine was given if "serious EPS" developed and required treatment. PPZ steady-state levels were not significantly correlated with global severity ratings of psychosis after 10 days of treatment in the total sample of 66 patients (r = -0.06), and the authors could not replicate the finding of optimal response in the 2-6 Nmol/l range. However, by summing the BPRS Hallucinations and Conceptual disorganization items, a threshold level of 2 Nmol/l was confirmed (the threshold of 2 Nmol/l produced the highest point biserial correlation of the levels tested; r = -0.56, p = 0.0001). The analysis of these two BPRS items suggested that antipsychotic
effect did not improve with plasma PPZ levels above 2 Nmol/l. Further, although plasma PPZ level and EPS were not significantly correlated, benztpine treatment was significantly more common in patients with higher PPZ levels. (Plasma PPZ in benztropine-treated patients was [mean ± SD] 8.7 ± 13.5 Nmol/l as opposed to 5.5 ± 8.3 in those patients not requiring benztpine; Mann-Whitney U, p = 0.005.) These data, therefore, are compatible with Bolvig-Hansen and Larsen's (1985) therapeutic range of 2-6 Nmol/l. Mazure et al. (1990) suggest that a plasma PPZ level may be useful in those in whom the distinction between EPS and worsening of psychosis is difficult to determine.

Thiothixene. Mavroidis et al. (1984a) randomly assigned 18 schizophrenic patients to thiothixene (THX) 16, 30, or 60 mg/day for 2 weeks. THX was measured by a gas chromatographic (GC) method, and clinical change was measured by the NHSI. A 40 percent or better improvement was observed in four of nine patients having plasma THX levels in the range of 0.45-1.0 ng/ml; in three of five having levels between 1.0 and 2.0 ng/ml; and in all of the four patients having levels between 2.5 and 10 ng/ml. One patient with a plasma level of 18.8 ng/ml demonstrated an “exacerbation of schizophrenic symptomatology,” and this patient determined the curvilinear correlation of 0.60. It is unknown whether this patient would have improved at a lower plasma level, but the authors suggested a therapeutic range of 2-15.0 ng/ml.

Yesavage et al. (1982, 1983) measured plasma THX 2.5 hours after a 30-mg oral dose in 28 schizophrenic patients who had been treated with 80 mg of THX for 7 to 10 days. A positive correlation (r = 0.51) was found between peak drug concentration and BPRS score. A similar correlation (r = 0.50) was found when the number of patients was increased to 48 (Yesavage et al. 1983).

Van Putten et al. (1983) treated 34 newly admitted schizophrenic patients with a fixed dose of THX (0.44 mg/kg) for 4 weeks. THX and its active metabolites were measured by an RRA. Improvement occurred over the entire range of recorded plasma levels, but the chances of substantial improvement appeared greater above 40 neuroleptic units. Side effects, however, precluded an increase in dosage in 11 nonresponders with plasma level < 40 neuroleptic units. Correlations between plasma THX level and clinical response were significant (p = 0.025) but weak (r = 0.36) for both the NOSIE and the doctor's global rating.

Since plasma levels of neuroleptics are usually obtained in the morning, 10-12 hours after the bedtime dose, only Mavroidis et al.'s (1984a) study with 18 patients and a GC method address the THX “therapeutic range.” The status of the RRA used by Van Putten et al. (1983) is uncertain.

Chlorpromazine (CPZ). Wode-Helgødt et al. (1978) randomly assigned 48 schizophrenic patients to 200, 400, or 600 mg/day of CPZ for 4 weeks. In a range of 0-145 ng/ml there were no significant correlations between plasma CPZ and clinical outcome. Six patients had plasma CPZ levels > 40 ng/ml and these six patients improved, suggesting a lower limit of 40 ng/ml. Three of these six patients had plasma levels between 100 ng/ml and 145 ng/ml. Plasma CPZ levels were strongly correlated (r = 0.68 at 4 weeks) with EPS as well as drowsiness (r = 0.46 at 4 weeks).

Alfredsson et al. (1984, 1985) treated 25 schizophrenic patients with CPZ 400 mg/day for 8 weeks. There was no correlation between CPZ levels and various ratings of clinical improvement; a threshold level of 40 ng/ml for the first 4 weeks of treatment was suggested by the authors, but no data were provided. The range of plasma CPZ levels was not given. Correlations between somnolence and plasma CPZ were significant during the first 4 weeks (r = 0.56 and 0.49), and patients with plasma levels above the median experienced significantly more EPS (p < 0.05). Patients with CPZ levels below the median tended to experience the greatest improvement in depression.

May et al. (1981) treated 48 newly admitted schizophrenic patients with CPZ 3 mg/lb (450 mg/day for a 65.7-kg person) for 4 weeks. There were no significant correlations between plasma CPZ level on the last
day of treatment and any of 10 clinical improvement variables. There was complete overlap in plasma CPZ levels between responders and nonresponders in a nondetectable to 700 ng/ml range (Van Putten et al. 1981). Dosage was subsequently increased in a range of 600 to 1,800 mg/day (mean = 1,333, SD = 423 mg/day) in 11 of the nonresponders. Six of the 11 patients eventually reached plasma levels > 100 ng/ml, but none improved. Four of these six patients became globally worse, and three became more bizarre, agitated, and hostile. One patient (plasma CPZ = 270 ng/ml) became more delusional, started to scream at cars, and struck a nurse without provocation. Another patient (plasma CPZ = 120 ng/ml) became agitated, more unpredictable, and cut his clothes into little pieces. The third patient (plasma CPZ = 110 ng/ml) became agitated and irascible, and struck a physician. When CPZ dosage was lowered these patients improved.

Three responders at the end of the fixed-dose period had plasma levels > 100 ng/ml and appeared overmedicated. A 46-year-old man taking 425 mg and with a plasma level of 215 ng/ml appeared sluggish and somewhat drowsy. A 25-year-old woman on 400 mg and with a plasma level of 165 ng/ml complained of postural hypotension, drowsiness, extreme blurring of vision, and photosensitivity. A 30-year-old man on 600 mg and with a plasma level of 110 ng/ml complained of tardive dyskinesia, and one had a trial of treatment with depot neuroleptics (which overcomes absorption problems and first pass metabolism), it is unlikely that decreased bioavailability explains much treatment resistance. Decreased bioavailability is more likely to occur with concomitant administration of such known enzyme inducers as carbamazepine, which can lower neuroleptic levels by 50 percent or more. Other interactions are likely to be detected.

Aberrantly high plasma levels are more problematic. Only in the case of HPL and CPZ is there a suggestion of an upper limit beyond which therapeutic response seems to diminish in at least some patients. In the case of CPZ, plasma levels above 100 ng/ml may be associated with behavioral toxicity (Van Putten et al. 1981). In the case of HPL, a plasma level above 12 ng/ml in a nonresponding patient should at least raise the possibility of reducing dose.

With FLU, PPZ, and HPL, side effects, particularly as subjectively experienced, are related to plasma levels. In the case of FLU, plasma levels > 2 ng/ml in a nonresponding patient should raise the possibility of subjective disabling side effects, which might compromise improvement. In the case of PPZ, optimal antipsychotic effect with minimal EPS appears in the range of 0.8–2.4 ng/ml. Above this range patients experience EPS with no gain (and possibly a loss) in antipsychotic effect (Bolvig-Hansen et al. 1982, Bolvig-Hansen and Larsen 1985). It may be that a plasma level is most useful when the distinction between side effects and worsening psychosis is unclear.

Table 7 summarizes reported therapeutic plasma concentrations for some antipsychotic drugs. These therapeutic plasma level concentrations cannot be regarded as established by any means, but they may help to identify aberrant plasma levels.

The utility of high neuroleptic plasma levels in the treatment-resistant patient has not been investigated. Studies that seek to establish a relationship between plasma level and clinical response must exclude treatment-resistant cases, as no relationship between clinical response and plasma level can be demonstrated if a substantial portion of the sample is truly treatment resistant. Further, the relationship between plasma level and clinical state in the chronic treatment-refractory patient is likely to be complicated. The setting and psychological requirements of the individual patient may affect plasma level requirements. Thus, in some treatment-resistant patients, particularly in poorly staffed institu-
Table 7. Reported therapeutic plasma concentration ranges for antipsychotic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic plasma concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>30–100¹</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.2–2.0²</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2–12¹</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>0.8–2.4²</td>
</tr>
</tbody>
</table>

¹Consider dosage reduction in patients with plasma level above upper limit.
²Range of concentrations in which good response without debilitating side effects has been found; no evidence that reduction of plasma levels above the upper limit improves antipsychotic effect.

Conclusions, high plasma levels are really used for “chemical restraint,” conceptualized as a combination of akinesia and sedation. Chemical restraint can also be the least restrictive form of treatment for a patient who is aggressive in response to intractable hallucinations or delusions. Also, some treatment-resistant patients actually prefer sedation and akinesia to dampen their misery or to help contain destructive impulses. Studies are needed in which treatment-refractory patients with high plasma levels are randomly assigned to plasma level reduction or to a control group in which plasma level remains the same.

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The Authors

Theodore Van Putten, M.D., is Staff Psychiatrist, West Los Angeles Veterans Affairs Medical Center, Brentwood Division, and Professor of Psychiatry, University of California, Los Angeles, CA. Stephen R. Marder, M.D., is Staff Psychiatrist, West Los Angeles Veterans Affairs Medical Center, Brentwood Division, and Associate Professor of Psychiatry, University of California, Los Angeles, CA. William C. Wirshing, M.D., is Staff Psychiatrist, West Los Angeles Veterans Affairs Medical Center, Brentwood Division, and Assistant Professor of Psychiatry, University of California, Los Angeles, CA. Manickam Aravagiri, Ph.D., is Assistant Research Pharmacologist, Veterans Affairs Medical Center, Brentwood Division, and University of California, Los Angeles, CA. Nicole Chabert, Ph.D., is Clinical Research Associate, Veterans Affairs Medical Center, Brentwood Division, Los Angeles, CA.