

the period of an examination, i.e., 10 minutes as opposed to 10 seconds.

The group generally agreed that the use of scores on rating scales to define a diagnosis was inappropriate. This is not a purpose for which rating scales are intended. The "diagnosis" of tardive dyskinesia should be a longitudinal process. Advances in validating diagnostic criteria will likely come from prospective assessment, as well as studies of pharmacological response patterns and long-term outcome.

In order to facilitate comparisons among studies of prevalence, treatment, and outcome, it was suggested that attention be given to parameters and variables which should be included in research reports. Suggestions included the following: age, sex, psychiatric diagnosis, drug treatment history, evidence of preexisting CNS dysfunction, duration of dyskinetic movements on and off medication, response to any pharmacological probes (e.g., dopaminergic or cholinergic manipulations), and characteristics of the dyskinesias (videotapes being highly desirable).

Participants agreed on the importance of an extended baseline drug-free period (e.g., 3 months) to establish the relative persistence of the disorder (particularly if a concurrent placebo group is not included) in interpreting the results of treatment studies because of the potentially high rates of spontaneous improvement or remission. In patients for whom drug withdrawal is not feasible, a similar period of observation on a constant dose of neuroleptics would be desirable.

Further work on scale construction in rating instruments is necessary. Work will be done to expand and modify the AIMS.

Further information on prevalence is needed in pediatric populations, the mentally retarded, and patients receiving neuroleptics for the treatment of nonpsychotic anxiety or other nonpsychotic indications.

The group concluded that both the amount and quality of research in this area has improved considerably in the past few years, and that it would be useful for such a group to provide an opportunity for investigators to meet and work on problems of common concern.

## Subjective Responses to Thiothixene and Chlorpromazine

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The subjective response to the first dose of antipsychotic

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medication is important. Those who see the drug effect as helpful and syntonically pose no particular problem, but those with a dysphoric response are a different matter. As the authors have previously reported, the patients' subjective response to a test dose of chlorpromazine (CPZ) was modestly predictive of short-term outcome after a sustained course of therapy with the same drug. In particular, an early dysphoric response seemed to augur a poor prognosis for further drug treatment (1,2).

This paper reports on schizophrenic patients' subjective response to a test dose of thiothixene. In addition, the authors ask if the aforementioned dysphoric responders to CPZ have deviant pharmacokinetics.

## Method

### General Design

Newly admitted schizophrenic patients were given an initial test dose of either CPZ or thiothixene by mouth. Blood and saliva drug levels and subjective responses were measured over the test-dose period prior to subsequent treatment with a controlled standardized course of drug therapy.

### Test Dose

An initial test dose of thiothixene, 0.22 mg/kg (0.1 mg/lb) or CPZ hydrochloride, 2.20 mg/kg (1 mg/lb) was given as oral concentrate.

### Subjective Response

Subjective response was assessed by a semistructured interview that asks the following questions: "How does the medication agree with you?" "Does it make you feel calmer?" "Does it affect your thinking?" and "Do you think this would be the right medicine for you?" The subjective response was graded on a syntonically-dysphoric continuum, as reported previously (1). Patients were divided according to their scores into *syntonically*, *indifferent*, and *dysphoric* responders.

### Assessment Measures

Patients were assessed by, among others, the Brief Psychiatric Rating Scale (BPRS) (3), the Global Assessment Scale (GAS) (4), the Camarillo Insight Rating Scale (5) and the Continuous Performance Test (CPT) (6).

### Chlorpromazine Assay

CPZ was estimated in plasma and saliva by gas chromatography-mass spectrometry (GCMS), using N, N-bis-perdeuteriomethyl CPZ( $^{2}\text{H}_6$ -CPZ) as an internal standard. Details of the collection and assay methods are given in a previous publication (7).

### Results

Patients varied widely in their subjective response to the test dose. Of the 63 patients who received thiothixene, 12 were noncommittal, 6 were inaccessible, 31 (49 percent) had a syntonic, and 14 (22 percent) had a dysphoric response.

#### *Implications of Dysphoric Response*

A dysphoric response to a test dose of thiothixene was a powerful and statistically significant predictor of early noncompliance (Chi-square significant at the  $p < .001$  level). Six of the 14 patients who had a dysphoric response vehemently refused to take another dose of thiothixene (or of any other antipsychotic drug), no matter how small the next dose offered.

#### *Prediction of Dysphoric Response*

At pretreatment, the dysphoric responders were rated as less symptomatic than the syntonic responders ( $p < .01-.05$ ) on 5 of the 22 physician's measures (GAS, unusual thought content, blunted affect, disorientation, total BPRS). There were no differences in age (30 vs. 35 years), lifetime length of psychotic symptoms (341 vs. 264 weeks), paranoid diagnosis (51 vs. 52 percent), or level of insight. The authors conclude that although, in general, dysphoric responders were somewhat less symptomatic at pretreatment, the overlap is such that only the extremes are useful for prediction in the individual case.

The CPT was the most powerful predictor. A perfect score (zero errors of omission) correctly identified 82 percent of dysphoric responders, but 22 percent of syntonic and 36 percent of noncommittal responders had a perfect score as well. (Overall Chi-square = 11.27,  $df = 2$ ;  $p < .01$ ).

#### *The Nature of Subjective Response*

Syntonic responders, at 4 and 24 hours after their first test dose of thiothixene, already tended to describe an improvement in thought disorder or mood. Some examples

are: "It's easier to concentrate on one thought," "I don't feel threatened anymore," "It brings my mind into focus," "I can cope with the voices better." Dysphoric responders, on the other hand, experienced the drug effect quite differently. Some examples are: "It makes everything slower," "It make me feel down," "It takes away motivation," "I can't think straight," "It makes me uptight," and one likened it to a "bad acid trip." Indeed, some dysphoric responders, although cooperative and calm to start with, actually panicked and became objectively more disorganized several hours after the first dose.

#### *Mechanisms of Dysphoric Response*

Dysphoric responders experienced significantly more extrapyramidal symptoms (EPS)—notably akathisia—during the 24 hours after their first dose. Of dysphoric responders, 64 percent experienced akathisia as opposed to 17 percent of syntonic and 17 percent noncommittal responders (Chi-square = 11.67,  $df = 2$ ;  $p < .001$ ).

#### *The Meaning and Significance of EPS*

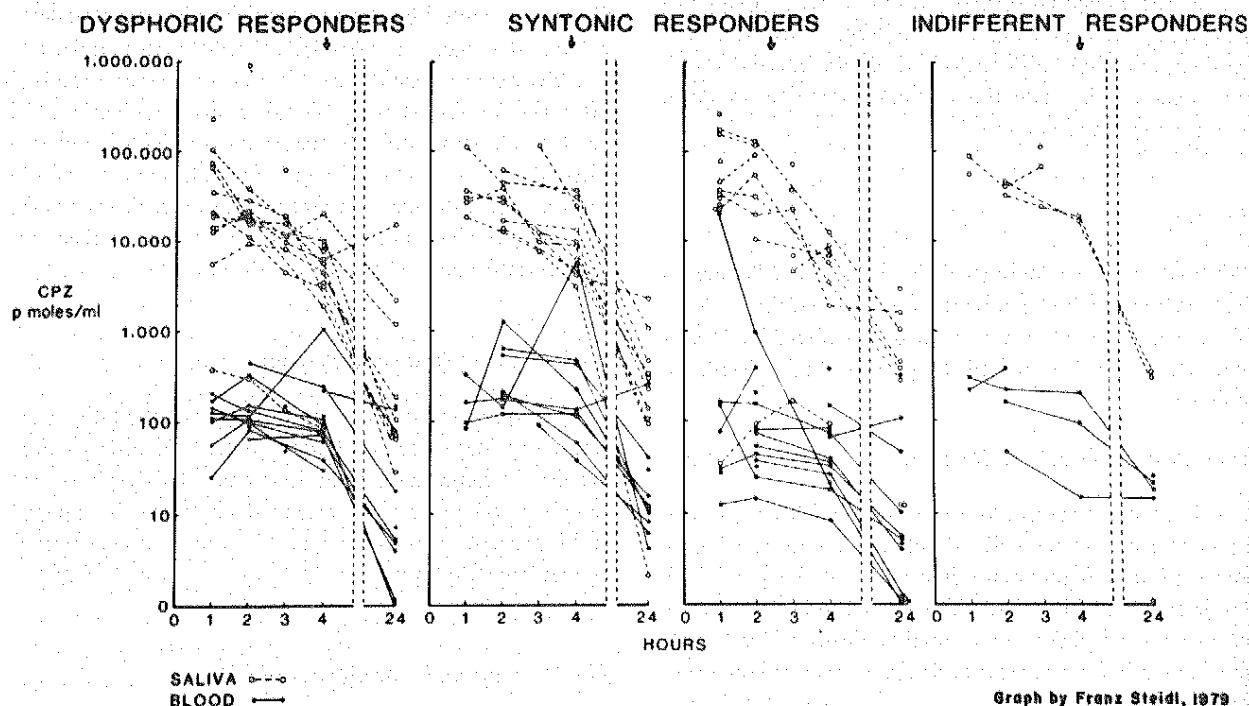
The fact that some syntonic responders also experienced EPS suggests that much may depend, as Sarwer-Foner has suggested (8), on the emotional meaning and significance that a side effect has for the individual patient. The six syntonic responders who had EPS regarded them as bothersome or annoying, but the dysphoric responders found EPS intolerable—an assault on their personality. For the dysphoric responder, side effects (usually an akathisia-like state) became the central drug experience.

#### *Subjective Response to CPZ and Plasma Level*

In the Figure, the logs of plasma and saliva CPZ are plotted against time for the dysphoric, indifferent, and syntonic responders. There does not appear to be any obvious relationship between subjective response and either blood or saliva levels. Certainly the dysphoric responders did not have higher blood or saliva levels than syntonic or indifferent responders; nor did they have differently shaped curves. Pearsonian correlations of subjective response at 4 and 24 hours with their respective plasma and saliva levels (whether raw or logarithmic) were not statistically significant.

Whatever the reason for dysphoric responses to CPZ, pharmacokinetics did not supply the answer.

## SUBJECTIVE RESPONSE vs BLOOD AND PLASMA LEVELS



Graph by Franz Steidl, 1979

Figure

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### A Double-Blind Controlled Study of Pimozide versus Chlorpromazine in Mania

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#### Introduction

Pimozide (PMZ) is a neuroleptic of the diphenylbutylpiperidine series. It is one of the most specific in its dopamine (DA) receptor-blocking activity and has little noradrenaline (NA) receptor-blocking action, as judged by the turnover of catecholamines (CA) (1).

In a previous pilot study of five manic patients, the authors found that PMZ led to improvement in all the symptoms rated and that the improvement was not asso-

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