Pharmacological Treatment of First Episode Non Affective Psychosis: Are Typical Doses of Haloperidol for Caucasians Appropriate for Asians?

By

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ABSTRACT

Pharmacological treatment for first episode of non-affective psychosis: are typical doses of haloperidol for Caucasians appropriate for Asians? By Jiahui Wong, Ph.D., 1999

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This study investigates possible Asian-Caucasian differences with respect to the metabolism and central nervous system (CNS) effect of haloperidol in the treatment of first episode non-affective psychosis. The two part study involved a 4-week active treatment phase and a 9-month follow-up. An attempt was made to control for other identified differences such as initial impairment, tolerance of symptoms, compliance and medication side effects.

Fifteen Asians and sixteen Caucasians participated in the four-week trial of treatment phase. Subjects were maintained on low oral doses of haloperidol(2mg./day) for the first week of treatment. Doses were increased weekly to 5mg., 10mg. and finally 20mg./day until *the optimal therapeutic dose* was achieved. This was defined as the point at which subjects: a) experienced significant clinical improvement; or, b) developed extrapyramidal side effects. On average, the same dose - 5mg./day - was optimal for both Asian and Caucasian subjects. At a fixed dose of 2mg haloperidol, Caucasian males had significantly lower plasma haloperidol levels than Asian males. No differences in plasma haloperidol levels were found between Asian and Caucasian females. There was no ethnicity effect or gender effect on plasma prolactin levels (change from baseline) after one week of treatment, implying that there were no differential prolactin response secondary to neuroleptic use.

At the end of 4 weeks, Asian subjects were responding less well to treatment than Caucasians. Covariance analysis demonstrated that this difference in initial improvement could be attributed to longer duration of illness onset, and greater proclivity to side-effects secondary to

neuroleptic treatment among Asian subjects. At 9-month open drug follow-up, Asian patients had improved to the point where their therapeutic gains matched those of the Caucasian subjects.

In conclusion, the study demonstrated Asian and Caucasian differences with respect to the metabolism of haloperidol in the treatment of first episode non-affective psychosis. There were no statistically significant ethnic differences in central nervous system (CNS) effect of haloperidol.

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CHAPTER 1

Introduction

Schizophrenia affects approximately 0.85 percent of the world's population (Eaton, 1986). It occurs in similar form and consistent rates across diverse cultures (Craig, 1997). The disorder probably has a multifactorial etiology that remains obscure. There is, however, considerable agreement that, whatever the complex of etiological factors, disorders in dopamine transmission play a role in the schizophrenia process. The effectiveness of many of the drugs used in the treatment of schizophrenia is attributed to their effect on dopamine pathways. However, despite the apparent cross cultural similarities in the phenomenology and distribution of schizophrenia, and despite the fact that the dopamine hypothesis is assumed to apply in all cultural groups, there appear to be ethnoracial differences in medication response (Potkin, 1984; Lin, 1983;1991; Ruiz, 1996). These differences are potentially important because prescribing guidelines for many drugs used for the control of schizophrenia are based on clinical trials that typically include only Caucasian male volunteers (Food and Drug Administration Guidelines 1977). The guideline has been changed recently in the U.S.A. to include women and ethnoracial minorities.

The current study investigates the response of Asians and Caucasians to the neuroleptic, haloperidol, and examines possible mechanisms to explain differential response. The study examines Asian-Caucasian differences in initial symptom impairment, tolerance of symptoms, compliance and medication side effects. It focuses also on differences in haloperidol plasma levels and prolactin levels secondary to haloperidol use.

Asians are one of the fastest growing ethnic groups in Ontario. Since this rapid growth is expected to continue, the majority of psychiatrists will be exposed to an increasing number of psychiatric patients of Asian descent. The Asian individual in his/her first episode of non-affective psychosis needs to be closely monitored since side effects could occur at a very low dose of antipsychotic drug (Lin, 1989). Intolerable side effects from neuroleptic medication can add further to stigmatization and treatment avoidance, unnecessarily prolonging suffering in those affected by the debilitating disorder. Increased understanding of the multiple ethnoracial influences on the success of pharmacological treatment for psychosis will help prevent this insidious cycle.

CHAPTER 2

Background

Etiology of Schizophrenia

Schizophrenia is a serious, debilitating illness that seems to exist worldwide. The WHO sponsored study, Determinants of Outcome of Severe Mental Disorders (DOSMD), aimed to identify every new case of schizophrenia in 12 sites in 10 different countries: Denmark, India, Colombia, Ireland, United States, Nigeria, Russia, Japan, United Kingdom and the Czech Republic during a two year period. Every person from age 15 through 54 who presented to a helping agency with signs or symptoms suggestive of a psychotic illness was assessed and diagnosed. The reliability and validity of the screening process was judged to be inadequate in 4 of the 12 sites. For the remaining 8 sites, the annual incidence rates for those cases with a restrictive core or nuclear schizophrenic symptom profile (characterized by positive symptoms) were remarkably similar (about 10 cases per 10,000 population) across sites. The DOSMD investigators concluded that restrictively defined schizophrenia occurs at a similar rate in diverse cultures and nations around the world.

Although the etiology of schizophrenia remains unclear, both genetic and environmental factors are thought to be implicated.

Biological relatives of patients with schizophrenia have a higher rate of schizophrenia and schizophrenia-like manifestations than the relatives of non-affected probands. The concordance rate for schizophrenia in monozygotic twins is between 40 and 50 percent. This concordance rate is four to five times higher than the concordance rate in dizygotic twins (14%) or in other siblings (10%). With two parents affected, the rate in children is 40%, with one parent affected, the rate 10%. Rate

in an affected offspring is 10%. Although environmental stressors including birth complications, and perhaps substance abuse during adolescence all contribute to the risk of schizophrenia occurrence, the heritability factor (i.e., the portion of risk attributable to genes) is estimated to be over 85% (Kendler, 1993).

Epidemiological data suggest a possible role for an infectious disease aetiology. Schizophrenia is associated with a winter birth excess which may be associated with a higher risk of viral infection during pregnancy (Bojholm et al., 1989). Infants born with a history of pregnancy or birth complications are at an increased risk for developing schizophrenia as adults (Barr et al., 1990). Possible explanations include: The genes that create vulnerability for schizophrenia may also alter early embryonic development in a manner that increases the likelihood of gestational and birth complications. Alternatively, adverse influences on the developing brain early in gestation may increase the risk of birth complications and subsequent schizophrenia. Finally, birth complications may traumatize the neonatal brain and lead to subtle impairment.

Other environmental factors may also play a role. Susser et al (1992) tested the hypothesis that first-trimester exposure to acute food deprivation was a risk factor for schizophrenia. A sharp and time- limited decline in the food intake of the Dutch population following a Nazi blockade in 1944 to 1945 created a tragic experiment of nature to test this hypothesis in three regions of Holland (west, north, and south). In the west, or famine region, birth cohorts exposed to severe food deprivation during the first trimester showed a substantial increase in hospitalized schizophrenia for women but not for men. Relative risks for women were 2.17 for "broad" and 2.56 for "restricted" schizophrenia. Moderate food deprivation during the first trimester was not associated with increased risk of schizophrenia in the famine region. It is possible that female fetus are more protected than

male fetus, that the male fetus who were exposed died. On the other hand, during this risk period, female brains may be developing at a faster pace and need more nutrition. These findings lend plausibility to the proposition that early prenatal nutrition can have a gender-specific effect on the risk of schizophrenia.

As already stated, regardless of etiology, there is considerable agreement that disorders in dopamine transmission play a role in the schizophrenia process. Evidence that the therapeutic basis of various drugs with antipsychotic efficacy correlates with the blockade of brain dopamine receptors was a key factor in the development of the dopamine hypothesis of schizophrenia. In its simplest form, this hypothesis states that symptoms are related to a relative excess of central dopaminergic activity in the mesolimbic system (e.g., nucleus accumbens, olfactory tubercle, and stria terminalis) which, in term, may inhibit other neurotransmitters and lead to both positive and negative symptoms. Several lines of evidence support the dopamine hypothesis.

1. All typical antipsychotic drugs block dopamine receptors in the striatum and their affinity for the dopamine 2 (D2) receptor correlates with their clinical potency (Seeman et al., 1976). Atypical antipsychotics also block D2 receptors but their clinical potency does not correlate as well with D2 blockade.
2. Drugs that increase dopaminergic activity and/or dopamine release, such as L-dopa, amphetamine, or cocaine, are psychotomimetic (lead to psychotic symptoms) which are blocked by D2 antagonists.
3. Postmortem studies in schizophrenic patients have shown increased striatal D2 receptor density (Seeman, 1987), but this increase may be due to prior neuroleptic treatments. Similar increases have been shown using positron-emission tomography (PET) brain scans in both treated and untreated schizophrenic patients (Pearlson et al., 1995; Wong et al., 1997), but these findings are hard to replicate.
4. Some studies have shown that chronic treatment with antipsychotic drugs gives rise to a transient increase in cerebrospinal fluid (CSF), plasma, and urine levels of the dopamine metabolite, homovanillic acid (Pickar et al., 1986). This finding is suggestive of an initial period of receptor blockade resulting in a compensatory increase in dopamine turnover and increased levels of metabolites.

Despite evidence supporting the dopamine hypothesis of schizophrenia, several inconsistencies suggest a need to reconsider the exclusive role of dopamine excess in schizophrenia and dopamine receptors as the sole targets of antipsychotic drug action.

First, although the administration of antipsychotic agents is immediately followed by dopamine blockage, full clinical response is not in evidence until days or even weeks following the initiation of treatment. Second, there appears to be a subgroup of patients with schizophrenia who are not responsive to typical antipsychotics. Third, there appears to be a relative lack of association between D2 receptor blockade and the antipsychotic effects of atypical antipsychotics such as clozapine (Farde, 1992). Finally, the brain dopaminergic systems do not function independently of other neurotransmitter systems. Serotonin interacts with dopamine and may have an important role in the regulation of dopaminergic function. A combined role for serotonin and dopamine in the etiology of schizophrenia has been suggested (Meltzer, 1989). Indirect evidence for this hypothesis is the superior therapeutic efficacy of clozapine and possibly several other atypical antipsychotic agents with high serotonin block compared with typical antipsychotics (Meltzer, 1989; Casey, 1996). The atypical antipsychotic agents exhibit relatively high affinity for the 5-HT2 receptor and relatively low affinity for the D2 receptor.

Other transmitters have been reported to interact with brain dopaminergic systems and have also been implicated in the pathophysiology of schizophrenia. These include norepinephrine (Van Kammen et al., 1991), glutamate (Kim et al., 1980), GABA (Harsing, 1997) and neuropeptides such as neurotensin (Garver et al., 1991).

Despite the possible role for other neurotransmitters in the genesis of schizophrenia, the evidence for abnormalities of dopamine metabolism remains compelling. The dopamine hypothesis

provides the framework for the current study, an investigation of ethnic differences in the pharmacokinetics and pharmacodynamics of antipsychotic medications. The classical dopamine blocker, haloperidol, is the drug of choice because it has fewer metabolites than most neuroleptics and these metabolites are relatively easy to measure.

Dopamine: Its Mode of Action:

Dopamine is initially formed from the amino acid tyrosine. It is then converted to dopa by tyrosine hydroxylase. Dopa decarboxylase decarboxylates dopa to form dopamine. Once dopamine is synthesized, it is stored and bound in vesicles. The process of vesicular storage protects dopamine from oxidation by intraneuronal monoamine oxidase (MAO) and serves as a transmitter depot that may be released upon the appropriate physiological stimulus. The arrival of the action potential promotes the fusion of the vesicle with the presynaptic membrane. Autoreceptors inhibit release when synaptic concentrations of transmitters are high and augment release when concentrations are low (Figure 1).

[See Figure 1 on page 7b]

The major enzymes involved in the metabolism of dopamine are MAO and catechol-O-methyltransferase (COMT). Intraneuronal MAO converts dopamine to its corresponding metabolites. The reuptake of neurotransmitters serves as a mechanism by which synaptic transmission is regulated. Dopaminergic receptors will also change with regard to their number and their affinity for the endogenous ligands in response to change of synaptic concentrations of neurotransmitters, for example, the number of DA receptors increases when synaptic concentration of DA decreases.

Figure 1

The key steps in the synthesis and degradation of dopamine (DA) and the sites of action of various psychoactive substances at the dopaminergic synapse. (Adapted from Cooper, Bloom, and Roth, 1986.)

1. *Enzymatic synthesis.* The conversion of tyrosine to DOPA (dihydroxyphenylalanine) by tyrosine hydroxylase is stimulated by L-DOPA and is blocked by the competitive inhibitor α-methyltyrosine.

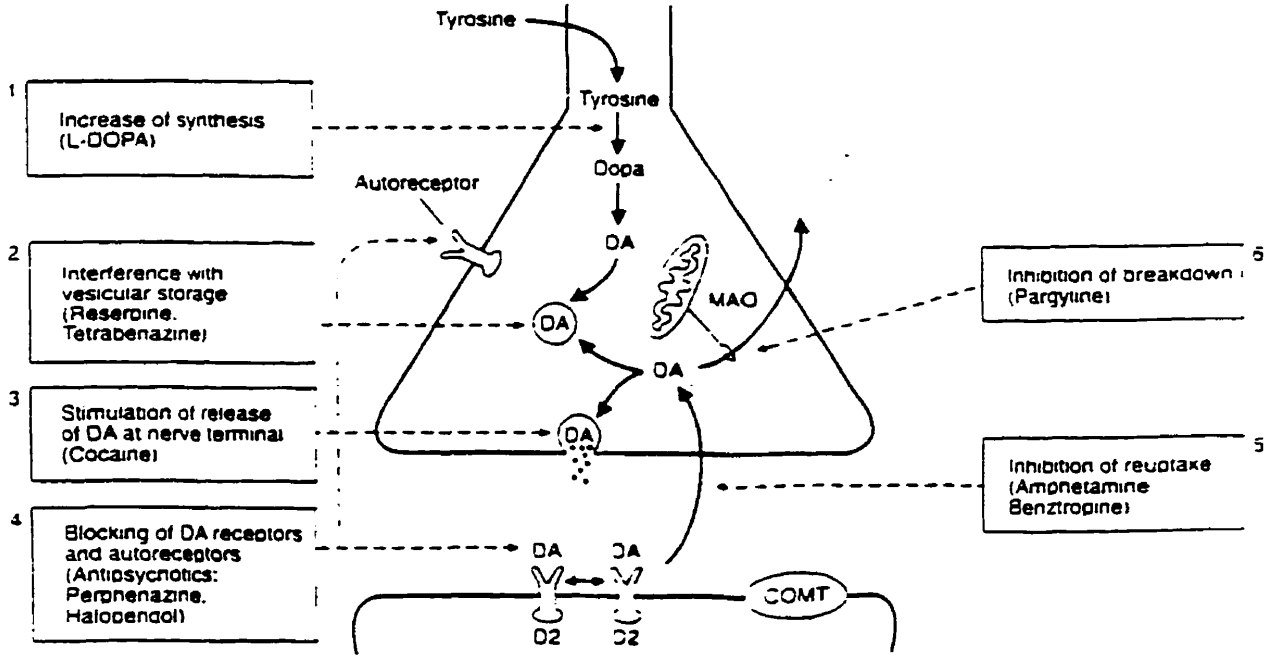
2. *Storage.* Reserpine and tetrabenazine interfere with the uptake and storage of dopamine by the storage granules. Reserpine is an effective antipsychotic drug; the depletion of dopamine by reserpine is long-lasting and the storage granules appear to be irreversibly damaged. Tetrabenazine also interferes with the uptake and storage mechanism of the granules, but only transiently.

3. *Release.* Cocaine releases dopamine from dopaminergic neurons by blocking reuptake.

4. *Receptor interaction.* Typical antipsychotics such as perphenazine and haloperidol are particularly effective in blocking the D_2 and the postsynaptic autoreceptors.

5. *Reuptake.* Dopamine activity is terminated when dopamine is taken up into the presynaptic terminal. Amphetamine, as well as the anticholinergic drug benzotropine, is a potent inhibitor of this reuptake mechanism. Amphetamine induces a psychosis that is reversed by antipsychotic drugs.

6. *Degradation.* Dopamine present in a free state within the presynaptic terminal can be degraded by the enzyme monoamine oxidase (MAO). Pargyline is an effective inhibitor of MAO. Some MAO is also present outside the dopaminergic neuron. Dopamine also can be inactivated by the enzyme catechol-O-methyltransferase (COMT), which is believed to be localized outside the neuron in the postsynaptic cell.



Dopamine antagonists such as haloperidol block post-synaptic dopamine receptors. The blockade increases dopaminergic cell activity, enhances dopamine turnover, increases dopamine catabolism and accelerates dopamine biosynthesis. The affinity of DA antagonists for DA receptors correlates with their clinical potency (Goodman, 1996; Kandel, 1996). It was thought that chronic administration of haloperidol would result in a chronically depolarized state to the extent that the spike-generating mechanism of neuron firing would become inactive. This mechanism, termed "depolarization block" was found to occur in both the A9 substantia nigra and the A10 ventral segmental dopamine neurons following chronic treatment with haloperidol (Kandel, 1991; Cooper, 1991; Goodman, 1996).

It has been hypothesized that the depolarization block of the A10 mesolimbic system is responsible for the therapeutic efficacy of typical antipsychotic drugs, whereas the decreased activity of the A9 substantia nigra neurons projecting to the caudate-putamen is responsible for the extrapyramidal side effects (EPS) (parkinsonism, dystonia, akathisia, and tardive dyskinesia) (Kaplan, 1995), although tardive dyskinesia is possibly due to neuronal death.

Antipsychotic use also causes adverse reactions that are not due to the antidopaminergic properties of the drug. These side-effects include:

1. sedation and orthostatic hypotension due to antimuscarinic and antiadrenergic properties;
2. tachycardia, dry mouth, and blurred vision due to anticholinergic properties;
3. neuroleptic malignant syndrome (NMS), a rare but serious side-effect, characterized by catatonia, muscle rigidity, and labile pulse and blood pressure. It occurs in 2% of all patients receiving neuroleptics. The etiology of NMS is unknown, but the mortality associated with it is very high (> 10%).
4. There are also metabolic and endocrine side effects secondary to the use of a neuroleptic, such as: weight gain, edema, lactation, gynecomastia, and menstrual irregularities.

In summary, it is thought that most antipsychotic drugs such as haloperidol function through dopamine receptor blockage. Haloperidol has been shown to be effective: (1) in managing acute symptomatic disturbances, (2) in inducing remission from psychotic exacerbation, (3) in maintaining the achieved clinical effect over prolonged periods of time (maintenance therapy), and preventing relapses or new episodes of symptom expression (prophylactic therapy).

Pharmacological treatment has been successful in controlling symptoms of schizophrenia. However, there is significant inter-individual variation in treatment response, and side effects have been major obstacles to treatment compliance. Despite extensive research efforts in the past, the dynamics of individual difference in treatment response and experience of side effects remain unknown (Lydiard et al., 1988).

Potential Predictors of Response to Treatment

Some factors that have been identified as potential predictors of response to treatment can be grouped into five categories: (1) initial illness impairment; (2) tolerance of symptoms; (3) compliance and medication side effects; (4) drug metabolism; and/or (5) CNS effect of antipsychotic medication.

Differential initial illness impairment: Schizophrenia begins early in life (Iacono et al., 1989), and it can cause significant and long-lasting impairment (Fenton et al., 1997). Impairment due to schizophrenia can occur mainly through the expression of *positive symptoms* or *negative* symptoms. Disorganized behaviour, cognitive symptoms and mood symptoms can also occur. Positive symptoms include distortions of thinking - delusions or false interpretations, distortions of perception – auditory, visual, tactile, olfactory, somatic hallucinations - and disorganized speech and

behavior. Negative symptoms include restrictions in the range and intensity of emotional expression, and in the fluency and productivity of thought and speech. The spectrum of negative symptom also includes decreases in motivation, sociability, energy, and interests and in the initiation of goal-directed behavior. Compared with positive symptoms, negative symptoms are more treatment resistant (Arndt, 1995).

Are there Asian-Caucasian differences in initial illness impairment? For example, is there a different distribution of symptoms? Are debilitating negative symptoms (restrictions in the range and intensity of emotional expression; poverty of thought and speech; decreases in motivation, sociability, energy, and interests) more common among Asians patients? Such differences in initial impairment might help explain differential outcome. Hence, they must be considered in any study of treatment response.

Although some investigators have observed Asian-Caucasian differences in the expression of mood disorders (Noh, 1992, Chung, 1995), differences with respect to symptom clusters in schizophrenia have not been reported.

Differential tolerance of symptoms: Previous studies have suggested that cultures define different boundaries for tolerable behaviour (Leff, 1990). Expectations for individual behaviour and values concerning the responsibility of the community to its members help to define the limits of tolerance(Leff, 1990). For example, Katz and Sankon (Katz, 1976; 1994) demonstrated that, of all the symptoms of schizophrenia, suspiciousness and agitation were the most disturbing to families of Asian patients. Helplessness, a salient symptom for families of Caucasian male patients, would not precipitate help-seeking for Asian families.

Although one must always remain cognizant of intra-cultural heterogeneity, it is possible to identify help-seeking trends that broadly distinguish ethnocultural groups. In general, the Asian community tends to be remarkably tolerant of psychotic behaviour, as long as the ill person remains quiet and non-violent. Asian families tend to wait much longer than Caucasian families to send a psychotic member to hospital. Asian families also tend to avoid the mental health treatment system, seeking help instead from family physicians or Asian traditional medicine (Lin et al., 1993; Gaw, 1992). In most cases of mental disturbance, Asian sufferers remain isolated within their home and family. When the family can no longer cope, a physician is summoned for treatment of a "physiological" ailment (Lin, 1982). Gaw (1992) has documented a range of factors accounting for the low utilization rates of mental health services among Asian patients. These include great concern about confidentiality, reluctance to use insurance coverage, showing up late or canceling the initial appointment, lack of support from family members regarding the usefulness of treatment or even outright refusal to seek treatment in the presence of overt psychotic symptoms.

Since a short psychotic history prior to admission predicts favourable response to treatment (McEvoy, 1991b), one might predict that the consequence of the Asian family's tendency to resist health care is patients whose illness has progressed to a point at which treatment is extremely difficult. It is also possible that differential tolerance of symptoms means that persons who seek care are a selected sample of all persons with schizophrenia. For example, if Asians tolerate negative symptoms such as withdrawal and isolation, Asian persons with schizophrenia might well fall into two major sub-groups -- those with violent behaviours, and those with illnesses so prolonged that they have exhausted family coping resources. As a result, the former sub-group may respond well to pharmacological treatment and later more treatment resistant. Caucasian patients are likely to

present at an earlier phase of their illness (Lin, 1993), and perhaps with more varied as well as more protean symptoms.

Differential compliance and medication side effects: The individual patient's acceptance or rejection of a prescribed pharmacological regimen is often the single greatest determinant of treatment effectiveness (Fenton et al., 1997). Between one quarter and two thirds of patients who unilaterally discontinue prescribed neuroleptic medicines cite side effects as their primary reason for noncompliance (Hoffman et al., 1974; del Campo et al., 1983). Patients from ethnic minorities are reported to have worse treatment compliance than their mainstream counterparts (Gaw, 1992).

The side-effect occurrence is closely related to wide individual and ethnic variation in the dose of medications that will lead to clinical improvement on the one hand, and side effects on the other (Lin et al., 1996). Some patients with schizophrenia will respond only when their dose of haloperidol, for example, is raised to 30 mg daily. Others will demonstrate intolerable side effects when they receive 2mg. daily (Lin et al., 1996; Jorgensen et al., 1994). Rapid advances in the field of clinical pharmacogenetics in the past few decades have led to better understanding of the mechanisms underlying these differences. For example, because of differences in metabolism related to the CYP2D6 enzyme, Asians may achieve higher concentrations of a given neuroleptic than Caucasians receiving the same dose of medication. This can produce more side effects (Lin, 1989).

Differential tolerance of side effects may also be a factor in non-compliance. In particular, it has been suggested that Asians tolerate visible extrapyramidal symptoms such parkinsonism, dystonia, akathisia, and tardive dyskinesia less well than Caucasians. As a result, Asians are more likely to stop their drug (Katz, 1976; 1994).

Differential drug metabolism: The existing literature suggests that racial differences in the speed of metabolism of neuroleptics (pharmacokinetics) and in target organ response to neuroleptics (pharmacodynamics) may be based on genetic variation (Yamamoto et al., 1995). The term pharmacokinetics refers to the rate of absorption, distribution, metabolism and elimination of pharmacological substances. Oral haloperidol, first absorbed via the stomach and intestines, undergoes first-pass metabolism in the liver, where it is converted to a lipid-soluable derivative and then re-enters the systemic circulation. Because it is lipid-soluble, haloperidol is sequestered in lipid compartments of the body where it may remain stored for a long time. As the blood flows through different organs, circulating haloperidol is either diffused through organs with which it comes into contact. It is actively transported to the brain, its site of action. Active transportation is different from diffusion: because of active transport mechanisms, haloperidol crosses the blood-brain barrier to achieve a concentration in the brain that is twice as high as the plasma level. In second pass metabolism, the liver converts the circulating haloperidol and converts it into hydrophilic forms so that it can be eliminated through the kidney.

In more detail, the metabolism of haloperidol in humans involves cleavage of the molecule by oxidative dealkylation at the C-N bond of the central chain to form piperidine metabolites and 4-fluorobenzoyl-propionic acid. Approximately one percent of haloperidol is excreted unchanged in the urine. Haloperidol is also metabolized via reduction at the benzylic ketone to an alcohol (reduced haloperidol). Electrophysiological studies showing that reduced haloperidol lacks the properties of a DA antagonist. It does not inhibit neuronal firing rates which suggests that it is an inactive metabolite of haloperidol (Kirch et al 1985). Biochemical studies have offered contradicting evidence regarding activity: reduced haloperidol has been shown to be one-fourth as potent as

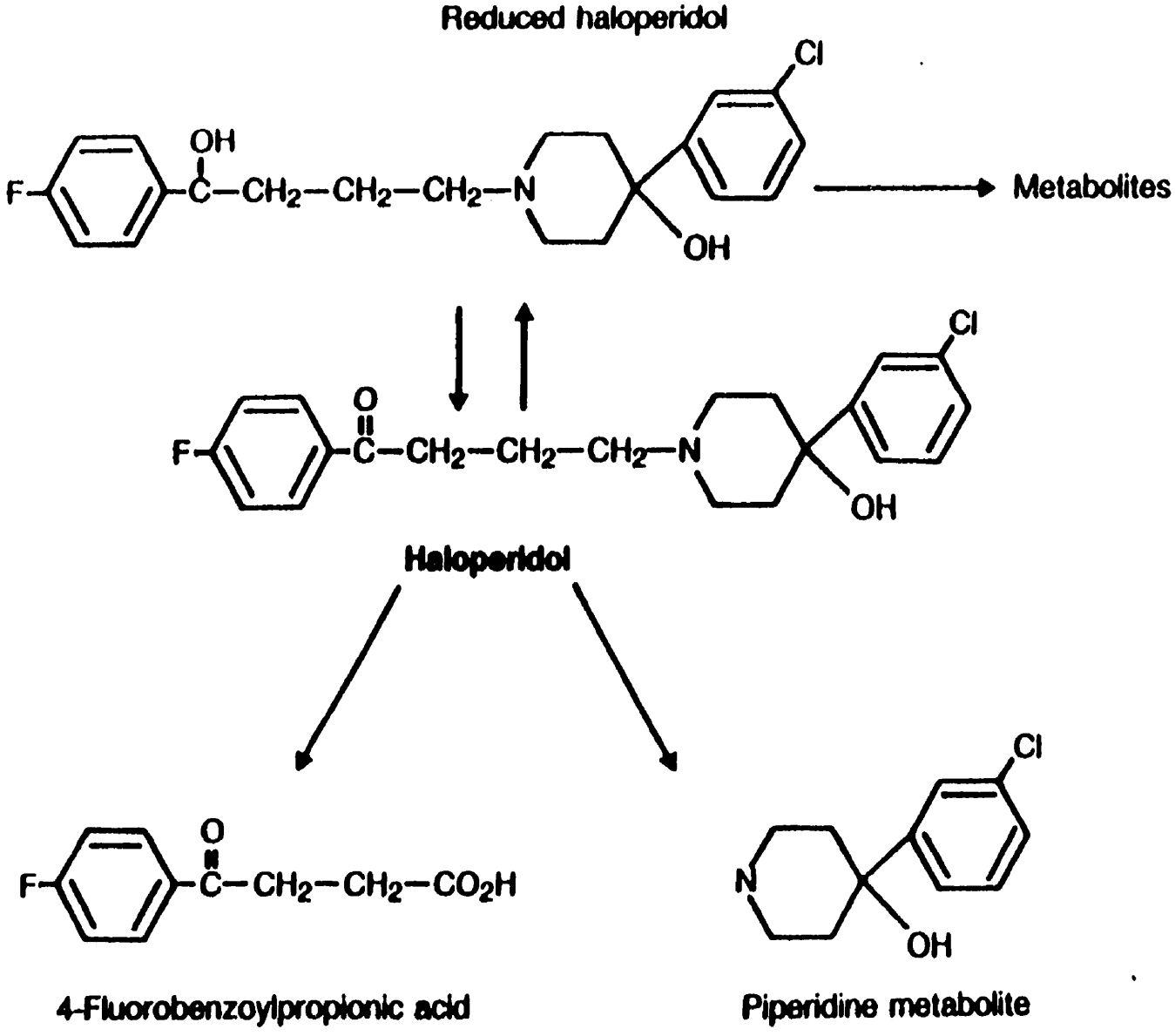
haloperidol in stimulating prolactin release in female rats (Hays et al 1980). Another biochemical investigation showed that the potency of reduced haloperidol in elevating levels of homovanillic acid (HVA) - a major metabolite of dopamine - was approximately one-half that of haloperidol (Chang, 1988). Reduced haloperidol was one fifth as potent as haloperidol in inhibiting apomorphine-induced stereotypy in rats (Browning, 1982). Reduced haloperidol has been shown to be oxidized back to haloperidol in guinea pigs and man (Korpi, 1985; Midha, 1987). Perhaps the biochemical and behavioural effects noted with respect to reduced haloperidol result, in part, from oxidation back to the active neuroleptic.

[See figure 2 on page 14b]

The liver is the major site of haloperidol metabolism (Korpi 1985). No correlations have been found between serum haloperidol concentrations and body surface area or body weight (Forsman 1977). Morselli at al (1983) and Jann (1985) also reported that body weight does not appear to influence clearance of haloperidol.

Individual variability in the rate of metabolizing a particular drug is, in part, genetically determined. All neuroleptics and most psychotropic drugs (exceptions are lithium and short-acting benzodiazepines) are metabolized by P450 liver enzymes. The enzyme systems responsible for the metabolism of psychotropic medications, whether through first or second pass action, are in part genetically controlled. Mutations in these genes often lead to the production of defective proteins that have little enzyme activity. People with such "defects" or "deficiencies" are commonly called poor metabolizers, in contrast to extensive metabolizers, who have normal genes and enzyme activity. The percentage of poor metabolizers often differs quite substantially across ethnic groups (Gonzalez, 1989; Kalow, 1993; Meyer et al., 1990; Wood et al., 1991). Some of the most dramatic

Figure 2 Metabolism of haloperidol (Forsman et al, 1977)



examples can be seen with the cytochrome P450 isozymes (CYP) (Shen et al., 1990).

The ancestral CYP enzyme from which all current ones have evolved came into existence over 1 billion years ago, a fact that underscores the biological importance of these enzymes to organisms, including man (Gonzalez et al., 1990; Gonzalez et al., 1992b). They are heme-containing mono-oxygenases responsible for much of the oxidative metabolism occurring in the body (Gonzalez, 1992a). Through N-dealkylation oxidation, and conjugation, haloperidol is broken down to more water soluble polar substances to be excreted through the kidney. The principal CYP enzyme involved in this metabolism is the isozyme debrisoquin hydroxylase (CYP2D6).

Research on liver cytochrome P450 isozymes reveals that these isozymes are highly polymorphic. A popular hypothesis posits that gene polymorphism occurs in response to environmental pressure (Gonzalez et al., 1990; Kalow, 1993). Ethnic variation in alleles of the CYP2D6 isozyme might be interpreted as the result of differences in the natural environments to which ancestors of different ethnic groups were exposed. The unique genotypic patterning of each group might have arisen, at least in part, as the imprint of interaction between a group's ancestors and the prehistorical environment in which they lived (Lin, 1996). About 7% of Caucasians but only 1% of Orientals are poor metabolisers (PMs) of debrisoquine. The most common mutated allele in Caucasian PMs, CYP2D6B, is almost absent from their Oriental counterparts. On the other hand, the mean activity of CYP2D6 in Oriental extensive metabolisers (EMs) is lower than that in Caucasian EMs. This is due to the frequent distribution of a partially deficient CYP2D6 allele causing a Proline34-->Serine amino acid exchange in 30% - 50% of Oriental alleles. Proline is a "bulky" amino acid which causes "kinks" in its segment of the DNA chain. When proline is replaced by serine, the "kinks" disappear and protein conformation changes subsequently. This change is

considered the molecular genetic basis for slower metabolism of antidepressants and neuroleptics observed in Oriental compared with Caucasian people, and for the consequent heightened sensitivity to these drugs (Bertilsson, 1995).

As briefly reviewed, genetically determined ethnic differences in the function of drug-metabolizing enzymes can significantly influence the pharmacokinetics of various psychotropic medications and may be partially responsible for ethnic differences in the pharmacokinetics of these substances (Lin et al., 1993).

A study of the pharmacokinetics of haloperidol compared Caucasian, American-born Asian and foreign-born Asian volunteers (Lin et al., 1988b). Subjects received same dose of oral and intramuscular haloperidol on two separate days, at least 2 weeks apart. Plasma levels of haloperidol in both Asian groups were significantly higher than in the Caucasians.

Potkin et al. (1984) compared Chinese schizophrenic patients residing in China with non-Asian-American schizophrenic patients. After each subject had received an identical dose per kilogram of body weight for 5 weeks, serum haloperidol levels in the Chinese were on average 52% higher than those in the Americans

According to another study conducted by Lin et al. (1989), Asian American patients required significantly smaller doses of haloperidol than non-Asians (6.5 versus 11.5 mg/day before reaching the extrapyramidal side effect threshold). There were also inter-ethnic differences in drug dosages required for clinical improvement measured by Brief Psychiatric Rating Scale (BPRS): Asians required 5.1 mg/day, versus 14.3 mg/day for Caucasians.

Environmental factors including diet, smoking, caffeine intake, exposure to alcohol, and concurrent use of other drugs and herbs can affect drug metabolism (Clark et al., 1988). These

factors likely exert their influences either through competition in absorption in the digestive system, in plasma protein binding, or by increasing or inhibiting liver enzymes, thereby facilitating or retarding the process of drug breakdown. The heterogeneity of the population with respect to these variables will require large sample sizes for adequate study.

Differential prolactin response to antipsychotic medication: Pharmacodynamics refers to medication effects on human physiology. As mentioned previously, the antipsychotic action of typical antipsychotic drugs such as haloperidol is thought to result from their ability to block the D2 receptor.

Existing literature indicates that pharmacodynamic differences can help account for variations in treatment response (Silverstone et al., 1984; Hu et al., 1983; Takahashi, 1979; Lin et al., 1988b). Lin et al. reported that intramuscular haloperidol injections lead to higher prolactin levels among Asians than Caucasians, suggesting an Asian-Caucasian difference in dopamine (DA) receptor response (Lin et al., 1988b). Since DA inhibits prolactin synthesis, treatment with DA antagonists like haloperidol should increase levels of serum prolactin. Serum prolactin thus provides an index of the sensitivity of central dopamine receptors to blockade (Rubin, 1980). These studies show that either pharmacokinetic or pharmacodynamic factors, or both are important in explaining ethnic differences in response to haloperidol in clinical studies. It should be noted that prolactin levels are also affected by other factors including gender, serotonin level, thyroid level, sleep/wake cyle, and time of the day.

Little is known about ethnic differences in response to the novel neuroleptics, such as clozapine and risperidone. However, because they are metabolized through the CYP2D6 pathway (Fischer et al., 1992; Huang et al., 1993), it is reasonable to expect such differences will likely exist.

In fact, Chang et al. (1993) have reported that clozapine is metabolized at a slower rate among Chinese as compared with Germans. These findings support the hypothesis that ethnic differences in pharmacokinetics may also affect clinical response to new atypical antipsychotic medications just as they do to older medications such as haloperidol.

Previous cross-cultural comparisons have limitations that the current study will try to overcome. The first issue is diagnosis. Previous cross-cultural comparisons have collected data from people with schizophrenia in different countries. The diagnostic criteria differed in each country from ICD to DSM to the modified DSM used in China. Lack of consistency in diagnosis compromises the replicability and the validity of study results. Second, previous studies have used acute and chronic populations. Ethnic differences in treatment response may have been confounded by variability in the chronicity of illness. Third, existing studies used a fixed dose treatment protocol. Fixed dose studies enable researchers to match plasma levels of neuroleptic to oral doses; on the other hand, the link to clinical application is less clear than with individually tailored optimal doses. Fourth, previous research has not taken into account the possible effects of demographic variables such as age and gender. These variables may affect drug metabolism and thus confound ethnic differences.

The Current Study

The current study recruited Asians and Caucasians residing in Metropolitan Toronto who were suffering from a first episode of psychosis, who were either not currently on medication, or who had received minimal previous treatment (either untreated or treated for a total duration of less than 6 months). Diagnosis was established by group consensus using DSM-III-R criteria.

The focus of this study was on cross-cultural differences in the metabolism and CNS effects of haloperidol. Predictors of response to treatment as revealed in the literature review were controlled through the following techniques. Impairment and severity of symptoms were directly assessed. Tolerance of symptoms was reflected in duration of untreated illness. These variables were used as covariables in the statistical analysis. Compliance was assessed through monitoring of weekly plasma levels. In order to reduce side effects and thereby encourage compliance, a low starting dose was chosen. Dosage was then stepped-up gradually, tailored to the individual in order to maximize response and minimize side effects.

The following questions were investigated:

1. Are there Asian-Caucasian differences in clinical response to treatment? Specifically, do Asians require lower doses of haloperidol than Caucasians to achieve therapeutic response? And do they develop EPS more readily than Caucasians?
2. Are there Asian-Caucasian differences in the metabolism of haloperidol as indicated by plasma haloperidol level?
3. Are there Asian-Caucasian differences in sensitivity to haloperidol by having different plasma prolactin level?
4. Are short-term treatment effects sustained during follow-up?

CHAPTER 3

Methods

The Asian/Caucasian study began in March 1993. It was conducted through the Culture, Community, and Health Studies Program and Schizophrenia Program of the Department of Psychiatry, University of Toronto. With more than 3.9 million residents, Toronto is the largest city in Canada. Toronto is also the most multi-cultural cities in the world with 48% of its residents coming from another country (Statistics Canada , 1996). Asians consist of 10% of total population in Toronto or 390,000.

The study involved Asians and Caucasians suffering a first episode of Non Affective Psychosis* in the Greater Toronto Area. After initial recruitment, each patient was placed on a 4 week regimen during which the optimal treatment dosage for haloperidol was ascertained. The regimen involved weekly blood draws, as well as monitoring of symptoms and side effects. A follow up series of ratings took place 9 months after entry to the study.

The Clarke Institute of Psychiatry, now a division of the Centre for Addiction and Mental Health, is a major teaching hospital of the University of Toronto. The centre emphasizes research, education and high quality patient care. The Clarke Division's clinical services include schizophrenia, mood and anxiety disorder, general psychiatry, forensic psychiatry, women's mental

* Although the study focuses on first-episode schizophrenia. it is difficult to make this diagnosis definitively in natural practice. The study sample includes a small number of persons with Non-Affective Psychosis other than schizophrenia. The essential features of Non-Affective Psychosis (NAP) are the presence of characteristic psychotic symptoms without co-occurrence of a full manic or depressive episode. NAP includes schizophrenia, delusional disorder and psychosis not elsewhere classified; the latter is further categorized as brief reactive psychosis, schizophreniform disorder. schizoaffective disorder and induced psychotic disorder (DSM-III-R). The justification for expanding the sample definition is that all NAP respond to antipsychotic treatment. Furthermore, the diagnosis of schizophreniform disorder is based on a conversion in the DSM system. Previous research of our own (Beiser, 1988; Zhang-Wong, 1995) demonstrated that most persons initially diagnosed as schizophreniform disorder are eventually re-diagnosed with schizophrenia.

health and child and adolescent psychiatry. The First Episode Psychosis Program is a tertiary care treatment program within the Schizophrenia Program of the Clarke Division. Developed to meet the needs of individuals experiencing a first episode of psychosis, the First Episode Program provides inpatient and outpatient services to patients from the Greater Metropolitan Toronto area.

Description of sample

The initial plan of the study was to recruit 100 Asians (0.03% of its population) suffering a first episode of psychosis in the Greater Toronto Area and a comparison sample of 100 Caucasian first episode patients. The study employed the following recruitment strategies:

1. Information packages describing the project were mailed out to the psychiatrists in charge at 35 hospitals in downtown Toronto, Oakville, Mississauga, Richmond Hill, Newmarket, Scarborough and Whitby. Follow-up phone calls were made to arrange for a presentation of the project to staff at the department of psychiatry in each of these hospitals. Information regarding the study was also sent to the University of Toronto and the York University student health centre where psychiatric services are provided to students.
2. A post-it sticker bearing the project name and referral contact telephone number was designed and distributed to all hospitals to be glued to telephones in the nursing stations. The purpose was to help staff on duty have easy access to contact numbers after identifying a potential subject.
3. As part of our efforts to recruit Asians suffering a first episode of non-affective psychosis, we obtained a list of 22 Chinese psychiatrists as well as a list of 249 Chinese general practitioners from the Canadian Chinese Medical Association. Information packages were mailed to them and follow-up phone calls were made by a Chinese speaking social worker to ensure that the mailing address was correct and to determine whether any additional information about the study was required by the physician.

First episode non-affective psychosis was defined as a non-affective psychosis for which a person had neuroleptic treatment for no more than six months prior to entering the study. All patients admitted to the First Episode Program inpatient unit who met the first episode psychosis criteria were approached for the study.

Exclusion criteria included:

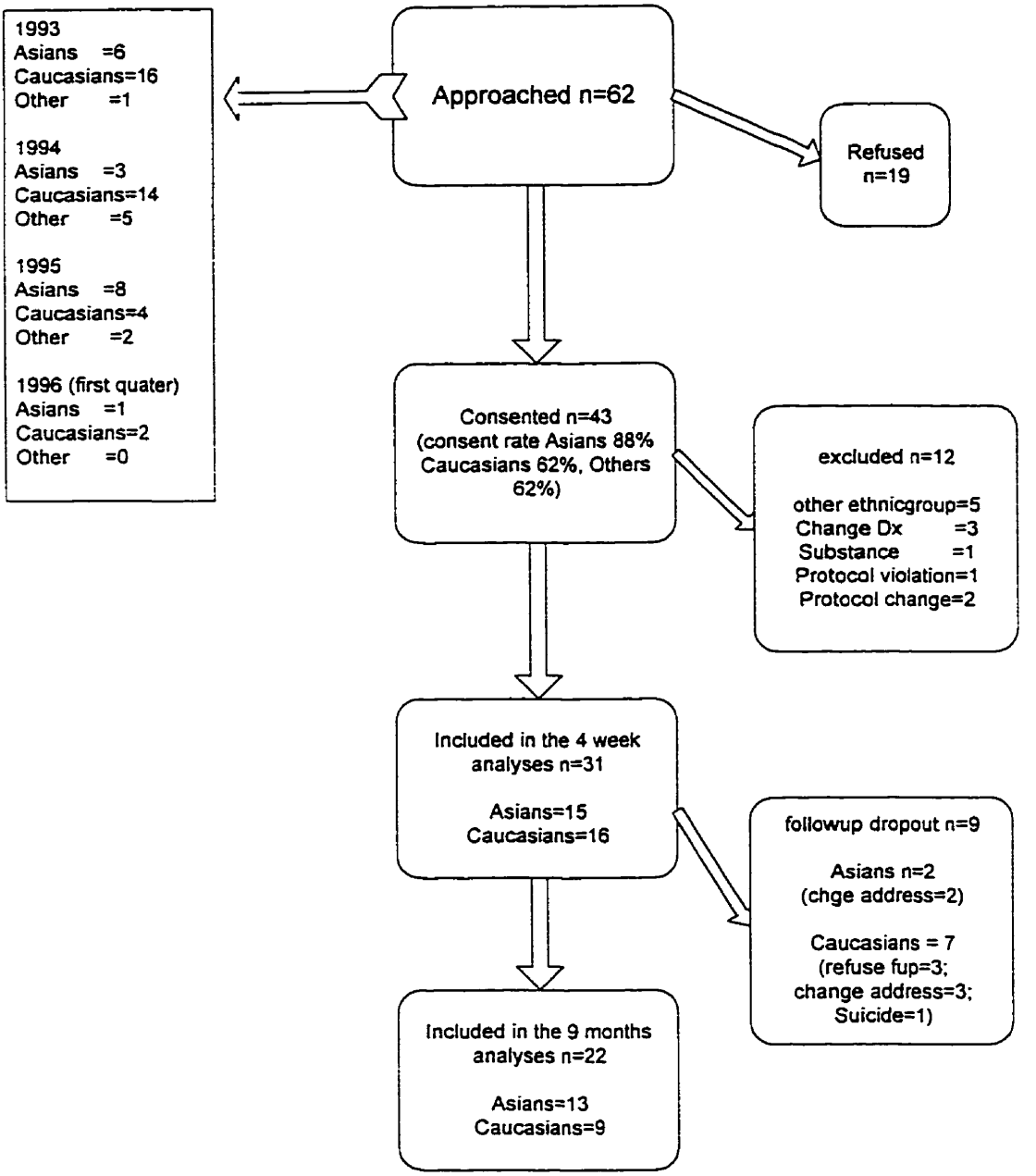
1. current substance abuse/dependency;
2. a crisis situation that required immediate medication treatment;
3. psychosis caused by a medical condition;
4. dementia, and other organic disorders such as seizure.

Over a three-year recruitment period, 62 subjects were approached, among whom 18 were Asian (Figure 3). Only 2 of the 18 Asians were referred by Chinese psychiatrists, and none came from general practitioners. Recruiting first episode patients proved more difficult than anticipated and it was even more so for Asian subjects. Forty-three patients (67% of those approached) signed an informed consent. The reasons cited by 17 patients who refused to participate in the study were: 1) discomfort with blood drawing and needles (n=8); 2) unwillingness to take any medication (n=6); and 3) unwillingness to participate in research (n=3). Another two patients were unable to consent due to cognitive difficulties.

[See Figure 3 on page 22b]

Among the 43 patients who signed a consent form, 7 either dropped out or were removed from the study. Reasons for subject attrition included: 1) drug abuse history (n=1); 2) inability to keep weekly visits as an outpatient for assessments and blood works (n=1); 3) change of diagnosis to affective disorder (n=3); and 4) complaints about treatment protocol (n=2). The subjects who dropped out citing complaints about treatment as the reason were the first two participants in the study. Based on early experiences, the treatment protocol was modified for the remainder of the study. At the time the study was initiated, there were no clear-cut guidelines for defining "optimal treatment doses". McEvoy et al (1991a) had offered a persuasive argument for defining optimal dosage as the dose when a subject first began to experience cog-wheel rigidity. Although it was not

Figure 3 Study recruitment chart



uncommon clinical practice to employ higher doses in order to control symptoms, McEvoy and his colleagues argued that one could expect no extra clinical improvement by employing drugs at a dose higher than those at which extrepyramidal symptoms appeared. According to McEnvoy (1991a), optimal treatment would consist of maintaining a patient at the dose at which side effects first emerged, while simultaneously employing an anticholinergic medication to handle side effects.

The first two subjects entered in the study experienced improvement at a low drug dose . When their medication was subsequently increased to a level which they experienced side effects, they objected to having to experience discomfort in order to adhere to the study protocol. Drawing on the experience with these two patients, the study protocol was modified and a second criterion, significant clinical improvement, was added to the definition of optimal dosage. The revised treatment protocol is detailed in a later section of this chapter. Because the protocol was modified after they entered the study, the first two subjects were excluded from the analyses.

The final sample consisted of a total of 36 individuals suffering from a first episode of non-affective psychosis, 32 inpatients and 4 outpatients. Due to very low rate of enrollment of Blacks (n=3) and South Asians (n=2), these ethnic groups were eliminated from the comparative study. The result was a comparison sample of 31 subjects. As a group, patients who dropped out of the study did not differ from participants with respect to age and gender. However, at the time of initial contact with the study, the dropouts had fewer symptoms than those who remained (Table 1).

[see Table 1 on page 23b]

Symptom severity ratings could obviously not be obtained for refusals. However, in order to compare the Asian/Caucasian study group with a benchmark sample, we reexamined the sample

Table 1 Description of Drop-Outs

	participants (N=36)	dropouts (N=7)	refusals (n=19)	statistics	p
Age (years): Mean (SD)	26.1(5.8)	26.1 (7.3)	24.6 (4.0)	F(2,61)=0.27	.76
Gender (number of cases)					
Male	19	5	13	$X^2(2)=1.72$	.17
Female	17	2	6		
Positive and Negative Syndrome Scale. Mean (SD)	99.8(20.6)	78.0(29.8)	n.a.	T(42)=2.38	0.02

of psychotic inpatients (n=101) Kay (1987) used to develop the positive and negative syndrome scale. Compared with that group, the Asian/Caucasian sample had higher scores on positive symptoms (t_{129}=2.42, p<0.05), and general pathology symptoms (t_{129}=3.13, p<0.01). There were no statistically significant differences in negative symptom scales. The Asian/Caucasian sample's mean symptom severity ratings were also comparable to those found for inpatients (n=127) taking part in the Canadian Multicenter Placebo-Controlled Study of Risperidone (Chouinard et al., 1997). Other demographic variables were also examined. Compared with Kay's study (age 36±11, gender male 70%) and Chouinard's study (age 37±10, male 71%), the Asian/Caucasian first episode sample (age 25±5, male 52%) was significantly younger (p<0.05), and more balanced according to gender, although the latter trend was not statistically significant (X^2=0.513, n.s.).

In summary, the 31 study participants were clinically comparable to psychotic patients taking part in other studies reported in the literature.

For this study, Asian subjects were defined as those whose parents were born in either China, Vietnam or Korea. Caucasian subjects consisted of those whose parents came from a variety of European backgrounds. Although these operational definitions would probably not suffice for a genetic study, we propose that, based on the premise that each of the study groups shared more within-group than between-group similarities, the samples are appropriate for the topic of this investigation.

Twenty (65%) of the subjects had never received neuroleptics prior to their enrolment in the study, 7 (23%) had been neuroleptic-free for at least two months, 2 (6%) for seven days and the remaining 2 (6%) for four days. Drug response among the Asian subjects (n=15: 11 Chinese, 1 Vietnamese, 3 Koreans) was compared with Caucasian first admissions who, like the Asian subjects,

had been treated for less than six months prior to entering the study (n=16).

Twenty-two of the 31 subjects in the current sample completed a 9 month follow-up. The follow-up strategies included monthly telephone contact to track subject whereabouts. Although Asian first episode patients were harder to reach than their Caucasian counterparts, they tended to have a higher consent rate and a lower dropout rate during follow-up. Two of the 15 Asian subjects changed addresses and could not be recontacted (one male returned to Hong Kong, the other female, brought in by police at intake, was discharged to her brother, the only relative and contact person in Canada. The address and phone number supplied to us was incorrect. This patient, an immigrant of 8 years, never had a family physician). Seven of the 16 Caucasians were lost to follow-up. Among this group, three male participants changed addresses, three females refused to participate in the follow-up and one male committed suicide. The three female refusals were all university students, each of whom responded to the treatment. They did not want to remain in the system after discharge. The three who changed addresses all moved out of the city (one back to Portugal, one to Calgary and one to Vancouver).

Mean SCI-PANSS total symptom ratings suggest that there were no clinically significant differences between retained and lost to follow-up samples (dropouts:60.3±32.3; retained: 75.7±27.6; t_{29}=1.34, p=0.19). Dropouts were slightly older than the retained sample (dropouts mean age 28.7±7.6; retained 24.5±4.0; t=1.60, p=0.14), and males appeared more likely than females to drop out during the follow-up (67% males in dropouts versus 45%male in retained, X^2=1.15, p=0.28). However, neither of these demographic differences was statistically significant.

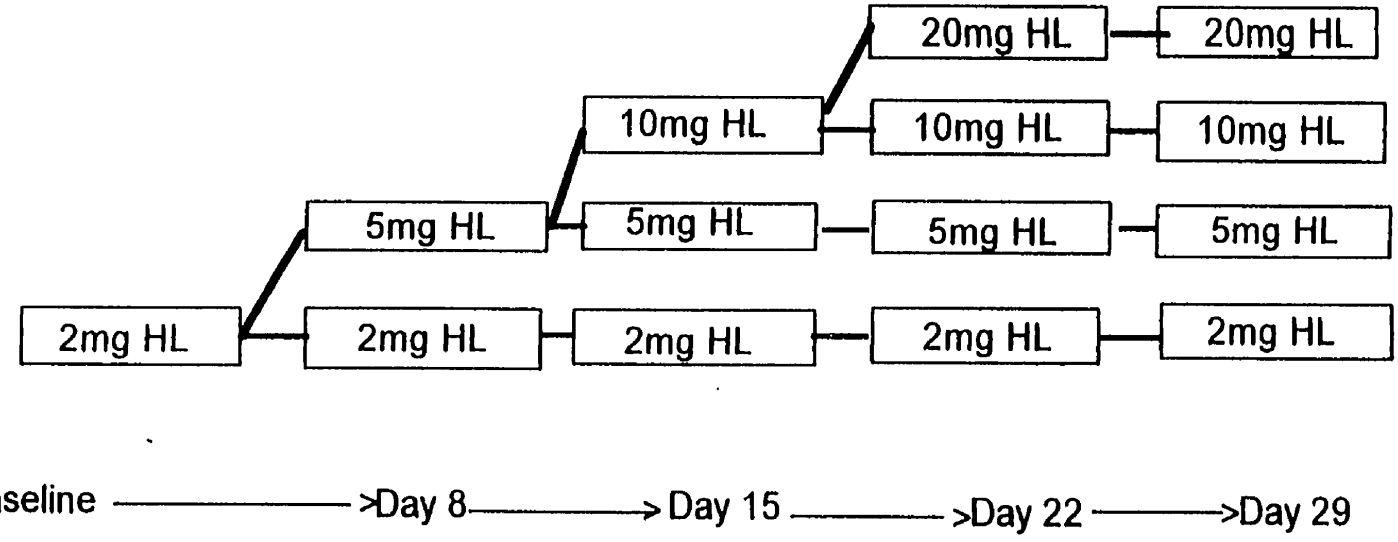
Treatment protocol

Optimal dosage was operationally defined as a decrease of 15 percent or greater in SCI-PANSS score from baseline, or the level at which individual patients developed slight increases in rigidity (Haase, 1961; McEvoy, 1986; McEvoy et al., 1991a). Each subject received 2 mg. of haloperidol daily during the first week of study. Doses were increased weekly until reaching the "optimal dosage", defined as the occurrence of either i) significant symptom reduction (15% or greater decrease in SCI-PANSS score from baseline) (Kay et al., 1987); or ii) development of cogwheel rigidity, akathisia or tremor as assessed by the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al., 1980), whichever came first. Dose increases were standardized as follows: 5mg. at day 8, 10mg. at day 15, and 20mg. at day 22. Once an individual reached his/her "optimal" dose, the dosage was frozen for the remainder of the four-week period (Figure 4). The acute treatment phase of the study terminated after week 4. Patients who had responded to the treatment protocol were prepared for discharge and for follow-up by outpatient psychiatrists at the Clarke Division, or by psychiatrists or general practitioners in the community. Patients who did not respond to the treatment protocol remained in the hospital and were treated with other antipsychotic medications.

[See Figure 4 on page 26b]

During the four week treatment period, all subjects received haloperidol as the drug of choice. No other antipsychotic medications were used during the initial 4 week study period. However, lorazepam up to 2 mg. four times a day was used in cases of extreme agitation. Because the occurrence of extrapyramidal side effects was one of the two criteria for optimal dosage, anticholinergic medication was not used until side-effects appeared. When present, side effects were

Figure 4 Treatment Protocol



Optimal dosage is defined as the occurrence of either

i) significant symptom reduction (15% or greater decrease in SCI-PANSS from baseline) or

ii)the patient develops cogwheel rigidity, akathisia or tremor as assessed by the Extra-pyramidal Side-effect Rating Scale ESRS.

Drug increases are standardized as 5mg at day 8, 10mg at day 15, and 20mg at day 22. Once an individual reaches his/her optimal dose, dosage is frozen for the reminder of the four-week period.

treated with Cogentin 2mg., up to twice a day.

In order to investigate Asian/Caucasian differences in plasma haloperidol and prolactin level, blood samples were drawn at intake and repeated at days 8, 15, and prior to any dosage adjustment. Procedures for the assessment of plasma levels of prolactin, haloperidol, and reduced haloperidol are described in the next section.

Measurements

A. Measurements of pharmacokinetic parameters: The plasma levels of haloperidol and one of its major metabolites, reduced haloperidol, were used as indicators of haloperidol metabolism in the liver. Plasma haloperidol analyses were conducted at the Psychopharmacology Laboratory at the Centre for Addiction and Mental Health, Queen Street Division. Plasma haloperidol levels were determined using a Fisons TRIO-1000 gas chromatograph-mass spectrometer (GC-MS). The mass spectrometer was operated in the electron impact mode using the following conditions: electron emission current 0.1mA, electron energy 70eV, and a source temperature of 250°C. The separations were carried out on an 8m x 0.25 mm I.D. fused silica capillary column coated with a 0.25 um layer of DB-5. The sensitivity of the assay was such that 0.09ng/mL of haloperidol could be detected with a coefficient of variation of 18%. Haloperidol was quantified at levels of 0.19 ng/mL with a coefficient of variation of 6.7%. At levels of 1.88ng/mL, the coefficient of variation was 3.2% for haloperidol.

B. Measurement of drug CNS effect (pharmacodynamics): Prolactin assays were conducted at the neuroendocrinology research laboratory of the Clarke Institute of Psychiatry using Synchron Enzyme Linked Immuno Sorbent Assay (SynElisa) method. The SynElisa prolactin method is based

on microtitre plate technology and uses a solid phase technique in which a new Transferable Solid Phase System (TSP=Synelisa Pin Plate) is employed. In contrast to the conventional microtitre plate technique, the SynElisa principle utilizes three different microtitre plates (MTP). The immunological reaction does not occur on the surface of the microplate wells but on the SynElisa pins. In the first step of the analysis, prolactin antibodies, immobilized on the SynElisa pins, bind specifically prolactin antigen in standards and samples (1st round bottomed plate). During the second step of the method, the antigen-antibody complexes that have formed on the SynElisa pin plate combine with a second enzyme labelled prolactin antibody into a sandwich complex (2nd round bottomed plate). In the third step, the enzyme labelled antigen-antibody complexes convert a substrate (which has to be added) to a coloured solution. The amount of colour of the chromogene is dependent on the enzyme quantity bound to the complex, and therefore proportional to the prolactin concentration to be determined (located on the flat bottom plate). By using the SynElisa pin plate as Transferable Solid Phase System, the starting and stopping of all reactions are synchronized, and conventional steps such as decanting and washing of the microtitre plate are eliminated.

C. Clinical measurements: These included The Structured Clinical Interview for DSM-III-R (SCID), Structured Clinical Interview - Positive And Negative Syndrome Scale (SCI-PANSS), Extrapyramidal Side-effect Rating Scale (ESRS), Premorbid Adjustment Scale (PAS) and Onset Questionnaire, described in detail below.

1) The Structured Clinical Interview for DSM-III-R Diagnosis (SCID)(Spitzer et al., 1990): The SCID is a structured clinical interview designed to establish a DSM-III-R diagnosis. It was developed by Spitzer et al. at the Biometrics Research Department at the New York State Psychiatric

Institute and Columbia University. The SCID interview includes modules covering all DSM-III-R Axis I diagnoses including psychosis, affective disorder, anxiety disorder to anorexia and adjustment disorder. Each module has its own specific questions directly mapped to the diagnostic criteria for each Axis I disorder in DSM-III-R. Differential diagnoses are also included for the study sample.

2) Structured Clinical Interview - Positive And Negative Syndrome Scale (SCI-PANSS) (Kay et al., 1987). A standardized scale used extensively in psychiatric research, the SCI-PANSS has demonstrated reliability and validity. Factor scores can be derived from this scale for positive, negative, general pathology and supplementary symptoms of schizophrenia. The positive symptom scale includes: delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution and hostility. The negative symptom measure includes: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. General pathology symptoms include: somatic concerns, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgement and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The last subscale, supplementary symptoms include: anger, difficulty in delaying gratification and affective lability.

Kay et al. (1987) reported high internal reliability and homogeneity among items, with coefficients ranging from .73 to .83 for each of the four sub scales. The discriminant and convergent validity of the SCI-PANSS dimensional scale was also assessed in relation to independent clinical, genealogical, psychometric, and historical measures. In contrast with the negative scale, the positive scale was more likely to be associated with rehospitalization during a 2 year follow-up

study, as well as greater likelihood of sociopathy among first degree relatives. By contrast, the negative scale was uniquely associated with slowed motor movement, deficits on affective measures, impoverished thinking, and family history of psychosis, but not affective disorders. Neither scale was related to extraneous variables such as race, cultural group, chronicity of illness, or depressive symptoms (Kay et al., 1987).

3) Extrapyramidal Side-effect Rating Scale (ESRS) (Chouinard et al., 1980): The ESRS was developed at the clinical psychopharmacology unit of the Allan Memorial Institute in Montreal. The ESRS has three components: rating for parkinsonism, rating for dystonia and rating for dyskinesia. The schedule covers the most common side effects caused by the blockade of dopamine transmission secondary to neuroleptic use. The Montreal group tested the scale's validity in 8 double-blind studies, 5 of them published: two comparing the extrapyramidal effects of different neuroleptics in the treatment of acute and chronic schizophrenia; two assessing the effects of neuroleptic withdrawal on the evolution of extrapyramidal symptoms; and one comparing Dispal with placebo in the treatment of tardive dyskinesia (Chouinard et al., 1980). The ESRS was found to be sensitive in its ability to detect changes in both parkinsonian and dyskinetic symptoms and to give results consistent with other scales such as the Involuntary Abnormal Movement Scale. Reports concerning inter-rater reliability coefficients range from 0.80 to 0.97.

4) Premorbid Adjustment Scale (PAS) (Cannon-Spoor, 1982): The scale assesses functioning prior to the onset of psychosis. The rating covers 9 areas: education, duration of employment, frequency of change of employment, establishment of independence, highest level of functioning achieved, sociability, interest in life, energy level and general functioning as a whole. Ratings for each dimension range from 0 (fully able to function successfully), to 6 (unable to function at all).

The total PAS score ranges from 0 to 54: the higher the score, the worse the functioning. Interrater reliability was determined in two studies. In the first study, two raters familiar with and experienced in the use of the PAS rated 11 patients. Both raters reviewed the patients' charts for psychosocial histories. After chart reviews and patient interviews were completed, the raters independently completed the PAS for each patient. The interclass correlation coefficient for the two raters was 0.85. In the second study, intrarater reliability among raters from another hospital who were unfamiliar with the scale and untrained to its use was investigated. The three untrained raters rated patients from chart histories alone. The chart histories were reviewed by the two experienced raters. The intraclass correlation coefficient for all five raters was 0.74. The validity was established by comparing PAS between a group of schizophrenic patients (n=86) with a normal population (N=76). The normals were significantly different ($p<0.01$, two tailed t-test) on average score from the patient population. The premorbid scale was used to investigate whether level of premorbid functioning affect treatment response.

5) Onset Questionnaire (Beiser et al., 1993): This semi-structured interview for patients and key informants allows an objective and reliable assessment of the onset of psychological impairments and symptoms. Three critical time points are defined: emergence of the first noticeable signs of illness (FNS); appearance of prominent psychotic symptoms (PPS) and time of precipitation of treatment seeking (PTS). Previous work by Beiser et al. (1993) has shown that the interval between the first noticeable signs of illness and onset of prominent psychotic symptoms (FNS-PPS) as well as the interval between the onset of prominent psychotic symptoms and the decision to seek treatment (PPS-PTS) show great inter individual variation. This finding was supported by Hafner et al. in their follow-up of first-episode schizophrenic patients (Hafner et al., 1992). Few research

investigations other than the current Asian/Caucasian study have examined the onset of non affective psychosis using two relatively homogeneous, ethnoculturally distinctive groups of subjects.

D. Nine month follow-up measurements: A nine-month follow-up was conducted to evaluate the clinical symptom and global functioning in both Asians and Caucasians. SCI-PANSS and ESRS ratings provided information about the maintenance of therapeutic benefits.

The study interviewers included the principal investigator, a research nurse and a Ph.D psychologist. SCID training was conducted prior to the recruitment of subjects for the study. SCID training tapes for schizophrenia were viewed by all raters and ratings were compared with the "gold standard" provided at the end of training tapes as well as among interviewers. In addition, selected patients attending outpatients services were approached for training interviews and interviewer/observer reliability was assessed. A similar approach was used in training with the ESRS. SCI-PANSS training was conducted during a training session in Toronto by one of the authors of the instrument, Dr. L.A.Opler. Training participants' ratings of videotaped patient interviews were compared with Dr. Opler's rating.

Thoughout the study, at least two raters, one interviewer and one observer, were present for each SCID, SCI-PANSS and ESRS assessment. This procedure provided a measure of inter-rater reliability. Inter rater correlation coefficients for SCI-PANSS assessment with the first six patients involved in the training were .92, .82, .89, .80 for positive, negative, general pathology and supplementary scales respectively.

The DSM-III-R diagnosis was established through case conference. The diagnostic process combined a "best-estimate" method (Leckman et al., 1982) with specified operational steps. Research and clinical staff held a clinical conference about each patient, reviewing hospital charts,

diagnostic interview SCID, symptom rating SCI-PANSS, and ancillary information. The team used the Operational Criteria (OPCRIT) (McGuffin et al., 1991) system to assemble data into diagnostic criteria, which were used to arrive at a DSM-III-R diagnosis. The diagnostic breakdown of the sample was: Asian subsample: 11 with schizophrenia, 1 schizophreniform, 2 schizoaffective, and 1 delusional disorder. Caucasian subsample: 11 with schizophrenia, 3 schizophreniform, and 2 delusional disorder.

Statistical consideration

Estimation of sample size requirements was based upon previous research reports. Since there were no reports on how neuroleptic metabolism among Asian first episode psychotic patients might differ from Caucasians, the study attempted to recruit as many subjects as possible. The recruitment was more difficult than anticipated. Instead of finding the hoped-for 100 Asians and 100 Caucasians which would have yielded a 80% power to detect an effect size of 0.2, the current, much smaller sample has only 80% power to detect an effect size of 0.48. This created a dilemma. A previous study using mixed acute and chronic patients (Lin et al., 1989) detected an inter-ethnic difference in "optimal haloperidol dosage" with a sample of 16 Asian schizophrenic patients and 13 Caucasian schizophrenic patients. This translates to an effect size of 0.49. Based on the assumption that a sample consisting entirely of first episode patients should yield group differences in optimal dosage at least as high as those found in a sample of mixed acute and chronic patients, it seemed reasonable to argue that a sample size of 31 would be sufficient to detect inter-ethnic differences.

Potkin et al (1984) studied serum haloperidol levels (HL) among eighteen chronic Chinese patients and 18 matched non-Asian American patients receiving a fixed dosage design of 0.4 mg.

haloperidol per day per kg. Potkin reported significantly higher plasma level of HL in Asians (effect size 0.44). Another study, conducted in Taiwan by Chang et al. (1992) found that Chinese patients had much lower reduced haloperidol/haloperidol ratios than Caucasians. Reduced haloperidol is the major metabolite of haloperidol, and the ratio of reduced and non-reduced haloperidol is an indicator of the speed of metabolism. Chang's sample consisted of 21 Asian subjects. They were compared with published reports on Caucasian samples. Lin et al.(1988b) detected a difference in plasma prolactin level between Asian and Caucasian subjects with a power of 80% and an alpha of 0.01 with sample sizes of only 17 per group.

Haloperidol is very effective in treating psychotic symptoms. An average change of psychotic symptom of 50% over one month has been reported in first episode studies(Geddes et al., 1994). This is a large effect size. Although it seems reasonable to expect significant rates of improvement in both Asian and Caucasian populations, there have been no previous investigations to establish whether one group improves more than another. The current study provides information on the rate of clinical improvement in two ethnic groups during short-term and medium term follow-up.

CHAPTER 4

Results

Description of the Sample

A. Baseline demographic variables: The best sample to examine ethnic similarities and/ or differences in treatment responses would be a weight and gender matched Asian-Caucasian sample. However, this ideal is difficult to achieve.

Despite repeated efforts to recruit as many as Asian subjects as possible, the sample remained unbalanced. As Table 2 shows, group differences in sex ratio were statistically significant in this sample. There were more women in the Asian group, and although the trend was not statistically significant, the Asians tended to weigh less.

There is a significant inter-individual variation in drug distribution throughout the body (Shulman, 1997). It relates to fat distribution because fat is the principal reservoir of psychotropic drugs. Although a mg/kg dosing method would have been ideal from a research standpoint. practical issues obviated that approach. The hospital pharmacy was unable to provide sufficient human resources to reassemble haloperidol in order to match each patient's weight. Therefore it was necessary to control statistically for weight in the analyses. Weight was not correlated with haloperidol plasma levels in either Asians (r=0.00) or Caucasians (r=0.21) in our sample. Nevertheless, it was controlled for in all our statistical analyses.

[See Table 2 on page 35b]

B. Clinical variables Because the distribution of duration of onset was skewed, this variable was log-transformed. Compared with Caucasians. Asians in our study exhibited a longer duration

Table 2 Sample description

	Asians (N=15)	Caucasians (N=16)	Statistics	p
Age (years): Mean (SD)	24(5.5)	27(5.4)	T(29)=-1.28	.22
Gender (number of cases)				
Male	5	11	$X^2(1)=3.88$	0.05
Female	10	5		
Weight (kg): Mean (SD)	59(9.1)	65(11.5)	T(29)=-1.55	.13
Positive syndromes: Mean (SD)	21(6)	20(4)	T(29)=0.23	.82
Negative syndromes: Mean (SD)	24(7)	23(9)	T(29)=0.18	.86
General pathological syndromes: Mean (SD)	42(11)	44(9)	T(29)=0.55	.59
Depression: Mean (SD)	8(2.4)	12(3.6)	T(29)=4.20	<0.01

between the emergence of first noticeable sign of illness and the onset of prominent psychotic symptoms (mean 6 years) compared with Caucasians (mean 36 weeks). Asians also had poorer premorbid functioning (see Table 3).

[See Table 3 on page 36b]

Study Question 1:

Are There Asian-Caucasian Differences in Clinical Response to Treatment?

The median optimal daily haloperidol dose for Asians and Caucasians was the same: 5 mg./day. Optimal dosages for the Asians were: 2 mg./day for 6 patients; 5 mg./day for 5 patients; 10 mg./day for 3 patients; and 20 mg./day for 1 patient. Optimal dosages for the Caucasians were: 2 mg./day for 6 patients; 5 mg./day for 5 patients; 10 mg./day for 4 patients; and 20 mg./day for 1 patient (X^2=0.11; df=3; n.s.) (figure 5)

Sixteen subjects (52%) reached their optimal dose before developing extrapyramidal side effects. The relationship between EPS and daily dose was curvilinear: only 1 of 12 subjects (8%) maintained on haloperidol 2 mg. developed EPS, compared to 6 of 10 subjects on 5 mg. (60%); 7 of 7 subjects on 10 mg. (100%); and 1 of 2 subjects on 20 mg. (50%).

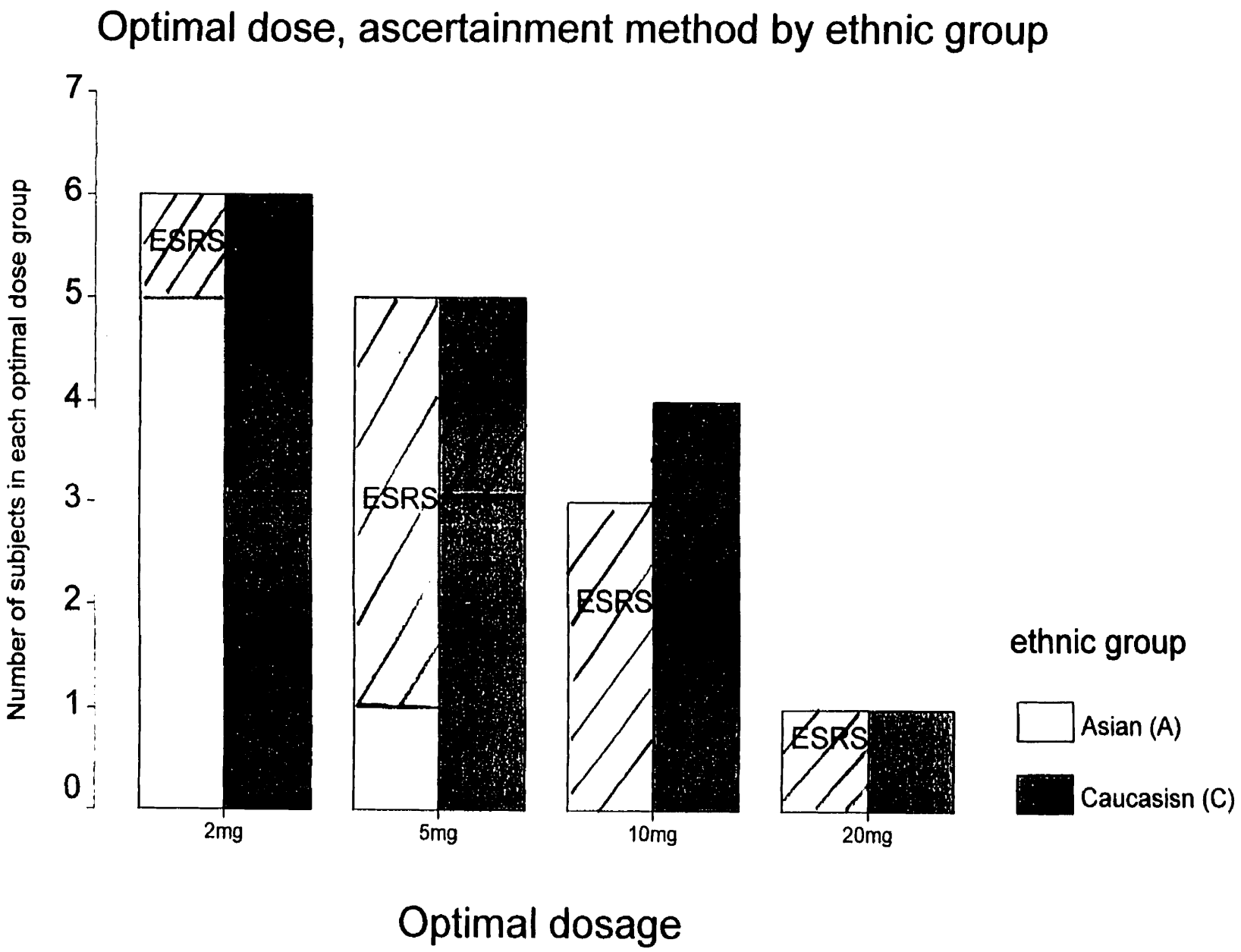
[See Figure 5 on page 36c]

Although the number of subjects in each optimal dosage group was similar for the Asian and for Caucasian group at week four, a higher percentage of Asian subjects (60%) reached their optimal dosage through the side effect criterion than Caucasian subjects (37.5%) (Fisher's exact test p=0.34). In particular, 4 of the 5 (80%) Asian males reached it through side effect compared with 4 out of 11

Table 3 Premorbid functioning and onset

	Asians (N=15)	Caucasians (N=16)	Statistics	p
duration of first noticeable signs to psychotic symptoms (lg years): Mean (SD)	2.52 (0.56)	1.61(1.31)	t(20)=2.54	0.02.
duration of psychotic symptoms to admission to the study (lg years): Mean (SD)	2.02 (0.89)	1.60 (0.87)	t(29) = 1.35	0.19
Premorbid functioning: Mean (SD)	26.9(10.36)	19.9(9.22)	t(29)=2.00	0.05

Figure 5


Optimal dose, ascertainment method by ethnic group
Number of subjects in each optimal dose group
0
1
2
3
4
5
6
7
ESRS
ESRS
ESRS
ESRS
2mg
5mg
10mg
20mg
Optimal dosage
ethnic group
Asian (A)
Caucasisn (C)

Caucasian males (36%) (Fisher's exact test p=0.14). Although these differences were not statistically significant, they may, as pointed out in the discussion, be clinically important.

Subjects who developed side effects could also have experienced symptom improvement. Table 4 describes the number of Asian and Caucasian subjects meeting one or both of the two optimal dose criteria in four optimal dose groups. At a 2mg. dose, 12 subjects (6 Asians and 6 Caucasians, 39% of the total sample) had significant improvement. One of the 6 Asians also developed side-effects. At 5mg and higher, 10 of the 10 Caucasian subjects responded to treatment (with or without side effects) while only 5 of the 9 Asian subjects did so. Four Asian subjects experienced side effects, but no clinical improvement. This difference in response to haloperidol between Asian and Caucasian subjects was statistically significant (fisher's exact test=0.03).

[See Table 4 on page 37b]

Study Question 2:

Are There Asian-Caucasian Differences in the Metabolism of Haloperidol?

All patients received 2 mg. of haloperidol per day for the first week of treatment. Thus, plasma haloperidol level measured at day 8 after the first week of treatment provided an opportunity to examine ethnic differences in response to a fixed dose of neuroleptics. At 2 mg./day of haloperidol, ethnic differences in plasma haloperidol concentration were not statistically significant. However, because there were differences in gender distribution (Asians 2/3 females, Caucasians 2/3 males), the results were reanalyzed using both gender and ethnicity. At equivalent levels of oral haloperidol, Caucasian males had lower plasma haloperidol levels (1.03ng/ml$\pm$0.51) than Asian males (1.93ng/ml$\pm$0.88) (t_{14}=2.62, p=0.02). The four subjects in the sample with the lowest plasma

Table 4 Distribution of subjects in method of ascertaining for optimal dose

optimal dose	SCI-PANSS improvement only without ESRS		SCI-PANSS+ESRS		ESRS only without SCI-PANSS improvement	
	Asian (n)	**Caucasian (n)**	**Asian (n)**	**Caucasian (n)**	**Asian (n)**	**Caucasian (n)**
2mg (n=12)	5	6	1	0	0	0
5mg (n=10)	1	3	3	2	1	0
10mg (n=7)	0	0	1	4	2	0
20mg (n=2)	0	1	0	0	1	0

haloperidol levels were all Caucasian males. There were no ethnic differences in haloperidol levels among females. Caucasian females (1.74ng/ml±0.66) and Asian females (1.96ng/ml±0.42) (t_{13}=0.70, n.s.) reached similar plasma haloperidol levels while receiving 2 mg. of oral haloperidol per day (figure 6). **[See Figure 6 on page 38b]**

As Table 5 demonstrates, after controlling for weight, the ethnicity x gender interaction remained significant. This difference was also clinically significant. Asian subjects appeared to be highly sensitive to developing side effects. Optimal dose was reached using the side effects rather than clinical improvement criterion in 4 out of 5 Asians males (80%) and 5 of 10 Asian females (50%), compared to 4 out of 11 Caucasian males (36%) and 2 out of 5 Caucasian females (40%).

[See Table 5 on page 38c]

In contrast to the differences observed in circulating haloperidol levels, regression analysis suggested that ethnic, gender differences in reduced haloperidol levels and their interaction after 1 week on a 2 mg. dose of haloperidol were not statistically significant (Ethnicity beta=.143, t=.482, n.s. Gender beta=.175, t=.606, n.s. Ethnicity x Gender beta=-.276, t=-.915, n.s.).

Study Question 3.

Are There Asian-Caucasian Differences in Prolactin Levels Following Administration of Haloperidol?

Prolactin levels at the end of the first week of treatment with haloperidol 2 mg./day were used to investigate possible ethnic differences in CNS responsiveness to haloperidol.

Figure 6 Plasma haloperidol level controlling for weight by ethnic group and by gender

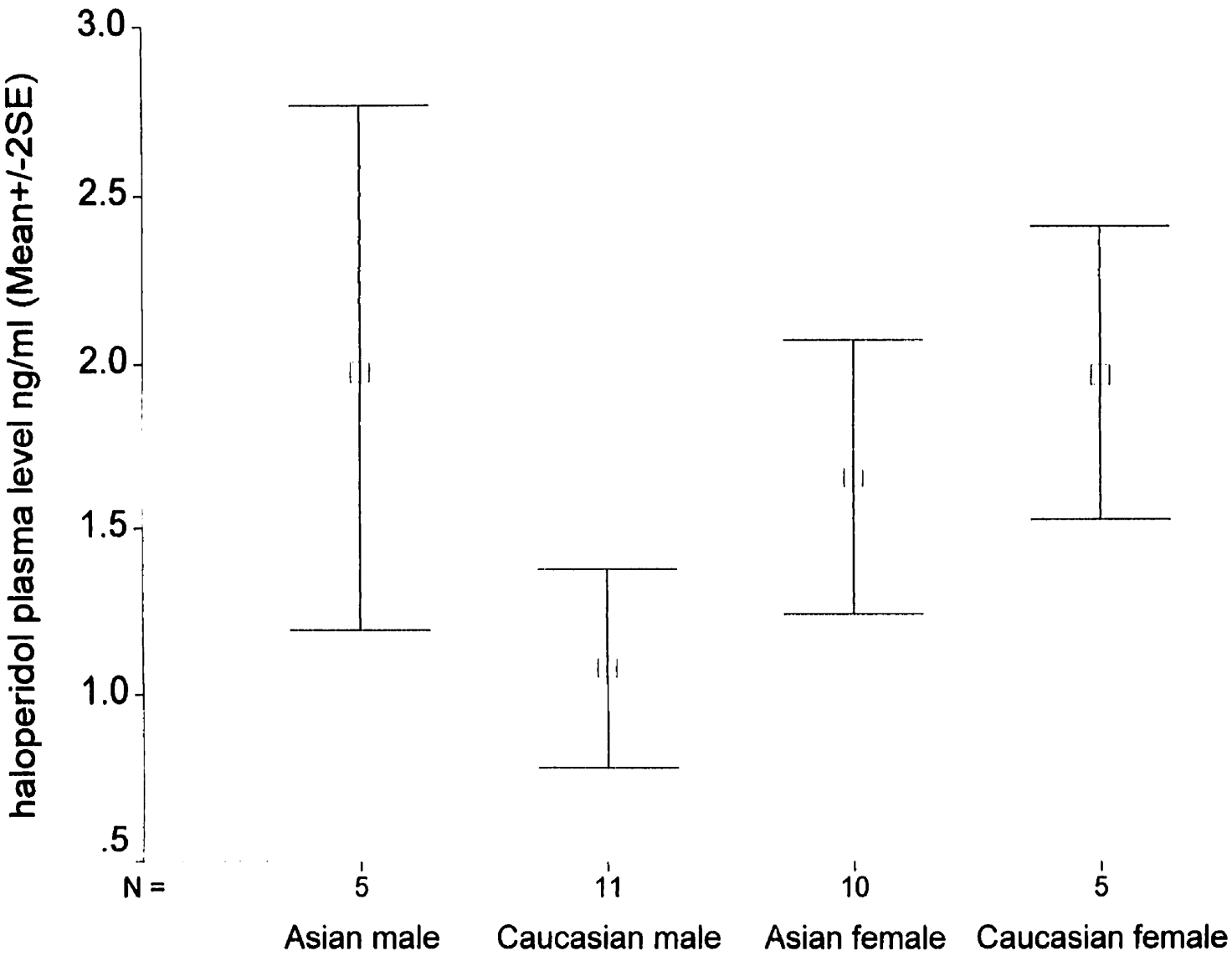


Table 5 Multiple regression predicting score on plasma haloperidol level at haloperidol 2mg/day (N=31) [a]

Variables	β	SE	p
Weight	-.088	.012	.63
Ethnicity (Asian=1, Caucasian=0)	-.189	.351	.46
Gender (male=1, female=0)	-.651	.342	0.01
Ethnicity by gender	.611	.487	0.02

a: R=0575, adjusted R^2 =.33, $F(4,26)= 3.21$, $p<0.05$

Regression analyses was used to examine the effect of ethnicity, gender, and their interaction on baseline prolactin (prior to initiating treatment). There was no statistically significant ethnic difference in plasma prolactin levels at baseline (beta=-0.66, t=-0.24, n.s) nor gender difference (beta=-3.24, t=-1.20, n.s.). Females tended to have higher baseline prolactin level, but the difference was not statistically significant. Ethnicity and gender interaction did not affect baseline prolactin levels (beta=.285, t=1.01, n.s.).

Step-wise regression was used to analyze the research question. Using prolactin levels at the end of the first week of treatment as the dependent variable, baseline prolactin was entered first in the regression model. Weight, ethnicity, gender and the interaction term were entered as step 2. As described in Table 6, after controlling for baseline prolactin level, plasma haloperidol was the only variable that remained significantly associated with plasma prolactin increase.

[See Table 6 on page 39b]

Study Question 4.

Are Short-term Effects Sustained During Follow-up?

SCI-PANSS scores were used to address treatment effects. Asians and Caucasian subjects had similar symptom ratings on the positive, negative and general pathology symptom subscales at intake (Table 2), but differed on the depression subscale. Asians had significantly lower depression score than Caucasians.

The relationship between haloperidol plasma level and therapeutic response across and within groups was examined using a repeated measures analysis. One- week improvement (measured by total SCI-PANSS) was statistically significant for the whole sample ($F_{1,28}$=5.27, p=0.03). However,

Table 6 Multiple regression predicting score on plasma prolactin level at haloperidol 2mg/day (N=31)

Step	Variables	β	SE	p
1[a]	Baseline prolactin	.669	0.237	<0.01
2[b]	haloperidol plasma level	.369	2.354	0.01
	Weight	-.031	0.149	0.82
	Ethnicity (Asian=1,Caucasian=0)	.256	4.269	0.17
	Gender (male=1, female=0)	.006	4.727	0.98
	Ethnicity by gender	-.328	6.554	0.12

a: R=0.669, adjusted R^2 =.429, F(1,29)=23.51, p<0.01

b: R=0.825, adjusted R^2 =.601, F(6,24)=8.53, p<0.01

an examination of interaction effects revealed that symptom improvement was related neither to ethnicity ($F1_{,28}$=0.11, n.s.) , nor to plasma haloperidol level after the first week of treatment with 2 mg. of haloperidol ($F_{1,28}$=0.024, n.s.).

As described in Figure 7, every study dose group experienced some improvement on average by week four. However, the amount of improvement varied by group. Subjects who responded to 2 mg. of haloperidol per day had an average 63% improvement in SCI-PANSS scores at the end of the 4 week trial, compared to 46%, 28%, and 21% for those treated with 5 mg., 10 mg., and 20 mg., respectively. A one-way ANOVA suggested that low-dose responders evidenced greater average improvement during the treatment period than persons whose optimal doses were higher (F(3,32)=3.10, p=0.04). Tukey post hoc tests suggested that the difference was accounted for primarily by differences between the 2mg response group and the 10 mg. response group (p=0.02).

[See Figure 7 on page 40b]

Ethnic group by total SCI-PANSS improvement interaction at week 4 was statistically significant ($F_{1,29}$=10.03, p=0.03). Interestingly, by the nine-month follow-up, Asians had apparently caught up with Caucasians; at this point, ethnic differences in improvement were no longer statistically significant (figure 8).

[See Figure 8 on page 40c]

Repeated measure analysis was used to assess symptom change over time in Asians and Caucasians. The following factors were considered as covariables:

Figure 7 Improvement of SCI-PANSS over time

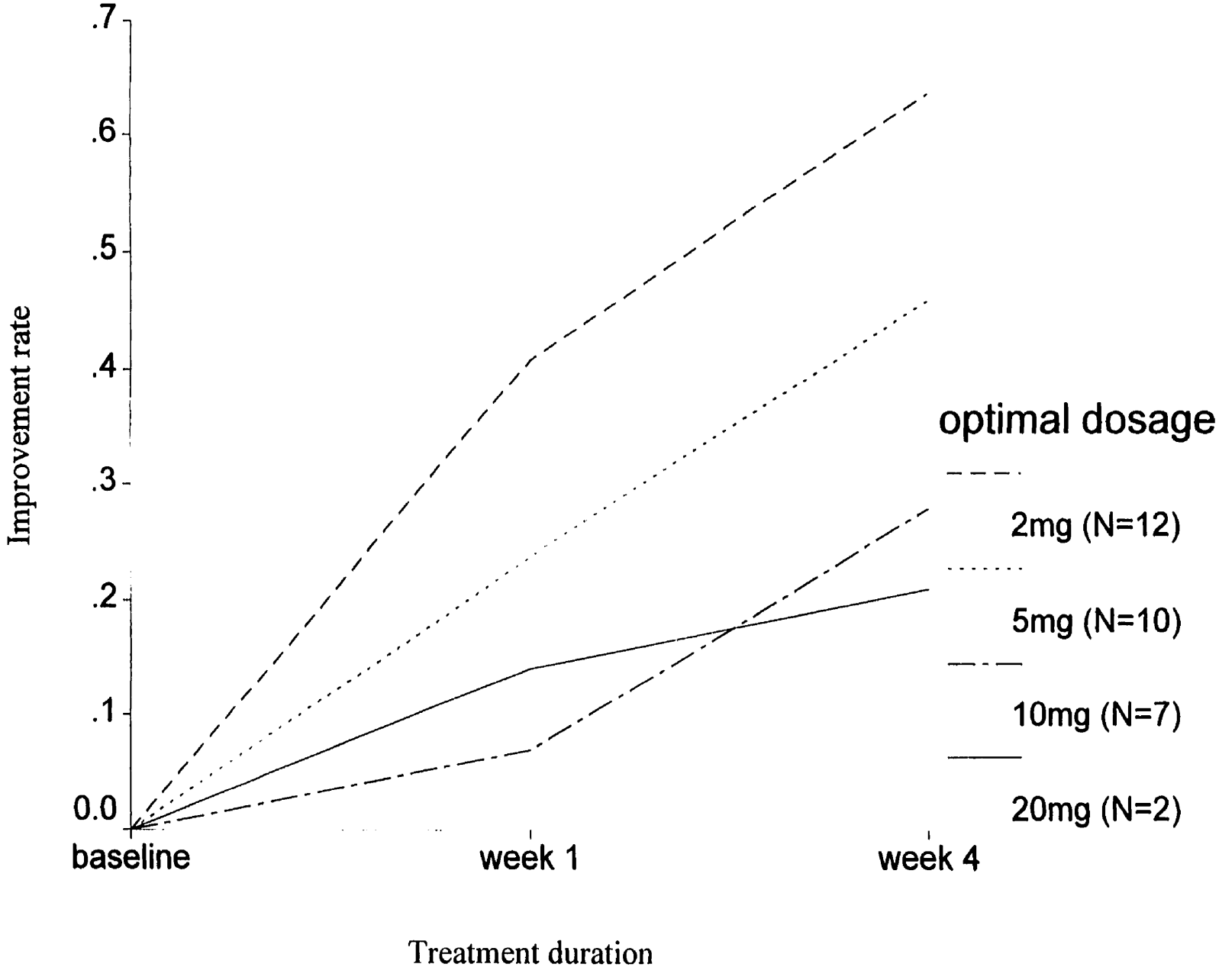
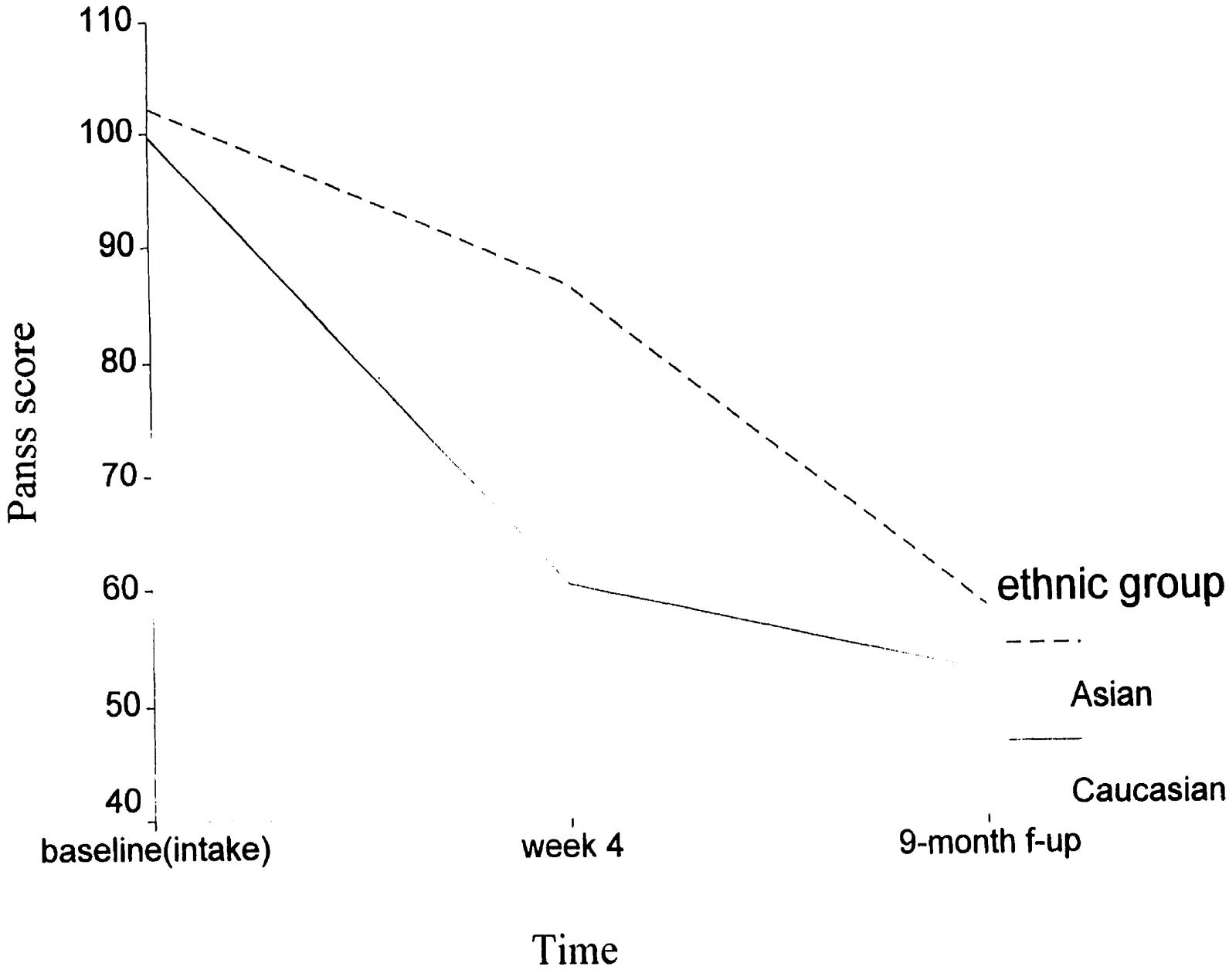


Figure 8 Symptom changes over time by ethnic group



1. Gender. During the first 15 years following the onset of psychosis, females have a better clinical course than males (Seeman, 1996);

2. Optimal medication dose. It may be that those who responded to a lower optimal haloperidol dose were better treatment responders in general;

3. Method of ascertaining optimal dosage. In comparison with Caucasians, more Asians subjects reached their optimal dose through side effects criteria rather than symptom improvement;

4. Duration of onset. Asians had longer duration of untreated illness than Caucasians. Premorbid functioning (PAS) was correlated with the onset variable at p=0.69. Although Asians had poorer premorbid functioning than Caucasians, the PAS was not included as a co-variable because of concerns of colinearity;

5. Different symptom profiles reported at intake. Depressive signs and symptoms during the course of schizophrenia are common and have been reported to be associated with impaired recovery (Tollefson, 1998). Since Asians reported significantly lower depression scores at intake, we might expect them to have a better recovery.

Table 7 describes changes in the SCI-PANSS positive scale, Table 8 describes changes in negative symptoms and Table 9 changes in the general pathology scale. Potential confounding effects are examined using Analysis Of Co-Variance (ANCOVA). ANCOVA is designed to be used for randomly assigned groups to avoid systematic bias despite random assignment. Requisite conditions for the use of ANCOVA include 1) the sample size must be large enough to accommodate the number of co-variables; 2) co-variables must be clinically significant and correlated with the outcome variables. The Asian/Caucasian study utilized ANCOVA, including variables based upon the above criteria. However, due to the fact that the study is a non-random open trial, the results of the ANCOVA analyses should be interpreted with caution.

[See Table 7-9 on page 41b,c,d]

Table 7 Repeated measures of positive symptoms change overtime controlling for covariables

variables		baseline to week4 (n=31, df=1,23)			baseline, week 4, 9 month (n=22, df=2, 28)		
		F	p	observed power	F	p	observed power
Time effect	change of positive symptoms	7.79	0.01	.76	2.00	0.15	.38
Interaction with time effect	gender(male=1, female=2)	0.91	0.35	.15	0.36	0.70	.10
	depression at intake	0.03	0.87	.05	1.93	0.16	.36
	optimal medication dose	0.76	0.39	.13	0.53	0.59	.13
	duration of FNS to PPS	0.00	0.97	.05	0.46	0.63	.12
	duration of PPS to PTS	0.00	0.98	.05	0.42	0.79	.08
	ascertaining method (by PANSS=1, by ESRS=2)	2.19	0.15	.29	1.26	0.30	.25
group X Time effect	ethnic group (Asian=1, Caucasian=2)	1.14	0.30	.17	0.46	0.63	.12

Table 8 Repeated measures of negative symptoms overtime controlling for covariables

	variables	baseline to week4 (n=31, df=1,23)			baseline, week 4, 9 month (n=22, df=2, 28)		
		F	p	Observed power	F	p	Observed power
Time effect	change of negative symptoms	3.70	0.06	.45	0.78	0.47	0.18
Interaction	gender(male=1, female=2)	0.08	0.78	,06	0.38	0.66	0.11
with time effect	depression at intake	0.57	0.46	.11	0.09	0.92	0.62
	optimal medication dose	1.25	0.28	.19	0.81	0.46	0.17
	duration of FNS to PPS	1.39	0.25	.21	0.11	0.90	0.06
	duration of PPS to PTS	0.87	0.36	.14	0.34	0.72	0.10
	ascertaining method (by PANSS=1, by ESRS=2)	3.92	0.06	.48	1.58	0.23	0.31
GroupX Time effect	ethnic group (Asian=1, Caucasian=2)	4.58	0.04	.54	1.13	0.34	0.23

Table 9 Repeated measures of general pathology symptoms overtime controlling for covariables

	variables	baseline to week4 (n=31, df=1,23)			baseline, week 4, 9 month (n=22, df=2, 28)		
		F	p	Observed power	F	p	Observed power
Time effect	change of general pathology symptoms	3.26	0.08	0.41	0.37	0.69	0.10
Interaction	gender(male=1, female=2)	0.47	0.50	0.10	0.03	0.97	0.05
with time effect	depression at intake	9.03	0.06	0.82	3.84	0.03	0.64
	optimal medication dose	0.09	0.77	0.06	1.41	0.26	0.27
	duration of FNS to PPS	0.07	0.79	0.06	0.22	0.80	0.08
	duration of PPS to PTS	7.93	0.01	0.77	2.86	0.07	0.52
	ascertaining method (by PANSS=1, by ESRS=2)	20.2	<0.01	0.99	2.86	0.07	0.52
GroupX Time effect	ethnic group(Asian=1, Caucasians=2)	0.52	0.48	0.01	0.29	0.75	0.09

As Table 7 shows, positive symptom change over 4 weeks was statistically significant. It was not associated with gender, dose, method of ascertainment, onset, or depression level at intake.

With respect to the negative symptoms, Asians experienced less improvement (Table 8). The covariable "method of ascertainment" was also significant - those who reached optimal dose through the side effects criteria had less improvement at week 4 than those whose optimal dose was marked by symptom relief. Difficulties in differentiating negative symptoms from drug induced side effects, such as sedation and flat affect may have introduced a confound in the assessment of negative symptom improvement.

The improvement of general pathology symptoms over 4 weeks was similar in Asians and Caucasians. Greater improvement was associated with shorter duration of onset and method of ascertainment. Those who reached their optimal dose through the side effects criteria had less improvement at week 4 than those demonstrating improvement in the SCI-PANSS. Depression was a confounding variable. Because general pathology symptoms includes a depression cluster, a lack of improvement in depression could result in a lack of improvement in general pathology. Asians were less depressed at intake than Caucasians and were less likely to improve. After controlling for this variable, Asians' improvement in general pathology equalled that of Caucasians.

Table 7 to 9 also address nine month outcome. Asians took longer to recover and recover best in their own milieu. Repeated measures analyses of positive, negative, general pathology symptoms in two ethnic groups was performed over three time points (baseline, 4 weeks, 9 months). Covariables were the same as those in the analyses of week four outcome: gender, optimal dosage, method of ascertainment, onset, and depression at intake.

Although 9 month follow up provided more time points (3 time points) compared with 4

week acute treatment phase (2 time points), subject attrition resulted in fewer subjects (n=22) being available for the 9 month than the 4 week assessments. Repeated measures for symptom change over the 9 month follow up did not reach statistical significance, perhaps because of sample size limitations. The interpretation of 9-month follow-up was further limited by the fact that 80% of the patients switched from haloperidol to other medications during the 9 month following discharge. At the time of the follow-up, atypical antipsychotics, such as risperidone which has the advantage of reducing the risk of extrapyramidal symptoms, had started to replace haloperidol as the drug of first choice for psychosis. Although subjects who were followed at 9-month follow-up maintained their therapeutic gain at the time of discharge, discrepancies in treatment regimes dictated by patient needs and by professional practice make the results difficult to interpret or to relate to the optimal dosage in effect at the conclusion of the 4 week trial with haloperidol.

CHAPTER 5

Discussion

Ethnicity and Optimal Dose

Contrary to previous reports, Asians and Caucasians in our study obtained an optimal therapeutic response at comparable doses of neuroleptic medication.

Sample characteristics may help explain differences between the current study and previous investigations. The Asian/Caucasian study sampled people suffering a first episode of psychosis, whereas previous investigations (Potkin, 1984; Lin, 1989; Jann, 1993) have typically used mixed samples of first episode and chronic cases. An unexpectedly large number of both Asians and Caucasians responded to haloperidol at both 2 mg. and 5 mg./day. The level of responsivity in such small samples militated against finding ethnoracial differences in oral optimal doses. Future studies permitting finer titration of optimal drug levels might well reveal that doses that are optimal for Asians are different from those that are optimal for Caucasians.

The fact that a large number of subjects responded to the initial dosage of medication raises the possibility that, for some at least, 2 mg. may have in fact exceeded the optimal therapeutic dose. In a study using positron emission tomography, Kapur et al (1996) reported that, at 2 mg. of haloperidol per day and plasma haloperidol levels ranging from 0.6 to 1.5ng/ml, the mean dopamine D2 receptor occupancy level was 67$\pm$7%, a level well beyond the 50% to 60% D2 occupancy defined as the threshold for a good clinical response (Nordstrom et al , 1993). Although our original study protocol called for initial doses of 1 mg., we were dissuaded by clinical staff and by the concerns

of the institutional review committee. However, the study results suggest that future investigations could justifiably begin with lower doses in order to permit finer titration of optimal drug levels.

Ethnicity, Gender and Haloperidol Metabolism

Our observation that Asian males obtained higher plasma haloperidol concentrations than Caucasian males at 2 mg./day is consistent with an earlier report (Lin, et al 1989) suggesting that Asian males metabolize drugs more slowly than Caucasians. In addition, our results raise the possibility that the Asian males would have responded to doses even lower than 2 mg. of haloperidol

Gender may also affect psychotropic drug metabolism. Women experience a higher frequency of adverse drug reactions than men (Domecq, 1980; Makka, 1993). There are reports of gender differences in some of the P450 enzymes that are responsible for the metabolism of most psychotropic drugs, and display a marked genetic polymorphism (Pollock, 1994). In addition, estrogen, oral contraceptives and menstrual cycle have been found to affect CYP450 metabolism (Abernethy, 1982,1984; Kimmel, 1992). Female patients in the Asian/Caucasian study were all in their child bearing age and menstruating during the four week treatment phase. The expression of CYP3A4 and CYP1A2, two subgroups of CYP450 that metabolize haloperidol, are highly responsive to environmental influences. Further analyses of the genotype of liver enzyme CYP450 would help to clarify the role of genotypes in explaining gender and ethnicity differences in neuroleptic metabolism.

Plasma level of reduced haloperidol, one of the major metabolites of haloperidol, supplies another index of ethnic or gender differences in metabolism. Previous research with a mixed acutely and chronically ill population of persons with schizophrenia (Jann et al, 1993) suggested slower drug

metabolism among Asians than among Caucasians. Based on these findings it was predicted that the Asian subjects in our study would have lower levels of reduced haloperidol. However, the extremely low levels of reduced haloperidol that resulted from 2 mg. of oral haloperidol made such analyses impractical in our study.

At the time of this study, the plasma haloperidol and reduced haloperidol were the most commonly used indicators of haloperidol metabolism. The values were easy to assess and the results easily compared with other studies in the literature. However, it is now clear that the best indicator of drug metabolism at the liver site is a measure of liver enzymes activity (Lin, 1996). Although we collected plasma with white cell-coating for all subjects at the time of the study, there were no facilities available to analyze genotypes of CYP enzymes at the Center for Addiction and Mental Health. Efforts will be made to contact other centers that have the facilities for genotyping in order to perform these analyses for future publication.

Ethnicity and Gender in CNS Sensitivity to Haloperidol

Study findings did not support the hypothesis that Asian CNS sensitivity to haloperidol in Asians is greater than among Caucasians. Gender was, likewise, not a significant predictor of CNS sensitivity. Small sample size may have compromised the findings. It should be noted that the proportion of females found in the Asian study sample is unexpectedly high. First episode studies usually report a predominance of males. This proportional difference may be as high as 3 to 1 (Iacono, 1992a, 1992b). Is this an oddity of our sample or is it that among Asians, first episode non-affective psychosis is more stigmatized for males than for females, leading to fewer Asian males being available for study recruitment? For example, Asian families consider male family members

as persons who will carry on the family lineage. Because of that, the existence of a mental illness in a male member would be more likely to be denied or kept secret by others in the family so that this individual would be able to get married and have children. In addition, mental illness in a male family member would more likely to be seen by others in the community as a familial vulnerability; this is less true for females who will join another family through marriage. Because help-seeking for psychosis is usually initiated by an ill individual's significant others, this pattern of gender specific stigmatization may lead to fewer Asian males than females seeking help in formal mental health care settings.

Methodological limitations may also have compromised the findings. Prolactin, an indicator of CNS response to haloperidol used in this study, is regulated by dopamine in the hypothalamic area outside the blood-brain barrier. It may not reflect D2 binding in other areas of the brain. Compared with plasma prolactin measurement, Positron Emission Tomography (PET) scan can provide direct mapping of haloperidol D2 binding in striatum. In 1993, when the study began, PET scan technology had just been introduced and was extremely costly. Now that PET scanning has become popular and less expensive, it offers a superior method for examining the potential effect of gender and ethnicity on CNS response to haloperidol in striatum.

Ethnicity and Clinical Improvement

Both Asians and Caucasians responded to haloperidol treatment. The improvement was significant in both groups. However, the longer duration of untreated illness with associated poorer premorbid functioning among the Asian group may have contributed to a less favourable response to treatment in Asians. This was evidenced by the observation that four subjects who did not have

clinical improvement at the time of the optimal dose threshold were all Asians. The fact that most Asian males reached optimal dose through the side effect criterion further complicated the issue. Side effects such as slower movement and restricted facial expression are difficult to separate from symptoms of schizophrenia.

Among the factors identified as contributing to the outcome and course of psychosis, depression has been frequently cited (Koreen, 1993). Depressive signs and symptoms in schizophrenia range from 7% to 65%, with a modal rate of 25%(Hirsh, 1989, Koreen 1993). Although the presence of affective features has, in past reports, been associated with good short term treatment response, recent literature has called this into question (Tollefson,1998). Tollefson (1998) reported that depressive signs and symptoms increased the likelihood of relapse and of suicide. Although Asian subjects had fewer depressive symptoms at intake, they had a worse 4 week course than Caucasians. Close examination of the study data revealed that Asians reported little or no depressed mood at intake and at week 4 of the treatment. Reporting bias may have contributed to the apparent paradox: despite being less depressed at intake, Asians had a worse outcome than Caucasians. One possible explanation is that the Asian score on the depression subscale may be artificially low due to ethnic differences in symptom expression (Noh, 1992; Chung, 1995). Another possibility is that SCI-PANSS was not sensitive to depression in Asians. The SCI-PANSS scale is primarily an instrument for measuring symptoms of schizophrenia.

Differences in depression scores may also help explain the relative lack of improvement in the general pathology symptom cluster among Asian subjects. The SCI-PANSS depression scale is made up of four questions: somatic concerns, anxiety, guilt feelings, and depression. Because the depression cluster represents 25% of ratings in the general pathology symptom cluster, a lack of

change in depression may have contributed to lack of change in the general pathology symptom cluster. Should the study be repeated in the future with a larger sample, a depression scale should be added to the instruments to examine whether Asians are different from Caucasians. Such a study should also provide information about the validation of the depression symptom cluster in the SCI-PANSS scale.

Why did the Asian subjects have less improvement in negative symptoms at the end of week 4 treatment period, but then catch up with their Caucasian counterparts at 9 month follow up? At 9 month follow-up, The total SCI-PANSS rating for the four Asian subjects who did not achieve symptom relief at 4 weeks were significantly improved. At 9 months, they had a 49% ±0.17 improvement rate compared with 69.6%± 0.23 for the remaining 9 Asian subjects and 68.5%±0.28 for 9 Caucasian subjects. The difference between four Asians and the remaining sample was not statistically significant (t=1.46, p=0.16). At 9 months, one of these apparently treatment-resistant Asians was taking 3mg haloperidol, one was on 8mg perphenazine, the third 30mg loxapine and the fourth 500 mg clozapine. If one of the major factors was the dose of haloperidol with side effects secondary to the use of this drug, then most subjects would be free from this condition during the follow-up when their medication was readjusted or switched (**Table 10, see page 49b**). Individually focused treatment plans are clearly superior to treatment dictated by a research protocol. Secondly, at the end of the recruitment in 1995, risperidone started to reach the Canadian market. This atypical antipsychotic causes fewer extrapyramidal side effects and it has been claimed that it is superior to haloperidol in reducing negative symptoms (Casey, 1996). The combination of individual tailored follow-up treatment and the availability of a new drug for Asian subjects may have contributed to their catching up at 9 months. Thirdly, it is also possible that the hospital where initial treatment

Table 10 Medication at 9 month follow-up

	Asian (N=13)	Caucasian (N=9)
haloperidol (2mg-3mg)	3	1
loxapine (15-60mg)	5	2
perphenazine (8mg)	0	1
risperidone (2.5-6mg)	4	1
clozapine (500mg)	1	0
No medication	0	4

occurred was a less familiar environment for Asians than for Caucasians. The context of unfamiliarity may have contributed to treatment resistance. After discharge, 70% of the Asian patients went to live at home, compared with only 30% of the Caucasians. The support offered by a familiar home environment may have created a post-discharge advantage for Asians, allowing them to make therapeutic gains sufficient to catch up with their Caucasian counterpart.

The catchup of Asian subjects to Caucasian subjects was not likely due to a difference in the attrition rate. The Asians who dropped out from follow up actually had lower symptom ratings than the Caucasian dropouts (Asians=51.5$\pm$3.53,(n=2); Caucasians=62.9$\pm$36.85,(n=7); t=0.42, p=0.69).

Study Limitations

A. Small sample size:In general, the Asian community tends to be remarkably tolerant of psychotic behaviour, as long as the ill person remains quiet and non-violent. In many cases, Asians suffering a mental illness remain isolated within their home and family. Despite efforts to recruit people from Asian background by repeatedly contacting Asian psychiatrists and family physicians and posting descriptions of the study in Chinese newspapers, radios and TV, very few Asian patients came to the Clarke Institute during the period of the study. The experience was consistent with reports in the literature: it was extremely difficult to recruit Asian patients suffering a first episode of psychosis who satisfied the study's inclusion criteria.

Modifying the inclusion criteria to include more chronic patients would have increased the sample size. However, as discussed in the literature review section, the inclusion of a more heterogeneous population might have produced a disproportionate number of poor responders and non-responders to medication thus reducing power to detect therapeutic response. Previous

treatment probably affects drug metabolism as well as CNS drug sensitivity (Geddes, 1994; Wiesel, 1994). Previous treatment history would compromise the ability to detect ethnoracial differences in drug metabolism.

B. Measurement issues: The primary outcome measures in this study were clinical symptom ratings over time. Other outcome measures, such as social functioning and/or occupational functioning were not included in the study. Persons suffering from a first episode of non-affective psychosis respond favourably to pharmacological intervention (Lieberman, 1993a, 1993b). However, unlike affective disorders in which psychosocial factors play a prominent role in the early phases of recovery, schizophrenic patients show less psychosocial responsivity. The recovery of social responsivity in schizophrenia may be delayed longer than in affective disorders (Beiser, 1994). Although the current study did not include measures for social/occupational functioning, it did capture symptom changes which are sensitive to pharmacological intervention, the major focus of this study.

C. Treatment protocol issues: Fixed dose vs step-up dose: Instead of randomized low versus high fix-dose in each ethnic group, the current study used a step-up dosing method. This design was chosen for two reasons: 1) existing literature suggested that Asians may not be able to tolerate high doses (Lin et al., 1991). 2) McEvoy (1991a) suggested in his study that even first episode Caucasian patients might not need doses as high as those commonly used for the treatment of schizophrenia. A step-up dosing method beginning from the lowest possible dose was used to determine optimal doses for Asian and Caucasian first episode patients. During the first 4 weeks of the study, about 40 percent of the subjects in the study had a good clinical response, and side effects were rare. This finding has important clinical implications: Using the current dosing method, treatment benefits

were maximized while side effects were minimized. The compliance to the treatment protocol was high. None of the subjects dropped out of the study after the modification of the initial protocol.

Although 2 mg./day haloperidol provides effective initial treatment for many patients, it might be argued that larger doses are necessary for sustained therapeutic gain. According to our results, however, further improvement occurred after setting the fixed therapeutic regimen at the operationally defined, and often very low, optimal dose. It may be that patients most likely to have a robust antipsychotic response are also most likely to respond to low doses. Conversely, those patients who do not respond well to small doses may be non-responsive to neuroleptic medication.

D. Non-response versus slow response: For example, although the study results suggest that low dose responders are also the best responders to neuroleptic treatment, design characteristics limit the strength of such an inference. Since the Asian/Caucasian study did not employ a fixed dose design, patients were treated with their final optimal dose for variable periods of time. It is possible that, had patients whose optimal daily dose was 5 mg., 10 mg. or 20 mg. of haloperidol per day received this level of medication for a full 4 week period -- as did patients on 2 mg. of haloperidol -- their improvement might have been greater. In other words, low dose responders may only have appeared to be the best responders because they were maintained at their optimal level for a longer period than people whose optimal dose was higher than 2 mg./day. The Asian patient who had improved at the 9 month follow-up while on 3mg. of haloperidol may be an example of someone who responds slowly, but who will respond to a relatively low dose. Although a fixed dose design might have shed light on this question, this approach has its own limitations, chief among them the danger of choosing a dose higher than optimal for some patients. As has been suggested by Freudenreich and McEvoy (1995), just as a large enough shoe will fit every foot, the amount of

medication that will guarantee a response in the highest number of patients is, by logical necessity, higher than the required dose for some patients in that group. Our titration method helped identify a substantial number of patients who responded to what many would consider very low doses of haloperidol. After initial resistance, the culture of the First Episode Service changed. The Service began to employ lower doses for everybody. The practice was later reenforced by Kapur et al's (Kapur, 1996) finding that, at 2 mg. of haloperidol per day, and plasma haloperidol levels ranging from 0.6 to 1.5ng/ml, the mean dopamine D2 receptor occupancy level was 67±7%, a level well beyond the 50% to 60% D2 occupancy defined as the threshold for a good clinical response (Nordstrom et al , 1993).

Clinical concerns inevitably constrain the design and conduct of research. For example, patients in this study who did not show improvement at a given level of medication after a seven-day period were routinely raised to the next higher dosage level. It is possible that, had the trial period at each level been extended, more people would have responded: for example, a two week trial at 2 mg./day might have revealed more low dose responders. However, the urgency of patient, family, and staff, to achieve symptomatic control obviated the possibility of a longer trial period at low dose levels.

E. Representativeness of the sample: No study can claim to have a representative sample of all persons with psychosis. It is, therefore, theoretically possible that sampling idiosyncrasies account for the current findings. This would be particularly problematic if the study subjects were less disturbed than the people typically found in inpatient settings. The data suggest otherwise: the subjects in this study were at least as severely disturbed as persons who typically take part in studies of antipsychotic medications.

Future Directions

If the study were to be repeated with a larger cohort in the future, the following recommendations would be helpful:

1) More efforts should be made to achieve a gender balance.

Pursuit of this goal would refocus attention on recruiting Asian males. A vigorous public education designed to de-stigmatize mental illness in this community would be one important strategy.

A recent paper by Hough et al (1996) suggests the following methods to improve recruitment and retention of difficult study populations:

a) Outreach as a model for participant recruitment. In our study, as often used in other projects, subjects were mainly recruited from psychiatrists and hospitals. None of the general practitioners responded to our mailing request for referrals. Family physicians and community counsellors are usually the primary care providers for a significant proportion of first episode patients who are too ill or suspicious to use mental health services. To get access to these patients, efforts need to be made to establish a good relationship with the front line community service providers by reaching and responding to their needs, such as giving lectures to staff and clients and providing consultations. This approach would help to improve the community services on one hand, and recruit first episode psychotic patients from the community on the other hand. Once a subject is recruited, the development of trust between researchers and participants is also very important.

b) Techniques specific to retention. The current study used monthly phone calls to track participants. More frequent contact and in particular, an anchoring method should further improve the retention rate. An anchor point is an item of information about where, or who may know where, a research participant may be found. For example, for the five subjects who were lost in the follow-up (most of them moving out of the city), an anchor point about their friends/relatives in the city other than the direct contact person (usually parents) would have helped to identify when and where these participants might come back to the city for a visit or stay.

Recruitment of individuals suffering from mental illnesses and individuals from certain ethnic groups will always require more efforts than the recruitment of participants from the general population. In addition, the greatest effort will always be required by the 10% of individuals who are most difficult to track. Learning from the current study, however, the recruitment could be improved with careful planning, persistence and flexibility.

2) Collect gender specific information.

Among the many factors associated with the course of non-affective psychosis, estrogens have been suggested as protective factors (Hafner et al., 1991; Riecher-Rossler et al., 1993; Seeman, 1981,1990). Supportive evidence includes improvement of symptoms during the high estrogen phase of the menstrual cycle and during pregnancy (Hallonquist, 1993; Riecher-Rossler, 1993; Hafner, 1994; Seeman, 1990, 1996). More directly, estrogen has been given to women with schizophrenia and has been able to hasten the response to neuroleptics in the acute phase of illness (Kulkarni et al., 1996). The improved neuroleptic response in women is generally thought to be related to dampening dopamine pathways over and above the dopamine blockade of neuroleptic medications (Hafner, 1991; DiPaolo T., 1994). In addition, estrogen, oral contraceptives and menstrual cycle have been found to affect CYP450 metabolism (Abernethy, 1982,1984; Kimmel, 1992). Thus, it is important to collect menstrual data as well as the use of the birth control pills.

3) Apply a finer dosing titration method

Fifteen subjects in our study developed side-effects. Among them, 11 had clinical improvement at the same time which suggests that their "real optimal dosage" would be lower than

the current one defined in the study. A dosing method starting from 1mg. of haloperidol and stepping up in 1 or 2mg. increments, rather than 5mg, would facilitate more accurate estimation of optimal dosage.

4) Use genotype for P450 liver enzymes in each ethnic group as measures for drug metabolism while controlling for other pharmacokinetic factors.

Liver metabolism is a powerful determinant for the plasma haloperidol level. Asians and Caucasians have different genetic mutations in CYP 2D6 which might contribute to different drug metabolism. Pharmacokinetic factors such as rate of absorption, distribution, and elimination may also affect plasma haloperidol level. Future studies comparing Asians and Caucasians on these variables would help advance our knowledge of how ethnic differences affect drug metabolism.

5) Use PET scans to quantify D2 blockade in different brain areas.

Functional brain imaging with positron emission tomography (PET) has opened up new avenues for the investigation of the pharmacodynamics of drug treatment in vivo. New strategies to study pharmacologic effects on the brain have been developed in recent years. The basic methods include measure of (a) blood flow or glucose metabolism, (b) parameters of specific receptor binding, or (c) neurotransmitter metabolism. Each of these can be performed either in a resting state or after perturbation with a pharmacologic challenge (Schloesser,1996). Functional imaging technology is providing increasing insights into schizophrenia and its treatment. Future research using such technology will provide a clear answer whether Asians and Caucasians differ in CNS sensitivities to the neuroleptic treatment.

6) Add a depression scale to the instruments

Another instrument sensitive to depression and validated in different cultural groups would help to examine Asian/Caucasian differences in depressive signs and symptoms in first episode non affective psychosis and to determine whether the affective component is associated with outcome in the same fashion in Asians and Caucasians. Culturally sensitive measures of depression developed by Beiser et al (1986, 1994) could be used for this purpose.

Relevance

Most drug trials conducted over the past three decades in North America have typically involved Caucasian male volunteers. Our study results strongly suggest that dosage recommendations based on trials limited to males from one ethnic group should be viewed with caution. It would appear that a large proportion of patients suffering a first episode of non-affective psychosis achieve optimal therapeutic benefit at neuroleptic levels lower than those established on the basis of clinical trials that rely on samples of Caucasian males.

Increasing ethnic diversity in Canada calls for societal adjustment - nowhere more so than in the health care system. Illnesses like schizophrenia do not respect ethnic boundaries. However, treatment approaches, including psychopharmacology, must take ethnocultural factors into account. If Canada is to have a truly culturally sensitive system of health care - and it must - results of studies such as the current one should find their way into prescribing manuals and into the training of health care professionals. The requirements for social equity and for ethical care and equitable care for all demand no less.

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[letter head]

Neuroleptic Dosage in First Episode Patients

I, _____ consent to participate in a clinical trial that will examine the effect of different medication doses on my condition. This study is under the direction of Dr. Morton Beiser and they or another member of their team have explained it to me and answered all my questions about the study.

1. PURPOSE

The purpose of the study is to assess the effect of medication on different ethnic groups. Patients will receive Haloperidol 2mg per day, a level which will be maintained for the first week of care. Haloperidol dosage will be increased, as required clinically, to 5mg at day 8. 10mg at day 15 and 20mg at day 22. Patients will be assessed for therapeutic effect and side effects of the drug and will be given extra medication if needed. Antiparkinsonian medication will be given as needed if side effects develop. If a patients does not tolerate the dose selected it will be decreased. An attempt will be made to maintain the minimal therapeutic dose of medication. Ratings of therapeutic effect and side effects of the drug and blood measurements for plasma levels of medication will be carried out weekly during the 4 week period of the study.

2. ADVANTAGES

Patient's treatment will be with standard medications normally used for their condition. They will be assessed by psychiatrists skilled in the treatment of their disorder. Eventual findings from this study may lead to improved treatment of people suffering from similar disorders. Patients will be required to spend approximately 30 minutes per visit beyond that needed for treatment.

3. RISKS

There will be the minor discomfort of having blood drawn for measurement weekly for 4 weeks. The dose of medication the patient receives will be assessed closely and effects of treatment include tremor, muscle rigidity, restlessness, fatigue. Rarely medical complications ensue. Tic-like movements may occur with long-term treatment in 10-20% of patients

4. CONFIDENTIALITY

All information obtained in this study is confidential and will be available only to the professional investigators involved in the work.

5. CONSENT

I understand that my participation in this clinical study is entirely voluntary, and that I may withdraw at any time without any prejudice to myself or my treatment. I have received a copy of this consent form.

Date the _____ day of _____, 19_____

Signature: _____

Witness: _____

I, Dr. Morton Beiser hereby certify that I have explained to the above mentioned patient the nature of the clinical trial, the known risks involved in participating in the study, and that the patient has the option of withdrawing from the study at any time.

Investigator: _____
Dr. Morton Beiser (979-4988)

PROTOCOL: SCHIZOPHRENIA IN ASIANS AND CAUCASIANS

The research project is previsedupon the clinical observation that compared with Caucasians, Asian patients require smaller doses of neuroleptics to control psychotic symptoms. This observation raises a number of questions: 1) Is the difference between dosage requirements due to differences in the absorption and/or metabolism of neuroleptics? 2) Is the difference between dosage requirements due to differences in the sensitivity of central receptors which mediate neuroleptic treatment?

The research project will investigate clinical response and psycho-physiological characteristics in two groups of patients during an acute phase (4 weeks) followed by a maintenance phase. Asian first-episode psychotic patients will be compared to a group of Caucasian first-episode psychotic patients. The objective of the acute treatment phase of the study is to determine the haloperidol level that produces maximal therapeutic response together with minimal side effects.

The drug protocol is based upon recommendations arising from the prephiatric literature. The reports suggest that the lowest neuroleptic dose at which patients develop slight increases in rigidity (crossing the neuroleptic threshold) is also the lowest dose at which these patients attain maximum antipsychotic benefit. For all patients enrolled in the study, treatment will be initiated with 2mg of Haloperidol, a level which will be maintained for the first week of care. Haloperidol dosage will be increased, as required clinically, to 5mg at day 8, 10mg at day 15 and 20mg at day 22.

Examples:

a) If no side effects are observed during the first week of treatment, Haldol will be increased to 5mg at day 8.

b) If slight side effects (criteria for the measurement explained in the following text) present during the first week of treatment, Haldol will be maintained at 2mg at day 8. Benztropine will be administered if necessary (the Benztropine will be given for the first time after the extrapyramidal symptoms rating scale has been administered, therefore not interfering in the rating of the latter).

c) If excessive rigidity (criteria for the measurement explained in the following text)presents during the 1st week of treatment, Haldol will be reduced to 1mg to yield minimal side effects and the reduced dose will be maintained at day 8. Benztropine will be administered in the same conditions mentioned above.

d) If, in the opinion of the treatment staff, the patient has severe psychotic symptoms and

requires more medications during the 1st week, lorazepam (2mg up to four time daily) can be added to potentiate maximum therapeutic response. Determination of neuroleptic threshold dosage and extra-pyramidal side effects assessments will be postponed for at least 24 hours after a dose of lorazepam. No other psychoactive medication (eg.lithium) will be permitted.

To determine the presence of extrapyramidal symptoms, the attending physician and a research assistant, using a standardized assessment tool (ESRS), will independently rate the patient. The neuroleptic threshold (NT) will be defined as a categorical increase in cogwheel rigidity from baseline (degree of rigidity ranges from normal muscle tone "0" to extremely severe rigidity-nearly frozen "6"). Slight side-effect equals to a mild rigidity (coded less than 3 for rigidity item in ESRS) while severe side effect equals to a severe rigidity (coded more than 4 for rigidity item)

This team will also rate each patient with the PANSS to assess response to treatment. To facilitate the evaluations and to ensured that the protocol is followed strictly, all patients will be admitted and treated during the acute phase at the Clarke .

At entry to the study, DSM-III-R diagnosis will be established by a structured clinical interview (SCID). Blood will be drawn to provide baseline measures of prolactin, Haloperidol and Reduced Haloperidol.

During each week of treatment, patients will be examined and rated for psychopathology as well as extrapyramidal side effects. Blood will be drawn in the early morning at day 8, day 15, day 22 and day 29 to determine levels of prolactin, Haloperidol and Reduced Haloperidol.

The quantity of blood needed for each patient for each weekly measurement will be: 20cc per sample (15cc for Haldol and Reduced Haldol, 4cc for prolactin).

TIME TABLE

BASELINE--ACUTE PHASE--FOLLOW-UP

- Baseline will be the time period to collect pre-treatment data.

- Acute phase will be the time period in which drug treatment started related tests will be administered.

- Follow-up phase will be the time period in which patients will receive a maintenance neuroleptic dosage and will be followed and evaluated by research team.

STRUCTURED CLINICAL INTERVIEW FOR DSM-III-R—PATIENT EDITION

SCID-P (Version 1.0)

Robert L. Spitzer, M.D.; Janet B. W. Williams, D.S.W.;
Miriam Gibbon, M.S.W.; and Michael B. First, M.D.

01
1-2

Study: _____ Study No.: — — — — 03-06

Subject: _____ I.D. No.: — — — — 07-10

Rater: _____ Rater No.: — — — 11-13

Rater is: Interviewer 1 14
Observer 2

Date of interview: — — — — — — 15-20
Mo. Day Year

Evaluation: Initial 1 21
Reevaluation 2

Time interview began _____

ended _____

Sources of information (check all that apply): 22

__ Subject
__ Family/friends/associates 23
__ Health professional/chart/referral note 24

____ Consultation with: _____ 25

Form No 01
79-80*

Edited and checked by: _____ Date: _____

*Keypunch: Duplicate on all cards; "b" = leave blank.

The development of the SCID has been supported in part by NIMH Contract #278-83-0007(DB) and NIMH Grant #1 R01 MH40511.

For citation: Spitzer Robert L., Williams Janet B. W., Gibbon Miriam, and First Michael B.: "Structured Clinical Interview for DSM-III-R—Patient Edition (SCID-P, Version 1.0)." American Psychiatric Press, Washington, DC, 1990

Baseline (drug free for at least 72 hs):

Two project staff(research assistant/ clinician/ nurse) will examine the patient using:

a)Interview and examination data:
-Complete physical exam and routine lab
-SCID

b)Rating scales :
-Side-Effect:-Extrapyramidal Symptom Rating Scale (ESRS)
-PANSS (Positive and Negative Symptoms Rating Scale)

c)Blood sample: 20cc from subject for prolactin, Haloperidol and Reduced Haloperidol.

ACUTE PHASE
(from day 1 to day 28)

First week (2mg haldol from day 1 to day 7. If excessive rigidity presents at the dosage of 2mg of Haloperidol daily, the dosage will be reduced to 1 or 0.5 mg per day to yield minimal rigidity):

a)Interview data (administered at day 3-5)
-Demographic questionnaire
-Onset questionnaire

b)Clinical rating scale (administered once a week):
-ESRS
-PANSS

c)Blood sample (20cc drawn on the morning of day 8 before new drug dosage)

d)No as-needed medication (Benztropine) administered if there is not any side-effect. If required, the ESRS should be administered before the Benztropine is given for the first time.

Second week (If patient hasn't shown side-effect by day 7, increase haldol to 5mg from day 8 to day 14. If patient has shown side-effect, keep 2mg dosage. If excessive rigidity presents at the dosage of 5mg of Haloperidol daily, the dosage will be reduced to yield minimal rigidity)

Repeat a)Clinical rating scale (administered once a week); b)Blood sample (20cc drawn on the morning of day 15); c)No as-needed medication (Benztropine) administered if there is not any side-effect. If required, the ESRS should be administered before the Benztropine is given for the first time.

Third week (If patient hasn't shown side-effect by day 14, increase haldol to 10mg from day 15 to

day 21. If patient has shown side-effect, keep 5mg dosage. If excessive rigidity presents at the dosage of 10mg of Haloperidol daily, the dosage will be reduced to yield minimal rigidity)

Repeat a)Clinical rating scale (administered once a week); b)Blood sample (20cc drawn on the morning of day 15); c)No as-needed medication (Benztropine) administered if there is not any side-effect. If required, the ESRS should be administered before the Benztropine is given for the first time.

Fourth week (If patient hasn't shown side-effect by day 21, increase haldol to 20mg from day 22 to day 28. If patient has shown side-effect, keep 10mg dosage. If excessive rigidity presents at the dosage of 10mg of Haloperidol daily, the dosage will be reduced to yield minimal rigidity)

Repeat a)Clinical rating scale (administered once a week); b)Blood sample (20cc drawn on the morning of day 15); c)No as-needed medication (Benztropine) administered if there is not any side-effect. If required, the ESRS should be administered before the Benztropine is given for the first time.

FOLLOW-UP PHASE

(from day 29 to the end of 9-month):

Rating scales administered at 9-month: Extrapyramidal SymptomRating Scale (ESRS) and PANSS

SPECIAL CASES

For patients who do not respond to Haloperidol during the acute phase:

A meeting between the patient's physician and research staffs will be set up to decide if changes to another drug is necessary.

For patients who relapse or are rehospitalized:

As mentioned in the literature, a significant amount of schizophrenic patients tend to relapse or to be rehospitalized after their first admission. In this study, patients, their parents and physicians (if not psychiatrists at the Clarke) will be informed to contact our research staff when there is any sign of relapse. For a patient who has a relapse, treatment will be arranged at the Clarke if the patient consents to this arrangement.

Information needs to be collected immediately after admission:(first priority)

-SCID
-PANSS
-ESRS
-Blood sample for Haldol and Reduced Haldol

SCID-P SUMMARY SCORE SHEET

Duration of interview (minutes): ___ ___ ___

DIAGNOSIS	LIFETIME PREVALENCE				MEETS SYMPTOMATIC DIAGNOSTIC CRITERIA PAST MONTH	
	INADEQUATE INFO.	ABSENT	SUB-THRESHOLD	THRESHOLD	ABSENT	PRESENT
MOOD DISORDERS						
01 Bipolar Disorder (D.1)	?	1	2	[3] →	1	3
[1] manic 2 depressed 3 mixed						
[1] mild 2 moderate 3 severe, without psychotic features 4 with mood-congruent psychotic features 5 with mood-incongruent psychotic features						
02 Other Bipolar Disorder (D.1)	?	1	2	[3] →	1	3
03 Major Depression (D.2)	?	1	2	[■] →	1	3
[1] mild 2 moderate 3 severe, without psychotic features 4 with mood-congruent psychotic features 5 with mood-incongruent psychotic features						

DIAGNOSIS		LIFETIME PREVALENCE					MEETS SYMPTOMATIC DIAGNOSTIC CRITERIA PAST MONTH	
		INADEQUATE INFO.	ABSENT	SUB-THRESHOLD	THRESHOLD		ABSENT	PRESENT
	MOOD DISORDERS (continued)							
04	Dysthymia (current only) (A.16)	?	1	2	3			
	1 primary 2 secondary							
05	Depressive Syndrome Superimposed on Chronic Psychotic Disorder (D.2)	?	1		[3]	→	1	3
	PSYCHOTIC DISORDERS							
06	Schizophrenia (C.5)	?	1	2	[3]	→	1	3
07	Schizophreniform Disorder (C.8)	?	1	2	[3]	→	1	3
	1 with good prognostic features 2 without good prognostic features							
08	Schizoaffective Disorder (C.9)	?	1	2	●	→	1	3
	1 bipolar type 2 depressed type							
09	Delusional Disorder (C.11)	?	1	2	[3]	→	1	3
10	Brief Reactive Psychosis (C.2)	?	1	2	[3]	→	1	3
11	Psychotic Disorder NOS (C.12)	?	1	2	[3]	→	1	3

DIAGNOSIS		LIFETIME PREVALENCE				MEETS SYMPTOMATIC DIAGNOSTIC CRITERIA PAST MONTH		
		INADEQUATE INFO.	ABSENT	ABUSE	DEPENDENCE	ABSENT	PRESENT	
	PSYCHOACTIVE SUBSTANCE USE DISORDERS							
12	Alcohol (E.4)	?	1	2	3 →	1	3	57 58
13	Sedative-Hypnotic-Anxiolytic (E.13)	?	1	2	3 →	1	3	59 60
14	Cannabis (E.13)	?	1	2	3 →	1	3	61 62
15	Stimulant (E.13)	?	1	2	3 →	1	3	63 64
16	Opioid (E.13)	?	1	2	3 →	1	3	65 66
17	Cocaine (E.13)	?	1	2	3 →	1	3	67 68
18	Hall./PCP (E.13)	?	1	2	3 →	1	3	69 70
19	Poly Drug (E.13)	?	1		[3] →	1	3	71 72
20	Other (E.13)	?	1	2	3 →	1	3	73 74

75-78 b
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79-80
Duplicate on all cards

DIAGNOSIS		LIFETIME PREVALENCE				MEETS SYMPTOMATIC DIAGNOSTIC CRITERIA PAST MONTH		
		INADEQUATE INFO.	ABSENT	SUB-THRESHOLD	THRESHOLD	ABSENT	PRESENT	
	ANXIETY DISORDERS							
21	Panic Disorder (F.2)	?	1	2	[3] →	1	3	16 17
	[1] without Agoraphobia [2] with Agoraphobia							18
22	Agoraphobia without History of Panic Disorder (AWOPD) (F.6)	?	1	2	[3] →	1	3	19 20
23	Social Phobia (F.9)	?	1	2	[3] →	1	3	21 22
24	Simple Phobia (F.11)	?	1	2	[3] →	1	3	23 24
25	Obsessive Compulsive Disorder (F.13)	?	1	2	[3] →	1	3	25 26
26	Generalized Anxiety Disorder (current only) (F.17)	?	1	2	3			27

02 duplicate 3
1-2 3-14 15

DIAGNOSIS		LIFETIME PREVALENCE				MEETS SYMPTOMATIC DIAGNOSTIC CRITERIA PAST MONTH		
		INADEQUATE INFO.	ABSENT	SUB-THRESHOLD	THRESHOLD		ABSENT	PRESENT
	SOMATOFORM DISORDERS							
27	Somatization Disorder (current only) (G.4)	?	1	2	3			
28	Somatoform Pain Disorder (current only) (G.5)	?	1	2	3			
29	Undifferentiated Somatoform Disorder (current only) (G.6)	?	1	2	3			
30	Hypochondriasis (current only) (G.7)	?	1	2	3			
	EATING DISORDERS							
31	Anorexia Nervosa (H.1)	?	1	2	[3]	→	1	3
32	Bulimia Nervosa (H.3)	?	1	2	[3]	→	1	3
33	**ADJUSTMENT DISORDER** (current only) (I.2)	?	1	2	3			
34	**OTHER DSM-III-R AXIS I DISORDER:**	?	1	2	[3]	→	1	3

Specify: _____

PRINCIPAL AXIS I DIAGNOSIS (i.e., the disorder that is [or should be] the main focus of current clinical attention).

Enter code number from left of diagnosis above: ___ ___
Note: Code 00 if no current Axis I disorder. Code 99 if unknown.

DIAGNOSTIC CERTAINTY FOR CURRENT DIAGNOSES

CODE CERTAINTY OF THE *PRESENCE* OF AT LEAST ONE DISORDER IN A DIAGNOSTIC CLASS, OR THE *ABSENCE* OF ANY DISORDER IN THAT DIAGNOSTIC CLASS

	Poor	Fair	Good	
MOOD DISORDERS	1	2	3	41
PSYCHOTIC DISORDERS	1	2	3	42
PSYCHOACTIVE SUBSTANCE USE DISORDERS	1	2	3	43
ANXIETY DISORDERS	1	2	3	44
SOMATOFORM DISORDERS	1	2	3	45
EATING DISORDERS	1	2	3	46
ADJUSTMENT DISORDER	1	2	3	47

INTERVIEWER'S DIAGNOSES, IF DIFFERENT FROM SCID DIAGNOSES:

_____ _____ _____

DSM-III-R AXIS V: GLOBAL ASSESSMENT OF FUNCTIONING SCALE

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Indicate appropriate code for the LOWEST level of functioning during the week of POOREST functioning in past month. (Use intermediate level when appropriate, e.g., 45, 68, 72.)

Code ___ ___ 48-49

90 | 81 **Absent or minimal symptoms** (e.g., mild anxiety before an exam), **good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g., an occasional argument with family members).

80 | 71 **If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., difficulty concentrating after family argument), **no more than slight impairment in social, occupational, or school functioning** (e.g., temporarily falling behind in school work).

70 | 61 **Some mild symptoms** (e.g., depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy, or theft within the household), **but generally functioning pretty well, has some meaningful interpersonal relationships.**

60 | 51 **Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g., few friends, conflicts with co-workers).

50 | 41 **Serious symptoms** (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job).

40 | 31 **Some impairment in reality testing or communication** (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).

30 | 21 **Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home, or friends).

20 | 11 **Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death; frequently violent, manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears feces) **OR gross impairment in communication** (e.g., largely incoherent or mute).

10 | 1 **Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene OR serious suicide act with clear expectation of death.**

0 **Inadequate Information**

INTRODUCTION TO OVERVIEW

I'm going to be asking you about problems or difficulties you may have had, and I'll be making some notes as we go along. Do you have any questions before we begin?

DEMOGRAPHIC DATA

SEX: 1 male 2 female 50

ETHNICITY: 1 Black, not of Hispanic origin; 2 Hispanic; 3 White, not of Hispanic origin; 4 American Indian or Alaskan native; 5 Asian or Pacific Islander 51

How old are you? AGE: ____ ____ 52-53

Are you married? MARITAL STATUS (most recent): 1 never married; 2 married once; 3 divorced; 4 divorced, remarried; 5 widowed; 6 widowed, remarried 54

IF NO: Were you ever?

Any children?

IF YES: How many? _____

Where do you live? _____

Whom do you live with? _____

EDUCATION AND WORK HISTORY

How far did you get in school? EDUCATION: 1 grade 6 or less; 2 grade 7 to 12 (without graduating high school); 3 graduated high school or high school equivalent; 4 part college; 5 graduated 2-year college; 6 graduated 4-year college; 7 part graduate/professional school; 8 completed graduate/professional school 55

IF FAILED TO COMPLETE A PROGRAM: Why didn't you finish? _____

_____

What kind of work do you do? (Do you work outside of your home?) _____

_____

Are you working now?

IF YES: How long have you worked there?

IF LESS THAN 6 MONTHS: Why did you leave your last job?

Have you always done that kind of work?

IF NO: Why is that?
What kind of work have you done?

How are you supporting yourself now?

IF UNKNOWN: Has there ever been a period of time when you were unable to work or go to school?

IF YES: When? Why was that?

OVERVIEW OF PRESENT ILLNESS

DATE ADMITTED TO INPATIENT OR OUTPATIENT FACILITY FOR PRESENT ILLNESS

Number of weeks since admission to facility
1 < 1 week
2 1–4 weeks
3 > 4 weeks

When did you come to the (hospital, clinic)?

CHIEF COMPLAINT AND DESCRIPTION OF PRESENTING PROBLEM

What led to your coming here (this time)? (What's the major problem you've been having trouble with?)

IF DOES NOT GIVE DETAILS OF PRESENTING PROBLEM: Tell me more about that. (What do you mean by . . . ?)

ONSET OF PRESENT ILLNESS OR EXACERBATION

When did this begin? (When did you first notice that something was wrong?)

When were you last feeling OK (your usual self)?

NEW SXS OR RECURRENCE

Is this something new or a return of something you had before?

(What made you come for help now?)

ENVIRONMENTAL CONTEXT AND POSSIBLE PRECIPITANTS OF PRESENT ILLNESS OR EXACERBATION
(USE THIS INFORMATION FOR CODING AXIS IV.)

What was going on in your life when this began?

Did anything happen or change just before all this started? (Do you think this had anything to do with your [PRESENT ILLNESS]?)

COURSE OF PRESENT ILLNESS OR EXACERBATION

After it started, what happened next? (Did other things start to bother you?)

Since this began, when have you felt the worst?

IF MORE THAN A YEAR AGO: In the last year, when have you felt worst?

TREATMENT HISTORY

When was the first time you saw someone for emotional or psychiatric problems? (What was that for? What treatment(s) did you get? What medications?)

(INQUIRE ABOUT ALL TREATMENT RECEIVED. THE LIFE CHART ON PAGE v OF OVERVIEW MAY BE USED TO SUMMARIZE A COMPLICATED HISTORY OF PSYCHOPATHOLOGY AND TREATMENT)

Have you ever been a patient in a psychiatric hospital?

IF YES: What was that for? (How many times?)

Number of previous hospitalizations (Do not include transfers) 0 1 2 3 4 5 (or more) 57

IF GIVES AN INADEQUATE ANSWER, CHALLENGE GENTLY: e.g., Wasn't there something else? People don't usually go to psychiatric hospitals just because they are tired or nervous.

OTHER CURRENT PROBLEMS

Have you had any other problems in the last month?

What's your mood been like?

How has your physical health been? Do you take any medications or vitamins (other than those you've already told me about)? (Have you had any medical problems?) USE INFORMATION TO CODE AXIS III.

How much have you been drinking (alcohol) (in the past month)?

Have you been taking any drugs (in the past month)? (What about marijuana, cocaine, other street drugs?)

CURRENT SOCIAL FUNCTIONING

How have you been spending your free time?

Whom do you spend time with?

MOST LIKELY CURRENT DIAGNOSES:

DIAGNOSES THAT NEED TO BE RULED OUT:

LIFE CHART

Age (or date)	Life history event	Symptoms or condition	Treatment

RETURN TO OVERVIEW PAGE iv, **OTHER CURRENT PROBLEMS**

B. *Psychotic and Associated Symptoms*

05 Duplicate 0
1-2 3-14 15

THIS MODULE IS FOR CODING PSYCHOTIC AND ASSOCIATED SXS THAT HAVE BEEN PRESENT AT ANY POINT IN THE PERSON'S LIFETIME.

FOR ALL PSYCHOTIC AND ASSOCIATED SYMPTOMS CODED "3," DETERMINE WHETHER THE SYMPTOM IS "NOT ORGANIC," OR WHETHER THERE IS A POSSIBLE OR DEFINITE ORGANIC CAUSE. THE FOLLOWING QUESTIONS MAY BE USEFUL IF THE OVERVIEW HAS NOT ALREADY PROVIDED THE INFORMATION:

When you were (PSYCHOTIC SXS), were you taking any drugs or medicines? Drinking a lot? Physically ill?

→ IF HAS NOT ACKNOWLEDGED PSYCHOTIC SXS: Now I am going to ask you about unusual experiences that people sometimes have.

→ IF HAS ACKNOWLEDGED PSYCHOTIC SXS: You have told me about (PSYCHOTIC EXPERIENCES). Now I am going to ask you more about those kinds of things.

DELUSIONS

False personal belief(s) based on incorrect inference about external reality and firmly sustained in spite of what almost everyone else believes, and in spite of what constitutes incontrovertible and obvious proof or evidence to the contrary. Code overvalued ideas [unreasonable and sustained belief(s) that is/are maintained with less than delusional intensity] as "2."

NOTE: A SINGLE DELUSION MAY BE CODED "3" ON MORE THAN ONE OF THE FOLLOWING ITEMS.

Did it ever seem that people were talking about you or taking special notice of you?

What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

Delusions of reference, i.e., personal significance is falsely attributed to objects or events in environment

DESCRIBE:

? 1 2 3 16

1 Poss der organic 3 Not org 17

What about anyone going out of the way to give you a hard time, or trying to hurt you?

Persecutory delusions, i.e., the individual (or his or her group) is being attacked, harassed, cheated, persecuted, or conspired against

DESCRIBE:

? 1 2 3 18

1 Poss der organic 3 Not org 19

Did you ever feel that you were especially important in some way, or that you had powers to do things that other people couldn't do?

Grandiose delusions, i.e., content involves exaggerated power, knowledge or importance

DESCRIBE:

? 1 2 3 20

1 Poss der organic 3 Not org 21

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

Did you ever feel that parts of your body had changed or stopped working? (What did your doctor say?)

Somatic delusions, i.e., content involves change or disturbance in body functioning

DESCRIBE:

? 1 2 3 22

1 Poss del organic 3 Not org 23

(Did you ever feel that you had committed a crime or done something terrible for which you should be punished?)

Other delusions, e.g., delusions of guilt, jealousy, nihilism, poverty

DESCRIBE:

? 1 2 3 24

1 Poss del organic 3 Not org 25

IF NEVER HAD A NON-ORGANIC DELUSION, CHECK HERE ____ AND GO TO **"Auditory Hallucinations,"** B.3. 26

Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against your will?

(Did you ever feel that certain thoughts that were not your own were put into your head?)

(What about taken out of your head?)

Delusions of being controlled, i.e., feelings, impulses, thoughts, or actions are experienced as being under the control of some external force (includes delusions of thought insertion and withdrawal)

DESCRIBE:

? 1 2 3 27

1 Poss del organic 3 Not org 28

Did you ever feel as if your thoughts were being broadcast out loud so that other people could actually hear what you were thinking?

Thought broadcasting, i.e., the delusion that one's thoughts are audible to others

DESCRIBE:

? 1 2 3 29

1 Poss del organic 3 Not org 30

[Are all of (DELUSIONS DESCRIBED SO FAR) related to each other in some way?]

Systematized delusions, i.e., a single delusion with multiple elaborations or a group of delusions that are all related by the individual to a single event or theme

DESCRIBE:

? 1 3 31

1 Poss del organic 3 Not org 32

[What is your understanding of why (CONTENT OF DELUSION)?]

Bizarre delusions, i.e., involving a phenomenon that the individual's subculture would regard as totally implausible (e.g., thought broadcasting, being controlled by a dead person)

DESCRIBE:

? 1 2 3 33

1 Poss del organic 3 Not org 34

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

"Auditory Hallucinations"

HALLUCINATIONS (PSYCHOTIC)
A sensory perception without external stimulation of the relevant sensory organ. (CODE "2" FOR HALLUCINATIONS THAT ARE SO TRANSIENT AS TO BE WITHOUT DIAGNOSTIC SIGNIFICANCE)

Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (Were you awake at the time?)

Auditory hallucinations when fully awake and heard either inside or outside of the head

DESCRIBE:

? 1 2 3 35

Go to "Visual Hallucinations," 8.4

1 Poss/def organic — 3 Not org 36

What did you hear? How often did you hear it?

More than two words heard more than twice with no apparent relation to depression or elation

NOTE: CODE "3" ONLY IF THERE ARE MORE THAN TWO WORDS HEARD MORE THAN TWICE AND EITHER (1) THERE HAS *NOT* BEEN ANY DEPRESSED OR ELATED MOOD OR (2) THE CONTENT OF THE HALLUCINATIONS IS UNRELATED TO DEPRESSION OR ELATION

? 1 2 3 37

Did it comment on what you were doing or thinking?

A voice keeping up a running commentary on the individual's behavior or thoughts as they occur

? 1 2 3 38

How many voices did you hear? Were they talking to each other?

Two or more voices conversing with each other

? 1 2 3 39

Visual Hallucinations

Did you ever have visions or see things that other people couldn't see? (Were you awake at the time?)

NOTE: DISTINGUISH FROM AN ILLUSION, I.E., A MISPERCEPTION OF A REAL EXTERNAL STIMULUS.

Visual Hallucinations

DESCRIBE:

? 1 2 3 40

1 Poss def organic 3 Not org 41

What about strange sensations in your body or on your skin?

Tactile hallucinations, e.g., electricity

DESCRIBE:

? 1 2 3 42

1 Poss def organic 3 Not org 43

(What about smelling things that other people couldn't smell?)

Other hallucinations, e.g., gustatory, olfactory

DESCRIBE:

? 1 2 3 44

1 Poss def organic 3 Not org 45

BASED ON OBSERVATION OR HISTORY OF OBSERVATION BY ANOTHER MENTAL HEALTH PROFESSIONAL

(Now I just need to stop for a moment to make a few notes.)

CATATONIC BEHAVIOR

Marked motor anomalies, including apparently purposeless excitement, negativism, rigidity, posturing, stupor, and waxy flexibility.

DESCRIBE:

? 1 2 3 46

1 Poss def organic 3 Not org 47

FLAT AFFECT

Virtually no affective expression, e.g., monotonous voice, immobile face.

DESCRIBE:

? 1 2 3 48

1 Poss def organic 3 Not org 49

GROSSLY INAPPROPRIATE AFFECT

Inappropriate affect is affect that is clearly discordant with the content of speech or ideation, e.g., smiling while discussing being persecuted.

DESCRIBE:

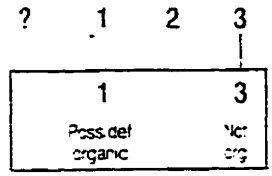
? 1 2 3 50

1 Poss def organic 3 Not org 51

? = inadequate information 1 = absent or false 2 = subthreshold 3 = threshold or true

INCOHERENCE

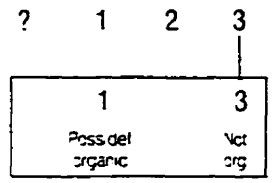
Speech that, for the most part, is not understandable because of lack of logical or meaningful connection between words, phrases, or sentences; excessive use of incomplete sentences; excessive irrelevancies or abrupt changes in subject matter; or idiosyncratic word usage.



DESCRIBE:

MARKED LOOSENING OF ASSOCIATIONS

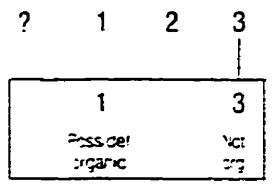
Thinking characterized by speech in which ideas shift from one subject to another that is completely unrelated or only obliquely related, without the speaker's showing any awareness that the topics are unconnected. When severe, speech is incoherent. Do not include when abrupt shifts in topic are associated with a nearly continuous flow of accelerated speech (as in flight of ideas).



DESCRIBE:

EMOTIONAL TURMOIL

Rapid shifts from one intense affect to another, or overwhelming perplexity or confusion, not due to a Mood Disorder.



DESCRIBE:

IF ANY DELUSIONS OR HALLUCINATIONS, NOTE DATES AND WHETHER PRESENT DURING PAST MONTH (E.G., "BIZARRE DELUSIONS, INTERMITTENTLY SINCE 1969 AND PERSISTENTLY FOR PAST SIX MONTHS").

DATES:

Check here if present within past month _____

C. DIFFERENTIAL DIAGNOSIS OF PSYCHOTIC DISORDERS

06 SUICIDE 5
1-2 3-14 15

NOTE: IN THE RARE CASE OF A PERSON WHO RECOVERS FROM ONE PSYCHOTIC DISORDER (E.G., DELUSIONAL DISORDER) AND LATER DEVELOPS A DIFFERENT PSYCHOTIC DISORDER (E.G., SCHIZOAFFECTIVE DISORDER), ONLY THE MOST RECENT DISORDER SHOULD BE CODED.

IF: THERE ARE NO ITEMS CODED "3" IN MODULE **B. PSYCHOTIC AND ASSOCIATED SYMPTOMS**, OR THE ONLY ITEM CODED "3" IS "EMOTIONAL TURMOIL," CHECK HERE ____ AND SKIP TO ***Mood Disorders,*** D.1. 16

IF A MAJOR DEPRESSIVE OR MANIC SYNDROME HAS EVER BEEN PRESENT: Has there ever been a time when you had (PSYCHOTIC SXS) and you were not (OWN EQUIVALENT FOR DEPRESSION AND/OR MANIA)?

Psychotic symptoms occur at times other than during mood syndromes

NOTE: CODE "3" IF NO MOOD SYNDROMES OR PSYCHOTIC SXS W/O BEING IN A MOOD SYNDROME. CODE "1" ONLY IF PSYCHOTIC SYMPTOMS OCCUR EXCLUSIVELY DURING UNEQUIVOCAL MOOD SYNDROMES.

? 1 3 17

? → Psychotic Mood Disorder Go to *Mood Disorders,* D.1

3 → Psychotic when no mood syndrome

Continue

NOTE: LIST OF PSYCHOTIC SXS (I.E., "A" CRITERION OF BRIEF REACTIVE PSYCHOSIS) OMITTED HERE BECAUSE THEY HAVE ALREADY BEEN CODED IN MODULE B. OTHER CRITERIA ARE IN DIFFERENT ORDER THAN IN DSM-III-R.

BRIEF REACTIVE PSYCHOSIS CRITERIA ? 1 3 18

? → Go to *Schizophrenia,* C.3

A. Duration of an episode of the disturbance from a few hours to one month.

NOTE: CODE "1" IF DURATION IS GREATER THAN ONE MONTH.

B. Emotional turmoil, i.e., rapid shifts from one intense affect to another, or overwhelming perplexity or confusion. ? 1 3 19

? → Go to *Schizophrenia,* C.3

C. Absence of the prodromal symptoms of Schizophrenia, and failure to meet the criteria for Schizotypal Personality Disorder before onset of the disturbance. ? 1 3 20

? → Go to *Schizophrenia,* C.3

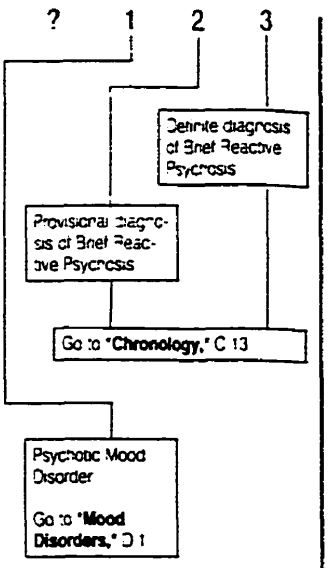
NOTE: SEE PAGE C.5 FOR LIST OF PRODROMAL SYMPTOMS

D. The psychotic symptoms (coded in Module B) appear shortly after and apparently in response to one or more events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture. ? 1 3 21

? → Go to *Schizophrenia,* C.3

E. Not due to a Psychotic Mood Disorder (i.e., no full mood syndrome is present during psychotic disturbance).

CODE "2" FOR A PROVISIONAL DIAGNOSIS OF BRIEF REACTIVE PSYCHOSIS IF THE EXPECTED RECOVERY HAS NOT YET OCCURRED. CODE "3" FOR A DEFINITE DIAGNOSIS IF THERE HAS BEEN A FULL RECOVERY.



DIFFERENTIAL DIAGNOSIS OF: SCHIZOPHRENIA, SCHIZOPHRENIFORM, SCHIZOAFFECTIVE, AND DELUSIONAL DISORDERS

SCHIZOPHRENIA CRITERIA

A. Presence of characteristic psychotic symptoms in the active phase: either (1), (2), or (3) for at least one week (unless the symptoms are successfully treated):

? 1 3 23

Go to "Delusional Disorder," C.10

(1) bizarre delusions (i.e., involving a phenomenon that the person's subculture would regard as totally implausible, e.g., thought broadcasting, being controlled by a dead person)

(2) prominent hallucinations [as defined in (3)(b) below] of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other

(3) two of the following:

(a) delusions

(b) prominent hallucinations (throughout the day for several days or several times a week for several weeks, each hallucinatory experience not being limited to a few brief moments)

(c) incoherence or marked loosening of associations

(d) catatonic behavior

(e) flat or grossly inappropriate affect

IF UNCLEAR: Has there ever been a time when you had (SXS FROM ACTIVE PHASE) at the same time that you were (depressed/high/OWN EQUIVALENT)?

B.(1) No major depressive or manic syndromes occurred during an active phase of the disturbance.

NOTE: CODE "3" IF NO MAJOR DEPRESSIVE OR MANIC SYNDROMES OR IF ALL MAJOR DEPRESSIVE OR MANIC SYNDROMES ARE DURING RESIDUAL OR PRODROMAL PHASES. CODE "1" IF ANY MOOD SYNDROMES OVERLAP WITH ACTIVE PSYCHOTIC SYMPTOMS.

NOTE: BECAUSE OF THE DIFFICULTY IN DISTINGUISHING THE PRODROMAL AND RESIDUAL SYMPTOMS OF SCHIZOPHRENIA (PAGE C.5) FROM A MAJOR DEPRESSIVE SYNDROME, THE RATER SHOULD RECONSIDER ANY PREVIOUSLY CODED MAJOR DEPRESSIVE SYNDROME TO BE SURE IT IS UNEQUIVOCAL.

? → Go to "Psychotic Disorder NOS," C.12

1

3 → Continue on next page

IF UNCLEAR: How much of the time that you have had (SXS FROM ACTIVE AND RESIDUAL PHASES) would you say you have also been (depressed/high/OWN EQUIVALENT)?

B.(2) The total duration of all mood syndromes has been *brief* relative to the *total* duration of the active and residual phases of the disturbance.

NOTE: CODE "1" IF TOTAL DURATION OF MOOD IS NOT BRIEF RELATIVE TO THE PSYCHOTIC DISTURBANCE OR IF TOTAL DURATION OF MOOD IS LONGER THAN DURATION OF PSYCHOTIC DISTURBANCE.

? → Go to "Psychotic Disorder NOS," C.12

1 → Go to "Schizoaffective Disorder," C.9

3 → Continue on next page

? = inadequate information 1 = absent or false 3 = threshold or true

NOW MAKE A DIFFERENTIAL DIAGNOSIS BETWEEN SCHIZOPHRENIA AND SCHIZOPHRENIFORM DISORDER

IF UNCLEAR: Between (MULTIPLE EPISODES), were you back to your normal self? How long did each episode last?

C. Continuous signs of the disturbance for at least six months. The six-month period must include an active phase (of at least one week, or less if symptoms successfully treated) during which there were psychotic symptoms characteristic of Schizophrenia (sxs in "A"), with or without a prodromal or residual phase, as defined below.

? 1 3 26

Go to "Schizophreniform Disorder," C 8

IF NOT ALREADY KNOWN: When you (HAD "A" CRITERION SXS), were you (working, having a social life, taking care of yourself)?

D. During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved before onset of the disturbance (or with onset in childhood or adolescence, failure to achieve expected level of social development).

? 1 3 27

Go to "Psychotic Disorder NOS," C 12

Schizophrenia

Continue with "Schizophrenia Types," next page

SYMPTOMS OF PRODROMAL AND RESIDUAL PHASES OF SCHIZOPHRENIA

Prodromal phase: A clear deterioration in functioning before the active phase of the disturbance that is not due to a disturbance in mood or to a Psychoactive Substance Use Disorder, and that involves at least *two* of the symptoms noted below.

Residual phase: Following the active phase of the disturbance, persistence of at least two of the symptoms noted below, these not being due to a disturbance in mood or to a Psychoactive Substance Use Disorder.

IF NOT ALREADY KNOWN: What kinds of difficulties were you having before or after (PSYCHOTIC EXPERIENCE)?

Prodromal or Residual Symptoms:

(1) marked social isolation or withdrawal

(2) marked impairment in role functioning as wage-earner, student, or homemaker

(3) markedly peculiar behavior (e.g., collecting garbage, talking to self in public, hoarding food)

(4) marked impairment in personal hygiene and grooming

(5) blunted, flat, or inappropriate affect

(6) digressive, vague, over-elaborate, or circumstantial speech, or poverty of speech or poverty of content of speech

(7) odd beliefs or magical thinking, influencing behavior and inconsistent with cultural norms, e.g., superstitiousness, belief in clairvoyance, telepathy, "sixth sense," "others can feel my feelings," overvalued ideas, ideas of reference

(8) unusual perceptual experiences, e.g., recurrent illusions, sensing the presence of a force or person not actually present

(9) marked lack of initiative, interests, or energy

Schizophrenia Types

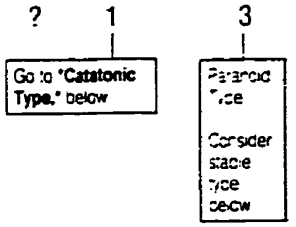
NOW DETERMINE THE CURRENT PHENOMENOLOGIC TYPE OF SCHIZOPHRENIA:

Paranoid Type

Paranoid Type: During the current episode, there is:

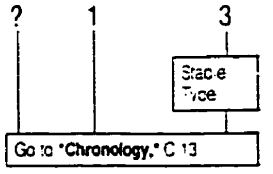
A. Preoccupation with one or more systematized delusions or with frequent auditory hallucinations related to a single theme.

B. *None* of the following: incoherence, marked loosening of associations, flat or grossly inappropriate affect, catatonic behavior, grossly disorganized behavior.



Stable Type:

The disturbance has met criteria "A" and "B" above during all (past and present) active phases.



Catatonic Type

Catatonic Type: During the current episode, the clinical picture is dominated by any of the following:

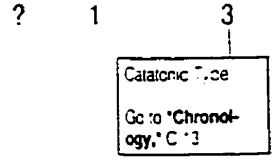
(1) catatonic stupor (marked decrease in reactivity to the environment and/or reduction of spontaneous movements and activity) or mutism

(2) catatonic negativism (an apparently motiveless resistance to all instructions or attempts to be moved)

(3) catatonic rigidity (maintenance of a rigid posture against efforts to be moved)

(4) catatonic excitement (excited motor activity, apparently purposelessness, and not influenced by external stimuli)

(5) catatonic posturing (voluntary assumption of inappropriate or bizarre postures)



"Disorganized Type"

Disorganized Type: During the current episode, there is:

A. Incoherence, marked loosening of associations.

B. Flat or grossly inappropriate affect.

? 1 3 31

Disorganized Type

Go to "Chronology," C.13

"Undifferentiated Type"

Undifferentiated Type: During the current episode, there are prominent delusions, hallucinations, incoherence, or grossly disorganized behavior.

? 1 3 32

Undifferentiated Type

Go to "Chronology," C.13

"Residual Type"

Residual Type: During the current episode, there is:

A. The absence of prominent delusions, hallucinations, incoherence, or grossly disorganized behavior.

B. Continuing evidence of the disturbance, as indicated by two or more of the residual symptoms listed on page C.6.

? 1 3 33

Residual Type

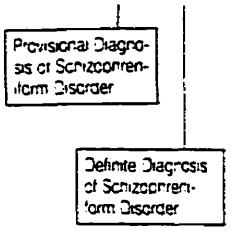
Go to "Chronology," C.13

Schizophreniform Disorder

SCHIZOPHRENIFORM DISORDER CRITERIA

CODE "2" FOR A PROVISIONAL DIAGNOSIS OF SCHIZOPHRENIFORM IF THE EXPECTED RECOVERY HAS NOT YET OCCURRED. CODE "3" FOR A DEFINITE DIAGNOSIS IF THERE HAS BEEN FULL RECOVERY.

An episode of the disturbance (including prodromal, active, and residual phases) lasts less than six months. (When the diagnosis must be made without waiting for recovery, it should be qualified as "provisional.") 2 3 34



NOW DETERMINE IF GOOD PROGNOSTIC FEATURES ARE PRESENT.

At least two of the following features that are generally associated with good prognosis:

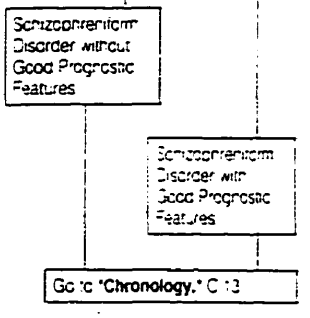
(1) onset of prominent psychotic symptoms within four weeks of first noticeable change in usual behavior or functioning ? 1 2 3 35

(2) confusion, disorientation, or perplexity at the height of the psychotic episode ? 1 2 3 36

(3) good premorbid social and occupational functioning ? 1 2 3 37

(4) absence of blunted or flat affect ? 1 2 3 38

AT LEAST TWO GOOD PROGNOSTIC FEATURES CODED "3" ? 1 3 39



? = inadequate information 1 = absent or false 2 = subthreshold or provisional 3 = threshold or true

"Schizoaffective Disorder"

SCHIZOPHRENIA AND SCHIZOPHRENIFORM DISORDER HAVE BEEN RULED OUT BECAUSE OF PROMINENT MOOD SYMPTOMS. NOW CONSIDER SCHIZOAFFECTIVE DISORDER.

IF NOT ALREADY KNOWN: Have there been any times when you had (PSYCHOTIC SXS) when you were not (MANIC OR DEPRESSED)?

SCHIZOAFFECTIVE DISORDER CRITERIA

A. A disturbance during which, at some time, there is either a major depressive or a manic syndrome concurrent with symptoms that meet the "A" criterion of Schizophrenia.

? 1 · 3 40

Go to "Psychotic Disorder NOS," C.12

B. During an episode of the disturbance, there have been delusions or hallucinations for at least two weeks, but no prominent mood symptoms.

? 1 3 41

Go to "Psychotic Disorder NOS," C.12

Schizoaffective Disorder

Psychotic Mood Disorder
Go to
"Mood Disorders,"
D.1

Phenomenologic Subtypes:

Manic syndrome present at some time during the course of the illness.

? 1 3 42

Depressive Type

Bipolar Type

Go to "Chronology," C.13

? = inadequate information 1 = absent or false 3 = threshold or true

Delusional Disorder

DELUSIONAL DISORDER CRITERIA

SCHIZOPHRENIA, SCHIZOPHRENIFORM, AND SCHIZOAFFECTIVE DISORDERS HAVE BEEN RULED OUT.

NOTE: THE ORDER OF THE CRITERIA BELOW DIFFERS FROM THAT IN DSM-III-R.

IF UNCLEAR: Has there ever been a time when you have been (DELUSIONAL) at the same time that you were (depressed/high/OWN EQUIVALENT)?

A.(1) No major depressive or manic syndromes occurred during the delusional disturbance.

NOTE: CODE "3" IF THERE WERE NO MAJOR DEPRESSIVE OR MANIC SYNDROMES OR IF ALL MAJOR DEPRESSIVE OR MANIC SYNDROMES OCCURRED AT TIMES OTHER THAN DURING DELUSIONAL PERIODS. CODE "1" IF THERE HAS BEEN OVERLAP WITH THE DELUSIONS.

? 1 3 43

? → Go to "Psychotic Disorder NOS," C.12

3 → Continue on next page

IF UNCLEAR: How much of the time that you have had (DELUSIONS) would you say you have also been (depressed/high/OWN EQUIVALENT)?

A.(2) The total duration of all episodes of the mood syndrome has been *brief* relative to the *total* duration of the delusional disturbance.

NOTE: CODE "1" IF TOTAL DURATION OF MOOD IS NOT BRIEF RELATIVE TO THE DELUSIONAL DISTURBANCE OR IF TOTAL DURATION OF MOOD IS LONGER THAN DURATION OF DELUSIONAL DISTURBANCE.

? 1 3 44

? → Go to "Psychotic Disorder NOS," C.12

3 → Continue on next page

IF UNCLEAR: Have you had (DELUSIONS) only at times when you were (depressed/high/OWN EQUIVALENT)?

Psychotic symptoms occur exclusively during mood syndromes.

? 1 3 45

? → Go to "Psychotic Disorder NOS," C.12

3 → Psychotic Mood Disorder

Go to "Mood Disorders," C.1

? = inadequate information 1 = absent or false 3 = threshold or true

B. Nonbizarre delusion(s) (i.e., involving situations that occur in real life, such as being followed, poisoned, infected, loved at a distance, having a disease, being deceived by one's spouse) of at least one month's duration. ? 1 3 46

Go to "Psychotic Disorder NOS," C.12

C. Auditory or visual hallucinations, if present, are not prominent ? 1 3 47

Go to "Psychotic Disorder NOS," C.12

NOTE: PROMINENT MEANING THROUGHOUT THE DAY FOR SEVERAL DAYS OR SEVERAL TIMES A WEEK FOR SEVERAL WEEKS.

NOTE: CODE "3" IF NO HALLUCINATIONS.

D. Apart from the delusion(s) or its ramifications, behavior is not obviously odd or bizarre. ? 1 3 48

Go to "Psychotic Disorder NOS," C.12

Delusional Disorder

Assign type below

SPECIFY TYPE ON THE BASIS OF PREDOMINANT THEME OF THE DELUSION(S), AND THEN GO TO **"Chronology,"** C.13. 49

1 **Persecutory** (belief that one is being maliciously treated in some way)

2 **Jealous** (belief that one's sexual partner is unfaithful)

3 **Erotomanic** (belief that one is romantically involved with a person of higher status)

4 **Somatic** (belief that one has some physical defect, disorder, or disease)

5 **Grandiose** (belief that one has inflated worth, power, special identity, or special relationship to a deity or famous person)

6 **Other** (cannot be subtyped in any of the previous categories, e.g., persecutory and grandiose themes without either predominating, delusion of reference without malevolent content)

Go to "Chronology," C.13

Psychotic Disorder NOS

PSYCHOTIC DISORDER NOS

This is a residual category for disorders in which there are psychotic symptoms (delusions, hallucinations, incoherence, marked loosening of associations, catatonic excitement or stupor, or disorganized behavior) that do not meet the criteria for any other non-organic psychotic disorder.

3
Psychotic Disorder NOS

DESCRIBE THE CLINICAL FEATURES BELOW AND THEN GO TO ***Chronology,*** C.13.

Chronology

CHRONOLOGY OF BRIEF REACTIVE PSYCHOSIS, SCHIZOPHRENIA, SCHIZOPHRENIFORM, SCHIZOAFFECTIVE, DELUSIONAL DISORDER, OR PSYCHOTIC DISORDER NOS

IF UNCLEAR: During the past month, have you had (PSYCHOTIC SXS CODED "3" OR, FOR SCHIZOAFFECTIVE DISORDER, DEPRESSIVE OR MANIC SXS CODED "3")?	Has met symptomatic criteria for the disorder during the past month, i.e., any psychotic symptom or, for Schizoaffective Disorder, has met full criteria for a Major Depressive or Manic Episode	? 1 3	51
When did you last have (PSYCHOTIC SXS OR, FOR SCHIZOAFFECTIVE DISORDER, EITHER DEPRESSED MOOD OR EUPHORIC OR IRRITABLE MOOD)?	Number of months prior to interview when last had psychotic symptoms (or, for Schizoaffective Disorder, when last had persistently depressed, euphoric, or irritable mood)	— — — (Go to "Past Five Years," C.14)	52-54

NOTE CURRENT SEVERITY OF PSYCHOTIC DISORDER, WORST WEEK OF PAST MONTH:

1	Mild:	Psychotic symptoms only intermittently present, **AND** have little influence on behavior
2	Moderate:	Symptoms or functional impairment intermediate between "mild" and "severe"
3	Severe:	Psychotic symptoms persistently present, **AND** markedly influence behavior
4	Nonpsychotic:	No psychotic symptoms (but currently meets full criteria for Major Depressive or Manic Episode)

55

CONTINUE ON NEXT PAGE

"Past Five Years"

During the past five years, how much of the time have you had (ANY SXS OF THE DISORDER)?

Would you say . . . [CODE DESCRIPTIONS]?

Approximate percentage of time during past five years that any symptoms of the disorder were present (including prodromal and residual symptoms)

1 Not all all (0%)

2 Rarely (e.g., 5–10%)

3 A significant minority of the time (e.g., 20–30%)

4 About half the time

5 A significant majority of the time (e.g., 70–80%)

6 Almost all the time (e.g., 90–100%)

9 Unknown

56

How old were you when you first had (PSYCHOTIC SXS)?

Age at onset of psychotic symptoms (CODE 99 IF UNKNOWN) — — 57-58

THE FOLLOWING ITEM APPLIES ONLY TO A DIAGNOSIS OF SCHIZOPHRENIA:

IF NOT ALREADY KNOWN: What kinds of difficulties were you having before you first had (PSYCHOTIC SXS)?

(Were you working, having a social life, taking care of yourself?) SEE PRODROMAL SYMPTOM LIST. C.5.

Age at onset of prodromal symptoms (if any) (CODE 99 IF UNKNOWN) — — 59-60

Number of episodes or exacerbations (CODE 99 IF TOO NUMEROUS OR INDISTINCT TO COUNT) — — 61-62

Positive and Negative Syndrome Scale

PANSS +/-

Manual

Stanley R. Kay, Ph.D.
Lewis A. Opler, M.D., Ph.D.
Abraham Fiszbein, M.D.

Published by Multi-Health Systems, Inc.

Positive Scale (P)

P1. Delusions. Beliefs which are unfounded, unrealistic, and idiosyncratic. ***Basis for rating:*** thought content expressed in the interview and its influence on social relations and behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Presence of one or two delusions which are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.
4	Moderate	Presence of either a kaleidoscopic array of poorly formed, unstable delusions or of a few well-formed delusions that occasionally interfere with thinking, social relations, or behavior.
5	Moderate Severe	Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations, or behavior.
6	Severe	Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations, and behavior.
7	Extreme	Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others.

Positive Scale (P)

P2. Conceptual disorganization. Disorganized process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations, non sequiturs, gross illogicality, or thought block. *Basis for rating*: cognitive-verbal processes observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Thinking is circumstantial, tangential, or paralogical. There is some difficulty in directing thoughts toward a goal, and some loosening of associations may be evidenced under pressure.
4	Moderate	Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.
5	Moderate Severe	Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevancies, disconnectedness, or loosening of associations even when not under pressure.
6	Severe	Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.
7	Extreme	Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which results in total failure of communication, e.g., "word salad" or mutism.

Positive Scale (P)

P3. ***Hallucinatory behavior.*** Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory, or somatic realms. *Basis for rating:* verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behavior.
4	Moderate	Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.
5	Moderate Severe	Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.
6	Severe	Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.
7	Extreme	Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations.

Positive Scale (P)

P4. Excitement. Hyperactivity as reflected in accelerated motor behavior, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. *Basis for rating*: behavioral manifestations during the course of interview as well as reports of behavior by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.
4	Moderate	Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.
5	Moderate Severe	Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.
6	Severe	Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating and sleeping.
7	Extreme	Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

Positive Scale (P)

P5. Grandiosity. Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. *Basis for rating*: thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.
4	Moderate	Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.
5	Moderate Severe	Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behavior.
6	Severe	Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.
7	Extreme	Thinking, interactions, and behavior are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power, and/or moral stature, which may take on a bizarre quality.

Positive Scale (P)

P6. Suspiciousness/persecution. Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. *Basis for rating*: thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behavior are minimally affected.
4	Moderate	Distrustfulness is clearly evident and intrudes on the interview and/or behavior, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.
5	Moderate Severe	Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavior.
6	Severe	Clear-cut pervasive delusions of persecution which may be systematized and significantly interfere in interpersonal relations.
7	Extreme	A network of systematized persecutory delusions dominates the patient's thinking, social relations, and behavior.

Positive Scale (P)

P7. Hostility. Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. *Basis for rating*: interpersonal behavior observed during the interview and reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.
4	Moderate	Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.
5	Moderate Severe	Patient is highly irritable and occasionally verbally abusive or threatening.
6	Severe	Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others.
7	Extreme	Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others.

Negative Scale (N)

N1. Blunted affect. Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. *Basis for rating*: observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.
4	Moderate	Reduced range of facial expression and few expressive gestures result in a dull appearance.
5	Moderate Severe	Affect is generally "flat," with only occasional changes in facial expression and a paucity of communicative gestures.
6	Severe	Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter.
7	Extreme	Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or "wooden" expression.

Negative Scale (N)

N2. Emotional withdrawal. Lack of interest in, involvement with, and affective commitment to life's events. *Basis for rating:* reports of functioning from primary care workers or family and observation of interpersonal behavior during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Usually lacks initiative and occasionally may show deficient interest in surrounding events.
4	Moderate	Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.
5	Moderate Severe	Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.
6	Severe	Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.
7	Extreme	Patient is almost totally withdrawn, uncommunicative, and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

Negative Scale (N)

N3. ***Poor rapport.*** Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. ***Basis for rating:*** interpersonal behavior during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Conversation is characterized by a stilted, strained, or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.
4	Moderate	Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.
5	Moderate Severe	Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.
6	Severe	Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.
7	Extreme	Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

Negative Scale (N)

N4. Passive/apathetic social withdrawal. Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living. *Basis for rating*: reports on social behavior from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.
4	Moderate	Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.
5	Moderate Severe	Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.
6	Severe	Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.
7	Extreme	Profoundly apathetic, socially isolated, and personally neglectful.

Negative Scale (N)

*N5. **Difficulty in abstract thinking.*** Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks. ***Basis for rating***: responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.
4	Moderate	Often utilizes a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.
5	Moderate Severe	Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.
6	Severe	Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.
7	Extreme	Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

Negative Scale (N)

N6. Lack of spontaneity and flow of conversation. Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. *Basis for rating*: cognitive-verbal processes observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.
4	Moderate	Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.
5	Moderate Severe	Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.
6	Severe	Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (E.g., "I don't know," "I'm not at liberty to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive.
7	Extreme	Verbal output is restricted to, at most, an occasional utterance, making conversation impossible.

Negative Scale (N)

*N7. **Stereotyped thinking.*** Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. *Basis for rating*: cognitive-verbal processes observed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.
4	Moderate	Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.
5	Moderate Severe	Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.
6	Severe	Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.
7	Extreme	Thinking, behavior, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication.

General Psychopathology Scale (G)

G1. Somatic concern. Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. *Basis for rating*: thought content expressed in the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.
4	Moderate	Complains about poor health or bodily malfunction, but there is no delusional conviction, and over-concern can be allayed by reassurance.
5	Moderate Severe	Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.
6	Severe	Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.
7	Extreme	Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.

General Psychopathology Scale (G)

G2. ***Anxiety.*** Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. ***Basis for rating:*** verbal report during the course of interview and corresponding physical manifestations.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some worry, over-concern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidence.
4	Moderate	Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.
5	Moderate Severe	Patient reports serious problems of anxiety which have significant physical and behavioral consequences, such as marked tension, poor concentration, palpitations, or impaired sleep.
6	Severe	Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.
7	Extreme	Patient's life is seriously disrupted by anxiety, which is present almost constantly and, at times, reaches panic proportion or is manifested in actual panic attacks.

General Psychopathology Scale (G)

G3. ***Guilt feelings.*** Sense of remorse or self-blame for real or imagined misdeeds in the past. *Basis for rating*: verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.
4	Moderate	Patient expresses distinct concern over his or her responsibility for a real incident in his or her life but is not preoccupied with it, and attitude and behavior are essentially unaffected.
5	Moderate Severe	Patient expresses a strong sense of guilt associated with self-deprecation or the belief that he or she deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.
6	Severe	Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he or she should receive harsh sanctions for the misdeeds and may even regard his or her current life situation as such punishment.
7	Extreme	Patient's life is dominated by unshakable delusions of guilt, for which he or she feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.

General Psychopathology Scale (G)

G4. Tension. Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. *Basis for rating*: verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.
4	Moderate	A clearly nervous appearance emerges from various manifestations, such as fidgety behavior, obvious hand tremor, excessive perspiration, or nervous mannerisms.
5	Moderate Severe	Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.
6	Severe	Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.
7	Extreme	Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

General Psychopathology Scale (G)

G5. ***Mannerisms and posturing.*** Unnatural movements or posture as characterized by an awkward, stilted, disorganized, or bizarre appearance. ***Basis for rating:*** observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Slight awkwardness in movements or minor rigidity of posture.
4	Moderate	Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.
5	Moderate Severe	Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.
6	Severe	Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods.
7	Extreme	Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.

General Psychopathology Scale (G)

G6. Depression. Feelings of sadness, discouragement, helplessness, and pessimism. ***Basis rating:*** verbal report of depressed mood during the course of interview and its observed influence on attitude and behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some sadness or discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.
4	Moderate	Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behavior or social functioning, and the patient usually can be cheered up.
5	Moderate Severe	Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.
6	Severe	Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.
7	Extreme	Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or actions.

General Psychopathology Scale (G)

G7. Motor retardation. Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. *Basis for rating*: manifestations during the course of interview as well as reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply. ··
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.
4	Moderate	Patient is clearly slow in movements, and speech may be characterized by poor productivity, including long response latency, extended pauses, or slow pace.
5	Moderate Severe	A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.
6	Severe	Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.
7	Extreme	Patient is almost completely immobile and virtually unresponsive to external stimuli.

General Psychopathology Scale (G)

G8. Uncooperativeness. Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. *Basis for rating*: interpersonal behavior observed during the course of interview as well as reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.
4	Moderate	Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.
5	Moderate Severe	Patient frequently is incompliant with the demands of his or her milieu and may be characterized by others as an "outcast" or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.
6	Severe	Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.
7	Extreme	Active resistance seriously impacts on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.

General Psychopathology Scale (G)

G9. Unusual thought content. Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical, and patently absurd. *Basis for rating*: thought content expressed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.
4	Moderate	Ideas are frequently distorted and occasionally seem quite bizarre.
5	Moderate Severe	Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving radio messages from outer space through a tooth filling).
6	Severe	Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet).
7	Extreme	Thinking is replete with absurd, bizarre, and grotesque ideas.

General Psychopathology Scale (G)

G10. Disorientation. Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. *Basis for rating*: responses to interview questions on orientation.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	General orientation is adequate but there is some difficulty with specifics. For example, patient knows his or her location but not the street address; knows hospital staff names but not their functions; knows the month but confuses the day of week with an adjacent day; or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the Mayor, Governor, or President.
4	Moderate	Only partial success in recognizing persons, places, and time. For example, patient knows he or she is in a hospital but not its name; knows the name of his or her city but not the borough or district; knows the name of his or her primary therapist but not many other direct care workers; knows the year and season but is not sure of the month.
5	Moderate Severe	Considerable failure in recognizing persons, place, and time. Patient has only a vague notion of where he or she is and seems unfamiliar with most people in his or her milieu. He or she may identify the year correctly or nearly so but not know the current month, day of week, or even the season.
6	Severe	Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his or her whereabouts; confuses the date by more than one year; can name only one or two individuals in his or her current life.
7	Extreme	Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.

General Psychopathology Scale (G)

G11. Poor attention. Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. *Basis for rating*: manifestations during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Limited concentration evidenced by occasional vulnerability to distraction or faltering attention toward the end of the interview.
4	Moderate	Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.
5	Moderate Severe	Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.
6	Severe	Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.
7	Extreme	Attention is so disrupted that even brief conversation is not possible.

General Psychopathology Scale (G)

G12. Lack of judgment and insight. Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of consequences, and unrealistic short-term and long-range planning. *Basis for rating*: thought content expressed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Recognizes having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.
4	Moderate	Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgment of being ill or little awareness of major symptoms which are present, such as delusions, disorganized thinking, suspiciousness, and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty.
5	Moderate Severe	Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.
6	Severe	Patient denies ever having had a psychiatric disorder. He or she disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.
7	Extreme	Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.

General Psychopathology Scale (G)

G13. Disturbance of volition. Disturbance in the willful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. *Basis for rating*: thought content and behavior manifested in the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.
4	Moderate	Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alternation in thinking, and in consequence verbal and cognitive functioning are clearly impaired.
5	Moderate Severe	Disturbance of volition interferes in thinking as well as behavior. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.
6	Severe	Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.
7	Extreme	Almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.

General Psychopathology Scale (G)

G14. Poor impulse control. Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about consequences. *Basis for rating*: behavior during the course of interview and reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.
4	Moderate	Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.
5	Moderate Severe	Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.
6	Severe	Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behavior and may also be sexually offensive and possibly respond behaviorally to hallucinatory commands.
7	Extreme	Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behavior. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

General Psychopathology Scale (G)

G15. Preoccupation. Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behavior. *Basis for rating*: interpersonal behavior observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.
4	Moderate	Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.
5	Moderate Severe	Patient often appears to be engaged in autistic experiences, as evidenced by behaviors that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.
6	Severe	Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself or herself.
7	Extreme	Gross absorption with autistic experiences, which profoundly affects all major realms of behavior. The patient constantly may be responding verbally and behaviorally to hallucinations and show little awareness of other people or the external milieu.

General Psychopathology Scale (G)

G16. Active social avoidance. Diminished social involvement associated with unwarranted fear, hostility, or distrust. *Basis for rating:* reports of social functioning by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient seems ill at ease in the presence of others and prefers to spend time alone, although he or she participates in social functions when required.
4	Moderate	Patient grudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.
5	Moderate Severe	Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.
6	Severe	Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he or she appears to isolate himself or herself from others.
7	Extreme	Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he or she avoids all interactions and remains isolated from others.

Supplementary Items for the Aggression Risk Profile

S1. Anger. Subjective state of displeasure and irritation directed at others. *Basis for rating:* verbal report of angry feelings during the course of the interview and, thereupon, corresponding hostile behaviors observed during the interview or noted from reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some irritation or ill feelings toward others but, otherwise, shows no emotional or behavioral signs of anger.
4	Moderate	Presents an overtly angry exterior, but temper remains under control.
5	Moderate Severe	Patient appears highly irritable, and anger is vented through frequently raised voice, occasional verbal abuse, or thinly veiled threats.
6	Severe	Patient appears highly irritable, and anger is vented through repeated verbal abuse, overt threats, or destructiveness.
7	Extreme	An explosive level of anger is evidenced by physical abuse directed or attempted at others.

Supplementary Items for the Aggression Risk Profile

S2. Difficulty in delaying gratification. Demanding, insistent that needs be satisfied immediately, and noticeably upset when fulfillment of needs or desires is delayed. *Basis for rating:* observation of behavior during the course of the interview as well as reports from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient is occasionally demanding and impatient but settles down quickly when spoken to.
4	Moderate	Demanding behavior occurs more than just occasionally or else has an insistent quality that makes the patient a "nuisance." No outbursts of hostility, however, typically follow, and the patient ordinarily can be managed without difficulty.
5	Moderate Severe	Demanding behavior is both frequent and persistent, resulting in occasional confrontations with other patients, staff, or family. As a rule, however, the patient regains control without serious incident.
6	Severe	Patient gets seriously upset whenever needs or demands are not met immediately. Explosive or violent behavior may once or twice ensue, and loss of control is an ever-present possibility.
7	Extreme	The failure to instantly cater to the patient's needs or demands tends to provoke explosive, violent, or impulsive behavior. Close supervision is typically required.

Supplementary Items for the Aggression Risk Profile

S3. ***Affective lability.*** Emotional expressions are unstable, fluctuating, inappropriate, and/or poorly controlled. *Basis for rating*: affective state observed during the course of the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some incongruous affective responses are observed or a few unexplained shifts in emotional tone may occur.
4	Moderate	Affect is frequently incongruent with thoughts (e.g., inappropriate silliness, anger, or worry), or there are several radical changes in emotional tone during the course of the interview.
5	Moderate Severe	Emotional expressions are highly unstable and occasionally seem beyond the patient's control. The affective picture may show sudden shifts to the extremes, with generally poor modulation.
6	Severe	Emotions appear to be uncontrolled during most of the interview and may be dominated by autistic or irrelevant stimuli. The affective state takes on a fleeting quality, with peculiar or kaleidoscopic changes. Primitive emotional discharge, e.g., displays of ecstasy or rage, may be seen.
7	Extreme	Patient seems to lack any control over his or her emotional state, which fluctuates freely in response to inappropriate external or internal events. Extreme emotional states, such as excitement or fury, at times dominate.

VISIT 2 (day 0)
BASELINE

25/3 baseline

EXTRAPYRAMIDAL SYMPTOM RATING SCALE
(ESRS, G. Chouinard, A. Ross-Chouinard, 1980)

I PARKINSONISM, DYSTONIA AND DYSKINESIA:
Questionnaire and Behavioral Scale
Answer questions by checking the appropriate box for each item

	Absent	Mild	Moderate	Severe
1. Impression of slowness or weakness, difficulty in carrying out routine tasks	☒	☐	☐	☐
2. Difficulty walking or with balance	☒	☐	☐	☐
3. Difficulty swallowing or talking	☒	☐	☐	☐
4. Stiffness, stiff posture	☒	☐	☐	☐
5. Cramps or pains in limbs, back or neck	☒	☐	☐	☐
6. Restless, nervous, unable to keep still	☒	☐	☐	☐
7. Tremors, shaking	☒	☐	☐	☐
8. Oculogyric crisis, abnormal sustained posture	☒	☐	☐	☐
9. Increased salivation	☒	☐	☐	☐
10. Abnormal involuntary movements (dyskinesia) of extremities or trunk	☒	☐	☐	☐
11. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips or face	☒	☐	☐	☐
12. Dizziness when standing up (especially in the morning)	☒	☐	☐	☐

VISIT 2 (day 0)
BASELINE

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (continued)

II ***PARKINSONISM : physician's examination***
Enter the appropriate score for each item

1. EXPRESSIVE AUTOMATIC MOVEMENTS: (facial mask/speech) [ ]
   - 0 : Normal
   - 1 : Very mild decrease in facial expressiveness
   - 2 : Mild decrease in facial expressiveness
   - 3 : Rare spontaneous smile, decrease blinking, voice slightly monotonous
   - 4 : No spontaneous smile, staring gaze, low monotonous speech, mumbling
   - 5 : Marked facial mask, unable to frown, slurred speech
   - 6 : Extremely severe facial mask with unintelligible speech

2. BRADYKINESIA: [ ]
   - 0 : Normal
   - 1 : Global impression of slowness in movements
   - 2 : Definite slowness in movements
   - 3 : Very mild difficulty in initiating movements
   - 4 : Mild to moderate difficulty in initiating movements
   - 5 : Difficulty in starting or stopping any movement, or freezing on initiating voluntary act
   - 6 : Rare voluntary movement, almost completely immobile

3. RIGIDITY:
   - Right arm [ ]
   - Left arm [ ]
   - Right leg [ ]
   - Left leg [ ]
   - 0 : Normal muscle tone
   - 1 : Very mild, barely perceptible
   - 2 : Mild (some resistance to passive movements)
   - 3 : Moderate (definite resistance to passive movements)
   - 4 : Moderately severe (moderate resistance but still easy to move the limb)
   - 5 : Severe (marked resistance with definite difficulty to move the limb)
   - 6 : Extremely severe (nearly frozen)

4. GAIT & POSTURE: [ ]
   - 0 : Normal
   - 1 : Mild decrease of pendular arm movement
   - 2 : Moderate decrease of pendular arm movement, normal steps
   - 3 : No pendular arm movement, head flexed, steps more or less normal
   - 4 : Stiff posture (neck, back), small step (shuffling gait)
   - 5 : More marked, festination or freezing on turning
   - 6 : Triple flexion, barely able to walk

VISIT 2 (day 0)
BASELINE

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (continued)

5. TREMOR:

			Occasional	Frequent	Constant or almost so
Right arm	[ ]	None : 0			
Left arm	[ ]	Borderline : 1			
Right leg	[ ]	Small amplitude :	2	3	4
Left leg	[ ]	Moderate amplitude :	3	4	5
Head	[ ]	Large amplitude :	4	5	6
Jaw/chin	[ ]				
Tongue	[ ]				
Lips	[ ]				

6. AKATHISIA : [ ]

0 : None
1 : Looks restless, nervous, impatient, uncomfortable
2 : Needs to move at least one extremity
3 : Often needs to move one extremity or to change position
4 : Moves one extremity almost constantly if sitting, or stamps feet while standing
5 : Unable to sit down for more than a short period of time
6 : Moves or walks constantly

7. SIALORRHEA : [ ]

0 : Absent
1 : Very mild
2 : Mild
3 : Moderate : impairs speech
4 : Moderately severe
5 : Severe
6 : Extremely severe : drooling

8. POSTURAL STABILITY : [ ]

0 : Normal
1 : Hesitation when pushed but no retropulsion
2 : Retropulsion but recovers unaided
3 : Exaggerated retropulsion without falling
4 : Absence of postural response, would fall if not caught by examiner
5 : Unstable while standing, even without pushing
6 : Unable to stand without assistance

VISIT 2 (day 0)
BASELINE

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (continued)

III *DYSTONIA: Physician's examination*
Enter the appropriate score for each item

1. ACUTE TORSION DYSTONIA:

Right arm	[ ]	Head	[ ]	0	: Absent
Left arm	[ ]	Jaw	[ ]	1	: Very mild
Right leg	[ ]	Tongue	[ ]	2	: Mild
Left leg	[ ]	Lips	[ ]	3	: Moderate
				4	: Moderately severe
				5	: Severe
				6	: Extremely severe

2. NON ACUTE OR CHRONIC OR TARDIVE DYSTONIA

Right arm	[ ]	Head	[ ]	0	: Absent
Left arm	[ ]	Jaw	[ ]	1	: Very mild
Right leg	[ ]	Tongue	[ ]	2	: Mild
Left leg	[ ]	Lips	[ ]	3	: Moderate
				4	: Moderately severe
				5	: Severe
				6	: Extremely severe

VISIT 2 (day 0)
BASELINE

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (continued)

IV DYSKINETIC MOVEMENTS: Physician's examination
Circle the appropriate score for each item

		Occasional*	Frequent**	Constant or almost so
1. Lingual movements (slow lateral or torsion movement of tongue)				
	None	0		
	Borderline	1		
	Clearly present, within oral cavity	2	3	4
	With occasional partial protrusion	3	4	5
	With complete protrusion	4	5	6
2. Jaw movements (lateral movement, chewing, biting, clenching)				
	None	0		
	Borderline	1		
	Clearly present, small amplitude	2	3	4
	Moderate amplitude, but without mouth opening	3	4	5
	Large amplitude, with mouth opening	4	5	6
3. Bucco-labial movements (puckering, pouting, smacking, etc.)				
	None	0		
	Borderline	1		
	Clearly present, small amplitude	2	3	4
	Moderate amplitude, forward movement of lips	3	4	5
	Large amplitude; marked, noisy smacking of lips	4	5	6
4. Truncal movements (rocking, twisting, pelvic gyrations)				
	None	0		
	Borderline	1		
	Clearly present, small amplitude	2	3	4
	Moderate amplitude	3	4	5
	Greater amplitude	4	5	6
5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)				
	None	0		
	Borderline	1		
	Clearly present, small amplitude, movements of one limb	2	3	4
	Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs	3	4	5
	Greater amplitude, movement involving two limbs	4	5	6
6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)				
	None	0		
	Borderline	1		
	Clearly present, small amplitude, movements of one limb	2	3	4
	Moderate amplitude, movement of one limb or movement of small amplitude involving two limbs	3	4	5
	Greater amplitude, movement involving two limbs	4	5	6
7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.)				
	None	0		
	Borderline	1		
	Clearly present, small amplitude	2	3	4
	Moderate amplitude	3	4	5
	Greater amplitude	4	5	6

* When activated or rarely spontaneous

** Frequently spontaneous and present when activated

VISIT 2 (day 0)
BASELINE

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (continued)

V CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA

Considering your clinical experience, how severe is the dyskinesia at this time ?

- [X] Absent
- [ ] Borderline
- [ ] Very mild
- [ ] Mild
- [ ] Moderate
- [ ] Moderately severe
- [ ] Marked
- [ ] Severe
- [ ] Extremely severe

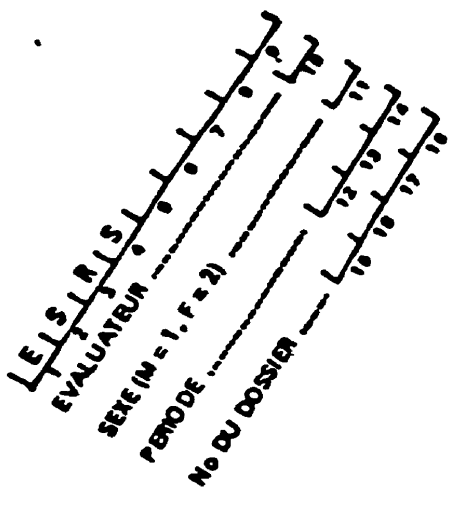
VI CLINICAL GLOBAL IMPRESSION OF SEVERITY OF PARKINSONISM

Considering your clinical experience, how severe is the parkinsonism at this time ?

- [X] Absent
- [ ] Borderline
- [ ] Very mild
- [ ] Mild
- [ ] Moderate
- [ ] Moderately severe
- [ ] Marked
- [ ] Severe
- [ ] Extremely severe

Investigator's signature

Date: 13 Jul 93
Day Month Year


E I S R I S
EVALUATEUR
SEXE (M = 1, F = 2)
PERIODE
No DU DOSSIER