Descriptive characteristics of inpatients with tardive dyskinesia as distinguished from inpatients without tardive dyskinesia

Lucy Glover Savage

College of William & Mary - School of Education

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DESCRIPTIVE CHARACTERISTICS OF INPATIENTS WITH TARDIVE DYSKINESIA AS DISTINGUISHED FROM INPATIENTS WITHOUT TARDIVE DYSKINESIA

The College of William and Mary in Virginia

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DESCRIPTIVE CHARACTERISTICS OF INPATIENTS WITH TARDIVE DYSKINESIA AS DISTINGUISHED FROM INPATIENTS WITHOUT TARDIVE DYSKINESIA

A Dissertation
Presented to
The Faculty of the School of Education
The College of William and Mary in Virginia

In Partial Fulfillment
Of the Requirements for the Degree
Doctor of Education

by
Lucy Glover Savage
October 1980
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by

Lucy Glover Savage

Approved October 1980 by

George Bass, Ph.D.

Richard Bloch, Ph.D.

Charles O. Matthews, Ph.D.
Chairman of Doctoral Committee
The energy necessitated by this research is dedicated to the individuals who have suffered tardive dyskinesia and to other workers trying to find a prevention or cure for this often debilitating movement disorder.
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a possibility and eventual reality. Dr. Ronald Savage served as an invaluable friend, mentor, and sounding board throughout my studies and writing; deepest appreciation is extended to him for his encouragement, support, and patience.
I. INTRODUCTION

Statement of the Problem

Tardive dyskinesia (TD) is a debilitating side effect of antipsychotic medications that is late in onset and often irreversible (Jeste et al., 1979). The etiology of TD, as well as the treatment for TD, remain elusive, although heavily researched (Jeste & Wyatt, 1979). Before comprehensive and conclusive research on the etiology and, therefore, treatment of TD can be accomplished, consistent findings about distinguishing characteristics of TD patients are needed in order for its precursors to be identified. It is the purpose of this study to investigate some of the characteristics which describe patients with TD. An attempt will be made to answer the question "Are there aspects of TD patients' drugs and behavioral histories which distinguish them from patients without TD?" The descriptive characteristics investigated were history of extrapyramidal side effects, initial psychiatric behavior pattern, psychiatric behavior patterns, history of antipsychotic drugs, history of antiparkinson agents, history of polypharmacy, history of drug-free periods, race, eye color, and dental status.

Need for the Study

Prevalence figures clearly indicate that TD is not uncommon among psychiatric patients. Statistics reflecting prevalence vary from study to study depending upon the intensity of measurements used
(Klawans, 1979). Reports have ranged as high as 36% (Fann et al., 1972) and 56% (Jus et al., 1976) for inpatients. Previously researchers assumed that TD occurred primarily among inpatients. However, with the advent of deinstitutionalization and long-term antipsychotic maintenance regimens, there are also increasing reports of TD in the outpatient population. Asnis et al. (1977) found a 43% prevalence of TD among outpatients and Chouinard et al. (1979) found a 31% prevalence among their outpatient sample. The development of TD often reduces a patient's ability to adjust to community life as its symptoms can be socially and vocationally disabling; also, patients "may have to remain in the hospital because of a complication of the therapy designed to get them out of the hospital" (Ayd, 1970, p. 306). Furthermore, TD has been associated with reduced life expectancy (Mehta et al., 1978) and suicide (Klawans, 1979).

Due to the possible irreversibility of TD, its growing incidence, and the adjustment problems it causes, it is imperative that the descriptive characteristics of TD patients are consistently delineated in order to identify the precursors of TD, for several reasons. Primary is the fact that no consistently effective treatment for TD has been discovered, thus the current emphasis is on preventing severe forms of TD through prompt recognition of early signs (Baldessarini & Tarsy, 1978). However, early warning signs are difficult to establish due to the syndrome's insidious on-set, individual differences in clinical display of symptoms, and the ability of antipsychotics to mask the clinical signs of TD. Consequently, research on the descriptive
characteristics of patients with TD is needed to identify precursors and eventually patients at high risk for developing TD. With such identifications made, precautions can be taken to prevent the syndrome's on-set rather than dealing with the syndrome after its occurrence.

Alexopoulos (1979) found that the outpatient schizophrenics diagnosed as having TD in his study did not complain about their symptoms to their therapist and only half of them were even aware of their symptoms. Similarly, Smith et al. (1979) report that only 8% of their inpatients diagnosed as having moderate TD were aware of their symptoms and only 3.5% reported distress about the symptoms. Due to increasing deinstitutionalization, non-medical personnel such as psychologists, counselors, and social workers are coming into greater contact with outpatients on antipsychotic regimens. These mental health workers have the greatest contact with outpatients and, in light of the findings of Alexopoulos and Smith et al. (1979), also have an increasing responsibility to be aware of the descriptive characteristics of patients with TD, the precursors of TD, and the symptoms of TD. This knowledge could greatly aid in reducing the incidence and/or severity of TD thus increasing community placement and adjustment for psychiatric patients. With the identification of these characteristics, and subsequently the precursors of TD, non-medical mental health workers could play an important role in identifying patients at high risk for developing TD. Referrals to the staff physician could then be made with consequential precautionary steps being taken. An efficient and effective multi-disciplinary approach to the prevention and curtailment
of TD could result.

Although there have been several epidemiological studies of TD, there have been few consistent findings due to several methodological problems. Ananth (1978), in reviewing etiological studies, points out that control groups are seldom used and suggests that "a more fruitful approach would be to understand the differences between those who develop dyskinesia and those who do not" (p. 34). Simpson et al. (1978) assert that merely using a control group is inadequate and that matching on age, sex, diagnosis, and length of hospitalization is necessary, although seldom done, for adequate epidemiological studies of TD as "direct comparisons... within matched patients should yield more definitive results" (p. 119). The proposed study meets these two methodological needs as a matched control group will be used. There are several reasons matching between experimental and control subjects on these control variables is recommended. The first lies in the consistent findings concerning these demographic variables, which are discussed in detail in Chapter 3. The second reason is a result of the restricted sample sizes retrospective, epidemiological studies of TD demand due to the enormous amount of data involved in studying such variables as drug and behavioral histories. A choice must therefore be made between having many subjects, unmatched, or having few-er subjects who are matched. The former choice has been made for this study as the variables under study either have not been studied with consistent depth and breadth--i.e., the drug variables, or they have not been studied at all--i.e., the behavioral variables. Consequently,
like Mallya et al. (1979), the "small sample . . . disadvantage [will] at least be partially offset by careful matching of controls" (p. 648). Ideally the future will see large matched groups in epidemiological studies of TD as the current trend in mental hospitals is toward computerized storage of drug information.

Theoretical Rationale

Empirical justification for predicting and researching the specific descriptive characteristics previously delineated is gained from a review of epidemiological research on TD. Replication of the findings on all variables under study is needed since matched control groups were used in only three previous studies (Mallya et al., 1979; Simpson et al., 1978; Pryce & Edwards, 1966). The majority of epidemiological research is descriptive, often reporting findings in percentages (Fann et al., 1972) and not testing for statistical significance. Recent findings have also raised some questions as to the accuracy of some of the previous findings and indicate alternative data collection methods, such as cutting-off data collection with the emergence of TD symptoms (Jus et al., 1976). Chapter 2. covers in depth the literature as related to each variable being studied, thus providing full empirical justification and further theoretical rationale.

Sample and Data Gathering Procedures

Two samples of psychiatric inpatients were studied, each with 26 subjects. This sample size is considered adequate as the studies
found that used matched controls had sample sizes of 21 (Pryce & Edwards, 1966), 28 (Mallya et al., 1979), and 40 (Simpson et al., 1978). The TD sample primarily includes patients at Eastern State Hospital identified by the medical staff in June, 1979 as having TD and who were concommitantly blind-rated by a psychiatrist as having TD. The No-TD sample was randomly selected from all remaining inpatients at Eastern State Hospital on the basis of the control variables of the TD sample; namely, age, sex, and diagnosis. They were also blind-rated by the psychiatrist to ensure the absence of TD.

The following information was obtained from the hospital records and ward charts of all subjects: initial admission date (in order to determine the initial psychiatric behavior pattern), history of antipsychotic medications, history of antiparkinson agents, history of polypharmacy, history of drug-free periods, history of extrapyramidal symptoms (EPS), initial psychiatric behavior pattern, psychiatric behavior pattern, race, eye color, dental status, diagnosis, birth date, sex, and (in order to determine data cut-off) the date of the first recorded TD symptom mention or diagnosis. This researcher collected all data listed above, excepting the ratings of initial psychiatric behavior pattern and psychiatric behavior pattern. Assistants, blind to the hypotheses of this study and the group membership of the subjects, collected data on and rated these variables. This was deemed necessary as the researcher is not blind to either of these factors; thus a blind rater was employed to guard against any
systematic bias that may have otherwise occurred.

Definition of Terms

Tardive dyskinesia (TD), a neurological side effect of antipsychotic medications, is an involuntary, hyperkinetic motor disorder. Two major subclassifications of symptom complexes within the syndrome of TD have been distinguished by Bell & Smith (1978) on the basis of anatomy area and population most affected. The first type involves the buccal-lingual-masticatory triad in which tongue protrusion, lip smacking, and facial tics are common manifestations. This symptom complex is found most commonly among elderly patients. The second type involves primarily the neck, trunk, and extremities in which choreoathetoid movements occur and is more prevalent a manifestation among younger patients.

Extrapyramidal symptoms (EPS) are reversible involuntary motor disturbances which are also side effects of antipsychotics. They occur earlier in treatment than TD and usually are one of two types. Tremor and akathisia are the hyperkinetic types; akinesia, rigidity, and dystonic reactions are the hypokinetic types (Choudhary et al., 1976). The symptom complex of tremor, rigidity, and akinesia is often referred to as parkinsonism or pseudoparkinsonism due to its similarity to the symptoms of idiopathic Parkinson's disease (Donlon & Stenson, 1976).

"Initial psychiatric behavior pattern" refers to behavioral notations made upon the patients' first admission to a psychiatric
facility. These are located in the hospital records under "Admission Notes."

"Psychiatric behavior pattern" refers to behavioral notations recorded by the staff after the patients were prescribed antipsychotic medications. Since these medications did not begin to be used until 1952 (Baldessarini, 1978), only notes recorded after this time will be used in this study. These notes are located in the records under "Interdisciplinary Notes" and "Semi-Annual Summaries"; their contents were rated beginning January, 1953 unless a subject was admitted subsequent to this time in which case data collection started with the first administration of antipsychotics to this patient.

Antipsychotics are used primarily to treat schizophrenia and other psychoses. They are not curative agents but rather treat the symptoms of the illnesses such as delusions, hallucinations, thought disorders, combativeness, agitation, psychotic excitement, and at times, seclusiveness. Improvement in insight, judgment, memory, and orientation, however, is less likely (Baldessarini, 1977). Although the mechanisms of actions of the antipsychotics are not completely understood, they are currently thought of as dopamine antagonists. Antipsychotics are believed to block dopamine receptors and possibly dopamine release or transmission which contributes to their antipsychotic effects (Baldessarini, 1977). Antipsychotics are also referred to as neuroleptics.

Antiparkinson medications are used to treat extrapyramidal side effects. These agents are anticholinergics which can produce their
own side effects, thus they should be used with some caution. Current practice involves only prescribing them when the EPS emerges, rather than prophylactically, and then for no longer than two months at the lowest possible dose. This practice partially results from their recently being implicated in worsening TD or possibly contributing to the risk of developing TD (Baldessarini, 1977).

Polypharmacy refers to the use of medication combinations. In examining the medication histories of the subjects, two types of polypharmacy were investigated. The first is the number of antiparkinson agents and antipsychotics prescribed to the subjects. The second is the summation of incidences where the subject was simultaneously prescribed two different drugs in various combinations, one of which was an antipsychotic. The four different forms of this type of polypharmacy are delineated in Appendix A.

Limitations

An ex post facto design has an inherent limitation concerning the establishment of causality. The independent variable (TD) has already occurred naturalistically, thus it cannot be manipulated--i.e., it is uncontrolled. Since identification of relationships between the independent and dependent variables is being accomplished on an after-the-fact basis, causality cannot be established; rather descriptive characteristics unique to the TD group are sought in an effort to identify areas in need of more direct testing. Thus, even when predicted relationships are found an assumption of causality
was not made. Instead the conclusion was drawn that the
descriptive characteristics found unique to the TD group are indicative
of potential precursors which need to be more directly tested.

Another limitation is the threat selection causes for internal
validity as group membership was determined by the criterion of
presence or absence of TD. The assumption was thus made in
contrast to the groups that they would have been equivalent on the
dependent variables if X (TD) had not occurred. However, "there are
. . . no formal means of certifying that the groups would have been
equivalent had it not been for the X" (Campbell & Stanley, 1963, p.
12). Also, antipsychotics can clinically mask symptom manifestations
of TD thus causing diagnostic validity problems for the absence of TD
in the control subjects. Thus, viewing findings as descriptive rather
than indicative of causation is further indicated.

In the case of external validity, any relationships found can
be reliably generalized to similarly aged inpatients, with severe TD,
and hospitalized in state mental institutions. The rationale for such
restricted generalizations lies in the fact that any patients who were
released from the hospital are not included in this study. To include
such individuals is clearly beyond the scope of this study due to the
amount of time it would involve to trace down such subjects in order
to ensure they have not developed TD or been treated for psychiatric
disturbances since their release and consequently have incurred the
risk of developing TD. The role that chronic institutionalization may
play in the development of TD can therefore not be addressed in this
As Crane (1973) points out, it is probably safe to assume that "the chronicity of a disease and/or institutionalization with the attendant emotional and physical deprivation" (p. 395) is not responsible for motor abnormalities such as TD. This assumption is backed up by several studies. Pryce & Edwards (1966), in studying inpatient samples, found that the incidence of TD and abnormal movements similar to TD was higher for patients treated with antipsychotics than for similar patients not treated with antipsychotics. Thus, TD has come to be understood as a result of antipsychotic medications rather than a result of chronicity or institutionalization. Furthermore, TD does occur among outpatient populations not previously hospitalized (Asnis et al., 1977; Chouinard et al., 1979). Given the state of uncertainty, however, concerning the etiology of TD—even in light of the above findings—the findings of this study can be generalized reliably to similarly aged patients who have severe TD, and are still institutionalized.

**General Hypotheses**

There will be differences between a group of inpatients with TD and a group of inpatients without TD on the descriptive characteristics of history of antipsychotic medications, history of antiparkinson agents, history of polypharmacy, history of drug-free periods, history of extrapyramidal symptoms (EPS), initial psychiatric behavior pattern, psychiatric behavior pattern, race, eye color, and dental status.
II. REVIEW OF RELATED LITERATURE

Summary of Rationale and Relationship to Problem

In 1973 the American College of Neuropsychopharmacology, Food and Drug Administration Task Force published editorials in psychiatric and medical journals concerning the side effects of antipsychotic medications. Until this time consistent definitions, descriptions, and labels for the side effects did not exist. The editorials served the purpose of initiating much research on the etiology of TD as a succinct definition of the syndrome and acknowledgement of its existence was provided. Prior to this time many authors had published work about the syndrome, but under a variety of different terms (Edwards, 1970; Roxburgh, 1970). The main thrust of initial research on TD concerned proving its existence and relating its occurrence to antipsychotics. Crane (1973) published the first review of literature on TD citing the inconsistencies in prevalence findings due to differences in defining the syndrome, in assessing the syndrome, in collecting information, and in the patient populations. Not much of this has changed in the past seven years as discrepancies still exist in the methodology and findings of research about TD. However, the syndrome of TD is more clearly defined, its existence is no longer questioned, and its occurrence is attributed to antipsychotic medications. This attribution is derived from prevalence studies finding the syndrome to be relatively common in drug-treated populations and relatively rare in
untreated populations (Crane, 1973). What remains unclear, however, is how TD develops and which individuals are at high risk for developing the disorder. Until these are understood, effective prevention strategies for tardive dyskinesia will remain, as they have to date, unclear and evasive (Jeste & Wyatt, 1979).

Although tardive dyskinesia is understood as a side effect of antipsychotics, it is not known for certain how the medications cause the syndrome. It is unlikely that this will be known until the mechanisms by which antipsychotics operate are more clearly understood. Currently, antipsychotic medications are thought to functionally deplete dopamine by blocking this neurotransmitter's receptors at several sites in the brain (Baldessarini, 1977). This framework derives from the dopamine surplus theory of schizophrenia, which is only one theory of the etiology for this psychosis, wherein the psychosis is understood as a neurochemical disorder (Lehman, 1975). However, this theory also provides a basis for understanding the development of TD. If schizophrenia is a state of dopamine-surplus and antipsychotics act by reducing dopamine, then TD can be understood as a dopamine level disturbance. This is hypothesized as resulting from a "state of denervation supersensitivity of . . . dopamine receptors" (Jeste & Wyatt, 1979, p. 252) due to a "prolonged blockage of dopaminergic mechanisms by the antipsychotic drugs" (Baldessarini, 1977, p. 47). Consequently, several epidemiological studies have focused on the drug histories of patients with TD expecting to find that they had received increased amounts of antipsychotics, either in dosages or length of
administrations, to account for the hypothesized dopamine supersensitivity.

Even if TD is proven to be a result of a neurological imbalance caused by the ingestion of antipsychotics, no explanation would be given as to why some individuals develop TD while others do not. Consequently, individual differences in susceptibility are hypothesized (Baldessarini & Tarsy, 1978; Crane, 1978). Epidemiological studies have investigated characteristics of individuals with TD in an effort to delineate precursors of the syndrome. However, research on the relationships of different variables to the occurrence of TD often encounters data-gathering and methodological difficulties. Inconsistent findings may, thus, follow from these design flaws and may be furthered by intervening variables, such as behavioral variables, which have been overlooked or inadequately examined. For example, variables such as age and sex have been found to be systematically related to TD (Smith et al., 1978). However many investigations of variables related to TD do not take these consistent findings into consideration by neglecting to use control groups which are matched on these variables. The following literature review focuses on methodological difficulties while summarizing findings on the relationship of drug histories and individual characteristics to the development of TD.

**Drug Histories**

A. Antipsychotic Dosages

Four antipsychotic dosage and administration variables are of research interest: cumulative dose, cumulative length of administra-
tion, daily dose, and maximum dose received per year. Interplay can and does occur between the first two variables. For example, two patients can have the same cumulative dose but one patient had high daily doses for a short period of time while the other had low daily doses for a long period of time. An alternative method involves examination of mean daily dosages (Simpson et al., 1978). Data on cumulative dose and length of administration of antipsychotics must still be collected and there are many problems in obtaining drug histories exact enough to determine daily dose averages for antipsychotics. Record-keeping practices are inconsistent and many patients are hospitalized in several locations with their past records not being forwarded to their current institution. Consequently, many studies look only at the current medications received (Bell & Smith, 1978; Fann et al., 1972) or choose not to examine drug histories at all (Asnis et al., 1977). Maximum antipsychotic dosage per year is another drug variable recently receiving research attention (Smith et al., 1978). This variable avoids confounding interactions which may occur among gross drug variables and which can obscure specific differences.

Questions remain as to the necessity and sufficiency of variables, such as the amount of antipsychotic dosage and the length of antipsychotic administration, for the development of TD. On the basis of the dopamine-blockage hypothesis, one could expect TD patients to have had higher cumulative dosages of antipsychotics than control patients. This has not been consistently found. The paradoxi-
cal ability of antipsychotics to mask TD symptoms, as well as cause them, may contribute to the diversity of findings (Turek et al., 1972). Some subjects in the control samples could, for example, actually have TD, but their symptoms may be masked by higher doses of antipsychotics. This could also explain why control groups have sometimes been found to have higher cumulative dosages of antipsychotics.

Another expectation, emerging from the dopamine-blockage hypothesis, is that the TD subjects will have longer histories of antipsychotic administration than control subjects. There are inconsistent relationships reported here as well. Unfortunately, only one study reviewed (Jeste et al., 1979) has made an attempt to stop data collection with the first emergence of TD. All other studies thus have both pre-TD and post-TD drug data in their analyses. This clearly confounds the data as antipsychotics are often adjusted in response to a patient developing TD. Ideally, the antipsychotic dosage would be lowered or the drugs discontinued (Jeste & Wyatt, 1979). Thus, lower cumulative and daily doses of antipsychotics and/or shorter lengths of antipsychotic administration may be found among TD subjects, contrary to expectation, due to their medications being adjusted once TD was recognized. Methodological problems result when this possibility is not dealt with by researchers as differences in dosage ingestions and durations between the two groups, which may have existed prior to the development of TD, are obscured. Recently Smith et al. (1978) have recognized such a dilemma and recommend that "it may
be more important to examine the schedule and concentration of anti-psychotic administration . . . rather than the total amount of medication a patient has received" (p. 1403).

There are several types of individual differences which can also act as intervening variables in the study of the relationship of drug history to TD development. Individuals differ greatly in the absorption of medications into their central nervous and blood systems and "the milligrams ingested may not give a totally accurate indication of what is actually occurring" in the patients' physiology (Simpson et al., 1978). Individuals who develop TD may have a lower tolerance to antipsychotic ingestion, and thus a lower TD threshold, than individuals who don't develop TD. Thus findings on antipsychotic usage may be contrary to the expectations generated by the dopamine-blockage hypothesis. To determine the existence of such a situation would require antipsychotic plasma monitoring as an assessment device which, perhaps, the future will see (Jeste & Wyatt, 1979). Individual differences in non-compliance with antipsychotic drug regimens is another possible intervening variable. Often patients surreptitiously do not take the medications administered to them (Van Putten, 1974). The dosages recorded as administered may not be an accurate reflection of the amount actually ingested by the patient. These two individual difference factors remain beyond experimental control at this time, yet are worthy of mention due to their explanatory value concerning conflicting findings.
Cumulative Dose

Three studies (Mallya et al., 1979; Pryce & Edwards, 1966; Simpson et al., 1978) have examined the differences in cumulative antipsychotic dose levels, comparing a TD sample to a No-TD sample. The groups were matched on age, sex, and diagnosis. Pryce & Edwards and Simpson et al. also matched on length of hospitalization. Pryce & Edwards (1966) were the only researchers to find a significant difference between the two groups; the TD sample received higher cumulative dosages than the No-TD sample. Simpson et al. (1978) found no significant differences between their TD and No-TD groups; in fact, the No-TD group actually had a slightly higher cumulative dosage (TD = 1266g.; No-TD = 1313g.). Pryce & Edwards (1966) and Simpson et al. (1978) used drug histories beginning in the early 1950s. The conflicting findings of these two studies could be explained by their using different methods to quantify cumulative dose; chlorpromazine conversion equivalents, which are readily available to today's researchers, were just emerging in 1966. Similarly, Mallya et al. (1979) found no significant differences between the two groups. Again the controls had a slightly higher cumulative dosage (TD = 616g.; No-TD = 644g.). Their findings are limited as they only studied cumulative dosages of four antipsychotics. Mallya et al. also did not mention how many years of drug data were gathered, but it appears that about eight years were utilized. One explanation of the conflicting findings may be that it was not realized until the early 1970s that antipsychotic dosages should be reduced or the drugs discontinued with
the occurrence of TD (Crane, 1973). The TD subjects in the 1978 and 1979 studies more than likely incurred antipsychotic dosage reductions once TD was recognized; this was probably not the case for the subjects of Pryce & Edwards' (1966) study. Also during the 1960s, one method of treating TD was the administration of increased amounts of antipsychotics due to their ability to mask TD symptoms being misunderstood as eradication of the symptoms. None of the studies determined the on-set of TD in order to avoid confounding the drug data with post-TD drug information. Simpson et al. (1978) did note that differences in dosage ingestion may have existed prior to the development of TD as they could not determine the time of on-set of TD.

Two studies examined the difference in cumulative antipsychotic dose between unmatched TD and No-TD groups. Brandon et al. (1971) did not find a significant relationship between the total amount of antipsychotics administered and the risk of developing TD. Likewise, Jus et al. (1976) found no significant differences between the TD and No-TD samples on cumulative antipsychotic dose. Again, neither study cut-off data input according to the on-set of TD. Jus et al. (1976) explicitly state that this probably affected their findings on this variable.

Three studies used only TD subjects in an attempt to correlate antipsychotic dosage with TD symptom severity. Crane & Smeets (1974) found a positive relationship between total antipsychotic intake and TD severity. Patients whose cumulative dosages were above the group median had significantly more pronounced TD symptoms than patients
whose cumulative dosages were below the group median. Turek et al. (1972) reported the lack of a relationship between symptom severity and total milligrams of antipsychotics ingested. However, they only used data from the patients' current hospitalization which could have clearly confounded the results if many of the subjects had the majority of their drug-treated years on a previous hospitalization. Smith et al. (1978) are the only researchers to find that TD was significantly negatively related to the total amount of antipsychotics a patient received; however, they only utilized drug data from 1968 on.

Crane (1970) appears to have conducted the closest there has been to a prospective study in this field. He was able to randomly assign patients to drug regimens of placebo, high dose antipsychotics, or low dose antipsychotics. Six months later the patients were assessed for the presence of TD. He found that the patients receiving high doses of antipsychotics had a significantly higher incidence of TD. Findings about the role cumulative antipsychotic dose may play in the development of TD are inconsistent. This variable merits further research, designed with regard to the methodological flaws of previous studies.

**Length of Antipsychotic Administration**

Since TD is late in on-set compared to other neurological side effects (ACN-FDA, 1973), it seems that several years of treatment with antipsychotics may be necessary before the syndrome emerges. This appears supported by the incidence of TD sharply increasing over the
age of 50, which is often believed to indicate chronicity (Chouinard et al., 1979; Fann et al., 1972; Jus et al., 1976). It can thus be expected that patients who develop TD will have a longer history of antipsychotic medication treatment than patients who don't develop TD (Crane, 1973). The literature has failed to support such an expectation, however.

In one of the three studies using controls matched on the variables previously delineated, longer drug histories for TD subjects were noted. Pryce & Edwards (1966) reviewed entire drug histories and found 19 of the 21 TD subjects had been on antipsychotics from 30 - 500 weeks compared to only 8 of the 21 No-TD subjects. Mallya et al. (1979) reviewed about eight years of treatment, but examined only four antipsychotics. They found no significant differences between the two groups although the TD subjects tended to have longer medication histories (97.5 mo.) than the controls (96 mo.). Simpson et al., (1978), studying 23 years of drug histories, did not find significant differences between the two groups (TD = 11.6 yrs.; No-TD = 12.5 yrs.). These last two (post - early 1970s) studies' failure to end data collection with the emergence of TD may explain their failure to find longer antipsychotic histories for the TD groups.

Four studies, using unmatched control groups, also investigated the relationship between TD and antipsychotic treatment duration. Brandon et al. (1971), utilizing entire drug histories, found no association between the incidence of TD and the total duration of antipsychotic treatment. Jus et al. (1976) examined fifteen years of
drug histories and report that the mean number of months of treatment did not differ significantly between the TD and No-TD groups. Two studies investigated outpatient populations. Asnis et al. (1977) found that the mean number of years on antipsychotics was actually slightly less in the TD group (TD = 4.59 yrs.; No-TD = 5.50 yrs.). However, the majority of their subjects had received medications for less than two years. Chouinard et al. (1979) found that the variable of length of antipsychotic administration did not enter into their regression equation as significant in predicting the incidence of TD. Yet, they did not examine the entire drug histories of their subjects.

Three studies did not use control groups in their examination of this variable. Turek et al. (1972) did not find a relationship between TD severity and years on medications. Crane (1973) reported that 18 out of 184 patients he examined twice a year for the presence of TD developed TD within that year. Fifteen of these patients had been on antipsychotics for five years or longer; three for only 3 years. This finding does support the contention that some history of antipsychotic administration is involved in the development of TD, but does not address the issue of TD subjects having longer drug histories. Fann et al. (1972) lent support to the contention that TD is more prevalent in chronic patients as 64% of the patients with TD had been hospitalized longer than ten years. They did not directly test the variable of antipsychotic medication duration, although lengthy hospitalizations may be thought of as indicative of equally
lengthy drug histories.

Despite the length of time on antipsychotics investigated, all of the studies (1966) failed to show a significant association between treatment duration and the development of TD. It is possible that the practice of antipsychotic discontinuation for patients with TD is an intervening variable not controlled for by ending data collection at the point of TD emergence. The fact that patients over 50 are at greater risk for developing TD may reflect an intervening variable of chronicity, which would imply longer antipsychotic treatment durations. However, this assumes that individuals over 50 have been hospitalized for many years, which is not necessarily the case.

Another variable that could intervene is age at initiation of antipsychotic treatment. Brandon et al. (1971) concluded that age was the most significant factor in determining the risk of TD as the risk increased dramatically for the subjects over 50. Jus et al. (1976) brought more specificity to this conclusion in finding that the prevalence of TD was significantly higher if the mean age was higher at the beginning of treatment with antipsychotics. They believe that individual susceptibility probably increases with age in conjunction with changes of dopamine metabolism in the brain due to aging. The dopamine balances of elderly individuals may be more easily disrupted so that the older patients are at treatment initiatives, the more likely they are to develop dopamine receptor supersensitivity in response to antipsychotic medications. In fact, Gerlach (1977), in an
attempt to clarify the pathogenesis of TD, concluded from his study "that the neurotoxic effect of neuroleptics is related to age-dependent changes in the ... basal ganglia" (p. 784) which would affect the dopamine-choline biochemical balance, perhaps in favor of the development of TD.

**Mean Daily Dose**

In an effort to avoid intervening interactions between length of antipsychotic administration and cumulative antipsychotic dose, the mean daily dose is a variable that may provide more specific information. Crane (1974) studied the relationship between daily dosages of antipsychotics and the development of TD in samples of patients over 55 and younger than 55. He found that TD prevalence and daily doses over 200 mg. were significantly correlated for patients over 55. A trend was noted for the younger patients with TD prevalence increasing with dosages over 1,000 mg. per day. He concluded that the maximum daily dose of antipsychotics is positively associated with TD. Simpson et al. (1978) examined 23 years of drug histories for a TD group and a matched control group. A significant difference was not found between the two groups on mean daily dose, although the TD group did have a slightly higher mean dose (TD = 298mg/day; No-TD = 289mg/day). Due to these conflicting findings and the need for more information on the role specific drug variables play in the development of TD, this variable merits further investigation. Precise and specific drug data is extremely time-consuming to gather and often unavailable, thus it is understandable that other gross drug variables are studied
more frequently.

**Maximum Antipsychotic Dosage Per Year**

The maximum antipsychotic dosage per year is another measure of the relationship between drug history variables and the development of TD. This is an important variable as the concentration of antipsychotic administration may be more informative than other more general drug variables. Two studies have examined this variable and the outcomes are consistent.

Crane (1974) found a significantly positive association between maximum dose of antipsychotics and TD (partial correlation $r = +.19$). Smith et al. (1978) did not find the total amount of antipsychotic medication a patient had received over many years to be the main variable related to TD severity. However, they did find a significantly positive association between the maximum amount of antipsychotics a patient had received in any year and TD severity (partial correlation $r = +.17$). This latter study only examined the variable's relationship to TD severity; however, the fact that they found the association to be positive and significant, which had not been the case for cumulative antipsychotic dose, indicates that equally close scrutiny should be carried out in any study of the relationship of drug variables to the development of TD. Although these studies were correlational and without matched controls, they do indicate a need to examine this variable more intensely.

**B. Antiparkinson Agents**

Previously antiparkinson agents were tried as a form of
treatment for TD because they worked well in reducing parkinsonism which, like TD, involves the extrapyramidal system. However, it was soon realized that these drugs did not improve TD (Turek et al., 1972) and actually aggravated the syndrome in some cases (Jeste & Wyatt, 1979). In fact, in an investigation of current medications, Bell & Smith (1978) found that patients receiving antiparkinson agents tended to have higher dyskinesia scores. Borison (1979) asserts that antiparkinson agents may promote the development of TD by increasing dopamine receptor hypersensitivity, currently hypothesized to mediate the development of TD. Consequently, more frequent treatment with antiparkinson agents could mediate the development of TD.

Simpson et al. (1978) studied four aspects of antiparkinson treatment history in their TD and No-TD groups matched on age, sex, diagnosis, and length of hospitalization: duration of administration, mean total amount, mean daily dose, and variety of antiparkinson agents. None of the differences found between the two groups were statistically significant. However, the TD subjects did tend to have a higher mean daily dose (TD = 2.8 mg; No-TD = 2.5 mg) and a greater variety of antiparkinson agents prescribed (TD mean = 1.9; No-TD mean = 1.6) than did the No-TD group. Simpson et al. did not cease gathering data upon the emergence of TD, however. Thus antiparkinson drugs used to treat TD may have confounded the data. Also, it is not uncommon for parkinsonism and TD to coexist (Crane, 1972; Fann & Lake, 1974). In such instances antiparkinson agents would have been administered to treat the parkinsonism.
Mallya et al. (1979) conducted the only other study found that used matched TD and No-TD groups matched on age, sex, and diagnosis. They found a statistically significant relationship between antiparkinson agent prescription and TD. The TD subjects had a significantly greater amount of antiparkinsons administered (TD = 4.51 g.; No-TD = 1.65 g.) for a significantly greater length of time (TD = 33.7 mo.; No-TD = 17.9 mo.). However, they only examined the average total amount administered and the average treatment duration of two antiparkinson agents.

Jus et al. (1976) found no differences between the unmatched TD and No-TD groups on history of antiparkinson agents. They caution, however, that they were not able to gather data solely prior to the development of TD as records did not document the onset of the syndrome. In light of the conflicting findings of the two studies using matched control groups and the failure of all three studies to cut-off data collection at the emergence of TD, the relationship between TD and antiparkinson medication history merits further examination.

C. Polypharmacy

In a survey on polypharmacy, Sheppard et al. (1974) concluded that the main cause of using more than one antipsychotic was a patient's responding poorly to his or her antipsychotic regime. The physician then adds a concomitant antipsychotic. Chouinard et al. (1979) found that little therapeutic improvement was a variable
significantly related to the presence of TD. When these two findings are combined, it could be expected that patients with TD will have a greater incidence of polypharmacy than patients not having TD.

Jus et al. (1976) investigated the role polypharmacy may play in the development of TD. They operationalized polypharmacy as instances in which patients "were treated with a simultaneous combination (cocktail) of two or more neuroleptics during at least one month and the monthly amount exceeded 3g of chlorpromazine equivalent" (p. 258). Such operationalization is necessary "because without restrictions to some time and quantity limits, the sporadic administration of only one additional neuroleptic during the whole course of treatment would be already labeled as cocktail and most if not all patients would have been evaluated as treated by cocktails" (Jus et al., 1979, p. 260). They found no significant differences between the unmatched TD and No-TD groups on the number of cocktails received. Unfortunately, drug data after the on-set of TD was included in their analysis. Furthermore, the criteria of 3g of chlorpromazine equivalents per month equals only 100 mg. per day which is much lower than the average amount of chlorpromazine equivalents administered to the majority of patients (Davis & Garver, 1978). If TD subjects do receive higher antipsychotic dosages, which may be administered in the form of polypharmacy—although possibly for shorter periods of time—then this may not be evident when studying such a broadly defined drug factor.

Borison (1979) asserts that combining an antiparkinson agent and an antipsychotic will promote dopamine receptor hypersensitivity.
It may be expected that increased incidence of polypharmacy involving an antipsychotic and an antiparkinson would be found in the drug histories of patients with TD. Jus et al. (1976) found no differences between the unmatched TD and No-TD groups on the mean total amount and mean duration of treatment with antiparkinson agents in addition to other antipsychotic treatment. However, it is unclear if they examined all instances of antiparkinson administration, or only those instances where both antipsychotic and antiparkinson drugs were simultaneously administered. In consideration of Borison's (1979) assertion, the findings reviewed earlier concerning antiparkinson agents in general, and the methodological generosities and uncertainties of Jus et al. (1976), it is necessary to examine further the relationship of antiparkinson and concomitant antipsychotic drug administration to the development of TD.

Nothing about two other categories of polypharmacy, antipsychotic(s) plus lithium and antipsychotic(s) plus tricyclic antidepressants, has been reported in the literature on the relationship of drug history variables and the development of TD. Lithium has been reported, in some cases, to improve TD (Simpson, 1973) and, in other cases, to aggravate TD (Rosenbaum et al., 1977). Tricyclic antidepressants have anticholinergic properties, like antiparkinson agents (Baldessarini, 1977), and are therefore implicated in the development of TD for the same reasons antiparkinson agents are (Borison, 1979). In fact, Rosenbaum et al. (1977) reported cases of TD that developed in patients with drug histories consisting
primarily of antidepressants or antianxiety agents. Fann et al. (1976) also reported the development of TD among some of their subjects as being associated with tricyclic antidepressant usage. These variables, if included in drug history studies, could possibly explain some of the inconsistent findings. They have been overlooked to date, although they are implicated on a neurochemical basis.

Simpson et al. (1978) studied the variable of polypharmacy but its operational definition was not similar to that of Jus et al. (1976). They defined polypharmacy as "two psychotropic drugs administered concurrently" (p. 120). "Psychotropic" refers to any drugs affecting mental activity and they analyzed all instances where neuroleptics, antiparkinson agents, antidepressants, and miscellaneous drugs were administered to the matched TD and No-TD groups. They did examine another type of polypharmacy; namely, the variety of antipsychotics administered to each group. The TD group received a mean of 5.4 different antipsychotics and the No-TD group received a mean of 5.0 different antipsychotics although no statistical test was reported on these differences.

D. Drug-Free Periods

As a preventative measure against TD, drug-free periods lasting from two days to two months have been advocated. These time periods would allow TD being masked by antipsychotics to be detected; they would also cut down on the cumulative doses and length of administration of antipsychotics (Ayd, 1970). Recently, Jeste et al. (1979) found that the best discriminator between TD patients whose
symptoms reversed after three months free of drugs and TD patients whose symptoms persisted was the number of intervals free of antipsychotic drugs. Paradoxically, the persistent group had a greater number of drug-free intervals of at least two months. This variable correctly classified 76% of the cases of dyskinesia into reversible and persistent groups. They only used data prior to the development of TD and set duration criteria of a two month period drug-free. Their finding is very disturbing as it indicated that a preventive measure previously advocated may instead actually be increasing the severity and/or irreversibility of TD.

Simpson et al. (1978) did gather data on the duration of documented time free of medication, but did not test for significant differences between the matched TD and No-TD groups as they used the information to determine polypharmacy duration. Although they did not address the issue of drug-free periods in their study, they did provide the findings in a table. The TD group had a mean of 3.7 years per subject of no medication, out of a mean of 15 years per subject when psychotropic medications could have been administered. The No-TD group had a mean of 2.5 years per subject of no medication, out of a mean of 14.3 years per subject when psychotropic medications could have been administered. This appears to be a sizable difference with the TD group having a greater period of time drug-free. However, data prior to and subsequent to the development of TD was used in this study. Also the drug-free periods referred to times when no psychotropics were administered rather than only time free of antipsychotics.
Given the disturbing findings of Jeste et al. (1979), closer examination of two drug-free variables is needed. Any differences between patients with TD and patients without TD on the number of incidences of drug-free periods--i.e., two months free of antipsychotics--merits additional attention. Also, differences between groups on the number of drug-free days needs further study.

Other Descriptive Characteristics

A. History of Extrapyramidal Symptoms (EPS)

There are conflicting findings concerning the relationship between EPS history and the subsequent development of TD (Sovner & DiMascio, 1978). This lack of consistency results, in part, from the lack of well-developed assessment methods for EPS (Mindham, 1976). In addition, the side effects are often not mentioned or specifically named in patients' records. Despite the conflicting findings, Crane (1972, 1978) has continually found a predisposing relationship. He has had excellent designs, controlling for intervening variables and rigorously assessing EPS, which are often lacking in other studies (McClelland, 1976). Crane, however, did not distinguish among the various types of EPS studying only the relationship between parkinsonism, which is a combination of rigidity, tremor, and akinesia, and the development of TD. Chouinard et al. (1979) are the first researchers to make such a distinction. They found an inverse relationship between parkinsonian symptoms and TD. They then excluded from the total parkinsonian score those for tremor and akathisia, the
hyperkinetic types of EPS, and found that the inverse relationship became more pronounced. Chouinard et al. (1979) postulate that the hyperkinetic types of EPS may be predisposing to the development of TD while the hypokinetic types of EPS may reduce the development of TD. However, their study examined only the current EPS of the subjects. Further exploration of subjects' EPS history is needed in order to test for a possible historical relationship similar to the findings of Chouinard et al. (1979).

B. Psychiatric Behavior Pattern

It is necessary to research both EPS history and psychiatric behavior patterns, rather than solely EPS history, due to the validity problem inherent in trying to investigate the relationship between EPS and the subsequent development of TD. Medical personnel and researchers often have difficulty differentially diagnosing EPS from psychiatric symptomology. Akathisia has been confused with psychotic agitation (Davis & Cole, 1975), tremor with anxiety (Donlon & Stenson, 1976), rigidity with anxiety accompanied by tension (Donlon & Stenson, 1976), dystonic reactions with hysteria (Lesser & Fahn, 1978), and akinesia with depression and apathy (Rifkin et al., 1975). The lack of a consistent relationship between EPS and TD may thus result from confusion between psychiatric symptoms and neurological side effects. To avoid this confusion the relationship between psychiatric behavior pattern and the development of TD should also be examined.
C. Initial Psychiatric Behavior Pattern

Friedhoff et al. (1960) determined that antipsychotics reduced motor activity in patients whose activity was previously quicker than average, but sped up patients whose motor activity had been retarded. Van Putten (1978) found that a hypokinetic type of EPS, akinesia, occurred more often in patients exhibiting high levels of excitation in their initial psychiatric behavior. These studies indicate that patients' initial psychiatric behavior patterns could possibly suggest the type of EPS, if any, they may develop in response to treatment with antipsychotics. Furthermore, in light of the findings of Crane (1972, 1978) and Chouinard et al. (1979), knowing the type of EPS a patient may be susceptible to may also indicate his or her risk of developing TD.

D. Miscellaneous Characteristics

Crane (1978) asserts that no data are available on genetic variables which could account for differences in individual susceptibility to TD. Brandon et al. (1971) reported an unexpected finding they felt indicated a role for genetics in the development of TD. In their study of dyskinesia among inpatients, they found a marked excess of blue-eyed males with dyskinesia that was not found among the female subjects. Gardos et al. (1978), however, were unable to replicate this finding and found no support for an association between eye color and dyskinesia. Furthermore, the finding of Brandon et al. peripherally addresses the question of what relationship, if any, exists between race and the incidence of TD as blue-eyed males would be caucasian.
It has been known for some time that edentulous elderly patients may appear to have TD in the buccal-lingual-masticatory triad due to the gumming movements this state often precipitates. Similarly, patients with ill-fitting dentures may move their mouth, tongue, and jaws in a manner found in TD patients. Consequently, a physician is warned to always check on the dental status of a patient when considering a diagnosis of TD (Sutcher et al., 1971). Occasionally, dental state has been found to be associated with the presence of TD. Asnis et al. (1977) found a significant association between the presence of dentures and dyskinesia in their TD group. Brandon et al. (1971) reported that edentulous patients were a high risk group for facial dyskinesia in their study. Consequently, the TD group in this study may potentially have more instances of missing teeth, with or without dentures.

**Summary**

Research on the relationship of various factors to the development of TD is increasing. Many of the findings are unclear and/or inconsistent. The primary reasons for this are methodological flaws such as the lack of matched control groups, failure to cut off gathering data with the emergence of TD, and the lack of clearly delineated criteria conducive to replication. Historical factors also confound results of studies investigating similar variables at different points in time since the treatment of TD has changed several times over the past two decades. Record-keeping procedures have also changed, thus making it possible to investigate variables on which
little information was formerly available. This study investigated the relationships discussed in the literature review while improving the major design flaws indicated.
III. METHODOLOGY

Population and Selection of the Samples

In June, 1979 the medical staff at Eastern State Hospital were asked to identify all patients they believed had tardive dyskinesia (TD). The total number of identified patients was 51. This original number was reduced, however, since several patients died or were discharged, resulting in a sample size of 47. Each patient was matched on age, sex, and diagnosis with another patient chosen from the hospital census (see Appendix B for matching procedure). A psychiatrist at Eastern State Hospital, blind to the group membership of the subjects, screened 37 patients from the TD group and 28 of the controls for the presence or absence of TD. The presence of TD was diagnosed in 17 of the screened TD subjects; the absence of TD was confirmed in 15 of the matched controls screened. The remaining controls were diagnosed as having TD. To increase the TD sample size, 9 of the controls diagnosed as having at least moderately severe TD were reassigned to the TD group. Of the TD subjects diagnosed as free of TD, 11 were reassigned to the control group on the basis of appropriate control variables and clear reasons for the staff misidentifying them as having TD. For instance, a patient identified by the staff as having TD was diagnosed by the psychiatrist as having abnormal movements secondary to a stroke. The TD and control groups each had a final sample size of 26.
Matching the groups on age, sex, and diagnosis was done as these variables are "the most likely sources of internal invalidity due to selection" (Tuckman, 1978, p. 105). The initial prevalence studies consistently found TD to occur more frequently among elderly, female, chronic schizophrenic inpatients (Crane, 1978). As TD became more clearly defined, assessment procedures more sophisticated, and samples larger, the findings became more discriminant. The 2:1 female to male ratio currently "appears to be true only for the more severe forms of tardive dyskinesia" (Smith et al., 1979, p. 921), which is a finding also supported by Jus et al. (1976). This ratio is also most evident in groups aged 59 and over (Smith et al., 1978; Bell & Smith, 1978). Tardive dyskinesia continues to be found more frequently among elderly subjects (Bell & Smith, 1978; Chouinard et al., 1979; Jus et al., 1976). The TD group identified at Eastern State Hospital was composed of severe TD cases, a 3:1 female to male ratio, and had an average age of about 70. Matching on age and sex thus assures that the No-TD subjects have the same risk factors etiologically as the TD subjects, yet had not developed TD. The No-TD subjects were also matched on the TD subjects' diagnosis due to findings indicating a relationship between organicity and TD (Brandon et al., 1971; Edwards, 1970). Diagnosis was also chosen as a control variable due to its implications concerning psychotropic treatment--i.e., manic-depressives receive primarily lithium.

Prior to the psychiatrist's screening, the samples were matched on sex and diagnosis; matching on age was within three years
and achieved according to year of birth. Following the psychiatrist's diagnoses, subjects were reassigned so that each was matched on sex and on the broad diagnostic categories of organic brain syndrome, schizophrenia, and other psychoses. All pairs were matched within eleven years on age. This was deemed acceptable as the rationale for matching on age was based on the consistent finding of a relationship between age over 55 and the occurrence of TD (Chouinard et al., 1979). It is most important, therefore, that TD subjects 55 years of age and older be matched with control subjects of the same age bracket. All but 4 subjects in this study were over 55 years of age; the other 4 were matched exactly on age. The control variables are depicted in Table 1.

Table 1
Control Variables of Samples

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Procedures

Under Chapter 13, Human Research, of the Code of Virginia, patient permission is not necessary as this study is considered epidemiological and does not involve an experimental treatment. All data collected was kept confidential as code numbers were used. Data was gathered from the hospital records and ward charts of all patients included in the study. The control variables of birth date, sex, and diagnosis were first gathered for the TD subjects to allow for subsequent matches to be found.

The date of the first TD symptom or diagnosis mentioned in the records was obtained so that data collection would be limited to the time preceding TD development. All TD subjects' cut-off dates were applied to their matched controls' data as well. This procedure prevented historical differences from affecting the data. For instance, if a TD subject's cut-off date was 1976 and the matched control's data had been collected through December 1979, the latter could have had more EPS incidences only because problem-oriented record-keeping procedures were introduced in the mid-1970s. Cut-off dates were determined for all but 5 of the TD subjects. For these five, and their matched controls, data was collected through December, 1979.

Data on the behavioral variables of initial and subsequent psychiatric behavior pattern was collected by assistants blind to group membership and hypotheses in order to guard against experimenter bias. Drug history data was collected starting in 1953, the year antipsychotics were first widely available. As recommended by Smith
et al. (1978), discrepancies between physicians' medication orders and nurses' records were resolved in favor of the nurses' records as they reflected the medications given. Data after the first mention of a TD diagnosis or one of the TD symptoms (Appendix C) was ignored as it is irrelevant to the descriptive characteristics prior to the development of TD.

"History of extrapyramidal side effects (EPS)" refers to recorded behavior treated with antiparkinson agents. A pre-study check of the hospital records indicated that extrapyramidal symptoms are not so-named—i.e., they are not recorded by form such as akathisia. The medical staff record daily behavior with problem numbers assigned and physicians then code prescriptions to these numbers. For example, if a behavior description of "restless, paces constantly" is coded as problem #3 and the physician prescribes antiparkinson medication coded to problem #3, then the behavior was recorded under "History of EPS." Symptom duration was determined by the length of antiparkinson medication administration. Prophylactic prescription of antiparkinson agents involves prescription prior to the emergence of extrapyramidal side effects (EPS) in an effort to prevent their occurrence. Consequently, such administrations of antiparkinson agents were not considered indicative of extrapyramidal side effects.

Instrumentation

The data gathered for all of the subjects are depicted on the Patient Information Sheet in Appendix D. The codes for the "General Information, Section I," are given in Appendix E. For
"Psychiatric Diagnosis" the current diagnosis of the subject was recorded in terms of DSM-II coding. The "First TD Symptom" is the first recorded symptom of TD found which corresponds with those listed in Appendix C. This was deemed necessary as initial symptoms are often recorded, but the diagnosis is withheld until the clinical picture becomes more evident. The symptoms listed in Appendix C were derived from the literature as well as an examination of about 50 hospital records. For "Dental Status" if code 2 is used (missing teeth), the number missing is recorded in parentheses. Fluctuating data was determined as of December 31, 1979--i.e., age, diagnosis, dental status.

The behavioral descriptions of EPS (Appendix F) were derived from the work of Donlon & Stenson (1976) and Sovner & DiMascio (1978). There are two hyperkinetic forms--akathisia and tremor--and three hypokinetic forms--akinesia, rigidity, and dystonic reactions. All behavior treated with antiparkinson agents was classified into one of five EPS forms, and coded in one of three types, hypokinetic, hyperkinetic, or mixed. The form of EPS was determined by reviewing the behavioral notations in the records for periods of time immediately preceding and immediately following the administration of antiparkinson agents. Initial administration and discontinuation of the antiparkinson agents determined on-set and off-set dates of the EPS occurrences. The descriptions and codes for the EPS histories are provided in Appendix F.

The "Psychiatric Behavior Pattern" was classified as hypokinetic, hyperkinetic, mixed, or none based on descriptors derived
from the work of Donlon & Stenson (1976) and Sovner and DiMascio (1978). In cases of inadequate information an "unknown" classification was used. Originally, an instrument measuring factors of psychopathology which included excitement and withdrawal scales was considered (Lorr et al., 1963). This instrument involved quite a bit of adaptation as it was designed to be used during an interview. After an extensive search an instrument specifically designed to assess psychiatric variables on the basis of sources such as nurses' notes was found (Spitzer et al., 1967). Once reviewed, however, it was realized that this instrument was designed to measure factors rather than behaviors, involved in psychopathology and therefore did not suit the needs of this study. Since differential diagnosis between psychopathology and extrapyramidal side effects is often difficult (Davis & Cole, 1975; Donlon & Stenson, 1976; Lesser & Fahn, 1978; Rifkin et al., 1975), it was deemed necessary to rate behavioral histories as hyperkinetic, hypokinetic, mixed, or none in case some instances of EPS were overlooked or misdiagnosed as psychopathology. Consequently, using an instrument designed to assess psychopathology was not found to be suitable. It was decided that rating the behavioral histories in terms of EPS descriptors would more directly satisfy the purpose of examining the behavioral variables. The descriptors and rating scale are presented in Appendix G.

The behavioral histories were blindly rated by assistants. Data collection began either from January 1953, when antipsychotics became widely available, or subsequent to the admission notations for
patients admitted after 1953. Data gathering for the control and TD subject pairs ended with the TD subject's first recorded TD symptom or diagnosis. For each six month period, beginning with January 1953 or subsequent to admission notations, the rater read the ward notes and semi-annual appraisal summaries in order to rate the patients' behavior. The five categories are defined on the Rating Form (Appendix G). The six month period was chosen as a pre-study check indicated that it was long enough to encompass the two sources of information and, thus, provides adequate information for a rating, yet was short enough to ensure sensitivity to changes in behavior patterns. An interjudge agreement ratio of 76% was achieved between the raters and is deemed acceptable as only one direct contradiction of ratings was found. Appendix H depicts training procedures and inter-judge agreement ratio findings.

Initial psychiatric behavior pattern refers to all notes made upon the subjects' first admission to a psychiatric facility. These notes may cover two to thirty days. The same rating procedure described above was used for this variable.

"Drug History" data was collected on four main variables; anti-psychotic medications, antiparkinson agents, polypharmacy, and drug-free periods.

Appendix A depicts the various names of medications, different medication abbreviations found in the hospital records, and chlorpromazine equivalents for the antipsychotics. These equivalents are primarily from the work of Davis and Garver (1978) and are necessary
for conversion of the various antipsychotics into equivalent dosages so comparisons can be made. Antiparkinson agents were converted into benzotropine mesylate equivalents obtained from Simpson et al. (1978) for the same purpose. All of the patients' dosages and lengths of administrations within these categories as well as all periods of time the patients did not receive medications, were recorded on the form depicted in Appendix I. Computer calculations then determined amounts for each of the following variables: cumulative dose of antipsychotics, cumulative length of administration of antipsychotics, average daily dose of antipsychotics, maximum antipsychotic dosage per year, cumulative dose of antiparkinson agents, cumulative length of administration of antiparkinson agents, average daily dose of antiparkinson agents, number of antiparkinson agents administered, number of incidences of polypharmacy, number of incidences per category of polypharmacy, number of antipsychotics administered, number of drug-free periods, and number of drug-free days.

The four types of polypharmacy investigated includes concurrent administration of an antipsychotic plus either another antipsychotic, an antidepressant, lithium, or an antiparkinson agent (see Appendix A). The duration criteria for the first three types was 2 months to ensure that actual polypharmacy was occurring rather than only a drug change-over. Duration criteria for an antipsychotic plus an antiparkinson agent was set at 3 months as 2 months is considered rational treatment while treatment beyond 3 months is considered inappropriate (Baldessarini, 1977). The four types of polypharmacy were computed using two
different chlorpromazine equivalence criteria: a lenient daily
criterion of any amount of antipsychotic in combination with another
drug and a daily criterion of at least 1,100 mg. of antipsychotic
in combination with another drug. Such a broad coverage was necessi-
tated by other investigators defining polypharmacy in a variety of
ways (Jus et al., 1976; Simpson et al., 1978). Another kind of
polypharmacy, the number of different antipsychotics and antiparkinson
agents administered to each subject, was also examined. A drug-free
period was defined as a 2 month or longer period of time during which
the subject received no antipsychotic medications. This criteria is
based on the Jeste et al. (1979) finding that antipsychotic-free
intervals of at least 2 months was the best discriminator between
persistent and reversible TD groups.

The psychiatrist examining the patients used a scale developed
by Van Putten (1974) which is intended for use in assessing the extent
of extrapyramidal involvement in response to pharmacotherapy. It was
adapted for use in this study to rate the extent of the presence or
absence of TD (Appendix J). Van Putten (1974) does not report relia-
bility ratings for assessment devices on disorders of the extrapyramidal
tract, including EPS and TD, as the syndromes fluctuate over time and
in response to medications (Gardos et al., 1977). This scale allowed
the psychiatrist's clinical judgment to be scaled. A rating of 1 or
above on TD was the criteria for the TD subjects' inclusion; the no-TD
subjects must have received a rating of 0 to remain in the study.
Design

This design is ex post facto as the phenomena to be examined have already occurred naturalistically--i.e., there is no manipulation of variables. This is a descriptive, retrospective study wherein the existence of relationships among variables was explored. Such a design is mandated by humanitarian reasons as the alternative method, a prospective study, would encompass observation of subjects until development of TD occurs with no attempt being made to prevent the occurrence of this debilitating syndrome. Such an approach would be highly unethical.

The criterion-group approach is the type of ex post facto design proposed. This involves "contrasting the characteristics of a state [TD] with the characteristics of its opposite state [No-TD]" in an attempt to "determine what characteristics are associated with the criterion and have presumably preceded the criterion" (Tuckman, 1972, pp. 149, 151). The criterion for group membership is the presence or absence of TD which is therefore the independent variable. The occurrence of the various descriptive characteristics will depend upon the subjects' group membership and are, therefore, the dependent variables.

This study has a methodological feature no other research on the role drug variables play in the development of TD has had: the cutting-off of drug data with the first recorded TD symptom or diagnosis mention. This was possible since the records at ESH are behavior-oriented, thus all entries are symptom-descriptive of the
patients' behaviors. Also, the records include a "Problem List" where side effects of drug regimes are often noted. Hopefully, this added methodological feature avoided obscuring differences in dosage ingestions between the two groups that may have existed prior to the development of TD. Also, unlike others (Asnis et al., 1977; Chouinard et al., 1976), entire drug histories beginning January 1953 were taken including any and all antipsychotics and antiparkinson agents administered. The length of antipsychotic administration does not include any days the subjects were off medications, which has not been taken into account by other investigators. These aspects of this study should have guarded against the confounding possibility of TD subjects having lower cumulative antipsychotic dosages or higher cumulative antiparkinson agent dosages due to antipsychotic dosage reductions or antiparkinson agent administration occurring in response to the development of TD.

Crane (1972, 1978) is the only investigator to examine the EPS histories of TD subjects. However, he did not distinguish between the 5 forms or 3 types of EPS as this study has. Chouinard et al. (1979) did make such distinctions yet only investigated concurrent EPS in their TD subjects. The current study makes the two distinctions and examines histories of, as well as concurrent, EPS. Furthermore, the safeguard taken against EPS being misdiagnosed or overlooked by investigating psychiatric behavior patterns, as well as EPS patterns has never been done in previous investigations. The conflicting findings reported in previous research relating various drug and
diagnostic variables to TD occurrences may have come, in part, from their lack of these procedures.

**Statistical Analysis**

The hypotheses about antipsychotic and antiparkinson drug dosages and administration duration (#1 - #7), polypharmacy (#8 - #11), drug-free periods (#12 - #13), EPS history (#17 - #18), and psychiatric behavior pattern (#20), involve interval measures of the dependent variables and nominal independent variables in a comparison of the means of each subject in a pair to determine if any mean differences found over all the pairs are statistically significant. Consequently, the t-test for dependent or paired samples was used to calculate the probability associated with the hypotheses (all are listed below).

The pair-wise matching carried out between the TD sample and control sample was done to control for extraneous influences in the variables being measured. Such experimental control reduces the effect of subject-to-subject variability and, usually, the variance and standard error of difference as well. Consequently, the sampling error is lowered, which allows more degrees of freedom in the answer (n-1) than an independent t-test (n-2) allows. Although pairing for t-tests most often occurs with pre- and post-test designs, it is also appropriate for this study's design wherein the pairs are correlated on the control variables and are consequently dependent rather than independent (Hays, 1963). A two-tailed test of statistical significance was applied as differences could occur in either direction.
A series of t-tests were chosen over an analysis of variance due to group membership being the only independent variable. Jeste et al. (1979) utilized discriminant analysis to determine which of the drug variables best distinguished between their two groups. This statistical technique is inappropriate for this study as there are too many variables involved according to the 1:10 variables-to-subjects guideline for use of discriminant analysis. Perhaps at a later date Pearson's correlation can be utilized to determine redundant variables and thus distinguish which five or six variables would be most informative in a discriminant analysis.

For the remaining hypotheses, chi-square was used to determine if systematic relationships exist among the variables. This statistic was chosen as it is used "with data in the form of frequencies" (Guilford, 1965, p. 227) "to determine whether or not the variables are statistically independent" (Nie et al., 1975, p. 218). The samples being compared can thus be judged as being essentially the same or different.

**Specific Hypotheses**

In an effort to answer the question "What are the descriptive characteristics of patients with tardive dyskinesia that distinguish them from patients without tardive dyskinesia (TD)" the following hypotheses were tested.
Drug Histories

A. Antipsychotics

1. $H_0$: No difference will be found in mean cumulative dose for antipsychotic medications between TD and No-TD groups.

2. $H_0$: No difference will be found in the mean cumulative length of antipsychotic medication administration between the TD and No-TD groups.

3. $H_0$: No difference will be found in mean daily dose of antipsychotic medications between the TD and No-TD groups.

4. $H_0$: No difference will be found in the maximum antipsychotic daily dosage for any year between the TD and No-TD groups.

B. Antiparkinson Agents

5. $H_0$: No difference will be found in the mean cumulative dose of antiparkinson agents between the TD and No-TD groups.

6. $H_0$: No difference will be found in the mean cumulative length of antiparkinson agent administration between the TD and No-TD groups.

7. $H_0$: No difference will be found in the mean daily dose of antiparkinson agents between the TD and No-TD groups.

C. Polypharmacy

8. $H_0$: No difference will be found in the mean number of total incidences of polypharmacy at the CPZE criterion dosage levels of 0 or 100 mg., between the TD and No-TD groups.

9. $H_0$: No difference will be found in the mean number of incidences in any of the four categories of polypharmacy--antipsychotic
plus an antipsychotic, antipsychotic plus an antiparkinson agent, antipsychotic plus an antidepressant, antipsychotic plus lithium—at the CPZE criterion dosage levels of 0 or 100 mg. between the TD and No-TD groups.

10. \( H_0: \) No difference will be found in the mean number of antipsychotics administered between the TD and No-TD groups.

11. \( H_0: \) No difference will be found in the mean number of antiparkinson agents administered between the TD and No-TD groups.

D. Drug-Free Periods

12. \( H_0: \) No difference will be found in the mean number of incidences of drug-free periods, lasting at least 2 months, between the TD and No-TD groups.

13. \( H_0: \) No difference will be found in the mean number of drug-free days between the TD and No-TD groups.

Other Descriptive Characteristics

A. Extrapyramidal Symptom(s) History

14. \( H_0: \) No difference will be found in the number of subjects experiencing extrapyramidal symptoms between the TD and No-TD groups.

15. \( H_0: \) No difference will be found in the number of extrapyramidal symptom incidences between the TD and No-TD groups.

16. \( H_0: \) No difference will be found in the number of extrapyramidal symptom incidences rated as hypokinetic, hyperkinetic, mixed, and more between the TD and No-TD groups.
17. $H_0$: No difference will be found in the mean number of days extrapyramidal symptoms rated as hypokinetic, hyperkinetic, or mixed occurred between the TD and No-TD groups.

18. $H_0$: No difference will be found in the mean cumulative days extrapyramidal symptoms occurred between the TD and No-TD groups.

B. Initial and Psychiatric Behavior Patterns

19. $H_0$: No difference will be found in the number of psychiatric behavior patterns rated hypokinetic, hyperkinetic, mixed, or more between the TD and No-TD groups.

20. If subsequent to having a hypokinetic initial psychiatric behavior pattern a patient has a hyperkinetic history or extrapyramidal symptoms, then he/she will be more likely to have TD than a patient who subsequent to having a hyperkinetic initial psychiatric behavior pattern has a hypokinetic history of extrapyramidal symptoms.

21. If subsequent to having a hypokinetic initial psychiatric behavior pattern a patient has a hyperkinetic psychiatric behavior pattern, then he/she will be more likely to have TD than a patient who subsequent to having a hyperkinetic initial psychiatric behavior pattern has a hypokinetic psychiatric behavior pattern.
C. Miscellaneous Characteristics

22. $H_0$: No difference will be found in eye color between the TD and No-TD groups.

23. $H_0$: No difference will be found in dental status between the TD and No-TD groups.

24. $H_0$: No difference will be found in race between the TD and No-TD groups.

Summary of Methodology

Two samples, each with N=26, were selected from current inpatients at Eastern State Hospital. The TD group included patients diagnosed by a psychiatrist as having TD. The No-TD group were randomly-chosen patients, based on their matching the TD subjects on age, sex, and diagnosis, and examined by the psychiatrist to ensure the absence of TD. The psychiatrist was blind to staff diagnosis or referral and used a rating scale adapted from Van Putten (1974) which is depicted in Appendix J.

The following data was gathered from the hospital records and ward charts of all subjects: history of antipsychotic medications, history of antiparkinson agents, history of polypharmacy, history of drug-free periods, history of extrapyramidal (EPS) symptoms, initial and subsequent psychiatric behavior patterns, race, eye color, dental status, diagnosis, birth date, sex, and date of first TD symptom or diagnosis mention. The Data Gathering Instrument and its codes are depicted in Appendices D - G. All subjects' names and data were kept confidential.
An Initial and Psychiatric Behavior Patterns Rating Form, using the extrapyramidal descriptors of Donlon & Stenson (1976) and Sovner & DiMascio (1978), was designed to rate the behavioral variables of "Initial psychiatric behavior pattern" and "Psychiatric behavior pattern." Two assistants, blind to the study's hypotheses and the group membership of the subjects, rated the behavioral variables. The interjudge agreement ratio of 76% (see Appendix H) was deemed acceptable. The extrapyramidal descriptors of Donlon & Stenson (1976) and Sovner & DiMascio (1978) were also used to determine the type and form of EPS incidences (Appendix F).

This study is an ex post facto design as the phenomena studied have already occurred naturally, thus the independent variable was not controlled or manipulated. The criterion-group approach is the type of design. The independent variable is the presence or absence of TD and the dependent variables are the descriptive characteristics being investigated. Descriptive characteristics of a TD group were contrasted with those of a No-TD group in an effort to determine which characteristics presumably preceded the criterion.

The hypotheses about antipsychotic and antiparkinson drug dosages and administration duration (#1 - #7), polypharmacy (#8 - #11), drug-free periods (#12 - #13), EPS history (#17 - #18), and psychiatric behavior pattern (#20) involve interval measures of the dependent variables and nominal independent variables. Consequently, t-test for dependent, or paired, samples was used to determine if any mean differences found, over all the pairs, were statistically significant.
Chi-square was used to determine the statistical significance of any systematic relationships among the variables tested in the remaining hypotheses.
IV. RESULTS

In this chapter, the results of the present study are listed by hypotheses.

Drug Histories

A. Antipsychotics

Hypothesis 1. No difference will be found in mean cumulative dose of antipsychotic medications between the TD and No-TD groups.

The TD group's mean cumulative dose of antipsychotic medications was 1348.27 grams of chlorpromazine equivalents; the No-TD group's mean cumulative dose of antipsychotic medications was 2565.68 grams of chlorpromazine equivalents (see Table 2). The t value was -2.12 and significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis is rejected as the No-TD group had a significantly greater mean cumulative dose of antipsychotic medications than the TD group.

Hypothesis 2. No difference will be found in the mean cumulative length of antipsychotic medication administration between the TD and No-TD groups.

The TD group's mean cumulative length of antipsychotic medication administration was 2890.19 days (7.92 years); the No-TD group's mean cumulative length of antipsychotic medication administration was 3200.23 days (8.77 years) (see Table 2). The t value
Table 2
Means and t Values of Antipsychotic (AP)
and Antiparkinson (ap) Medication Variables
(dependent t with 25 DF)

<table>
<thead>
<tr>
<th>DRUG VARIABLE</th>
<th>MEAN</th>
<th>NO-TD</th>
<th>t</th>
<th>p</th>
<th>Reject</th>
<th>Null?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cum. dose of APs (in CPZE)</td>
<td>1348.27 g</td>
<td>2565.68 g</td>
<td>-2.12</td>
<td>.044</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mean cum. length of AP administra-tion</td>
<td>2890.19 days</td>
<td>3200.23 days</td>
<td>-.53</td>
<td>.597</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mean daily dose of APs (in CPZE)</td>
<td>323.58 mg</td>
<td>493.81 mg</td>
<td>-2.12</td>
<td>.044</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mean max. AP daily dose for any year (in CPZE)</td>
<td>1514.18 mg</td>
<td>2306.17 mg</td>
<td>-1.54</td>
<td>.14</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mean cum. dose of aps (in BME)</td>
<td>4g</td>
<td>10.23 g</td>
<td>-1.90</td>
<td>.07</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mean cum. length of ap administration</td>
<td>393.96 days</td>
<td>950.73 days</td>
<td>-2.12</td>
<td>.04</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mean daily dose of aps</td>
<td>7.42 mg</td>
<td>12.79 mg</td>
<td>-1.71</td>
<td>.10</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Legend:  
Cum    = cumulative  
Max    = maximum  
CPZE   = Chlorpromazine equivalents  
BME    = Benztropine mesylate equivalents
was -.53 and not significant at the .05 level for two-tailed tests (with 25 degrees of freedom). The null hypothesis is accepted.

Hypothesis 3. No difference will be found in mean daily dose of antipsychotic medications between the TD and No-TD groups.

The TD group's mean daily dose of antipsychotic medications was 323.58 mg of chlorpromazine equivalents; the No-TD group's mean daily dose of antipsychotic medications was 493.81 mg of chlorpromazine equivalents (see Table 2). The t value was -2.20 and significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis is rejected as the No-TD group had a significantly greater mean daily dose of antipsychotic medications than the TD group.

Hypothesis 4. No difference will be found in the maximum antipsychotic daily dosage for any year between the TD and No-TD groups.

The TD group's mean maximum antipsychotic daily dosage per year was 1514.18 mg of chlorpromazine equivalents; the No-TD group's mean maximum antipsychotic daily dosage per year was 2306.17 mg of chlorpromazine equivalents (see Table 2). The t value was -1.54 and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis can not be rejected.

B. Antiparkinson Agents

Hypothesis 5. No difference will be found in the mean cumulative dose of antiparkinson agents between the TD and No-TD groups.

The TD group's mean cumulative dose of antiparkinson agents was 4.00 grams of benztropine mesylate equivalents; the No-TD group's
mean cumulative dose of antiparkinson agents was 10.23 grams of benztropine mesylate equivalents (see Table 2). The t value was -1.90 and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis can't be rejected.

**Hypothesis 6.** No difference will be found in the mean cumulative length of antiparkinson agent administration between the TD and No-TD groups.

The TD group's mean cumulative length of antiparkinson agent administration was 393.96 days (1.08 years); the No-TD group's mean cumulative length of antiparkinson agent administration was 950.73 days (2.61 years) (see Table 2). The t value was -2.12 and significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis is rejected as the No-TD group had a significantly greater mean cumulative length of antiparkinson agent administration than the TD group.

**Hypothesis 7.** No difference will be found in the mean daily dose of antiparkinson agents between the TD and No-TD groups.

The TD group's mean daily dose of antiparkinson agents was 7.42 mg of benztropine mesylate equivalents; the No-TD group's mean daily dose of antiparkinson agents was 12.79 mg of benztropine mesylate equivalents (see Table 2). The t value was -1.71 and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis can not be rejected.
C. Polypharmacy

Hypothesis 8. No difference will be found in the mean number of total incidences of polypharmacy, at either of the two chlorpromazine equivalents criterion dosage levels (0 & 100), between the TD and No-TD groups.

The TD group's mean number of total incidences of polypharmacy was 1.77 at the 0 mg chlorpromazine equivalents (CPZE) criterion level and 1.77 at the 100 mg CPZE level. The No-TD group's mean number of total incidences of polypharmacy was 3.0 at the 0 mg CPZE criterion dosage level and 2.77 at the 100 mg CPZE criterion level (see Table 3). The t values were -1.72 at 0 mg and -1.42 at 100 mg and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis can not be rejected.

Hypothesis 9. No difference will be found in the mean number of incidences in any of the four categories of polypharmacy--antipsychotic plus an antipsychotic, antipsychotic plus an antiparkinson agent, antipsychotic plus an antidepressant, and antipsychotic plus lithium--at the CPZE criterion dosage levels of 0 or 100 mg, between the TD and No-TD groups.

As depicted in Table 3, no significant differences were found in the mean number of incidences in any of the four categories of polypharmacy, at the CPZE criterion dosage levels of 0 or 100 mg, between the TD and No-TD groups. The null hypothesis can not be rejected.

Hypothesis 10. No difference will be found in the mean number of antiparkinson agents administered between the TD and No-TD groups.
Table 3

Means and t Values of Polypharmacy Incidences
(dependent t with 25 DF)

<table>
<thead>
<tr>
<th>DOSAGE LEVEL OF CPZE</th>
<th>TYPE OF POLYPHARMACY</th>
<th>MEAN</th>
<th>TD</th>
<th>No-TD</th>
<th>t</th>
<th>p</th>
<th>Reject Null?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>AP/AP</td>
<td>1.38</td>
<td>2.30</td>
<td>-1.62</td>
<td>.12</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>AP/ap</td>
<td>.38</td>
<td>.61</td>
<td>-.97</td>
<td>.34</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>AP/ad</td>
<td>.0</td>
<td>.08</td>
<td>-1.44</td>
<td>.16</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>AP/L</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Total</td>
<td>1.77</td>
<td>3.0</td>
<td>-1.72</td>
<td>.09</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>AP/AP</td>
<td>1.38</td>
<td>2.19</td>
<td>-1.43</td>
<td>.16</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>AP/ap</td>
<td>.38</td>
<td>.54</td>
<td>-.66</td>
<td>.52</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>AP/ad</td>
<td>.0</td>
<td>.03</td>
<td>-1.00</td>
<td>.33</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>AP/L</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Total</td>
<td>1.77</td>
<td>2.77</td>
<td>-1.42</td>
<td>.17</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Legend: AP = antipsychotic
ap = antiparkinson agent
ad = antidepressant
L = lithium
The TD group received a mean of 1.08 (SD=.80) different antiparkinson agents. The No-TD group received a mean of 1.81 (SD=1.17) different antiparkinson agents (see Table 4). The t value was -2.56 and significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis is rejected.

Hypothesis 11. No difference will be found in the mean number of antipsychotics administered between the TD and No-TD groups.

The TD group received a mean of 4.23 different antipsychotics. The No-TD group received a mean of 5.65 different antipsychotics. The t value was -1.67 and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom) (see Table 4). The null hypothesis can not be rejected.

D. Drug-Free Variables

Hypothesis 12. No difference will be found in the mean number of incidences of drug-free periods, lasting at least two months, between the TD and No-TD groups.

Both the TD and the No-TD groups had a mean of 3.04 drug-free periods lasting at least two months. The t value was .00 and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom) (see Table 5). The null hypothesis can not be rejected.

Hypothesis 13. No difference will be found in the mean number of drug-free days between the TD and No-TD groups.

The TD group's mean number of drug-free days was 1780.42 days (4.88 years); the No-TD group's mean number of drug-free days was 1855.42 days (5.08 years) (see Table 5). The t value was -.17 and
Table 4
Means and t Values of Number of Antipsychotic (AP) and Antiparkinson (ap) Medications Administered (dependent t with 25 DF)

<table>
<thead>
<tr>
<th>MEAN (SD)</th>
<th>TD</th>
<th>No-TD</th>
<th>t</th>
<th>p</th>
<th>Reject Null?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of APs administered</td>
<td>4.23</td>
<td>5.65</td>
<td>-1.67</td>
<td>.11</td>
<td>No</td>
</tr>
<tr>
<td>Number of aps administered</td>
<td>1.08</td>
<td>1.81 (.80)</td>
<td>-2.56</td>
<td>.02</td>
<td>Yes</td>
</tr>
</tbody>
</table>
not significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis is accepted.

**Other Descriptive Characteristics**

**A. History of Extrapyramidal Symptoms**

**Hypothesis 14.** No difference will be found in the number of subjects experiencing extrapyramidal symptoms between the TD and No-TD groups.

In the TD group, 14 subjects had a history of extrapyramidal symptoms as compared to 18 subjects in the No-TD group (see Table 6). The results of the $X^2$ test were not significant ($X^2 = 1.3$, df = 1, $p = NS$), thus the null hypothesis cannot be rejected.

**Hypothesis 15.** No difference will be found in the number of extrapyramidal symptom incidences between the TD and No-TD groups.

There were 23 incidences of extrapyramidal symptoms in the TD group as compared to 46 incidences of extrapyramidal symptoms in the No-TD group (see Table 7). The results of the $X^2$ test were significant ($X^2 = 4.62$, df = 1, $p < .05$) indicating that a greater number of extrapyramidal symptom incidences were found in the No-TD group. The null hypothesis is rejected.

**Hypothesis 16.** No difference will be found in the number of extrapyramidal symptom incidences rated as hypokinetic, hyperkinetic, or mixed between the TD and No-TD groups.

Of the 23 extrapyramidal symptom incidences found in the TD group, 8 were rated as hypokinetic, 11 were rated as hyperkinetic, and
Table 6
Summary of Descriptive Characteristics Results

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TD</th>
<th>No-TD</th>
<th>ANALYSIS</th>
<th>REJECT NULL?</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Ss developing EPS</td>
<td>14</td>
<td>18</td>
<td>$X^2=1.3$, df=1, p=NS</td>
<td>No</td>
</tr>
<tr>
<td># of EPS incidences</td>
<td>23</td>
<td>46</td>
<td>$X^2=4.62$, df=1, p &lt; .05</td>
<td>Yes</td>
</tr>
<tr>
<td># of EPS incidences rated:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypo</td>
<td>8 (19.92)</td>
<td>19 (57.88)</td>
<td>$t=-1.79$; TD, SD=52; TD+SD=117</td>
<td>No</td>
</tr>
<tr>
<td>hyper</td>
<td>11 (88)</td>
<td>20 (181.92)</td>
<td>$t=-1.05$; TD, SD=222; TD, SD=395</td>
<td>No</td>
</tr>
<tr>
<td>mixed</td>
<td>4 (8.69)</td>
<td>7 (25.50)</td>
<td>$t=-1.07$; TD, SD=35; TD, SD=70</td>
<td>No</td>
</tr>
<tr>
<td>(w/mean # days)</td>
<td></td>
<td></td>
<td>(df=25, p=NS)</td>
<td></td>
</tr>
<tr>
<td>Mean cum. days EPS occurred</td>
<td>116.62</td>
<td>265.31</td>
<td>$t=-1.52$, df=25, p=NS</td>
<td>No</td>
</tr>
<tr>
<td># of PBPs rated:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypo</td>
<td>60</td>
<td>54</td>
<td>$X^2=1.97$, df=3, p=NS</td>
<td>No</td>
</tr>
<tr>
<td>hyper</td>
<td>55</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed</td>
<td>46</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>121</td>
<td>149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo IPBP w/ Hyper EPS (Hyper PBP)</td>
<td>1</td>
<td>1</td>
<td>$X^2=0$, df=2, p=NS</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>(0)</td>
<td>($X^2=2.52$, df=2, p=NS)</td>
<td>No</td>
</tr>
<tr>
<td>Hyper IPBP w/ Hypo EPS (Hypo PBP)</td>
<td>1</td>
<td>1</td>
<td>$X^2=0$, df=2, p=NS</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>(1)</td>
<td>($X^2=2.52$, df=2, p=NS)</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 7
Comparison of Extrapyramidal Symptom (EPS) Incidences

<table>
<thead>
<tr>
<th></th>
<th>EPS</th>
<th>NO EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>23 (27)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>NO-TD</td>
<td>46 (42)</td>
<td>8 (12)</td>
</tr>
</tbody>
</table>

(Expected cell frequency) \( X^2 = 4.62, \ df=1, p < .05 \)
4 were rated as mixed. Of the 46 extrapyramidal symptom incidences found in the No-TD group, 19 were rated as hypokinetic, 20 were rated as hyperkinetic, and 7 were rated as mixed (see Table 6). The results of the $X^2$ test were not significant ($X^2 = .2766$, df = 2, $p = NS$). The null hypothesis can not be rejected.

**Hypothesis 17.** No difference will be found in the mean number of days extrapyramidal symptoms rated as hypokinetic, hyperkinetic, or mixed occurred between the TD and No-TD groups.

A comparison of the means of the two groups on number of days the different ratings of extrapyramidal symptoms occurred follows:

- Rated hypokinetic (TD: $\bar{X} = 19.92$, SD = 52; No-TD: $\bar{X} = 57.88$, SD = 117),
- Rated hyperkinetic (TD: $\bar{X} = 57.88$, SD = 222; No-TD: $\bar{X} = 181.92$, SD = 395), and mixed (TD: $\bar{X} = 8.69$, SD = 35; No-TD: $\bar{X} = 25.50$, SD = 70). The t values were -1.79, -1.05, and -1.07, respectively. They are not significant at the .05 level for two-tailed tests (with 25 degrees of freedom), thus the null hypothesis can not be rejected.

**Hypothesis 18.** No difference will be found in the mean cumulative days extrapyramidal symptoms occurred between the TD and No-TD groups.

The TD group's mean cumulative days on which extrapyramidal symptoms occurred was 116.62; the No-TD group's mean was 265.31 days (see Table 6). The t value was -1.52 and not significant at the .05 level for a two-tailed test (with 25 degrees of freedom). The null hypothesis can not be rejected.


B. Psychiatric Behavior Patterns

Hypothesis 19. No difference will be found in the number of psychiatric behavior patterns rated hypokinetic, hyperkinetic, mixed, or none between the TD and No-TD groups.

Of the 282 known psychiatric behavior patterns for the TD group, 60 were rated hypokinetic, 55 were rated hyperkinetic, 46 were rated mixed, and 121 were rated as having no predominant pattern. Of the 317 psychiatric behavior patterns for the No-TD group, 54 were rated hypokinetic, 62 were rated hyperkinetic, 52 were rated mixed, and 149 were rated as having no predominant pattern (see Table 6). The results of the $X^2$ test were not significant ($X^2 = 1.97$, df = 3, $p = NS$). The null hypothesis can not be rejected.

C. Initial Psychiatric Behavior Patterns

Hypothesis 20. If subsequent to having a hypokinetic initial psychiatric behavior pattern a patient has a hyperkinetic history of extrapyramidal symptoms, then he/she will be more likely to have TD than a patient who subsequent to having a hyperkinetic initial psychiatric behavior pattern has a hypokinetic history of extrapyramidal symptoms.

Of the 26 TD subjects, 1 displayed a hypokinetic initial psychiatric behavior pattern followed by a hyperkinetic history of extrapyramidal symptoms and 1 displayed a hyperkinetic initial psychiatric behavior pattern followed by a hypokinetic history of extrapyramidal symptoms. This was also the case for the No-TD group. There were not enough cases for statistical analysis.
Hypothesis 21. If subsequent to having a hypokinetic psychiatric behavior pattern a patient has a hyperkinetic psychiatric behavior pattern, then he/she will be more likely to have TD than a patient who subsequent to having a hyperkinetic initial psychiatric behavior pattern has a hypokinetic psychiatric behavior pattern.

A hypokinetic initial psychiatric behavior pattern followed by a hyperkinetic psychiatric behavior pattern was displayed by 2 TD subjects and none of the No-TD subjects. A hyperkinetic initial psychiatric behavior pattern followed by a hypokinetic psychiatric behavior pattern was displayed by 2 TD subjects and 1 of the No-TD subjects. There were not enough cases for statistical analysis.

D. Miscellaneous Characteristics

Hypothesis 22. No difference will be found in eye color between the TD and No-TD groups.

In both the TD and No-TD groups, there were 12 subjects with blue eyes and 14 subjects with brown eyes (see Table 8). The results of the $X^2$ were not significant ($X^2 = 0$). The null hypothesis can not be rejected.

Hypothesis 23. No difference will be found in dental status between the TD and No-TD groups.

In the TD group, 5 subjects had teeth or dentures; 21 of the subjects had no teeth and no dentures. In the No-TD group, 12 subjects had teeth or dentures; 14 had no teeth and no dentures; 14 had no teeth and no dentures.
Table 8

Summary of Miscellaneous Characteristics' Results

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TD</th>
<th>NO-TD</th>
<th>$X^2$</th>
<th>Reject Null?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Color:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Brown</td>
<td>14</td>
<td>14</td>
<td>df=1, p=NS</td>
<td></td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>10</td>
<td>8</td>
<td>.34</td>
<td>No</td>
</tr>
<tr>
<td>White</td>
<td>16</td>
<td>18</td>
<td>df=1, p=NS</td>
<td></td>
</tr>
<tr>
<td>Dental Status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teeth</td>
<td>5</td>
<td>21</td>
<td>4.28</td>
<td>Yes</td>
</tr>
<tr>
<td>(including</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dentures)</td>
<td></td>
<td></td>
<td>df=1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; .05</td>
<td></td>
</tr>
<tr>
<td>No Teeth</td>
<td>12</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(no dentures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The results of the $X^2$ were significant ($X^2 = 4.28$, df = 1, $p < .05$). The null hypothesis is rejected.

**Hypothesis 24.** No difference will be found in race between the TD and No-TD groups.

There were 10 black subjects and 16 white subjects in the TD group. In the No-TD group there were 8 black subjects and 18 white subjects (see Table 8). The results of the $X^2$ were not significant ($X^2 = .34$, df = 1, $p = NS$). The null hypothesis can't be rejected.

**Summary**

Four antipsychotic variables were tested: mean cumulative dose, mean cumulative length of administration, mean daily dose, and maximum dose in any year. Significant differences, with the control group having greater means, were found on the variables of mean daily and cumulative dose of antipsychotics (see Table 2). As a further measure of possible differences between the groups on concentration and schedule of antipsychotic administration, the number of incurred changes in antipsychotic dosage levels and frequencies of administration was tested. No significant difference was found on this variable either. Three antiparkinson agent variables were tested: mean cumulative dose, mean cumulative length of administration, and mean daily dose. A significant difference, with the control group having a greater mean, was found on the mean cumulative length of antiparkinson agent administration (see Table 2).
Table 9
Comparison of Dental Status

<table>
<thead>
<tr>
<th></th>
<th>Teeth (including dentures)</th>
<th>No Teeth (no dentures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>5 (8.5)</td>
<td>21 (17.5)</td>
</tr>
<tr>
<td>NO-TD</td>
<td>12 (8.5)</td>
<td>14 (17.5)</td>
</tr>
</tbody>
</table>

(Expected cell frequencies) $X^2 = 4.28$, df=1, $p < .05$
No significant differences were found on any of the polypharmacy variables. A trend was noted for the No-TD group having a greater number of incidences of polypharmacy. No significant differences were found between the TD and No-TD groups on the variables of 2 month periods or mean number of days free of antipsychotic medications (see Table 5).

A significant difference was found between the TD and No-TD groups on the number of extrapyramidal symptom incidences; the No-TD group had a greater number of incidences (see Table 7). No significant differences were found on the remaining extrapyramidal symptom variables (see Table 6). On the variable of number of psychiatric behavior patterns rated as hypokinetic, hyperkinetic, mixed, or none, no significant difference was found between the groups (see Table 6). Likewise, no significant differences were found on the initial psychiatric behavior pattern and the subsequent psychiatric behavior pattern or subsequent extrapyramidal symptom pattern (see Table 6).

No significant differences were found on the variables of eye color or race between the TD and No-TD groups (see Table 8). The TD group had a significantly greater number of subjects without teeth than the No-TD group (see Table 9).
V. SUMMARY AND CONCLUSIONS

This chapter is designed to summarize and interpret the present study and its results. Conclusions, limitations, and implications for further research are also included.

Summary

Tardive dyskinesia (TD) is a debilitating side effect of antipsychotic medications that is late in on-set and often irreversible (Jeste et al., 1979). The etiology of TD, as well as the treatment for TD remain elusive, although heavily researched (Jeste & Wyatt, 1979). Before comprehensive and conclusive research on the etiology and, therefore, treatment of TD can be accomplished, consistent findings about distinguishing characteristics of TD patients are needed in order for its precursors to be identified. It was the purpose of this study to investigate some of the characteristics which describe patients with TD. An attempt was made to answer the question "Are there aspects of TD patients' drug and behavioral histories which distinguish them from patients without TD?"

The general hypothesis of this study is that there are no differences between a group of inpatients with TD and a group of inpatients without TD on the descriptive characteristics of history of antipsychotic medications, history of antiparkinson agents,
history of polypharmacy, history of drug-free periods, history of extrapyramidal symptoms (EPS), initial psychiatric behavior pattern, psychiatric behavior pattern, race, eye color, and race.

Due to the possible irreversibility of TD, its growing incidence among inpatients (Jus et al., 1976) and outpatients (Asnis et al., 1977), and the community adjustment problems it often causes (Ayd, 1970), it is imperative that the descriptive characteristics of TD patients are consistently delineated. Although there have been several epidemiological studies of TD, there have been few consistent findings due to several methodological problems. Ananth (1978), in reviewing etiological studies, points out that control groups are seldom used and suggests that "a more fruitful approach would be to understand the differences between those who develop dyskinesia and those who do not" (p. 34). Simpson et al. (1978) assert that merely using a control group is inadequate and that matching on age, sex, diagnosis, and length of hospitalization is necessary, although seldom done, for adequate epidemiological studies of TD as "direct comparison . . . within matched patients should yield more definitive results" (p. 119). The present study met these two methodological needs as a matched control group was used.

Empirical justification for predicting and researching the specific descriptive characteristics previously delineated was gained from a review of epidemiological research on TD. Replication of the findings on all the variables studied was needed since matched control groups were used in only three previous studies (Mallya et al., 1979;
The occurrence of TD is attributed to antipsychotic medications due to prevalence studies finding the syndrome to be relatively common in drug-treated populations and relatively rare in untreated populations (Crane, 1973). What remains unclear, however, is how TD develops as well as how the medications cause the syndrome. It is unlikely that this will be known until the mechanisms by which antipsychotics operate are more clearly understood. Currently, antipsychotic medications are thought to functionally deplete dopamine by blocking this neuro-transmitter's receptors at several sites in the brain (Baldessarini, 1977). This framework derives from the dopamine-surplus theory of schizophrenia, which is only one theory of the etiology for this psychosis, wherein the psychosis is understood as a neurochemical disorder (Lehman, 1975). However, this theory also provides a basis for understanding the development of TD. If schizophrenia is a state of dopamine surplus and antipsychotics act by reducing dopamine, then TD can be understood as a dopamine level disturbance. This is hypothesized as resulting from a "state of denervation supersensitivity of ... dopamine receptors" (Jeste &
Wyatt, 1979, p. 252) due to a "prolonged blockage of dopaminergic mechanisms by the antipsychotic drugs" (Baldessarini, 1977, p. 47). Consequently, several epidemiological studies have focused on the drug histories of patients with TD expecting to find that they had received increased amounts of antipsychotics, either in dosages or length of administrations, to account for the hypothesized dopamine supersensitivity.

Even if TD is proven to be a result of neurochemical imbalance caused by the ingestion of antipsychotics, no explanation would be given as to why some individuals develop TD while others do not. Consequently, individual differences in susceptibility are hypothesized (Baldessarini & Tarsy, 1978; Crane, 1978). Epidemiological studies have investigated characteristics of individuals with TD, in an effort to delineate precursors of the syndrome.

Four antipsychotic dosage and administration variables were of research interest: cumulative dose, cumulative length of administration, daily dose, and maximum dose received per year. On the basis of the dopamine-blockage hypothesis one could expect TD patients to have had higher cumulative dosages of antipsychotics than control patients. This has not been consistently found. Three studies (Mallya et al., 1979; Pryce & Edwards, 1966; Simpson et al., 1978) examined the differences in cumulative antipsychotic dose level, comparing matched TD and No-TD samples. Only one study (Pryce & Edwards, 1966) found a significant difference with the TD sample receiving higher cumulative dosages than the No-TD sample. Since TD
is late in onset compared to other neurological side effects (ACN-FDA, 1973), it seems that several years of treatment with antipsychotics may be necessary before the syndrome emerges. It can thus be expected that patients who develop TD will have a longer history of antipsychotic medication treatment than patients who don't develop TD (Crane, 1973). The literature has failed to support such an expectation (Mallya et al., 1979; Pryce & Edwards, 1966; Simpson et al., 1978).

In an effort to avoid intervening interactions between length of antipsychotic administration and cumulative antipsychotic dose, the mean daily dose is a variable that may provide more specific information. However, findings on this variable have been inconsistent (Crane, 1974; Simpson et al., 1978). The maximum antipsychotic dosage per year is another measure of the relationship between drug history variables and the development of TD. Two studies have examined this variable and the outcomes are positive and consistent (Crane, 1974; Smith et al., 1978). Although these studies were correlational and without matched controls, they do indicate a need to examine this variable more intensely.

Previously, antiparkinson agents, which are used to treat extrapyramidal symptoms (EPS), were tried as a form of treatment for TD since both disorders involve the extrapyramidal system. However, it was soon realized that these drugs did not improve TD (Turek et al., 1972) and actually aggravated the syndrome in some cases (Jeste & Wyatt, 1979). Borison (1979) asserts that antiparkinson agents may promote the development of TD by increasing dopamine receptor hyper-
sensitivity, currently hypothesized to mediate the development of TD. Consequently, frequent treatment with antiparkinson agents could mediate the development of TD. The two studies using matched control groups in examining this variable had conflicting findings (Mallya et al., 1979; Simpson et al., 1978).

In a survey on polypharmacy, Sheppard et al. (1974) concluded that the main cause of using more than one antipsychotic was a patient's responding poorly to his or her antipsychotic regimen. The physician then adds a concomitant antipsychotic. Chouinard et al. (1979) found that little therapeutic improvement was a variable significantly related to the presence of TD. When these two findings are combined, it could be expected that patients with TD will have a greater incidence of polypharmacy than patients not having TD. Four psychotropic combinations were investigated in this study: an antipsychotic plus an antipsychotic, an antipsychotic plus an antiparkinson agent, an antipsychotic plus lithium, and an antipsychotic plus a tricyclic antidepressant. When the relationship of the first two types of polypharmacy to the development of TD has been studied, operational definitions differed between studies (Jus et al., 1976; Simpson et al., 1978); no significant differences were found between the experimental and control groups in either study. Nothing has been reported in the literature on the relationships of the other two categories of polypharmacy to the development of TD.

As a preventative measure against TD, drug-free periods lasting from two days to two months have been advocated. These time periods
would allow TD being masked by antipsychotics to be detected; they would also cut down on the cumulative doses and length of administration of antipsychotics (Ayd, 1970). Recently, Jeste et al. (1979) found that the best discriminator between TD patients whose symptoms reversed after three months free of drugs and TD patients whose symptoms persisted was the number of intervals free of antipsychotic drugs. Paradoxically, the persistent group had a great number of drug-free intervals of at least two months. Given this disturbing finding, closer examination of two drug-free variables was merited; namely, number of drug-free periods of at least two months duration and total number of drug-free days.

There are conflicting findings concerning the relationship between extrapyramidal symptom (EPS) histories and the subsequent development of TD (Sovner & DiMascio, 1978). This lack of consistency results, in part, from the lack of well-developed assessment methods for EPS (Mindham, 1976). Despite the conflicting findings, Crane (1972, 1978) has continually found a predisposing relationship. He has had excellent designs, controlling for intervening variables and rigorously assessing EPS; however, distinction among the various types of EPS was not made. Chouinard et al. (1979) are the first researchers to make such a distinction and concluded that the hyperkinetic types of EPS (akathisia and tremor) may be predisposing to the development of TD while the hypokinetic types of EPS (akinesia, rigidity, dystonic reactions) may reduce the development of TD. However, their study examined only the current EPS of the subjects. Further exploration
of subjects' EPS histories is needed in order to test for a possible historical relationship similar to their findings.

It is necessary to research both EPS history and psychiatric behavior patterns rather than solely EPS history as medical personnel and researchers often have difficulty differentially diagnosing EPS from psychiatric symptomology (Davis & Cole, 1975; Donlon & Stenson, 1976; Lesser & Fahn, 1978; Rifkin et al., 1975). The lack of a consistent relationship between EPS and TD may thus result from confusion between psychiatric symptoms and neurological side effects.

Friedhoff et al. (1960) determined that antipsychotics reduced motor activity in patients whose activity was previously quicker than average, but sped up patients whose motor activity had been retarded. Van Putten (1978) found that a hypokinetic type of EPS, akinesia, occurred more often in patients exhibiting high levels of excitation in their initial psychiatric behavior. These studies indicate that patients' initial psychiatric behavior patterns could possibly suggest the type of EPS, if any, they may develop in response to treatment with antipsychotics. Furthermore, in light of the findings of Crane (1972, 1978) and Chouinard et al. (1979), knowing the type of EPS a patient may be susceptible to may also indicate his or her risk of developing TD.

Crane (1978) asserts that no data are available on genetic variables which could account for differences in individual susceptibility to TD. Brandon et al. (1971), however, reported an excess of blue-eyed males with dyskinesia which they felt indicated a role for
genetics in the development of TD. Gardos et al. (1978), however, were unable to replicate this finding. The finding of Brandon et al. peripherally addresses the untested question of what relationship, if any, exists between race and incidence of TD.

It has been known for some time that edentulous elderly patients may appear to have TD in the buccal-lingual-masticatory triad due to the gumming movements this state often precipitates. Similarly, patients with ill-fitting dentures may move their mouth, tongue, and jaws in a manner found in TD patients (Sutcher et al., 1971). Occasionally, dental state has been found to be associated with the presence of TD (Asnis et al., 1977; Brandon et al., 1971).

Many of the research findings on the relationship of the factors reviewed to the development of TD are unclear and/or inconsistent. The primary reasons for this are methodological flaws such as the lack of matched control groups, failure to cut-off data gathering with the emergence of TD, and the lack of clearly delineated criteria conducive to replication. Historical factors also confound results of studies investigating similar variables at different points in time since the treatment of TD has changed several times over the past two decades. Record-keeping procedures have also changed, thus making it possible to investigate variables on which little information was formerly available. This study investigated the relationships discussed while improving as much as possible the major design flaws indicated.

Two samples, each with N=26, were selected from current
inpatients at Eastern State Hospital. The TD group included patients diagnosed by a psychiatrist as having TD. The No-TD group were randomly chosen patients, based on their matching the TD subjects on age, sex, and diagnosis, and examined by the psychiatrist to ensure the absence of TD. The psychiatrist was blind to staff referrals and used a rating scale adapted from Van Putten (1974) which is depicted in Appendix H.

An Initial and Psychiatric Behavior Patterns Rating Form, using the extrapyramidal descriptors of Donlon & Stenson (1976) and Sovner & DiMascio (1978), was designed to rate the behavioral variables of "Initial psychiatric behavior pattern" and "Psychiatric behavior pattern." Two assistants, blind to the study's hypotheses and the group membership of the subjects, rated the behavioral variables. The interjudge agreement ratio of 76% (see Appendix E) was deemed acceptable. The extrapyramidal descriptors of Donlon & Stenson (1976) and Sovner & DiMascio (1978) were also used to determine the type and form of EPS incidences (Appendix D).

This study is an ex post facto design as the phenomena studied had already occurred naturalistically, thus the independent variable was not controlled or manipulated. The criterion-group approach is the type of design. The independent variable is the presence or absence of TD and the dependent variables are the descriptive characteristics investigated. Descriptive characteristics of a TD group were contrasted with those of a No-TD group in an effort to determine which characteristics presumably preceded the criterion.
The hypotheses about antipsychotic and antiparkinson drug dosages and administration duration (1-7), polypharmacy (8-11), drug-free periods (12, 13), EPS history (17, 18), and psychiatric behavior pattern (20) involve interval measures of the dependent variables and nominal independent variables. Consequently, t-test for dependent, or paired, samples was used to determine if any mean differences found, over all the pairs, were statistically significant. Chi-square was used to determine the significance of any systematic association among the variables tested in the remaining hypotheses.

Conclusions

The variables of length of drug and psychiatric histories were tested to determine if they may be intervening variables affecting the present study's results. The mean length of the TD group's drug history was 15.93 years; the No-TD group's drug history was 15.62 years. The TD group's mean length of hospitalization, representing psychiatric history, was 12.79; the No-TD group's length of hospitalization was 13.84. No significant differences were found between the TD and No-TD groups on these two variables, thus they are not considered intervening variables capable of confounding this study's results.

Due to the necessity of group reassignments, the independence of the samples was examined in terms of the 17 intervally measured drug variables. The 5 significant correlations generated by a dependent t-test are depicted in Table 10. The first two are desirable correlations as very dissimilar lengths of hospitalization and drug history
Table 10

Significant Correlations Generated By Dependent T-Test

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CORRELATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of psychiatric history</td>
<td>.67 (.000)</td>
</tr>
<tr>
<td>Length of drug history</td>
<td>.61 (.001)</td>
</tr>
<tr>
<td>Number of days received antipsychotics</td>
<td>.49 (.01)</td>
</tr>
<tr>
<td>Daily dose of antipsychotics</td>
<td>.60 (.001)</td>
</tr>
<tr>
<td>Total cumulative dose of antipsychotics</td>
<td>.62 (.001)</td>
</tr>
</tbody>
</table>
may have introduced artificial differences into the statistical analysis of the drug variables. The remaining 3 correlations are also desirable as they indicate that the two samples received similar treatment with antipsychotics, which was part of the rationale for matching on diagnosis. The two groups were not significantly correlated on the remaining 12 variables, indicating their independence. Within group homogeneity was examined by an independent t-test on the 17 drug variables of the subgroups of each sample. No significant differences were found within the TD sample between the original TD subjects (n=17) and the reassigned controls (n=9). One significant difference was found within the control group between the original controls (n=15) and the reassigned TD subjects (n=11). The number of drug-free periods was significantly greater for the reassigned TD subjects. This particular variable never proved significant in later analyses and is therefore not considered indicative of lacking homogeneity in the control sample.

A listing of this study's findings, by hypothesis number, is provided below in order to help the reader see unquestionably what was found herein.

Drug Histories

A. Antipsychotics

1. Significant differences were found in mean cumulative dose of antipsychotic medications; the No-TD group's mean was greater than the TD group's mean.
2. No significant differences were found in the mean cumulative length of antipsychotic medication administration between the TD and No-TD groups.

3. Significant differences were found in mean daily dose of antipsychotic medications; the No-TD group's mean was greater than the TD group's mean.

4. No significant differences were found in the maximum antipsychotic daily dose for any year between the TD and No-TD groups.

B. Antiparkinson Agents

5. No significant differences were found in the mean cumulative dose of antiparkinson agents between the TD and No-TD groups.

6. Significant differences were found in the mean cumulative length of antiparkinson agent administration; the No-TD group's mean was greater than the TD group's mean.

7. No significant differences were found in the mean daily dose of antiparkinson agents between the TD and No-TD groups.

C. Polypharmacy

8. No significant differences were found in the mean number of total incidences of polypharmacy, at either of the two chlorpromazine equivalents criterion dosage levels of 0 mg. and 100 mg., between the TD and No-TD groups.

9. No significant differences were found in the mean number of incidences in any of the four categories of polypharmacy—antipsychotic plus an antipsychotic, antipsychotic plus an antiparkinson agent, antipsychotic plus an antidepressant, and antipsychotic plus
lithium--at either of the chlorpromazine equivalents criterion dosage levels of 0 mg. or 100 mg., between the TD and No-TD groups.

10. Significant differences were found in the mean number of antiparkinson agents administered between groups; the No-TD group received a greater variety of antiparkinson agents.

11. No significant differences were found in the mean number of antipsychotics administered between the TD and No-TD groups.

D. Drug-Free Variables

12. No significant differences were found in the mean number of incidences of drug-free periods, lasting at least two months, between the TD and No-TD groups.

13. No significant differences were found in the mean number of drug-free days between the TD and No-TD groups.

Other Descriptive Characteristics

A. Extrapyramidal Symptoms

14. No significant differences were found in the number of subjects experiencing extrapyramidal symptoms between the TD and No-TD groups.

15. Significant differences were found in the number of extrapyramidal symptom incidences between the TD and No-TD groups; a greater number of extrapyramidal symptom incidences were found in the No-TD group.

16. No significant differences were found in the number of extrapyramidal symptom incidences rated as hypokinetic, hyperkinetic,
or mixed.

17. No significant differences were found in the mean number of days extrapyramidal symptoms rated as hypokinetic, hyperkinetic, or mixed occurred between the TD and No-TD groups.

18. No significant differences were found in the mean cumulative days extrapyramidal symptoms occurred between the TD and No-TD groups.

B. Initial and Psychiatric Behavior Problems

19. No significant differences were found in the number of psychiatric behavior patterns rated hypokinetic, hyperkinetic, mixed, or none between the TD and No-TD groups.

20. No significant differences were found in initial psychiatric behavior pattern ratings and subsequent extrapyramidal symptom ratings between the TD and No-TD groups.

21. No significant differences were found in initial psychiatric behavior pattern ratings and subsequent psychiatric behavior pattern ratings between the TD and No-TD groups.

C. Miscellaneous Characteristics

22. No significant differences were found in eye color between the TD and No-TD groups.

23. Significant differences were found in dental status; the TD group had significantly more edentulous subjects.

24. No significant differences were found in race between the TD and No-TD groups.
Discussion

This section addresses the findings of this study as related to the empirical justifications provided in Chapter II.

Drug Histories

A. Antipsychotics

The No-TD group had significantly greater grams and milligrams, respectively, of chlorpromazine equivalents on the variables of mean cumulative dose and mean daily dose of antipsychotic medications. No significant differences were found between the groups for the variables of mean length of antipsychotic medication administration and mean maximum antipsychotic daily dose for any year (see Table 2).

Pryce & Edwards (1966) are the only researchers who used a matched control group and found a significantly higher intake of antipsychotics for the TD group, which is in direct contrast to this study's results. In 1966 chlorpromazine equivalents were not available, causing Pryce & Edwards to utilize the standard weekly dose of each antipsychotic studied as a common unit. Length of antipsychotic intake ranges were determined and chi-square was used to test for significant differences. A possible explanation of the differing results is their method of quantifying cumulative antipsychotic dose. It differs from the one used by the present study, as well as the other two studies using matched control groups to investigate this variable (Mallya et al., 1979; Simpson et al., 1978). Mallya et al. and Simpson et al. found no significant differences between the matched...
TD and No-TD groups on the variable of cumulative antipsychotic dosage; however, both studies found slightly higher cumulative dosages for the control groups. Simpson et al. assert that "the simplest explanation for these findings is individual vulnerability" (1978, p. 123). They also point out that differences in cumulative dosages may have existed prior to the development of TD as they were unable to discontinue data collection with the emergence of TD. The current study did utilize data cut-off and found a significantly higher cumulative antipsychotic dosage for the No-TD subjects. Consequently, greater support is provided for the assertion of Simpson et al. Furthermore, Brandon et al. (1971) and Jus et al. (1976), using unmatched control groups, did not find significant differences between the TD and No-TD groups on cumulative antipsychotic dosages.

The only study to investigate differences between matched TD and No-TD groups on the variable of mean daily dose is Simpson et al. (1978). No difference was found between the groups, although the TD group had a slightly higher mean daily dose. The present study found a significantly greater mean daily antipsychotic dose for the control group. The inclusion by Simpson et al. of post-TD drug data may reflect the prior method of treating TD with an increase in antipsychotic dose. Consequently, the present study's results clarify as significant the trend of higher antipsychotic mean daily dose among TD subjects noted by Simpson et al.

The findings of greater mean cumulative antipsychotic dose and greater mean daily antipsychotic dose for this study's control group
parallel each other, indicating that the total gram intake of chlorpromazine equivalents was greater for the control group. This is further indicated by the lack of significant difference between this study's TD and No-TD groups on mean length of antipsychotic administration. This finding is in concurrence with the literature as all studies utilizing control groups in their investigation of this variable failed to show a significant association between treatment duration and the development of TD (Asnis et al., 1977; Brandon et al., 1971; Chouinard et al., 1979; Jus et al., 1976; Mallya et al., 1979; Pryce & Edwards, 1966; Simpson et al., 1978). Furthermore, a trend was noted wherein this study's control group had a greater mean length of antipsychotic administration, which was also noted by Asnis et al. (1977) and Simpson et al. (1978). The present study investigated this variable as prior studies included post-TD drug data. Such methodologies consequently failed to guard against the possible intervening variable of antipsychotic discontinuation or increases for patients developing TD. The replication of the finding with this study's improved methodology indicated that such confounding apparently did not occur and confirms the accuracy of previous findings.

The variable of maximum antipsychotic dosage per year was investigated to determine if the concentration and schedule of antipsychotic administration provided information not available from examination of the more gross drug variables discussed above (Smith et al., 1978). Smith et al. and Crane (1974) found a small positive correlation between maximum amount of an antipsychotic a subject
received in any year and the severity of TD. Their findings merited replication in relation to the occurrence of TD due to their specificity and consistency. This study found no significant differences between the TD and No-TD groups; in fact, the No-TD group had a higher mean. As a further measure of possible differences between the experimental and control groups on concentration and schedule of antipsychotic administration, the number of incurred changes in antipsychotic dosage levels and frequencies of administration was tested. The TD group's mean number of such changes was 25.19; the No-TD group's mean was 42.42. The t value was -1.60 and not significant at the .05 level for two-tailed test (with 25 degrees of freedom). Apparently, what may exist in regard to TD severity does not exist in regard to TD occurrence. The two specific variables investigated appear to only provide additional information on the control group's antipsychotic administrations as a trend for this group to receive greater maximum antipsychotic dosages per year and more concentration and schedule changes is noted. This trend is consistent with the trends and significant findings of the antipsychotic variables already discussed.

It is important to note that the present study found greater means for the No-TD group on all antipsychotic variables investigated herein. Such trends were also found by Simpson et al. (1978) and Mallya et al. (1979) for the variable of cumulative antipsychotic dose. Likewise, Simpson et al. and Asnis et al. (1977) noted similar trends for the variable of cumulative length of antipsychotic administration.
These trends, in conjunction with the results discussed above, are considered strongly supportive of the role individual differences play in the development of TD. The conclusion is drawn that individual sensitivity interacting with a critical ingestion of antipsychotic medications is more related to the development of TD than the specific quantities of the drug variables tested. Confirmation is provided for the assertion of Simpson et al. (1978) that individuals differ greatly in the absorption of medications into their central nervous and blood systems, thus "the milligrams ingested may not give a totally accurate indication of what is actually occurring in the brain" (p. 123).

The conclusion drawn by both Brandon et al. (1971) and Jus et al. (1976), who investigated the relationship of drug variables to the occurrence of TD, that age was the most significant factor in determining the risk of developing TD is illustrative of such individual vulnerability postulated by Simpson et al. (1978). The relationship between individual susceptibility and the development of TD is supported by the neurochemical basis hypothesized for TD. Neurochemically, TD is understood as a primary dopamine deficiency, due to the antipsychotics blocking some of this neurotransmitter's receptor-sites in the brain, and a secondary dopaminergic hypersensitivity. Such a decline in the dopamine system occurs organically with increasing age as well and the ingestion of antipsychotics are believed to accelerate this age-related change in the brain (Gerlach, 1977). Consequently, the older patients are at the initiation of antipsychotic treatment or as patients receiving long-term treatment with antipsychotics age, the higher the risk of developing TD.
Strength for concluding that individual susceptibility is of greater importance in the development of TD than specific antipsychotic drug variables is drawn from the main methodological improvement of the present study. Namely, ceasing data collection on the TD subjects with the emergence of TD. This method is credited for the consistent trend of greater antipsychotic variable means for the No-TD group as the two groups did not differ significantly on the length of drug and psychiatric histories.

B. Antiparkinson Agents

Like the antipsychotic variables, the three antiparkinson agent variables tested in this study—mean cumulative dose, mean daily dose, and mean length of administration—evidenced a trend of greater means for the No-TD group (see Table 2). The control group's mean length of antiparkinson administration was significantly greater than that of the TD group. These findings parallel those of Simpson et al. (1978) as they also noted the trend of greater mean cumulative dose and mean length of administration for their matched control group. They noted a very slight, and insignificant, higher mean daily dose for the TD group. Conversely, Mallya et al. (1979) found mean cumulative dose and mean length of antiparkinson administration to be significantly greater for the TD group than for the matched control group. This discrepancy more than likely reflects methodological differences as the investigation of Mallya et al. was limited to only two antiparkinson agents over about eight years
of treatment while Simpson et al. (1978) and the present study were more comprehensive, examining all antiparkinson agents administered throughout the subjects' entire treatment histories (about 15 years for both studies).

The present study found greater mean differences between the TD and No-TD groups' antiparkinson variables, with higher means for the control group. These findings are more definitive than the similar trend noted by Simpson et al. (1978); this difference in specificity is attributed to the discontinuation of data collection for the TD subjects in this study with the emergence of TD. The investigation of Simpson et al. was completed in 1977 when the treatment of TD with antiparkinson agents was still widely practiced (Jeste & Wyatt, 1979). Their inclusion of post-TD antiparkinson agent histories more than likely accounts for their finding a slightly higher antiparkinson mean daily dose for the TD group. It's interesting to note that even with the inclusion of post-TD data, Simpson et al. did not find significantly more antiparkinson agent usage for the TD group. In fact, they noted trends for the control group to have greater means on the antiparkinson agent variables.

There are several reasons researchers could expect to find significant relationships between the occurrence of TD and antiparkinson agent usage. Currently the strongest rationale is psychopharmacological as antiparkinson agents are anticholinergics which could exaggerate an imbalance between the cholinergic and dopaminergic systems resulting in further increased dopamine relative to the
decreased acetycholine (Borison, 1979). Another rationale is the correlation reported between parkinsonism and TD (Crane, 1972) indicating that patients developing TD have had a greater history of EPS, which is treated with antiparkinson agents, than patients not developing TD.

The present study provides no support for, and consequently raises questions about, such rationales. This study's findings of antiparkinson agent usage to be more related to the absence of TD than to the presence of TD has some psychopharmacological implications. Mallya et al. (1979) viewed their finding a strong relationship between antiparkinson agent usage and the development of TD as clinical confirmation of the work of Klawans & Rubovits (1974). Klawans & Rubovits hypothesize that antiparkinson treatment may increase the occurrence of TD by reducing the threshold for the development of TD. The present study's results do not support such a causal relationship between antiparkinson agent usage and the incidence of TD. It appears that Mallya et al. (1979) were overly conclusive given their failure to discontinue data collection for the TD subjects with the emergence of TD. This is of great importance given that administration of antiparkinson agents was previously a standard treatment for TD.

This study's results provide further evidence that TD most probably results from a functional primary dopamine deficiency, with a secondary dopamine hypersensitivity (Gerlach, 1977), due to individual vulnerability to the dopamine-depleting mechanisms of antipsychotics rather than a dopamine excess in relation to an antiparkinson agent-
induced cholinergic reduction. Such an interpretation does not negate the hypothesis of Klawans and Rubovits (1974) that antiparkinson agents may increase the severity of TD as this was not examined herein. This hypothesis of increased severity is in concurrence with the individual susceptibility interpretation provided as Klawans and Rubovitz specify that increased severity is most likely to occur with "anticholinergic therapy in patients prone to developing TD" (p. 941). If antiparkinson agents do mediate the development of TD, this relationship would be, as is true for antipsychotics, a matter of individual vulnerability rather than quantitative amounts of antiparkinson agent variables.

This study's finding of greater antiparkinson usage for the control group is understood as a result of the control group also having a significantly greater number of EPS incidences as well as a trend towards greater amount of days on which extrapyramidal symptoms were experienced. Such findings indicate that antiparkinson medications are probably more related to the incidence of EPS than to the presence or absence of TD. This interpretation is further supported by the trend for all antipsychotic variables tested to be greater for the control group. This is indicative of the relationship often evidenced between greater usage of antipsychotics and increased EPS occurrences resulting in greater antiparkinson agent usage (Simpson et al., 1978).
C. Drug-Free Periods

No difference was found between the TD and No-TD groups on either the mean incidences of two month periods free of antipsychotics or on the mean days free of antipsychotics; a trend was noted for the No-TD group to have more drug-free days. It is concluded, therefore, that the number of drug-free two month periods and cumulative number of drug-free days are not related to the presence or absence of TD.

Jeste et al. (1979) found the cumulative number of drug-free two month periods to be the best discriminator between reversible and persistent TD groups. To date, no epidemiological study has determined if this finding is applicable in differentiating between TD and No-TD groups. The present study's results indicate that it is not applicable as both the TD and No-TD groups incurred a mean of 3.04 drug-free two month periods. This study's findings also indicate that drug-free periods or drug-free days are not an effective preventative measure against TD as the control and experimental groups did not differ significantly on these variables.

Jeste et al. (1979) point out that increases in these drug-free variables may indeed increase the risk of developing persistent TD for patients already predisposed to developing the disorder. They postulate a "kindling" effect--i.e., increased sensitization--that occurs in response to intermittent administration of antipsychotics as an explanation of their findings. The conclusions of Jeste et al. and of the present study indicate that lengthy antipsychotic treatment interruptions should be avoided in favor of consistent, maintenance
treatment with only short interruptions, when necessary, curtailed to a span of several days or more.

D. Polypharmacy

Four types of polypharmacy were investigated: an antipsychotic plus an antiparkinson agent, an antipsychotic plus an antidepressant, and an antipsychotic plus lithium (see Appendix A). Another kind of polypharmacy, the number of different antipsychotics and different antiparkinson agents administered to each subject, was also examined.

No significant differences were found between the TD and No-TD groups in the mean number of incidences, in any of the four categories, of polypharmacy at either of the two daily chlorpromazine equivalents (CPZE) criterion dosage levels of 0 mg. and 100 mg. This was also the case for the mean number of total incidences of polypharmacy at each of the daily CPZE criterion levels (see Table 3). A very consistent trend was noted wherein the No-TD group had higher incidences of polypharmacy in every category, and totally, for each dosage level. Further analyses indicated this trend is true for CPZE criterion dosage levels of 500 mg. and 1000 mg. as well. The mean duration of polypharmacy on any of the four categories, at all four daily CPZE dosage levels, was also examined. No significant differences were found between the TD and No-TD groups. Also there was not a significant difference between the two groups in the number of subjects receiving polypharmacy of any category at any dosage level. Consequently, support is provided for the finding of Jus et al. (1976) of no
significant difference between their unmatched TD and No-TD groups on the number of "cocktails" received (concomitant administration of two or more antipsychotics). Their finding was questioned as the operationalization of "cocktail" was quite lenient necessitating only a one month administration of polypharmacy with daily CPZE of at least 100 mg. The present study used a more rigorous operationalization as a two month administration of polypharmacy was necessary. Furthermore higher (500 & 1000 mg.) daily CPZEs and mean duration of polypharmacy of all CPZE levels were also investigated. This study was more inclusive as the four different categories of polypharmacy were investigated and all were included in the total incidences variable. Examining polypharmacy at a daily CPZE of 0 mg.--i.e., no criterion dosage level--also expanded this study's investigation of polypharmacy as compared to that of Jus et al. (1976). Finally, post-TD drug data was not included for either the TD or No-TD groups, thus providing greater certainty that the study's results are not confounded by treatment changes made. In light of the present study's additional methodological features, expanded investigative focus, and the findings being supportive of Jus et al., it is very probable that the administration of polypharmacy as defined herein is not related to the occurrence of TD.

The rationale for examining polypharmacy was primarily based on the expectation that greater antipsychotic usage would be found among patients with TD to account for the dopamine supersensitivity hypothesized as the neurochemical basis of TD (Jeste & Wyatt, 1979).
The above findings on polypharmacy do not negate such a neurochemical basis. They do, however, provide cause to question a predisposing relationship between greater antipsychotic usage and the occurrence of TD. This parallels all the drug variable findings discussed in the previous sections. This study has consistently found less antipsychotic and antiparkinson agent usage—whether in the form of dosage levels, lengths of administration, or polypharmacy—among the TD subjects. The results of the polypharmacy analyses are therefore interpreted as further support for the relationship of TD to individual vulnerability rather than specific drug quantities or combinations. The fact that a trend was noted for greater polypharmacy among the No-TD subjects is interpreted as paralleling the findings of greater antipsychotic and antiparkinson agent usage in general for the No-TD group (see Table 2).

No significant difference was found in the mean number of different antipsychotics administered between the TD and No-TD groups (see Table 4). In fact, a trend was noted for the controls to receive a greater number. Again, this is reflective of the greater antipsychotic usage found in general for the No-TD group. The control group did receive a significantly greater number of antiparkinson agents than the TD group (see Table 4). This is considered reflective of the significantly greater number of incidences of extrapyramidal symptoms (EPS) and the significantly greater length of antiparkinson agent administration found for the No-TD groups. It's quite possible that, given more EPS and antiparkinson agent treatment, the No-TD
subjects were treated by a variety of physicians who preferred prescribing different agents. Also, since the No-TD subjects were treated over a longer period of time, it is possible that new agents became available to prescribing physicians.

**Other Descriptive Characteristics**

**A. History of Extrapyramidal Symptoms (EPS)**

Crane's (1974, 1978) predisposing relationship between EPS and the development of TD was not supported by the present study. The No-TD group evidenced a trend of more subjects developing EPS for longer periods of time than the TD group (see Table 8). In fact, the control group had a significantly greater number of EPS incidences than the TD group. One explanation of this result may lie in the finding of mean number of drug-free days. A "reverse tolerance" phenomenon is hypothesized by Sovner & DiMascio (1978) wherein interrupted antipsychotic treatment regimens may increase the occurrence of EPS. Also, the mean daily antipsychotic dose of the control group was significantly greater than that of the experimental group. Consequently, if the incidence of EPS is dose-related, as often hypothesized (Simpson et al., 1978), it follows that the No-TD group would have a greater number of subjects developing more incidences of EPS which lasted for longer periods than is true for the TD group.

Another possible explanation of this result may be due to record-keeping procedure changes. About 2 years ago, Eastern State Hospital adopted a problem-oriented system of recording patient infor-
mation. This procedure involves an increase in symptom descriptions which results in a greater amount of information. Data collection ceased for the majority of TD subjects (n=17) prior to 1978; the control subjects' data collection also ceased according to their matches' cut-off dates. Such equalization of cut-off dates makes this explanation unlikely.

A final explanation of the control group's greater EPS incidence lies in the possibility that individual's prone to the development of TD may develop a very brief form of EPS that is less likely to be mentioned in the hospital charts. Dystonic reactions occur within 1 to 3 days of treatment initiation or changes. They can be effectively treated immediately with an injection of an antiparkinson agent (Swett, 1975). Only one instance of this form of EPS was detected in the recording of EPS histories for this study; it was incurred by a TD subject. This is an extremely low incidence of 1% when compared to Swett's (1975) finding the incidence of dystonic reactions among inpatients to be 10.1%. Consequently, it is very probable that unrecorded dystonic reactions occurred among the present study's subjects. Furthermore, it is postulated that dystonic reactions may be more common among patients prone to developing TD (Simpson et al., 1978). This form of EPS, like TD, is age-, sex-, and individual sensitivity-related (Sovner & DiMascio, 1978). Unlike the other forms of EPS, dystonic reactions differ in etiology from the dopaminergic-cholinergic balance hypothesis which asserts that a shift to cholinergic excess results in EPS. Conversely, dystonic reactions are currently
understood as a result of the "hyperactivity of dopaminergic neurons caused by the initial increase in the turnover and synthesis of dopamine" (Sovner & DiMascio, 1978, p. 1025). This is also the hypothesized neurochemical state of TD (Jeste & Wyatt, 1979). In fact, dystonic reactions were once commonly referred to as transient dyskinesias as this form of EPS presents in a manner very similar to TD. Unfortunately, data enough to test the possible existence of a precursory relationship of dystonic reactions to the eventual development of TD was not generated by the present study. Nonetheless, this final explanation of the finding of significantly more EPS incidences for the No-TD group is the one asserted herein.

According to the findings of Chouinard et al. (1979) concerning the relationship of EPS type to the eventual development of TD, the TD subjects should evidence a preponderance of extrapyramidal symptoms rated as hyperkinetic and the control subjects extrapyramidal symptoms rated as hypokinetic. No significant differences were found between the control and experimental groups on the ratings of EPS incidences. Trends, however, were noted. As a group, the TD subjects did have more EPS incidences and more days of hyperkinetic than hypokinetic or mixed extrapyramidal symptoms (see Table 8). The control subjects, however, did not have more hypokinetic than hyperkinetic or mixed symptoms. Furthermore, such trends were not noted between the groups. Since Chouinard et al. (1979) investigated only the current EPS of their subjects, the most recent EPS occurrences of this study's subjects were also examined. The TD group again evidenced a trend for their
most recent incidences of EPS to be rated hyperkinetic; the control
group did not have a trend of their recent EPS episodes being rated
hypokinetic. No significant differences between groups were found.
Due to the trends found for the TD group, some support for Chouinard
et al.'s postulate of hyperkinetic types of EPS being precursors of
TD is provided. Due to the lack of similar trends for the control
group, support was not found for Chouinard et al.'s proposal that
hypokinetic types of EPS might reduce the occurrence of TD.

An explanation of this study's lack of support for Chouinard
et al.'s findings more than likely is related to their focus on EPS
coexisting with TD and this study's focus on the historical relation-
ship between EPS and the development of TD. Another factor that may
have produced this lack of support is the fact that this study
attempted to determine EPS occurrences from behavioral notations and
doctor's notes in the hospital charts. On the other hand, Chouinard
et al. were able to directly, and probably more accurately, assess
the current type of EPS their subjects were experiencing. A final
explanation is that individuals don't always experience the same form
or type of EPS each time they develop EPS. However, this explanation
is doubtful as the most recent EPS episodes of the TD and No-TD groups
herein were tested as was the mean number of days on which extra-
pyramidal symptoms were experienced. These variables would have more
than likely tapped any information overlooked by the broader variable
of EPS incidences. Consequently, the conclusion is drawn that,
although trends similar to those of Chouinard et al. were found for
the TD group, the design and methodology of both this and Chouinard et al.'s study are inadequate. In order to determine the existence of a predisposing or inverse relationship between EPS history and the development of TD, a prospective study is necessary. Confidence could then be gained about the exact form and type of extrapyramidal symptoms experienced by patients who subsequently develop TD. Only then could causal relationships be proposed.

B. Psychiatric Behavior Pattern (PBP)

The variable of psychiatric behavior pattern was investigated to guard against differential diagnostic difficulties that are inherent in the assessment of EPS. Such assessment is obviously necessary for an investigation of the relationship between EPS and the subsequent development of TD (David & Cole, 1975; Donlon & Stenson, 1976; Lesser & Fahn, 1975; Rifkin et al., 1975). Recognizing these difficulties as present for diagnosing current EPS, it was realized that the difficulties would be even greater when attempting to determine historical EPS episodes from hospital records. Furthermore such records seldom label EPS as such; instead symptom descriptions are provided.

Psychiatric behavior patterns were rated as hypokinetic, hyperkinetic, mixed, none, or unknown. Significantly more of the TD subjects' psychiatric behavior patterns (n=242) were rated unknown as compared to the No-TD subjects' psychiatric behavior patterns (n=173) ($X^2=12.39; DF=1; p < .01$). Consequently, calculations between the two groups were only carried out on the known psychiatric behavior patterns (see Table 8).
There were no significant differences between the TD and No-TD groups' number of known PBPs rated hypokinetic, hyperkinetic, mixed, or none. In fact, there was a trend for the TD subjects to have more PBPs rated hypokinetic than hyperkinetic. This trend is in direct contrast to the predisposing and inverse relationship of, respectively, hyperkinetic and hypokinetic extrapyramidal symptoms to the subsequent development of TD postulated by Chouinard et al. (1979).

As with the EPS histories, the most recent PBPs of this study's subjects were examined due to Chouinard et al.'s investigating only current EPS. A within group trend similar to the relationship identified by Chouinard et al. was found for the TD subjects as more of the recent PBPs were rated hyperkinetic than hypokinetic; however, the majority of these PBPs were rated mixed. Furthermore, the No-TD group's majority of recent PBPs were rated hyperkinetic, rather than hypokinetic as could be expected from the findings of Chouinard et al.

More than likely the fact that 46% of the TD subjects and 35% of the No-TD subjects PBPs were rated as unknown is responsible for the findings on this variable. Although calculations were corrected for this lack of information by using only known ratings, this does not change the fact that a major amount of information was found lacking in the hospital charts. Consequently, not much weight can be given to these results.
C. Initial Psychiatric Behavior Pattern (IPBP)

The relationship of initial psychiatric behavior patterns to subsequent extrapyramidal symptoms and psychiatric behavior patterns was examined to determine if particular behavior patterns were related to the presence or absence of TD. Based on the works of Friedhoff et al. (1960), Van Putten (1978), Crane (1972, 1978), and Chouinard et al. (1979), it was hypothesized that patterns involving hypokinetic IPBPs followed by hyperkinetic extrapyramidal symptoms or psychiatric behavior patterns would be found more often in the histories of TD subjects. Likewise, based on the same works cited, it was hypothesized that patterns involved in hyperkinetic IPBPs followed by hypokinetic extrapyramidal symptoms and psychiatric behavior patterns would be found more often in the histories of the No-TD subjects. Evidence for the existence of either of these patterns was not provided by this study. Table 8 indicates how compromising the results are. One explanation for the lack of significant findings is the large amount of inadequate information found for the PBPs.

Although this study failed to demonstrate the relationship of a historical contingent initial psychiatric behavioral and extrapyramidal pattern to the eventual development of TD, further investigation is merited for two reasons. First, the initial psychiatric pattern and subsequent psychiatric/extrapyramidal patterns did not indicate a predominant hypokinetic-hyperkinetic pattern for the TD subjects or hyperkinetic-hypokinetic pattern for the No-TD subjects as hypothesized. However, trends for these hypothesized patterns are noted when
psychiatric behavior and extrapyramidal symptom patterns are examined (see Table 8). TD subjects display a pattern of hypokinetic psychiatric behaviors and hyperkinetic extrapyramidal symptoms. The No-TD subjects display a pattern of hyperkinetic psychiatric behaviors and hypokinetic extrapyramidal symptoms. Rather than initial psychiatric pattern, it is possible that patients' predominant psychiatric behavior—i.e., predominant behavior pattern observed while not experiencing EPS—may indicate the form of EPS they may develop and therefore their risk for developing TD. Secondly, the present study's retrospective focus clearly may have led to compromising results. As with the investigation of a relationship between EPS history and subsequent development of TD, a prospective study is the design necessary to investigate the existence of contingent behavioral and extrapyramidal patterns within groups eventually developing and not developing TD. Such a design would involve current, on-going monitoring of behavioral and extrapyramidal patterns and therefore provide much more accurate and reliable information.

D. Miscellaneous Characteristics

Crane's (1978) assertion that no data are available on genetic variables which could account for differences in individual susceptibility to TD is supported by the present study's findings. No difference was found between the TD and No-TD groups on eye color or race (see Table 9), which may have indicated a role for genetics in the development of TD.
The TD group was found to differ significantly from the No-TD group on the variable of dental status (see Table 9). One TD subject had all of her teeth and 4 TD subjects had some missing teeth, without dentures. The remaining 21 subjects had no teeth and no dentures as compared to only 14 No-TD subjects. This finding supports those of Asnis et al. (1977) and Brandon et al. (1971) who found significant associations between edentulousness and the presence of TD. The implications of such findings remain unclear. It has been proposed that teeth act as a barrier to tongue protrusion, a primary symptom of the buccal-lingual-masticatory form of TD (BLM) (Sutcher et al., 1971). Consequently, early BLM symptoms in patients who have the majority of their teeth may go unrecognized. Dental status often raises the question of differential diagnosis as well. Edentulous elderly patients may appear to have TD in the BLM triad due to the gumming movements this state often precipitates. The majority of the edentulous TD subjects in the present study were rated as displaying TD symptomomologies in their limbs and extremities as well as in the BLM triad. Therefore this finding on dental state is not considered as indicating differential diagnostic problems. It is not possible to clarify the interpretation of this finding at this time as research in this area is rare. The conclusion is drawn, however, that clinicians need to be aware of this relationship of dental state to the presence of TD and not dismiss BLM movements in an edentulous patient as non-indicative of the presence of TD.

Several other non-hypothesized variables were investigated.
Chouinard et al. (1979) found antipsychotic ineffectiveness—i.e., treatment resistant psychosis—to be significantly related to the occurrence of TD. Consequently, any statements made about antipsychotics being ineffective for subjects in this study were recorded. Such statements were found for 5 of the TD subjects and 2 of the No-TD subjects. This difference is not significant, however, a trend similar to the findings of Chouinard et al. is noted. This lends credence to the recommendation of Chouinard et al. that patients not responding effectively to antipsychotic treatment should probably be tried on another treatment regimen.

The relationship of electroconvulsive therapy (ECT) to the occurrence of TD has been addressed by several studies (Brandon et al., 1971; Pryce & Edwards, 1966). Brain damage was once thought to predispose patients to the development of TD (Edwards, 1970); consequently, ECT treatment became implicated as well. A relationship between ECT treatment and the development of TD was not supported by the present study as 6 subjects in each group had histories of ECT treatment. Furthermore, no significant differences were found in the number of ECT treatments received by the TD subjects (189) and No-TD subjects (200). This finding, consistent with those of Brandon et al. and Pryce & Edwards, implies that ECT is not an intervening variable in the development of TD.

Limitations

In the case of external validity, any relationships found can be reliably generalized to similarly aged inpatients, with severe TD,
and hospitalized in state mental institutions. The rationale for such restricted generalizations lies in the fact that any patients who were released from the hospital are obviously not included in this study. To include such individuals is clearly beyond the scope of this study due to the amount of time it would involve to trace down such subjects in order to ensure they have not developed TD or been treated for psychiatric disturbances since their release and consequently have incurred the risk of developing TD. The role that chronic institutionalization may play in the development of TD can therefore not be addressed in this study. As Crane (1973) points out, it is probably safe to assume that "the chronicity of a disease and/or institutionalization with the attendant emotional and physical deprivation" (p. 395) is not responsible for motor abnormalities such as TD. This assumption is supported by Pryce & Edwards (1966) finding the incidence of TD and abnormal movements similar to TD to be higher for inpatients treated with antipsychotics than for similar inpatients not treated with antipsychotics. Thus, TD has come to be understood as a result of exposure to antipsychotic medications rather than a result of chronicity or institutionalization. Furthermore, TD does occur among outpatient populations (Asnis et al., 1977; Chouinard et al., 1979). Given the state of uncertainty, however, concerning the etiology of TD—even in light of the above findings—the results of this study can be generalized reliably to similarly aged patients, who have severe TD, and are still institutionalized. Due to the ex post facto design of this investigation, the results are considered
indicative of potential precursors of TD which need to be more directly tested. Consequently, no conclusions about causal relationships between the descriptive characteristics studied herein can be drawn on the basis of this investigation's results.

**Implications for Future Research**

As asserted by Simpson et al. (1978), the direct comparison within matched pairs of patients with TD and patients without TD apparently yields more definitive results. Although no conclusions about causality can be drawn due to this study's ex post facto design, the consistent findings clearly indicate areas in need of further investigation. Furthermore, the finding of significant differences on variables previously displaying only trends in the direction of this study's results indicates the necessity of discontinuing data collection with the emergence of TD.

Consistent results of greater quantities on the variables concerning antipsychotic usage, antiparkinson agent usage, and extrapyramidal symptom incidence were found for the control group. These findings indicate that future research efforts need to be focused on the possibility of individual differences in susceptibility to the development of TD. TD is clearly related to exposure to antipsychotic medications (Crane, 1978); however, this study's findings of greater antipsychotic usage in the control groups lends further support to the postulation that individual vulnerability accounts for the occurrence of TD more than greater quantities of antipsychotics do (Simpson et al., 1978). To investigate the existence of such a situation
requires the monitoring of plasma levels. This is necessary in order to determine if individuals developing TD do indeed have a lower tolerance to antipsychotic ingestion, and thus a lower TD threshold, than individuals who don't develop TD (Jeste & Wyatt, 1979).

The most reliable design by which TD precursors could be investigated involves objective diagnostic criteria as well as prospective data collection. However, to date, no such criteria have been delineated although the near future may witness such a delineation (Jeste & Wyatt, 1979). Prospective studies incur ethical problems given the possibility of irreversible TD and lack of effective treatment. However, such a decision must be weighted in relation to this risk as well as the benefit to be gained from locating definite precursors of TD. Only a prospective study is capable of determining the existence of causal relationships between extrapyramidal symptom histories and/or individual vulnerability—i.e., specific plasma levels in response to antipsychotic administration. The finding of such relationships would represent a greatly needed method for preventing the development of TD. The pharmacological treatment of patients determined to be at high risk for the development of TD could be altered in order to reduce this risk significantly. Furthermore, the recent findings that the identification of early warning signs can reduce the occurrence of severe and/or irreversible TD brings greater credence to a prospective design (Baldessarini & Tarsy, 1978). Under such a design patients would be monitored at least bi-monthly for physiological changes, the development of EPS, and the
development of early TD symptoms. Such close monitoring specifically directed towards the diagnosis of TD is far greater attention than patients not in such a study would receive. In light of this close scrutiny and the great potential benefits, the question of ethics becomes a highly relative issue.

If such a design becomes a possibility, it is recommended that dystonic reactions be given specific attention. This suggestion is based on their neurochemical similarity to TD and their early appearance in response to the initiation of antipsychotic treatment (Sovner & DiMascio, 1978).

The relationship of TD symptom severity to the antipsychotic variables was not investigated herein. However, in light of finding greater usage of antipsychotics in the control subjects' histories, research focus on the relationship of these variables to TD severity is recommended. Severity has been found to be significantly related to cumulative antipsychotic dose (Crane & Smeets, 1974) and maximum antipsychotic dose per year (Smith et al., 1978). It is possible, therefore, that individual vulnerability to the ingestion of antipsychotics may determine the development of TD while specific quantities of antipsychotic variables determine its severity. Consequently, such research focus could aid in reducing the severity of TD, should it develop, while other research efforts are directed towards determining the precursors of TD.
Appendix A

DRUG HISTORY CODES

0 - Drug-free period: Documented time free of antipsychotics lasting at least two months.

1 - Antipsychotic + antipsychotic: 2 or more antipsychotics for a period of at least two months where:
   a. total combined CPZE is 0 mg per day,
   b. total combined CPZE is at least 100 mg per day,
   c. total combined CPZE is at least 500 mg per day, and
   d. total combined CPZE is at least 1,000 mg per day.

2 - Antipsychotic(s) + Lithium: Antipsychotic plus lithium for a period of at least two months where:
   a. total combined CPZE is 0 mg per day,
   b. total combined CPZE is at least 100 mg per day,
   c. total combined CPZE is at least 500 mg per day, and
   d. total combined CPZE is at least 1,000 mg per day.

3 - Antipsychotic(s) + tricyclic antidepressant: Antipsychotic plus a tricyclic antidepressant for a period of at least two months where:
   a. total combined CPZE is 0 mg per day,
   b. total combined CPZE is at least 100 mg per day,
   c. total combined CPZE is at least 500 mg per day, and
   d. total combined CPZE is at least 1,000 mg per day.

4 - Antipsychotic(s) + antiparkinson agent: Antipsychotic plus an antiparkinson agent for a period of at least three months where:
   a. total combined CPZE is 0 mg per day,
   b. total combined CPZE is at least 100 mg per day,
   c. total combined CPZE is at least 500 mg per day, and
d. total combined CPZE is at least 1,000 mg per day.

**CPZE = Chlorpromazine Equivalence**

**CPZE CONVERSION EQUATION:**
1) Equivalence factor = 100/antipsychotic equivalent
2) Antipsychotic dosage X Equivalence factor

(See following pages for antipsychotic equivalents)

**CODES FOR OTHER MEDICATIONS:**
- L - Lithium
- ad - Tricyclic antidepressant
- ap - Antiparkinson agent

**MEDICAL ABBREVIATIONS:**
- b.i.d. - 2 times a day
- t.i.d. - 3 times a day
- q.i.d. - 4 times a day
- p.o. - by mouth
- h.s. - at bedtime
- p.r.n. - as needed
- stat - immediately

**NOTE:** Any discrepancies between physicians' orders and nurses' records are to be resolved in favor of the nurses' records.

## ANTIPSYCHOTICS

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<th>AVG. DAILY DOSE (mg)*</th>
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<th>TRADE NAMES</th>
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**NONPHENOTHIAZINES:**

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<td>RES</td>
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<td>Kemadrin</td>
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**ANTIDEPRESSANT DRUGS**

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**ANTIMANIC DRUG++**

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<td>PSYCHOTROPIC DRUG COMBINATIONS++</td>
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<tr>
<td>Perphenazine + Amitriptyline</td>
<td>Triavil</td>
<td>TRI</td>
<td>Titrated</td>
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<tr>
<td>Chlordiazepoxide + Amitriptyline</td>
<td>Limbitrol</td>
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<td>Titrated</td>
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</table>

* Davis & Garver (1978)
** Baldessarini (1977)
+ Klerman (1974)
++ Newton et al. (1978)
MATCHING PROCEDURE

The TD subjects were matched with the control subjects on age, sex, and diagnosis. The April 1980 Patient Census of Eastern State Hospital was used to identify appropriate matches based on the previously recorded control variables of the TD subjects. A random numbers table (Tuckman, 1978) was used to systematically choose patients and determine if their demographics matched any of the TD subjects' control variables. If the chosen patient was unsuitable, the name was crossed off and another patient was chosen at random. This procedure continued until all required control subjects were identified.
LISTING OF TARDIVE DYSKINESIA SYMPTOMS

Mouth hanging open with tongue lolling out
Involuntary twitching of the mouth that stops when resting
Constant chewing movements of the mouth
Tongue protrudes from mouth with constant drooling
Involuntary tongue movements
Tongue cannot be controlled
Tongue moves constantly
Tongue sticks out slightly
Lip smacking or puckering
Cheek puffing
Moves mouth constantly
Choreiform movements of the trunk
Choreiform movements of extremities
Involuntary movements of the body
Jerking of the extremities that increases with anxiety
Involuntary movements of the hands and feet
Constant rocking motion of head and body
Involuntary movements or restlessness of limbs
Constant jerking movements of the entire body
PATIENT INFORMATION SHEET

I. GENERAL INFORMATION (use codes)
   Today's
   ID #:____ Initial Admission Date: _____ Date:____________
   Birth
   Date (Age):____(____) Sex:____ Psychiatric Diagnosis:____
   Race:_____ Eye Color:____ Dental Status:_________ (____)
   First TD Symptom,
   Mention or Diagnosis:___________ # of Drug-Free Periods:____
   # of Drug-Free Days: ____

II. HISTORY OF EXTRAPYRAMIDAL SYMPTOMS: Record only symptoms coded
to antiparkinson agents using length of their administration as
on-set and off-set dates. Record form, specific symptom, and
type.

   DATES FORM SPECIFIC SYMPTOMS TYPE
   From:  to

III. PSYCHIATRIC BEHAVIOR PATTERN(S): For each 6 month period, after
1953 or subsequent to admission, read Interdisciplinary notes and
Semi-Annual Summaries; rate on Rating Form using Rating Descriptors
Sheet.

IV. INITIAL PSYCHIATRIC BEHAVIOR PATTERN: Read Admission Notes and
rate on Rating Form using Rating Descriptors Sheet.

V. DRUG HISTORY: Record all antipsychotics, antiparkinson agents,
antidepressants and lithium prescribed including dates and doses.
Use data sheets for collection. Enter computer calculations
below.
ANTIPSYCHOTICS

__________ Average daily dose
__________ Cumulative dosages
__________ Cumulative length of administration
__________ Average maximum yearly dose

POLYPHARMACY

__________ # of PP incidences

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<tr>
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</thead>
<tbody>
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</table>

__________ # of incidences of PP by Category

__________ # of APs prescribed cumulatively

__________ # of aps prescribed cumulatively

ANTIPARKINSON AGENTS (aps)

__________ Average daily dose
__________ Cumulative dose
__________ Cumulative length of administration
### GENERAL INFORMATION CODES

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<td></td>
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<td>3 - black</td>
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<tr>
<td></td>
<td>4 - Oriental</td>
<td>4 - green</td>
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**DIAGNOSIS**

Use DSM-II code number; use current and primary diagnosis.

**DENTAL STATUS**

1 - all teeth
2 - missing teeth (record number)
3 - edentulous (no teeth)
   a. - with dentures
   b. - without dentures

**DATE TD DIAGNOSED:** For validation purposes; record date psychiatrist diagnosed TD.

**FIRST TD SYMPTOM:** Date of first recorded TD symptom mention or diagnosis.

**NUMBER OF DRUG-FREE PERIODS:** Number of two-month periods free of antipsychotics.

**NUMBER OF DRUG-FREE DAYS:** Total number of days free of antipsychotics.
EXTRAPYRAMIDAL DESCRIPTORS AND CODES

FORM:

1 - Pseudoparkinsonism
   a - Akinesia
   b - Tremor
   c - Rigidity

2 - Akathisia

3 - Acute Dystonic Reactions

TYPE:*

0 - Hypokinetic: akinesia, rigidity, acute dystonic reactions

R - Hyperkinetic: akathisia, tremor

N - neither; no pattern

M - mixed

NOTE: Refer to following pages for specific symptom codes.

* Chouinard et al. (1979)
1. Pseudoparkinsonism (Fully developed cases of parkinsonism =
generalized slowing of volitional movements
--akinesia, tremor at rest--especially involving
distal upper extremities, and rigidity. Elderly
females most susceptible.)

A. Akinesia (Hypokinesia; reduction in physical activity; decreased
motor activity.)

1. Slowness in initiating motor tasks (bradykinesia).

2. Fatigue when performing activities requiring repetitive
movements (bradykinesia).

3. Lessening of spontaneity; apathy--blunting of interest and
drive; slow mental activity.

4. Paucity of gestures.

5. Diminished conversation; impairment of vocalizations
(mutism).

6. Cramped handwriting (micrographia).

7. Mask-like, apathetic appearance with little facial
expression (hypomimia).


9. Gross muscle weakness with loss of associated movements that
accompany gait (amimia).


11. Psychological state without neurological signs simulating
depression, demoralization, residual schizophrenia, and
drug-induced sedation with effect of drowsiness.

12. May have somatic over-concern.

B. Tremor (Rhythmic 4-8/sec., oscillating resting tremor.)

1. Pill-rolling tremor of hands and fingers.

2. Oscillating resting tremor in head, trunk, or legs.

3. Rabbit syndrome: oscillating resting tremor of the
periocular (mouth area).
C. Rigidity ("Chemical strait jacket")

1. Stiffness and slowness of voluntary movements.
2. Cogwheel rigidity: presence of both tremor and rigidity.
3. Shuffling, festinating gait (an involuntary acceleration of gait when walking).
4. Slow, monotonous speech.
5. Stooped posture.
7. Plastic hypertonicity of both axial and limb musculature; "lead-pipe" variety of rigidity (state of tissues having excessive tension in response to stimuli).

D. Dysfunctions of the Autonomic Nervous System

1. Sialorrhea: excess of salivation; drooling.
2. Hyperhidrosis: generalized or localized excessive sweating.
3. Heat intolerance.
4. Seborrhea: functional disturbance of the sebaceous glands; characterized by increased secretion and discharge of sebum (oily/greasy material) that produces an oily appearance of the skin and the formation of greasy scales.
5. Hyperthermia/Hyperpyrexia: exceptionally high fever either in comparison to fever usually accompanying a particular disease or absolutely.

2. Akathisia (May be confused with agitated depression, psychiatric excitement, or anxiety; subjective desire to be in constant motion, inability to sit or stand still; favors no age group.)

1. Rocking and shifting of weight while standing.
2. Tapping of feet while sitting.
3. Pacing.
4. Fidgeting.
5. Disturbance in sleep with initial insomnia.
6. Hyperactivity—patients report worsening of their discomfort with physical inactivity.

7. Complaints of:
   a. restlessness
   b. impatience
   c. jitters
   d. nervousness
   e. panic
   f. vague feelings of discomfort

3. Acute Dystonic Reactions (Approximately 90% of the reactions occur within 72 hours of neuroleptic treatment initiation; occurs most frequently in children and young adults, especially males.)

1. Mild symptoms experienced as tightness of the throat or tongue.

2. Exaggerated and unusual posturing of the head, neck, and jaw that may present as:
   a. Torticolis: wryneck; abnormal twisting of the head; spasms of the neck.
   b. impairment of jaw movements.
   c. spasms with cramp-like pain.

3. Tongue protrusion or curling.

4. Facial distortions and grimacing.

5. Spasms of the musculature of the face or throat.


7. Dysphasia: loss of or deficiency in use of language.

8. Oculogyric crisis: fixed upward gaze; severe rolling of the eyes.

9. Less frequently, muscles of the extremities and back may be
involved and produce:

a. opisthotonus: spasm of the muscles of the back causing head and lower limbs to bend backward and trunk to arch forward.

b. scoliosis: lateral (crooked) curvature of the spine.

c. lordosis: abnormally exaggerated forward curvature of the spine.

d. bizarre gait.

10. Dystonic symptoms may be accompanied by automatic signs, such as:

a. profuse sweating

b. pallor

c. occasionally, fever

11. Repetitious, alternating rhythm of movements.
RATING DESCRIPTORS SHEET

HYPOKINETIC (Abnormal reduction in movement)

Slowness in initiating motor tasks

Reduction in physical activity

Decreased motor activity

Fatigue when performing activities requiring repetitive movements

Lessening of spontaneity

Slow mental activity

Apathy - blunting of interest and drive

Paucity of gestures

Diminished conversation

Mutism - Impairment of vocalization

Micrographia - Cramped handwriting

Hypomimia - Mask-like, apathetic appearance with little facial expression

Zombie-like appearance

Joint and muscle pain

Stiffness and slowness of voluntary movements

Cogwheel rigidity

Shuffling gait

Festinating gait - An involuntary acceleration of gait when walking

Slow, monotonous speech

Stooped posture
Dysarthria - Difficulty in articulating words

"Lead-pipe" variety of rigidity

Complaints of tightness of the throat or tongue

Exaggerated and unusual posturing of the head, neck, or jaw (frozen vs. rhythmical)

Abnormal twisting of the head (frozen vs. rhythmical)

Spasms of the neck (frozen vs. rhythmical)

Impairment of jaw movements (frozen vs. rhythmical)

Bizarre gait

Spasms with cramp-like pain (frozen vs. rhythmical)

Spasms of the musculature of the face or throat (frozen vs. rhythmical)

Dysphagia - Difficulty in swallowing

Oculogyric crisis - Fixed upward gaze; severe rolling of the eyes

HYPERKINETIC (Abnormal excess in movement)

Rocking and shifting of weight while standing

Tapping of the feet while sitting

Pacing

Fidgeting

Initial insomnia w/restless behavior(s) (i.e., night-time activity such as pacing, chain-smoking, etc.)

Overactivity

Restlessness

Impatience

Jitters

Nervousness
Feelings of panic

Parkinsonian (resting) tremor of the head, legs, or hands (in the hands, may be referred to as pill-rolling tremor)

Patient reports feelings of discomfort that worsen with physical inactivity (i.e., patient complains about discomfort that results if she/he does not remain constantly active)
INITIAL & PSYCHIATRIC BEHAVIOR PATTERNS RATING FORM

Subject #: 
Name: ___________________________  Data cut-off date: ________________

<table>
<thead>
<tr>
<th>IPBP</th>
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**INSTRUCTIONS:** Initial Psychiatric Behavior Pattern (IPBP): Record date(s) of admission notes above IPBP column. Read hypokinetic and hyperkinetic descriptors on Rating Descriptors Sheet.
Read admission notes; check which category the behavior notations fall into. (NOTE: admission notes may span one month.) Psychiatric Behavior Pattern (PBP): Record time period number at top of each column. Read hypokinetic and hyperkinetic descriptors on Rating Descriptors Sheet. Beginning January 1953 (or one month subsequent to admission for patients admitted after 1/53), for each 6 month period read Semi-Annual Summaries and Interdisciplinary Notes; check which category the behavioral notations fall into. NOTE: Record inclusion dates of all missing records.

Key

Hypokinetic = Behavior notations are consistent with descriptors under "Hypokinetic" on RDS.
Hyperkinetic = Behavior notations are consistent with descriptors under "Hyperkinetic" on RDS.
Mixed = Behavior notations are consistent with descriptors under both "Hyperkinetic" and "Hypokinetic" of RDS.
None = Detailed behavior notations available, but are not consistent with either listing on RDS.
? in None = No behavior notations provided on which to base a rating.
Appendix H

TRAINING PROCEDURES FOR RATER

1. The rater was given the Rating Descriptors Sheet to read over.

2. Differences between hypokinetic (abnormal reduction in movement) and hyperkinetic (abnormal excess in movement) descriptors were discussed.

3. Descriptors were defined and discussed.
   The following instructions were given:

4. The interest lies in behavioral descriptions found in the records; NOT in cognitive (i.e., thought disorders), affective (i.e., inappropriate or flat), or physiological (i.e., incontinency) descriptions.

5. The etiology of the movements is not of interest--i.e., involuntary, catatonia, etc.

6. The starting date for data collection on "Initial psychiatric behavior patterns" is the date of the subjects' first admission to a psychiatric institution. The data used for this pattern are the admission notes; these notes may span 2 days to 1 month.

7. The starting date for data collection on "Psychiatric behavior patterns" is January 1, 1953. If a subject is admitted after this time, starting date is one month after admission to (1) avoid confusion of "Initial psychiatric behavior pattern" data with "Psychiatric behavior pattern" data and (2) ensure initiation of antipsychotic medication.

8. The cut-off date will be given to the rater prior to the start of data collection for each subject. The rater is not to look at records subsequent to this date.

   Note: The assistant was informed, before collecting data on a subject of the cut-off date of that subject. This way the assistant should not have encountered any mention of TD or its symptoms which could have confounded the data and biased the rater. Initially it was believed that the rater should be uninformed about TD. However, during training questions occurred on the part of the rater concerning TD mentions seen in the records. Thus, to avoid confounding the ratings with any possible TD symptoms overlooked, it was deemed best to instruct the rater on
the symptoms of TD as well as this study's lack of interest in TD symptoms being included in the behavioral ratings. This was needed as any rating of TD would more than likely be categorized as "Hyperkinetic" and therefore confound the pre-TD behavioral ratings. Also, it was realized that the rater's knowledge of TD symptomology would better ensure that only pre-TD data was included in this study by the raters double-checking the original determination of TD on-set, while still remaining blind to the purpose of this study. The rater was instructed to record any symptoms encountered which may have been related to TD, as well as the date of the record entry, on another sheet of paper. The reason for this was explained as being potentially instructive for a future project unrelated to this study. The TD symptom(s) and date recorded by the rater were actually used by the author to adjust the data cut-off dates, prior to computer entry, in cases where the author overlooked earlier recorded TD symptoms or diagnoses.

9. In cases where records are missing, inclusion dates are to be recorded on the Rating Form in a column.

10. Consistency is important in the judgments of the ratings. The following are guidelines for the use of the four categories:

   Hyperkinetic: Majority of notations are congruent with the descriptors listed under this category on the Rating Descriptors Sheet.

   Hypokineti c: Majority of notations are congruent with the descriptors listed under this category on the Rating Descriptors Sheet.

   Mixed: Notations are congruent with the descriptors under both hyperkinetic and hypokinetic on the Rating Descriptors Sheet to the point that no judgment of hyper- or hypo- is possible.

   None: Notations are neither hyper- or hypo-.

11. In cases where detailed information is available but no behavioral descriptions are provided in the records for the "Initial psychiatric behavior pattern" or any 6 month period(s) of the "Psychiatric behavior pattern," a question mark (?) is to be placed in the None category as no information was provided on which to make a rating. This directive also applies in cases where no information is available—i.e., no entries were made in the patients' records during these time periods.
12. The rater had no idea of the nature or hypotheses of this study. The purpose of the ratings was simply explained as necessary to determine the subjects' various behavior patterns while receiving mediations. (The rater understood he would be de-briefed at the completion of this study.)

13. The rater had no knowledge of the medications the subject received during the time periods for which the subject's behavior was being rated.

14. The rater was trained for 5 hours in the following manner:
   a) Record usage was explained; the location of Admission Notes, Semi-Annual Summaries, and Interdisciplinary Notes was shown.
   b) Using a subject not in this study, the rater rated "Initial psychiatric behavior pattern" and "Psychiatric behavior patterns." We discussed the ratings and once again reviewed the irrelevancy of etiology as well as cognitive, affective, and physiological descriptions.
   c) The importance of his being consistent and staying within the descriptors provided--i.e., not adding to them, was emphasized.

Interjudge Agreement

The original rater quit after rating about 50% of each sample. Consequently, another rater was hired and then trained by the original rater to ensure consistency. She re-rated 3 subjects previously rated by the original rater which equalled 58 ratings or 29 years of behavioral histories. The ratings are discontinuous data, thus an intrarater correlation was not appropriate. Of the 58 ratings 44 were agreements, resulting in an interjudge agreement ratio of 76% (see Table 11). Of the 14 disagreements, 72% (10) were hyperkinetic or hypokinetic ratings rated as neither; 21% (3) were hyperkinetic or hypokinetic ratings rated as mixed; 7% (1) was a direct contradiction of ratings--i.e., a hypokinetic rating rated as hyperkinetic.

Table 11
Interjudge Variance Graph

<table>
<thead>
<tr>
<th>Rater 2</th>
<th>Rater 1</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyper</td>
<td>Hypo</td>
<td>Mixed</td>
<td>Neither</td>
</tr>
<tr>
<td>Hyper</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The interjudge agreement ratio is deemed acceptable as only one instance, out of 58 possibilities, involved a direct contradiction. The other disagreements involved one rater judging the behavior notations as reflecting hyperkinetic or hypokinetic behavior, while the other rated the notations as neither of or a mixture of the two behavior types. These disagreements are most likely the result of difficulties in reading the handwriting of the record entries and in locating necessary information. Many different individuals recorded behavioral information in the records and illegibility was a continuous problem. It was not uncommon for one of us to be able to read something another could not.
<table>
<thead>
<tr>
<th>DATES</th>
<th>DRUG</th>
<th>DOSAGE</th>
<th>FREQUENCY</th>
<th>COMMENTS</th>
</tr>
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<tr>
<td>2/3/55</td>
<td>TDL</td>
<td>16</td>
<td>2</td>
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<tr>
<td>1/23/55</td>
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<td>CPZ</td>
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<td>10/21/61</td>
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</table>
# PSYCHOMOTOR SYMPTOM SCALE

For each disorder listed below, check the space provided in the appropriate column for symptom severity.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Absent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>None</td>
<td>Patient feels</td>
<td>More intense</td>
<td>Restlessness to point of agitation. Cannot sit still for even a few minutes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nervous or</td>
<td>subjective complaints,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>uptight, may</td>
<td>inability to</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>have restless</td>
<td>feel comfortable in any</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>postural changes.</td>
<td>position.</td>
<td></td>
</tr>
<tr>
<td>Akinesia</td>
<td>None</td>
<td>Patient feels</td>
<td>More intense</td>
<td>Loss of facial expression.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dead inside, tired</td>
<td>subjective complaints,</td>
<td>Obvious decrease of associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all the time,</td>
<td>loss of associated</td>
<td>movements, definite motor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weakness. May</td>
<td>movement, diminution</td>
<td>expression, slow movements.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>appear apathetic.</td>
<td>of facial slowing.</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>None</td>
<td>Seldom or intermittently present.</td>
<td>Intermittently usually present.</td>
<td></td>
</tr>
<tr>
<td>Rigidty</td>
<td>None</td>
<td>Intermittent resistance to passage movement.</td>
<td>Cogwheeling effect in passive movement of the limbs in both directions.</td>
<td>Strong resistance to passive movement of the limbs.</td>
</tr>
<tr>
<td>Dystonia</td>
<td>None</td>
<td>Occasional and self-limiting oculogyric crises. Mild torticollis, trismus.</td>
<td>More severe dystonic reaction that requires IM or IV medications.</td>
<td>Psychiatric emergency that is life threatening.</td>
</tr>
<tr>
<td>TARDIVE DYSKINESIA</td>
<td>None</td>
<td>Occasional movements of tongue, vermicular movements, blinking, cheek puffing.</td>
<td>More frequent movements of tongue and lips, blepho-aspasm, occasional choreoathetotic movements in fingers or toes.</td>
<td>Choreoathetotic movements of limbs, trunk, and orofacial muscles.</td>
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</tr>
<tr>
<td>ABNORMAL MOVEMENTS</td>
<td>None</td>
<td>Occasional tic, twitch, or rocking movement. Would not be socially stigmatizing.</td>
<td>More frequent and socially stigmatizing movements.</td>
<td>Severe and obvious bizarre movements strongly suggesting a need for treatment.</td>
</tr>
</tbody>
</table>

Adapted from Van Putten (1974)
BIBLIOGRAPHY


Alexopoulos, G. S. Lack of complaints in schizophrenics with tardive dyskinesia. The Journal of Nervous and Mental Disease, 1979, 167, 125-127.


Roxburgh, P. Treatment of persistent phenothiazine-induced oral


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Birthplace: Lima, Ohio

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in Education
Doctor of Education

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Bachelor of Science

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Danville, Virginia

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Williamsburg, Virginia

1975-1977 Guidance Counselor
Newport News Public Schools
Newport News, Virginia
Abstract

DESCRIPTIVE CHARACTERISTICS OF INPATIENTS WITH TARDIVE DYSKINESIA AS DISTINGUISHED FROM INPATIENTS WITHOUT TARDIVE DYSKINESIA

Lucy Glover Savage, Ed.D.

The College of William and Mary, October 1980

Chairman: Charles O. Matthews, Ph.D.

The purpose of this study was to investigate the relationship of the presence or absence of tardive dyskinesia (TD) to drug and behavioral history variables. The author hoped to determine if there were descriptive characteristics, unique to patients with TD, which could merit further investigation as precursors of TD. Two samples, with 26 subjects each, were drawn from patients identified at Eastern State Hospital and screened by a psychiatrist. The TD and No-TD groups were matched on age, sex, and diagnosis. Entire drug histories were recorded and entire behavioral (hospitalization) histories were rated. Data collection was discontinued, for both subjects, with the emergence of TD symptoms in the TD subject. This was an ex post facto design.

It was hypothesized that significant differences would be found between the two groups on history of antipsychotic and antiparkinson medications, history of polypharmacy, history of drug-free days and periods, history of extrapyramidal symptoms (EPS), history of psychiatric behavior patterns, race, eye color, and dental status. A trend was noted for the No-TD group to have consistently higher means on all of the drug variables. Significantly higher means for the No-TD group were found for mean cumulative and mean daily dose of antipsychotics, mean length of antiparkinson agent administration, and in the number of EPS incidences. The TD group had significantly more edentulous subjects than the No-TD groups.

Although TD is clearly related to antipsychotic ingestion, apparently it is not related to the quantity of antipsychotics ingested. Future study should, therefore, focus on the relationship of individual vulnerability to the development of TD rather than on drug variables such as those investigated in this study. Further investigation of the behavioral precursors is indicated. A prospective design is recommended in order to clarify relationships, such as EPS history and the development of TD, that remain unclear in retrospective investigations.