ALPHA-TOCOPHEROL IN THE TREATMENT OF TARDIVE DYSKINESIA

Christian L. Shriqui M.D., F.R.C.P.(C)*
Department of Psychiatry
McGill University
Montréal, Québec

A Thesis submitted to the Faculty of Graduate Studies and Research, McGill University, in partial fulfillment of the requirements for the degree of Master of Science, September 1990.

* Supported in part by a Research Development Award from the Canadian Psychiatric Research Foundation to Dr. C. Shriqui, and a research grant from St. Mary's Hospital Foundation.

ALPHA-TOCOPHEROL IN THE TREATMENT OF TARDIVE DYSKINESIA

Christian L. Shriqui, M.D., F.R.C.P.(C)

ABSTRACT

Free radicals are consistently implicated in the physiology of normal aging and in the pathophysiology of neuropsychiatric disorders such as Tardive Dyskinesia (TD).

Alpha-tocopherol (Vitamin E), a potent antioxidant, was compared to Placebo in a double-blind randomized crossover study among thirty-three subjects with TD. Six subjects terminated prematurely while the remaining twenty-seven subjects (17 female; 10 male) had a mean age ± SD of 42.9 ± 12.6 and an age range of 19-69. Twenty-two subjects satisfied DSM-III-R criteria for schizophrenia and five subjects met DSM-III-R criteria for bipolar disorder. All subjects satisfied Research Diagnoses Criteria (Schooler and Kane) for at least mild TD. Patient's psychopathology and psychotropic regimen remained stable throughout the study.

Subjects were randomly assigned to two 6 week treatment periods, each with Vitamin E and Placebo. A 2-3 week Placebo washout was conducted between each 6 week treatment period. Vitamin E or Placebo was administered double-blind on a fixed dosage schedule of one 400 I.U. capsule of Vitamin E, or one identical placebo capsule, three times daily.

The Abnormal Involuntary Movement Scale (AIMS) and the Extrapyramidal Symptom Rating Scale (ESRS) served as primary outcome measures. Scores on the ESRS subscales I-VI and AIMS total score, at termination of Vitamin E and Placebo treatment, from analysis of variance for the two-period crossover design, revealed no significant differences (with alpha levels set at .05). These results suggest that Vitamin E, at the dosage level used, confers no consistent short term symptomatic benefit to patients with TD. This finding does not replicate those of two previous reports where Vitamin E, administered for a four week period, showed a significant effect over Placebo. Possible reasons for these differences are discussed. Nevertheless, further research with a long-term follow-up cohort of newly treated schizophrenics with neuroleptics, is a likely step to clarify the prophylactic use of Vitamin E alone, or in combination with other antioxidants.

RÉSUMÉ

Les radicaux libres sont impliqués dans le vieillissement normal ainsi que dans la physiopathologie de désordres neuropsychiatriques tels que la Dyskinésie Tardive (DT).

L'alpha-tocophérol (Vitamine E), un antioxidant reconnu, a été comparé au Placebo dans une étude chassé-croisé randomisée en double aveugle auprès de trente-trois sujets ayant une DT. Six sujets ont interrompus l'étude, alors que les vingt-sept restants (17 femmes; 10 hommes) avaient un age moyen $\pm$ écart-type de 42.9 $\pm$ 12.6 et un age variant de 19-69. Selon les critères du DSM-III-R, vingt-deux sujets avaient un diagnostique de schizophrénie et cinq sujets un diagnostique de trouble bipolaire. Tout les sujets répondaient à des critères de recherche établis (Schooler et Kane) pour définir une DT au moins légère. La psychopathologie et le régime psychotrope des sujets sont demeurés stables tout au long de l'étude.

Chaque sujet fut exposé à deux périodes de traitement, d'une durée de six semaines chacunes, avec de la Vitamine E et du Placebo. L'administration d'un Placebo, pendant deux à trois semaines, est survenu entre chaque période de traitement. La Vitamine E ou Placebo fut administrée en double aveugle avec un dosage fixe d'une capsule de 400 U.I. de Vitamine E, ou d'une capsule identique de Placebo, trois fois par jour.

L'**Abnormal Involuntary Movement Scale** (AIMS) et le **Extrapyramidal Symptom Rating Scale** (ESRS) ont servies d'échelles de mesure principales. Les résultats aux sous-échelles I à VI du ESRS et au score total à l'AIMS, à la fin d'une période de six semaines d'un traitement à la Vitamine E et au Placebo n'a révélé aucune différence significative (avec un niveau de signification de .05) à l'analyse de variance pour une étude à deux périodes avec chassé-croisé.

Cette étude suggère que la Vitamine E, aux doses utilisées, ne confère aucune éfficacité claire à court terme auprès de sujets souffrant de DT. Ce résultat ne corrobore pas celui de deux études antérieures ou la Vitamine E, administrée pendant une période de quatres semaines, s'est révélée supérieure au Placebo. Des raisons possibles pour cette divergence de résultats sont discutées.

Néanmoins, une étude contrôlée menée auprès d'une cohorte de patients nouvellement traités aux neuroleptiques, élucidera le rôle prophylactique de la Vitamine E seule ou combinée avec d'autres antioxidants.

ALPHA-TOCOPHEROL IN THE TREATMENT OF TARDIVE DYSKINESIA

1.0 INTRODUCTION

1.1 SCHIZOPHRENIA

i) Clinical Features:

Schizophrenia is a chronic mental disorder which affects about one percent of the world population (1). Its social costs are considerable since the disorder typically appears during adolescence or early adulthood. Essential features of the disorder are the presence of characteristic psychotic symptoms during the acute phase of the illness and impairment in several areas of routine daily functioning such as work, social relations and self-care (2). It is a heterogenous condition with clear genetic, biological, environmental, familial, psychological and social factors, which in varying degrees, confer an individual's susceptibility to the onset of the disease (2-8). The long-term outcome of schizophrenia is variable. A ten-year longitudinal follow-up study of first admission cases reported that 58 % of a cohort of eighty-eight schizophrenics had no social or intellectual deficits, 51 % had normal economic productivity, and 69 % had a good or fair social adjustment (9). In this cohort, only 8 % had an unremitting course requiring institutionalization. Possible reasons for the improved prognosis in schizophrenia are: short initial hospitalization, use of community services (psychiatric and social), and the use of maintenance antipsychotic drug treatment (9).

Several classification systems have been suggested in

schizophrenia amongst which DSM-III-R criteria for schizophrenia (2), listed in the Appendices. Schizophrenia has also been divided into two important clinical syndrome profiles, Type I and Type II, which, although generally regarded as independent of each other, are not mutually exclusive (10-13). The Type I syndrome is characterized by positive symptoms such as delusions, hallucinations and thought disorder. The Type II syndrome is manifested by a predominance of negative symptoms such as cognitive impoverishment, affective flattening, social withdrawal and avolition. Central nervous system structural abnormalities on computerized tomography and a more chronic course have often been associated with the Type II syndrome. The latter syndrome has been associated with tardive dyskinesia (14) and is also believed to be less responsive to conventional neuroleptics. However, recent findings challenge the notion of neuroleptic resistance in Type II schizophrenics (15-16).

ii) Neurobiological Hypotheses:

The dopamine hypothesis of schizophrenia, which has dominated biological psychiatry research for more than two decades, proposes that schizophrenia results from some form of hyperdopaminergic activity in the mesolimbic or mesocortical DA nerve terminal regions (17-19). This assumption is based on the following observations: 1) that antipsychotic drugs are dopamine (DA) antagonists and their

potency is correlated with DA receptor blockade; and 2) DA agonists such as amphetamine induce psychotic states similar to paranoid schizophrenia (17-21). This DA hyperactivity could result from several possible mechanisms such as: dysregulation of DA synthesis, increased DA release from terminals, impaired DA removal from nerve ending terminals, or an elevation of either the number of receptors or their sensitivity. There is however no direct evidence supporting inherent DA neuron hyperactivity in schizophrenia. Dopamine metabolite levels of homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) in the cerebrospinal fluid (CSF) of schizophrenics have not been shown to be higher than in normal controls (22). Furthermore, measurements of DA metabolites such as HVA in either plasma or CSF, as indicators of dopamine activity, are currently unable to tease out the central versus peripheral nervous system contributions to plasma HVA, nor can they adequately extrapolate on mesolimbic dopamine activity (as opposed to cortical or nigrostriatal) from cerebrospinal fluid HVA . Support for DA hyperactivity in schizophrenia originates from receptor studies where D_2 dopamine receptors have a high affinity with antipsychotic drug binding. D_2 receptors have been found, although not consistently, to be increased in the postmortem brains of schizophrenic patients (23). An important issue remains whether brain DA receptor density is elevated in schizophrenia, independent of the increase which

would be expected as an adaptive response to long-term neuroleptic drug treatment. Despite technical controversy, an increase in D_2 receptor density has however been reported in drug-naive schizophrenics (24). Little is known about the role of the D_1 dopamine receptors (25). However, it has been suggested that D_1 receptors normally exert some influence on D_2 receptors, but a dysfunction of this communication would occur in schizophrenia (26). Despite recent progress, there is still little understanding of the physiological and psychological roles of dopamine tracts in the central nervous system and the quest for a clinically measurable indicator of central dopamine activity continues. Current research is devoting attention on the interactions between dopamine and other neurochemical systems such as serotonin, acetylcholine, cholecystokinin (CCK), neurotensin, substance P, and the prostaglandins (PG) (27-33). The development of certain atypical antipsychotics, such as clozapine, which have a relatively weak affinity for D-2 receptors, yet significant serotonin 5-HT_2 receptor antagonist properties, emphasize the presence of more than one unique neurotransmitter system abnormality in schizophrenia (34-38).

1.2 BIPOLAR DISORDER

i) Clinical features:

The lifetime risk for bipolar disorder in industrialized

nations is less than one percent for both sexes (39). The illness usually manifests itself in the early 20s, and commonly has serious consequences such as: marital instability, job loss, financial recklessness, alienation of family, alcohol abuse, and death by suicide (2). Varying degrees of genetic, biological, environmental, familial, psychological and social factors play a role in its development. The essential clinical features of bipolar disorder are one or more manic episode usually accompanied by one or more major depressive episode. DSM-III-R criteria for bipolar disorder are generally used in clinical practice and research (2). These criteria are listed in the Appendices. Psychosis is a common yet complicating factor in the management of bipolar disorder (40). Classical " schizophrenic" symptoms, including many types of hallucinations, delusions, catatonic symptoms, and Schneiderian first-rank symptoms have been reported in 20 % to 50 % of cases of bipolar illness (41). The presence or absence of psychosis further suggests the disorders heterogeneity in clinical, biological, and treatment response characteristics.

ii) Neurobiological hypotheses:

The monoamine hypothesis of affective disorders emerged following a greater understanding in the 1960s of the action of psychotropic drugs on the biogenic amines norepinephrine

(NE), serotonin (5-HT), and to a lesser degree, epinephrine and dopamine (42,43). Tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors, used principally for treating major depressive episodes, acutely increase the availability of biogenic amine transmitters to postsynaptic receptors through two distinct mechanisms. TCAs block presynaptic autoreceptors, thus promote neurotransmitter release, and block their reuptake into the presynaptic terminal (44). MAO inhibitors inhibit the intracytoplasmic enzyme important in the metabolic degradation of biogenic amine neurotransmitters and therefore increase vesicular and cytoplasmic concentrations of monoamines (45). These drug actions led to the monoamine hypothesis that a deficit in the amount of norepinephrine or serotonin available to postsynaptic receptors results in depression, and an excess leads to mania. Support for this hypothesis is provided by measurements of the urinary excretion of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) which has been reported to be low in depressed patients and elevated in manic patients (46). A subgroup of depressed patients have been identified with low CSF levels of the serotonin metabolite, 5-hydroxyindolacetic acid (5-HIAA) (47). However, in addition to difficulties in measuring monoamines and their metabolites, the CNS contribution to levels measured in serum or urine is controversial. A revised version of the monoamine hypothesis, based on receptor down-

regulation at postsynaptic receptor sites, takes into account the fact that the brain normally compensates for acute pharmacologic effects (44). While the monoamine hypothesis of affective illness focused largely on norepinephrine, altered functional dopaminergic activity in both depressed and manic patients have been suggested (48). In a subgroup of depressed patients there would be a reduced level of dopamine activity while the opposite would occur in manic patients. Support for an increase in dopamine function in mania originates from clinical and pharmacological observations with dopamine agonists and antagonists. Amphetamine has activating and mood-elevating effects which can, after prolonged use, lead to psychotic states that are treatable by dopamine antagonists (48). These behavioral effects bear similarities to mania whose response to neuroleptic drugs is also linked to dopamine receptor blockade (48).

1.3 DRUG TREATMENT OF SCHIZOPHRENIA AND BIPOLAR DISORDER

A cornerstone for the treatment of schizophrenia has been antipsychotic drug maintenance therapy since the introduction of these agents in clinical practice in 1952. However, currently used antipsychotic drugs do not constitute a cure for schizophrenia, and have additional limitations: 1) limited effectiveness in a significant number of patients (up to 20 percent); 2) poor efficacy in

improving social and interpersonal functioning; 3) lack of neurotransmitter specificity with actions on serotonergic, muscarinic and noradrenergic systems in addition to dopamine receptor blockade; 4) poor regional dopamine specificity with actions not only on the mesocortical/mesolimbic systems (regarded as the neuronal substrates for psychopathology), but also on the hypophyseal system (accounting for neuroendocrine abnormalities such as hyperprolactinemia and amenorrhea), and on the nigrostriatal system causing extrapyramidal side-effects, which will be the subject of further discussion (36, 49,50).

With its proven efficacy, lithium is the primary treatment for acute mania, and for the prophylaxis of bipolar disorder (40,51,52). However, because of its delayed therapeutic onset of action, many clinicians often combine lithium with antipsychotic agents in the acute management of mania, especially when there are associated psychotic symptoms and/or severe agitation (40,53,54).

In order to decrease exposure to antipsychotic drugs, benzodiazepines such as clonazepam and lorazepam, may play a significant role, either alone or in combination with other psychotropics, in controlling mania (55-59). While it is not usual to prescribe maintenance antipsychotic drug treatment to bipolar patients, such a treatment alternative can be necessary in controlling the underlying psychopathology in severely affected patients whose compliance or clinical

response to lithium is poor, e.g., rapid cyclers, and patients with coexistent psychotic features (40). In such patients, carefully documenting the reasons for maintenance neuroleptic treatment is essential since affective disorder patients may be at increased risk of developing Tardive Dyskinesia (60--66).

1.4 NEUROLOGICAL SIDE-EFFECTS OF ANTIPSYCHOTIC DRUGS

Neurological, particularly extrapyramidal side-effects (EPSEs) are the most common troublesome adverse reactions to antipsychotic drug treatment (67,68). Conventional antipsychotics share an equal propensity to induce EPSEs. Novel antipsychotics such as clozapine have a significantly lower incidence of EPSEs (34,36-38). In the case of clozapine, because of its higher risk of agranulocytosis, its use is mostly targeted for treatment-resistant schizophrenics to conventional neuroleptics (69,70).

The pathophysiology of these neurological side-effects remains poorly understood, although dopamine-mediated systems in the basal ganglia are believed to be involved. These syndromes can be divided in the following five categories (50,60,62,71-77):

a) Acute dystonia: Acute dystonias usually occur within the first few days of treatment and are associated with the use of high-potency neuroleptics (60,71,76,77). They may be triggered by a single dose of medication regardless of the

route of administration. Acute dystonias consist of involuntary muscle spasms of the neck and oro-facial areas but may involve virtually any striated muscle producing oculogyric crisis, torticollis, retrocollis, opisthotonos, and carpopedal spasm. Acute dystonia can mimic a seizure disorder, tetany or tetanus, and a conversion reaction (60,71,77). Dystonia occurs more frequently in younger, male patients (71,77). Laryngeal dystonia, a potentially life-threatening medical emergency, is fortunately rare in its severe form (77). The treatment by injection of an antiparkinsonian medication has both diagnostic and curative values and is usually dramatically effective (60,71,77).

b) Drug-induced parkinsonism: Drug-induced parkinsonism usually occurs weeks to months after the initiation of treatment (60,71,77). Women and the elderly are at increased risk (71,77). The syndrome may be clinically indistinguishable from idiopathic or post-encephalitic parkinsonism and consists of a triad of signs: bradykinesia or akinesia, rigidity, and tremor (60,71,77). The latter is typically greater at rest than during activity and has a frequency of four to eight cycles per second. The bradykinetic patient can present a clinical picture of cogwheel rigidity of upper and lower joints, stooped posture, festinant gait and mask-like inexpressive facies (60,71,77). Seborrhea and hypersalivation are common associated features. The rabbit syndrome, characterized by

an isolated perioral tremor mimicking the facial expression of a rabbit chewing a carrot, is a late occuring variant of drug-induced parkinsonism which can be mistaken for tardive dyskinesia (60,71,77). Unlike the latter, the rabbit syndrome usually responds favorably to antiparkinsonian agents. Some "tolerance" to drug-induced parkinsonism develops in certain patients with a fading of clinical signs over two or three months (71,77). The syndrome can be improved by a decrease in the dosage of neuroleptics to the minimal effective dose when possible, but frequently its treatment requires the use of antiparkinsonian agents such as benztropine mesylate (Cogentin) or procyclidine (Kemadrin)(71,77). Antiparkinsonian agents should be gradually discontinued after one to three months while monitoring for a possible reemergence of symptoms (77).

c) Akathisia: Akathisia is one of the most important of the neuroleptic side effects (50,60). Women are more commonly affected than men (77). Subjectively, patients relate a sensation of increased tension, inner restlessness, and a drive or compulsion to move about. Objectively, the syndrome is characterized by actual motor restlessness, fidgeting, pacing, and "restless legs". The feeling of restlessness is not only unpleasant to the patient, but the associated dysphoria can lead to non-compliance to drug treatment. The "akathisia triad" of insomnia, hypermotility, and psychic

discomfort are frequently mistaken as an exacerbation of the patient's psychosis which results in an inappropriate increase of neuroleptic medication (60,77). This in turn magnifies the patient's initial complaint. For many years, akathisia was thought to be a typical neuroleptic-induced side effect treatable by antiparkinsonian agents. However, the treatment of akathisia is frequently disappointing. Antiparkinsonian anticholinergic antihistamine drugs and benzodiazepines provide only minimal relief in the majority of cases (60). Lowering the dose of the neuroleptic or switching from a high-potency to a low-potency agent are possible strategies to decrease the syndrome's severity (60,71). These latter approaches are not feasible for a majority of patients whose psychoses are controlled with their current neuroleptic drug treatment. The current treatment of choice for akathisia are beta-blockers, such as the lipophilic selective $beta_1$-blocker metoprolol (Betaloc,Lopresor)(50,78).

d) Neuroleptic malignant syndrome: Neuroleptic malignant syndrome (NMS) is a life-threatening complication of neuroleptic treatment (50,60,74-76). The main symptoms of NMS are muscle rigidity, fever, diaphoresis, and autonomic instability (50,60,74-76). In most cases these symptoms are present together. Other symptoms such as tremor, dystonia, dyskinesia, sialorrhea, incontinence, muteness and stupor may be present. The values of creatine phosphokinase are

usually very high and leucocytosis is common (50,74,75). Symptoms of NMS have been reported without the full-blown syndrome. The mortality rate related to NMS is approximately 20% (60), but this figure may actually reflect severe forms of the disorder. Despite the frequent use of neuroleptics in clinical practice, the incidence of NMS is fortunately low, but in recent years, there has been a steady increase in the number of reported cases (75). The syndrome is more frequent in young males but also affects the elderly (74,75). Other risk factors include: the number of intramuscular doses of neuroleptic, the first few days of a first dose or a rapid increase in neuroleptic dose (79). The immediate withdrawal of neuroleptics in a patient with suspected NMS is a first step to treatment (60). Evaluating the efficacy of specific therapeutic agents in NMS is complicated by the small number of single case reports. Nevertheless, dantrolene and bromocriptine have demonstrated therapeutic effects as well as amantadine, levodopa, and benzodiazepines in a few cases (74-76). The use of electroconvulsive therapy for NMS is a controversial approach (74,75).

e) Tardive Dyskinesia: Tardive dyskinesia (TD) is a major complication of long-term neuroleptic drug treatment (50,60,62,71-73,76) and is discussed in the following section.

2.0 TARDIVE DYSKINESIA

2.1 Introduction

Tardive dyskinesia (TD) is a hyperkinetic syndrome of heterogenous abnormal movements, which occurs in predisposed individuals during or following the cessation of long-term neuroleptic drug therapy, and which is not attributable to other causes (60,62,71). TD's significant prevalence, conservatively estimated at 15-20 %, potential for irreversibility, lack of effective treatment, and legal implications are a concern to clinicians prescribing maintenance neuroleptic drug therapy (60-64,71-73). The reversibility of the syndrome was recognized since its early descriptions (80), nevertheless, a persistent course is not uncommon.

2.2 Clinical manifestations and outcome:

Clinically, TD is characterized by involuntary, repetitive, purposeless hyperkinetic movements of choreoathetotic and dystonic nature varying in location and intensity (60,62,71). The initial descriptions emphasized oro-facial signs particularly amongst elderly patients (60,63,72,73). Oro-facial signs include tongue protusion, puckering, smacking, pouting, chewing and lateral jaw movements, but TD can also involve the upper and lower extremities, neck, trunk as well as virtually any muscle group (60). At times,

the fingers and toes move in a repetitive pattern that resembles an invisible piano (60,62,63,71,72). Mild forms of respiratory dyskinesias with irregular respiratory rates and grunting noises are not that uncommon but are seldomly diagnosed (60,81).

Early reports of TD in children emphasized axial features such as hemiballism but recent evaluations suggest a greater similarity to the adult presentations (60,62,72). Atypical forms of TD like tardive dystonia and tardive akathisia have been reported but it is unclear if these sub-types have their own underlying pathophysiology or represent symptom clusters of one unique syndrome (60,62). TD frequently coexists with other movement disorders such as parkinsonism and akathisia (60,82,83).

Three types of dyskinesia have been described with respect to their time of onset (60,62,84,85). **Covert dyskinesia** is unmasked when neuroleptic drugs are reduced or discontinued. **Withdrawal dyskinesias** appear under similar circumstances but, by definition, resolve spontaneously within 3 months. **Overt dyskinesia** is present during the course of neuroleptic treatment.

Research diagnostic criteria for TD have been widely accepted in clinical practice and research and include three prerequisites: 1) at least three months of cumulative neuroleptic exposure, 2) at least moderate abnormal involuntary movements in one or more body areas or mild

movements in two or more body areas, and 3) the absence of other conditions that produce involuntary hyperkinetic dyskinesias (85).

The long-term outcome of TD is unpredictable and varies widely across studies (60,62,83,86,87). However, recent findings support the conclusion that once TD develops, its course is not unremittingly progressive and can actually improve with or without cessation of medication (83,88-90). A recent 5-year longitudinal study in a cohort of 169 schizophrenic outpatients found that the prevalence of TD increased from 22 to 44 % (83). Of those 131 patients who did not have TD at the start of the study, 35 % developed it, at an annual incidence rate of 8.4 % . Nine of the 38 cases who had TD 5 years previously did not have it at the follow-up examination.

Defining persistent TD as irreversible if the dyskinetic syndrome is of twelve months duration or greater is inappropriate when taking into account its varying long-term outcome (62).

Factors that influence the improvement of TD are: patient variables (age, sex, and psychiatric diagnosis), treatment parameters (drug dosage, cumulative exposure, discontinued versus continued treatment), and temporal aspects (duration of TD, length of follow-up) (60,62-64,73,83,86,87,91,92).

2.3 Differential diagnosis:

Tardive dyskinesia (TD) must be distinguished from other EPSEs of neuroleptics. Even though TD has been reported following brief periods of neuroleptic drug treatment, it is rare for the syndrome to develop before three to six months of treatment (60).

In recent years, increasing concern about tardive dyskinesia has increased awareness among clinicians. The latter should be careful however to not overdiagnose the syndrome. A diagnosis of TD should be considered in any patient with abnormal involuntary movements who has a history of taking neuroleptic medication for at least three months (91). A careful neuropsychiatric evaluation and detailed laboratory assessment including thyroid function studies are necessary since there are no clinical or laboratory tests that are pathognomonic for TD (60). Since the diagnosis of TD is made largely by exclusion, knowledge of it's differential diagnosis, listed in Table I of the Appendices, is essential (60,62,71,91,93).

INSERT TABLE I ABOUT HERE

L-DOPA and amphetamines can induce dyskinetic movements that resolve following the cessation of medication (60). Tricyclic antidepressants, rarely associated with persistant

TD, have almost always occured in patients who had a history of antipsychotic drug treatment (60). Metoclopramide (Maxeran), a drug frequently used in gastroenterology, with a chemical structure similar to the antipsychotic sulpiride, has been reported to cause TD (94,95). Spontaneous dyskinesias, with an estimated prevalence of 4 to 7 % , are usually orofacial in their distribution, and occur chiefly in elderly individuals (72,96). Stereotyped movements in schizophrenics have a symbolic meaning to patients who, usually, are aware of them (60).

2.4 Epidemiology:

a) Prevalence and incidence:

The American Psychiatric Association Task Force Report on Tardive Dyskinesia reported prevalence rates of TD varying between 0.5 to 65 percent, with an estimated mean of 20 percent (71). This wide variability was related to several factors: heterogenous patient populations, differences in diagnostic criteria for TD, methods of case ascertainment and neurological assessment (71).

A retrospective analysis of 34 555 patients enrolled in 56 studies published from 1959 to 1979, estimated a 20 percent mean prevalence rate of TD (64). However, several studies have reported higher prevalence and incidence rates (65,83,97-101).

b) Risk factors:

A recent study evaluated 50 schizophrenics never treated

with neuroleptics and failed to find any cases of TD (102). This report further establishes the central role of neuroleptics in the etiology of TD.

Amongst the many suggested, advancing age is the single most consistent risk factor for TD, with younger patients likely to show the greatest improvement (60,62-64,71-73,86,87,91,92). Female sex is the second most frequently suggested risk factor (60,62,71,86,87,91,92). Several reports note that affective disorders may be a risk factor for TD, yet it is not clear if schizophrenia is a risk or a protective factor for the disorder (60,62,64-66,99). Recent data suggest that clinically significant parkinsonism constitutes a risk factor for TD (83,91,103). Furthermore, recent evidence shows a cumulative increase in the incidence of TD with longer duration of neuroleptic exposure, at least during the first 4 to 5 years of treatment (83,103,104).

2.5 Physiopathology:

Despite considerable research efforts, the pathophysiology of tardive dyskinesia (TD) remains largely unknown (60). Amongst the several hypotheses suggested, the one that has received the most attention is that of TD which is characterized by a functional hyperdopaminergic state with striatal postsynaptic dopamine receptor supersensitivity (60,62,71,87,105-109). By blocking postsynaptic dopamine receptors, neuroleptics would create a chemical state

analogous to surgical denervation. Prolonged receptor blockade would either "sensitize" postsynaptic dopamine receptors, or increase their numbers, or both. In long-term neuroleptic treated rats, dopamine receptor supersensitivity clearly occurs (105-106). In primates, such as monkeys and humans, this supersensitivity only occasionally produces clinically manifest dykinesias (62,105-109). Neuroleptic withdrawal emergent dyskinesias may result from a supersensitivity mechanism more than persistent forms of TD (107). This is supported by the observation that supersensitivity is often short lived and can be elicited after only a single injection of a neuroleptic (106,107).

TD's heterogeneity both in its clinical manifestations and response to various agents makes it likely that apart from dopamine, other neurotransmitters particularly norepinephrine, L-Gamma-Aminobutyric acid (GABA), acetylcholine, and serotonin may be involved in its pathophysiology (60,62,105-110). Both noradrenergic hyperactivity and hypoactivity, as evidenced by plasma and CSF dopamine-bêta-hydroxylase [DBH - the enzyme that catalyzes the formation of norepinephrine from dopamine] levels, have been reported in subsets of TD subjects (60,105,106).

GABA is frequently implicated in the pathophysiology of TD (60,62,87,105,106,111,112). The inhibitory effect of GABA on DA neurons is the rationale for increasing GABA activity as

a treatment for TD (62). Now, however, clinical use of GABAmimetic drugs is based on the critical role GABAergic neurons play in the substantia nigra pars reticulata in mediating dyskinetic movements (113). These substantia nigra pars reticulata GABA-containing neurons form an important inhibitory efferent pathway from the basal ganglia (112). In the experimental animal, disruption of these GABAergic efferents can produce hyperkinetic involuntary movements (114). Chronic neuroleptic treatment in animals has resulted in a loss of striatal neurons (which could be GABA-ergic) and in a reduction of glutamic acid decarboxylase (GAD - the enzyme which catalyzes the synthesis of GABA) activity in the substantia nigra (105,106,115). In an experimental model, monkeys chronically treated with neuroleptics that developed a dyskinetic syndrome, demonstrated a reduction in GAD activity, whereas similarly treated animals without dyskinesia did not (115). Treatment with GABA-ergic drugs such as clonazepam, muscimol, and gamma-acetylenic GABA have reduced symptom severity in patients with TD (105,106,112,116). These observations have led to the proposal that a GABA-ergic dysfunction may be an important underlying mechanism in tardive dyskinesia (106,112,116-118).

An overlapping of neurochemical and neuroanatomical abnormalities may be important factors in the development of TD (105-107). While dopaminergic supersensitivity may be a

common feature amongst neuroleptic-treated subjects, as well as in the development of withdrawal emergent dyskinesias, other neurochemical abnormalities (e.g., noradrenergic hyperactivity, GABA-ergic hypoactivity, or cholinergic hypoactivity) may be important for the occurence of specific subtypes of persistent TD (60,62,105,106).

Computerized axial tomography (CAT) scans have been inconsistent in showing significant differences between TD and non-TD patients (60,62,87,105). Some neuropathological studies have reported higher rates of nigral degeneration and gliosis in TD subjects while others have concluded that these changes are non specific and age related (62,119). Basal ganglia alterations in rodents chronically treated with neuroleptics have been reported (120) but this is not a consistent finding (62). The precise mechanisms underlying neuronal damage in persistent TD are unknown but may involve the action of cytotoxic free radicals (120-128).

2.6 Prevention:

Because of lack of effective treatment, prevention of TD is essential (60). Primary prevention includes: limiting the indications of long-term neuroleptic drug therapy to essentially schizophrenia (60,61). Prior to initiation of neuroleptic drugs, patients should be examined to determine the presence of any preexisting movement disorder and should be reexamined at periodic intervals. Secondary prevention

consists of: 1) limiting the duration of neuroleptic treatment especially amongst first break episode patients, and 2) using the lowest possible dose for maintenance treatment (60,61,91,129). Early detection with commonly used rating scales such as the Abnormal Involuntary Movement Scale (AIMS) (130) or the Extrapyramidal Symptom Rating Scale (ESRS) (131) used every six months may help contain the progression or increase the likelihood of reversibility of the syndrome.

2.7 Treatment:

Despite several dozen clinical trials with numerous agents (60,62,71,87,91,105,132,133), the present treatment of choice for tardive dyskinesia is gradual reduction of antipsychotic drug treatment when possible (60). Discontinuing drug treatment generally stabilizes or improves TD but this is not a realistic alternative for a majority of chronic schizophrenic patients (86). Maintenance neuroleptic drug therapy at low to moderate doses (300-600 mg/day of chlorpromazine equivalents or less) frequently stabilizes or improves TD symptoms (60,86,90).

Pharmacological strategies:

Dopamine

Increasing the dosage of neuroleptics consistently masks TD (60,62,105,132). This antidyskinetic effect of neuroleptics

appears to be separate from their sedative and antipsychotic effects (132). This strategy is primarily indicated in patients who present a moderate to severe form of TD which is unresponsive to other agents, and who need continued neuroleptic drug treatment. Clozapine treatment has led to various improvements in patients with TD (133-136). Its use may become an important alternative strategy in patients with moderate to severe TD who need continued antipsychotic drug therapy.

Agents that decrease presynaptic DA activity via depletion or false transmission such as reserpine, tetrabenazine, alpha-methyl-paratyrosine have produced variable changes in TD severity (62,107,132). Desensitizing hypersensitive DA receptors by temporarily increasing dopamine levels is an appealing research strategy still under investigation (137).

Acetylcholine

Anticholinergic drugs may be of benefit in subtypes of TD with tardive dystonia (132). However, these agents usually have no effect or aggravate more typical forms of TD (62,132). Augmenting cholinergic function with physostigmine, an acetylcholine esterase inhibitor, has had inconsistent results which could be related to subtypes of TD or to side effects of physostigmine (62). Clinical results with choline precursors such as deanol, choline, and

lecithin, were initially encouraging but later studies were relatively unsuccessful (60,62,71,72,138,139).

GABA

GABAmimetic treatments vary in their antidyskinetic effects. Studies with putative GABAergic drugs such as baclofen and valproic acid have been inconsistent in their antidyskinetic action (62,112,132). Encouraging results with the potent $GABA_A$ agonist muscimol, and with direct (e.g., progabide) and indirect (e.g., Gamma-vinyl GABA) GABA agonist drugs have been reported (111,112,116). However, despite an effective antidyskinetic action, side effects of several specific GABA agonists have precluded their further clinical applicability (112).

Benzodiazepine receptors, with a subpopulation of $GABA_A$ receptors, form the GABA-benzodiazepine-chloride ion channel complex (140). Benzodiazepines act at this site as indirect $GABA_A$ agonists. In a recent 12-week, double-blind, placebo-controlled, randomized crossover trial in 19 chronically ill patients with TD, clonazepam treatment led to a 35 % decrease in dyskinesia ratings (112). The authors observed that tolerance to clonazepam's antidyskinetic effect developed after long-term use of the drug, but a 2-week clonazepam-free period was able to recapture the drugs antidyskinetic effect.

Other

Miscellaneous agents used to treat TD such as tryptophan and 5-hydroxy-tryptophan (both serotonergic agonists), cyproheptadine (a serotonergic antagonist), lithium, propranolol, estrogen, and many others have been generally unsuccessful (62,105,132). Clonidine, a presynaptic alpha$_2$-adrenergic receptor agonist, has shown some efficacy in patients with TD (105,106). In a recent open pilot study, verapamil, a calcium channel blocker, was successful in four out of six patients with severe TD (141). Alpha-tocopherol in the treatment of TD is a novel research strategy which, so far, has had encouraging results (123,142).

3.0 FREE RADICALS

Free radicals (e.g., superoxide, hydroxyl radicals) are consistently implicated in the physiology of normal aging and in the pathophysiology of neuropsychiatric disorders such as Parkinson's disease, Alzheimer's disease, schizophrenia, and tardive dyskinesia (120-128,143,144-147). They are highly reactive compounds, with short half-lives, containing at least one unpaired electron, and are produced by a wide variety of "in vivo" reactions which include water formation (120-126,148,149). Although not a free radical itself, hydrogen peroxide, when reacting with transition metals (e.g., iron, copper, manganese) forms in hydroxyl

radicals (148). These metals, found in mammmalian brain regions rich in catecholamines (e.g., substantia nigra, basal ganglia) may contribute to enhance free radical reactions (126,143,150,151). There are no laboratory methods available to directly measure the activity level of free radicals in vivo. However, thiobarbituric acid (TBA) reactivity assays (152-154) constitute an index of free radical induced lipid peroxidation. Cells depend on elaborate and often mutually supportive systems to protect themselves from oxidative damage. Antioxidants such as alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), glutathione, superoxide dismutase, catalase and peroxidase protect cells from oxidative stress (122). When the oxidative demands of free radicals exceed the threshold of available protective systems, membrane lipid peroxidation chain reactions can occur and result in membrane destabilization and cell death (149,155,156). This process in the central nervous system could contribute to structural neuropathological changes observed in some patients with persistent forms of TD (122).

4.0 EVIDENCE FOR FREE RADICAL INVOLVEMENT IN TARDIVE DYSKINESIA:

Striatal damage in TD could result from the destabilizing effects of cytotoxic free radicals whose production would be increased by the autoxidation of catecholamines, especially

dopamine and norepinephrine (120-128,148,149). An increase in catecholamine turnover, and biochemical alterations such as noradrenergic hyperactivity, in a subgroup of TD patients, could lead to a progressive build-up of free radical activity, resulting in neuropathological alterations in the nigro-striatal basal ganglia system. This process could underly the disruption of inhibitory efferent pathways from the basal ganglia, e.g., GABA-ergic efferents, important in the modulation of voluntary motor control. The basal ganglia, by virtue of its high lipid and oxygen consumption, elevated concentration of transition metals, and high metabolic activity derived from hydrogen peroxide formation, are an ideal site for the degenerative actions of free radicals (157). Thus, the basal ganglia would be particularly vulnerable to the cytotoxic effects of lipid peroxidation.

With neuroleptics increasing catecholamine turnover (158), more catecholamines would be available for enzymatic and non-enzymatic degradation, which would increase production of oxidative free radicals.

Autoxidation of catecholamines such as 6-hydroxydopamine (6-OHDA) leads to superoxide radical formation (143,148). Antioxidants such as alpha-tocopherol attenuate the toxic effects of intrastriatal injection of 6-hydroxydopamine (6-OHDA) in rats (159). Furthermore, 6-OHDA stimulates lipid peroxidation in rat brain synaptosomes by generation of

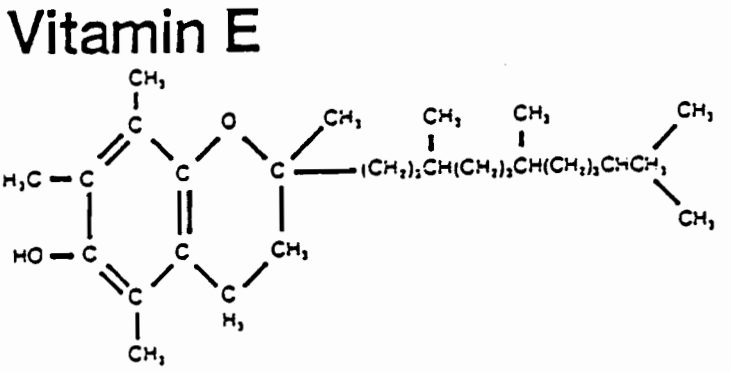
superoxide anion-radicals (127,160). With the use of thiobarbituric acid (TBA) reactivity assays (152-154), rodents exposed to six months administration of neuroleptics showed a marked increase of lipid peroxidation in the cortex and hypothalamus, which decreased to control levels with simultaneous administration of alpha-tocopherol (127,160). Increased TBA reactivity in the peripheral lymphocytes, plasma, and cerebrospinal fluid (CSF) of schizophrenics receiving neuroleptics is an increasingly consistent finding (127,160,161-164). In a study with thirty-two schizophrenic subjects on neuroleptics, TBA reactivity in plasma and peripheral lymphocytes was significantly increased ($p < .01$) when compared to a group of 35 healthy controls (127,160). When the same schizophrenic subjects received simultaneously six weeks of alpha-tocopherol (400 mg daily dose), TBA reactivity in both plasma and peripheral lymphocytes decreased to the levels of healthy controls (127,160).

Further pre-clinical support for free radical involvement in tardive dyskinesia is provided by a study where a movement disorder in rodents was induced following an injection with the neurotoxin iminodipropionitrile (IDPN) (165). Since IDPN toxicity and vitamin E deficiency states share similar neuropathological features, the underlying neurochemical basis of both conditions could involve free radical production. Indirect support was provided when injection of the antioxidant alpha-tocopherol partially reversed the

dyskinetic syndrome (165).

In a double-blind placebo controlled crossover study on fifteen schizophrenic or schizo-affective patients with tardive dyskinesia treated with alpha-tocopherol for a four week period, Abnormal Involuntary Movement Scale (AIMS) scores were significantly reduced after treatment with alpha-tocopherol but not after placebo (123). The mean reduction in the AIMS score with alpha-tocopherol was 43 percent, and seven patients had a greater than 50 percent reduction in their dyskinesia rating (123). A more recent study, in a smaller number of patients (n=8) found alpha-tocopherol superior to placebo in reducing AIMS scores (142). These findings support the potential value of antioxidant supplementation in suppressing the long-term side effects of neuroleptic drug therapy.

5.0 VITAMIN E



Vitamin E (Tocopherol)
Alpha Tocopherol: 5,7,8-trimethyltocol, or 2,5,7,8-tetra-methyl-2-(4' 8' 12'-trimethylcecyl)-6-chromanol

The only major function known of Vitamin E in human metabolism is that of an antioxidant capable of protecting

unsaturated lipids of degradation from free radical chain reactions (147,155,156,166-170). Vitamin E has been shown to be more potent than other common antioxidants (155). Of the four fat soluble tocopherols, alpha-tocopherol is the major chainbreaking antioxidant present in mammalian lipid. The chroman ring plays a crucial role in the antioxidant efficacy of tocopherol (170). Absorption of Vitamin E from the gastrointestinal tract depends on the presence of bile and about 20-60% of the vitamin obtained from dietary sources is usually absorbed (169). Vitamin E is metabolized in the liver and excreted primarily in bile (169). Plasma concentrations of the tocopherols vary among individuals but plasma measurements in normal adults range between 0.8 and 1.4 mg per 100 mL (167). Normal requirements for Vitamin E are estimated at 25-30 mg daily. One mg of alpha-tocopherol is approximately equivalent to 1 I.U. of alpha-tocopherol. In experimental animals, the amount of vitamin E required in the diet to prevent signs of deficiency depend on: 1) the amount of dietary polyunsaturated fatty acids, and 2) the presence of other natural or synthetic fat-soluble antioxidants in the diet (166,167).

The richest dietary sources of Vitamin E are certain seed oils such as corn, peanut, and soybean oil, wheat germ, liver, and eggs (167). Vitamin E deficiency states in adults, with or without fat malabsorption , can induce neurological abnormalities producing symptoms of ataxia, and

areflexia (171-173). Low levels of Vitamin E can be found in abetalipoproteinaemia, malabsorption syndromes in cystic fibrosis, short bowel and blind loop syndromes, and in cholestatic liver disease (171-173). In malabsorption states, suggested replacement therapy averages 100 mg per kilogram per day, and a dose of one to two grams daily of alpha-tocopherol has been considered as effective antioxidant therapy (143,145,146,166). However, doses of 900 I.U. daily or lower of alpha-tocopherol may also represent effective antioxidant therapy (174). Adverse reactions have rarely been reported with large doses (greater than 300 I.U. daily) of alpha tocopherol (167,169,175). Rare adverse reactions include: nausea, diarrhea, intestinal cramps, fatigue, weakness, headache, blurred vision, rash, all of which are known to disappear after discontinuing the vitamin (169).

Nutritionists have long been opposed to vitamin supplementation in adults, stating that intake of vitamins above levels of the Recommended Dietary Allowance are of no appreciable benefit (176). While this is true of vitamins that are only functional components of enzymatic systems, it is not the case for antioxidants such as vitamin E (176). Biological requirements for antioxidants are dependent on the concentrations of free radicals and other oxidants, and the polyunsaturated fatty acid content of body tissues (167,168,176).

6.0 STUDY OBJECTIVES

In relation to a previous study (123)[1], the objective of the current study was to replicate the short term efficacy of alpha-tocopherol in the treatment of tardive dyskinesia in a larger sample of patients.

7.0 HYPOTHESIS TO BE TESTED:

With the premise that tardive dyskinesia may involve a neurodegenerative process resulting from a cytotoxic effect of free radicals, it is hypothesized that short-term antioxidative supplementation therapy with alpha-tocopherol may be of benefit to patients suffering from tardive dyskinesia who have, to some degree, reversible free radical-induced neuromembrane alterations.

8.0 METHOD

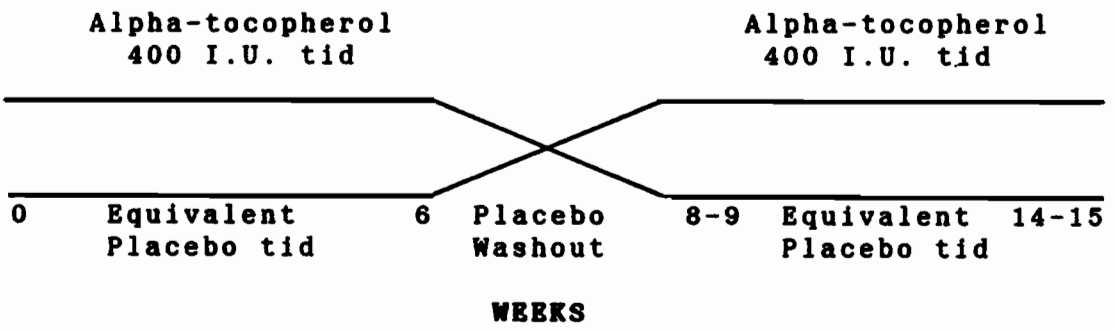
8.1 Design:

The study was double-blind, placebo controlled, with a crossover period. Each subject was randomly assigned to an initial 6 week treatment period with either alpha-tocopherol or placebo. This first period was followed by a two or three week placebo washout depending on each subjects medication

---

[1] This study was carried out prior to the publication of the study by Elkashef A. M. et al: Vitamin E in the treatment of tardive dyskinesia, Am J Psychiatry, April 1990, 147: 505-506.

interval, for example, if subjects were on depot neuroleptics every 2 or 3 weeks. The placebo washout before the start of the second period was done in order to minimize the possibility of a carryover effect of alpha-tocopherol (if received in the first period) during the second period of the crossover. A second 6-week crossover treatment period followed during which subjects received alpha-tocopherol if they had initially been on placebo, or placebo if they had initially received active medication. The design of the study is illustrated below:



8.2 Subjects:

Thirty-three outpatients recruited from St. Mary's Hospital Center, Montréal, and the Royal Ottawa Hospital, Ottawa, were selected for participation in the study as they became available.

Inclusion criteria included: 1) subjects had a primary diagnosis of schizophrenia or bipolar disorder according to DSM-III-R criteria (2), 2) met Research Diagnoses Criteria (Schooler and Kane 1982) for at least mild TD (85), 3)

subjects were of either sex and between the ages of 18 to 70 years, 4) subjects had a stable level of psychopathology not requiring medication changes in the last two months, 5) subjects had stable psychotropic drug regimens for at least two months prior to study entry, 6) subjects had adequate educational levels capable of understanding the study and giving informed consent.

Exclusion criteria included: 1) significant neurological or systemic disease (apart from tardive dyskinesia and parkinsonism), 2) use of any drugs with significant movement disorder inducing potential (except antipsychotic and antiparkinsonian medications), 3) signs of organic brain syndrome, 4) ECT treatment within the last five years, 5) history of drug or alcohol abuse/dependance in the last six months, 6) family history of illnesses associated with a movement disorder (e.g., Huntington's disease, Wilson's disease), 7) for study design purposes, subjects receiving monthly depot neuroleptic injections.

8.3 Medication Schedule:

Alpha-tocopherol or placebo was administered double-blind on a fixed dosage schedule. All drugs were prepared in identical capsules which contained 400 I.U. each of alpha-tocopherol or an equivalent placebo (Novopharm Ltd.). All subjects received either one 400 I.U. capsule of alpha-tocopherol, or one identical placebo capsule, three times

daily (tid). In between the two treatment periods, a placebo washout was administered with a dosage regimen of one placebo capsule, three times daily (tid). To ensure compliance, capsule count was verified at each visit.

With regard to the subjects regular psychotropic medications, no changes in these medications occured throughout the study. Neuroleptics, antiparkinsonian agents, benzodiazepines, lithium, were permitted as long as each patient had been on stable doses of medication at least two months prior to study entry.

8.4 Assessment:

For the first three months of the study, patients were jointly assessed by the candidiate (C.S.) and the thesis supervisor (J.B.) until concordance in ratings had been reached. Following this standardized training period, all patients were subsequently evaluated by the candidate.

Involuntary movements were assessed with the **Abnormal Involuntary Movement Scale** (AIMS) (130) and the **Extrapyramidal Symptom Rating Scale** (ESRS) (131) at baseline and every 2 or 3 weeks thereafter (depending on the injection schedule of each subject, if on depot neuroleptics) until study completion. These evaluations were carried out under the following standardized conditions: 1) for subjects on depot neuroleptics, TD assessments were conducted just prior to their next neuroleptic injection, 2)

due to possible diurnal fluctuations in TD severity, an effort was made to assess each subject at similar times during the study visits.

The **Brief Psychiatric Rating Scale** (BPRS) (130,177) and the **Global Assessment Scale** (GAS) (130,178) were used to assess the level of psychopathology and functioning of each subject at baseline and at study termination. Side effects related to the study medication were recorded at each visit.

8.5 Study measures:

a) Clinical evaluations: A neurological examination was performed for each patient prior to study entry.

b) Rating scales:

i) The Abnormal Involuntary Movement Scale (AIMS):

The AIMS scale, a frequently used 12-item clinical rating scale, designed to record in detail the occurence of dyskinetic movements, has a detailed standardized examination procedure (130). The AIMS total score is obtained by the addition of individual results for each item. All items, except for two items concerning the subject's dental status, range from none to severe or 0 to 4. In 1976, the AIMS scale was made available through the ECDEU Assessment Manual for Psychopharmacology without formal interrater reliability and validation studies. To the

candidate's knowledge, specific validity and reliability data for the scale have not been published. A copy of the AIMS scale is included in the appendices.

ii) <u>The Extrapyramidal Symptom Rating Scale (ESRS):</u>

The ESRS consists of a parkinsonism, dystonia, and dyskinesia questionnaire and behavioral scale, a physician's examination of parkinsonism and dyskinetic movements, and a clinical global impression of severity of dyskinesia and parkinsonism. The 12-item questionnaire allows the patient to report on extrapyramidal symptoms and other neuroleptic side effects at periods other than the time of their examination.

The questionnaire item scores range from " absent " to " severe " or 0 to 3. The evaluation of parkinsonism includes an 8-item subscale, and each parkinsonism item score ranges from 0 to 6. Tardive dyskinesia is rated following a standard procedure designed to activate or uncover covert dyskinesias. Dyskinetic movements in each of the commonly involved muscle groups are rated according to their frequency (occasional, frequent, constant or almost so) and amplitude with each item having a score range of 0 to 6. The scale also includes two clinical global impression of severity scales for dyskinesia and parkisonism each ranging in scores from " absent " to " extremely severe " or 0 to 8. The last subscale of the ESRS, concerning the stage of parkinsonism, was not appropriate for use in this

study. The ESRS has been validated in 8 double-blind studies and was found to be sensitive in its ability to detect changes in both parkinsonian and dyskinetic symptoms and to give results consistent with those from studies using standard scales such as the AIMS. Inter-rater reliability coefficients have ranged from 0.80 to 0.97 (130). The ESRS is a sensitive and reliable instrument for measuring parkinsonian and dyskinetic symptoms. A copy of the ESRS is included in the appendices.

iii) <u>The Brief Psychiatric Rating Scale (BPRS):</u>

The BPRS consists of 18 symptom constructs or items that are rated on a 7-point scale of severity. Each item score ranges from "not present" to "extremely severe" or 1 to 7. This scale provides a rapid and efficient evaluation of psychopathology and is frequently used in clinical drug trials. Brief instructions for rating each item are printed on the scale itself, but to increase communality in interpretation, the items are defined in greater detail in the ECDEU Assesment Manual for Psychopharmacology (130). In its original 16-item version, interrater reliability was established with an r range varying from .62 to .87 (177). A copy of the BPRS is included in the appendices.

iv) <u>The Global Assessment Scale (GAS):</u>

The GAS evaluates the overall functioning of a subject on a continuum from psychological or psychiatric illness to health with values ranging from 01, the hypothetically

sickest possible individual, to 100, the hypothetically healthiest. The scale is divided into ten equal intervals: 01-10, 11-20, 21-30, and so on to 91-100. The defining characteristics of each 10 point interval comprise the scale. Specific guidelines for the proper rating of the GAS are found in the ECDEU Assessment Manual for Psychopharmacology (130) and in a procedure detailed by the authors of the scale (178). In five interrater reliability studies, the GAS was found to have a good reliability, with an intraclass correlation coefficient of reliability ranging from 0.69 to 0.91. (178). A copy of the GAS in included in the appendices.

v) Side effect checklist:

A side effect checklist, derived from side effects having been reported with Vitamin E, was completed at each study visit. A copy of this checklist is included in the appendices.

c) Laboratory measures: All subjects underwent a detailed laboratory assessment which included thyroid function studies.

Willing subjects had blood drawn for measurement of plasma tocopherol levels at baseline, and blindly during active and placebo periods (Clinical Nutrition, Pharma Industry Unit, Department of Human Nutrition and Health, F. Hoffmann La Roche & Co. Ltd., Vitamins and Fine Chemicals Division,

Basle, Switzerland).

8.6 Ethical considerations:

Subjects participated only after the nature of the study had been explained and written informed consent had been obtained. The study was approved by the Health Protection Branch of Health and Welfare Canada and by the Ethics Review Committees of St. Mary's Hospital, Montréal, and of the Royal Ottawa Hospital, Ottawa. A copy of the informed consent form is included in the Appendices.

8.7 Statistical Analysis:

Scores for ESRS and AIMS scores at termination of Vitamin E and Placebo treatment were examined using analysis of variance for the two-period cross-over design (179). Mean end point changes from baseline were analysed for all 27 subjects at termination of Vitamin E and Placebo treatments. The breakdown of sum of squares in the analysis of variance table is reported in Table II.

INSERT TABLE II ABOUT HERE

9.0 RESULTS

9.1 Patient Characteristics:

The sample consisted of thirty-three subjects, six of whom terminated prematurely (see section below). The remaining twenty-seven subjects (17 female; 10 male) had a mean age $\pm$ SD of 42.9 $\pm$ 12.6 and an age range of 19-69. Twenty-two subjects satisfied DSM-III-R criteria for schizophrenia and five subjects met DSM-III-R criteria for bipolar disorder (2). Twenty-one subjects were on injectable neuroleptics, five subjects were on oral neuroleptics, and one subject received no neuroleptics. Eighteen subjects (67%) received concomitant antiparkinsonian agents; thirteen subjects (48%) received concomitant benzodiazepine medication; and four subjects (all bipolars) were on concomitant lithium therapy. One bipolar and one schizophrenic subject also received therapy with carbamazepine. Twenty subjects (74%) had an illness duration greater than ten years. A majority of these patients were on continued neuroleptic drug therapy for an equally long period. The patients' psychopathology remained stable throughout the entire study period as there were no significant ($p < .05$) differences between baseline and end point scores on the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment Scale (GAS).

9.2 Drop-outs:

Apart from the 27 subjects who completed the study, five schizophrenic patients discontinued their participation due to noncompliance unrelated to adverse effects of treatment, and one elderly bipolar patient was forced to withdraw her participation for medical reasons unrelated to the use of the study medication. Due to the crossover nature of the study, none of these six patients was included in the statistical analyses.

9.3 Treatment response:

Scores for Extrapyramidal Symptom Rating Scale (ESRS) and Abnormal Involuntary Movement Scale (AIMS) total score at baseline and at the end of the placebo washout (week 8-9), is shown in Table III.

INSERT TABLE III ABOUT HERE

Scores for ESRS and AIMS total score in subjects first treated with Vitamin E and subjects first treated with Placebo are shown in Tables IV and V.

INSERT TABLE IV ABOUT HERE

INSERT TABLE V ABOUT HERE

Scores for ESRS I-VI, ESRS total score, and AIMS total score in subjects first treated with Vitamin E and subjects first treated with Placebo are illustrated in Figures 1-8.

INSERT FIGURES 1-8 ABOUT HERE

Scores on the ESRS subscales I-VI and AIMS total score, at termination of Vitamin E and Placebo treatment, from analysis of variance for the two-period crossover design, revealed no significant differences (with alpha levels set at .05) as shown on Table VI.

INSERT TABLE VI ABOUT HERE

Differences from baseline scores on the mean AIMS total score at termination of Vitamin E and Placebo treatments were significant ($p < .05$, paired t test). At termination of Vitamin E, the mean AIMS total score dropped 48 % from baseline levels. At termination of Placebo, AIMS total score dropped 45 % from baseline levels. When both treatment

groups were compared, no significant (p < .05) differences emerged on any of the individual items of the ESRS (IV) dyskinesia subscale (i.e., no differential treatment effect was observed with regard to the affected body region). Period effect analysis (period 1: initial six weeks, period 2: last 6 weeks of the study), irrespective of drug treatment, using analysis of variance for the two-period crossover design, showed no significant differences except on parkinsonism (ESRS II) and on the Clinical Global Impression (CGI) of Severity of Parkinsonism (ESRS VI) scores as shown on Table VII.

INSERT TABLE VII ABOUT HERE

9.4 Side effects:

Side effects reported while receiving Vitamin E and Placebo are shown in Table VIII. Side effects are reported as they occured in each subject. If a particular side effect occured more than once in the same subject, the side effect is reported only once for that given subject.

INSERT TABLE VIII ABOUT HERE

In all subjects, the side effects were short lived, mild in severity, and seldom occured more than once. No side effects required any particular treatment. A surprisingly high number of subjects (33 %) reported mild diarrhea while on Placebo.

9.5 Plasma tocopherol levels and change in dyskinesia scores:

Twenty out of the twenty-seven subjects agreed to have blood drawn at baseline and at the end of each 6 week treatment period for determination of plasma tocopherol levels. Mean levels $\pm$ SEM were 27.19 $\pm$ 3.7 micromol/L (or 11.55 $\pm$ 1.32 g/ml) at baseline, and 62.02 $\pm$ 6.6 micromol/L (or 26.53 $\pm$ 2.88 g/ml) after six weeks of tocopherol administration (paired t-test = -6.41, $p < 0.001$). The increase in the tocopherol/cholesterol ratio after 6 weeks of treatment with vitamin E was equally significant (paired t-test = -6.98, $p < 0.001$). Results of tocopherol plasma levels and tocopherol/cholesterol ratio at baseline and following 6 weeks of tocopherol administration are illustrated in **Figure 9**. A correlation analysis, between plasma tocopherol levels and change in severity of dyskinesia ratings on the ESRS and AIMS total score failed to show any significance (with alpha level set at .05).

INSERT FIGURE 9 ABOUT HERE

9.6 Statistical Power Analysis:

Table IX shows the minimum detectable treatment differences for this study with 80% and 90% power (using a two-tailed test at p=0.05), as based on the study results. For instance, at 80% power, the study could detect a treatment difference of 2.91 scale points in the ESRS IV scores (total scores for tardive dyskinesia), which represents a 29.5% difference from the observed placebo endpoint mean score. Similarly, the minimum detectable difference in AIMS scores at 80 % power was 22.5%. As the sample size was estimated in order to detect 25% differences in tardive dyskinesia scores at 80% power, it is reasonable to conclude that the actual power of the study was close to its original aim. The power calculations were made using the method described by Lachin (1981) (180).

INSERT TABLE IX ABOUT HERE

10.0 DISCUSSION

The results of this study suggests that alpha-tocopherol, at the dosage level used, confers no consistent short term symptomatic benefit to patients with tardive dyskinesia. This finding does not replicate those of two previous reports where alpha-tocopherol, administered for a four week period, showed a significant effect over placebo (123,142). In both these studies, the small sample size raises the issue of how representative the samples were of a wider population of TD subjects. Furthermore, these diverging results may reflect a pharmacokinetic drug interaction between tocopherol and neuroleptic drug levels. Most of the patients in this study were on injectable neuroleptics and were regularly assessed just prior to their next neuroleptic injection. The timing of assessment may have added a withdrawal emergent component to their dyskinesia for which antioxidative therapy may be of little or no benefit. Alternatively, the subjects in both previous studies (123,142) were mostly on oral neuroleptics. Since alpha-tocopherol undergoes hepatic metabolism, high tocopherol plasma levels may have interfered with neuroleptic metabolism in the liver. This effect may have been less prominent amongst the injectable neuroleptic treated subjects of this study since injectable neuroleptics do not undergo a first pass effect in the liver. Such a drug interaction could have led to a higher increase in

neuroleptic plasma levels, despite the constant dose received, amongst patients on oral neuroleptics. This effect could of partly covered up their dyskinesia and led to a falsely positive result (181). The finding of markedly increased tocopherol levels following 6 weeks of tocopherol administration indicates a necessity to clarify the possible significance of a drug interaction between tocopherol and neuroleptic metabolism. Subjects in this study had comparable plasma tocopherol levels at baseline and following tocopherol administration to those reported in the study by Lohr et al (123). The significant increase in tocopherol plasma levels is also consistent with an overall good compliance amongst the patients who completed the study.

Demographically, subjects were also comparable with regard to age and illness duration to those in the study by Lohr et al (123). Due to deficiencies in record taking, poor historical reliability of subjects, and frequent anosognosia of TD movements, it was not possible to adequately determine the duration of tardive dyskinesia for each patient. This is regretful since a correlation analysis between TD duration and treatment response could have clarified some aspects pertaining to the expected greater reversibility of TD in patients with a relatively early onset of movement disorder.

Since there were no clear differences in side effects in both treatment groups (alpha-tocopherol and placebo), it

is difficult to tease out which treatment emergent symptoms were really related to alpha-tocopherol. Factors such as the excipients in the capsule preparation, and suggestibility of patients when warned of possible side-effects, could have played a role in the occurence of treatment emergent symptoms.

The placebo effect observed has been reported in other TD controlled studies (105,132). Several of the subjects enrolled in this study were " vitamin friendly " and had engaged in taking vitamin supplements in the past. This factor could represent an unintentional selection bias which could of played a role in the placebo response.

The period effect noticed only for parkinsonism in the ESRS II and VI subscales raises the possibility of a pharmacokinetic drug interaction between the excipients in the capsule preparation and anticholinergic antiparkinsonian medication . Stress may also have played a greater role in parkinsonism scores during the second period of the study. Since the remaining findings were consistent, it is unlikely that the period effect observed on parkinsonism reflects an inconsistancy in ratings.

11.0 LIMITATIONS AND FUTURE DIRECTIONS OF THE FREE RADICAL MODEL IN TARDIVE DYSKINESIA

The evidence supporting free radical toxicity in the development of tardive dyskinesia is steadily increasing. A

significant shortcoming remains the inability to directly measure free radical activity in the central nervous system. Nevertheless, assay techniques using thiobarbituric acid (TBA) reactivity, measuring lipid peroxidation in plasma, peripheral lymphocytes and in the CSF, clearly suggest increased free radical activity in neuroleptic treated subjects.

At this time, the free radical model is unclear as to why only a percentage of patients receiving chronic neuroleptic drug therapy develop tardive dyskinesia. Pre-clinical and clinical findings (123,142,159,161,163,164,165) support the notion that Vitamin E may neutralize the toxic effects of free radicals in the central nervous system.

Although it seems paradoxical for free radicals to play a role in the development of clinically opposite motor conditions, it is possible that patients with tardive dyskinesia have in common with patients with Parkinson's disease endogenously low levels of free radical scavenging enzymes (144,157,182). In individuals predisposed to the development of TD, neuroleptics could suppress the activity of protective enzymes and lead to increasing free radical activity which could progressively lead to basal ganglia neuropathology. The hypokinetic or hyperkinetic nature of the movement disorder would depend on the location(s) of structural damage (e.g., basal ganglia, substantia nigra) as well as on which efferent pathway or combination of pathways

(e.g., dopaminergic, GABAergic) is affected.

Despite these equivocal findings, further research with a long-term follow-up cohort of newly treated schizophrenics with neuroleptics, is a likely step to clarify the prophylactic use of alpha-tocopherol alone, or in combination with other potent antioxidants, for example, deprenyl.

12.0 REFERENCES

1. Jablensky A. Epidemiology of Schizophrenia: A European Perspective. Schizo Bull, 1986; 12: 52-73.

2. Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM-III-R), 1987; 97-163, 187-198, 208-211, 213-226, American Psychiatric Association, Washington, D.C.

3. Brown G. W., Birley J. L. T., Wing J. K. Influence of family life on the course of schizophrenic disorders: A replication. Br J Psychiatry 1972; 121: 241-258.

4. Bassett A. S., McGillivray B. C., Jones B. et al. Partial trisomy chromosome 5 co-segregating with schizophrenia. Lancet 1988; 1: 799.

5. Sherrington R., Brynjolfsson J., Petursson H., et al. Localization of a susceptibility locus for schizophrenia on chromosome 5. Nature 1988; 336: 164-167.

6. Wong D. F., Wagner H. N., Tune L. E., et al. Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. Science 1986; 234: 1558-1563.

7. Falloon I. R. H. Family stress and schizophrenia: Theory and practice. Psychiatric Clin N Am 1986; 9: 165-182.

8. Hogarty G. E., Anderson C. M., Reiss D. J., et al. Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. I. One-year effects of a controlled study on relapse and expressed emotion. Arch Gen Psychiatry 1986; 43: 633-642.

9. Bland R. C., Parker J. H., Orv H. Prognosis in Schizophrenia: A 10-year follow-up of first admissions. Arch Gen Psychiatry 1976; 33: 949-954.

10. Crow T. J. Molecular pathology of schizophrenia: more than one disease process ? British Medical Journal 1980; 280: 66-68.

11. Crow T. J. Positive and negative schizophrenia symptoms and the role of dopamine. Br J Psychiatry 1980; 137: 383-386.

12. Grossman L. S., Luchins D. J., Harrow N. Positive and negative symptoms and the neurology of schizophrenia. Current Opinion in Psychiatry 1989; 2: 20-25.

13. Carpenter W. T., Buchanan R. W. Domains of psychopathology relevant to the study of etiology and treatment in schizophrenia. In: Schizophrenia: Scientific Progress 1989; Chap. 1: 13-22, S. C. Schulz & C. A. Tamminga Eds., Oxford University Press.

14. Waddington J. L., Youssef H. A., Dolphin C., et al. Cognitive dysfunction, negative symptoms, and tardive dyskinesia in schizophrenia. Arch Gen Psychiatry, 1987; 44: 907-912.

15. Kay S. R., Singh M. M. The positive-negative distinction in drug-free schizophrenic patients, stability, response to neuroleptics, and prognostic significance. Arch Gen Psyhiatry 1989; 46: 711-718.

16. Breier A., Wolkowitz O. M., Doran A. R., et al. Neuroleptic responsivity of negative and positive symptoms in schizophrenia. Am J Psychiatry 1987; 144: 1549-1555.

17. Losonczy M. F., Davidson M., Davis K. L. The dopamine hypothesis of schizophrenia. In: Psychopharmacology: The Third Generation of Progress 1987; Chap. 70: 715-726, H. Y. Meltzer Ed., Raven Press, New York.

18. Crayton J. W. The dopamine hypothesis of schizophrenia. Current Opinion in Psychiatry 1990; 3: 19-22.

19. Reynolds G. P. Beyond the dopamine hypothesis - The neurochemical pathology of schizophrenia. Br J Psychiatry 1989; 155: 305-316.

20. Sachar E. J. Disorders of thought: the schizophrenic syndromes. In: Psychopharmacology: The Third Generation of Progress 1987; Chap. 53: 704-716, H. Y. Meltzer Ed., Raven Press, New York.

21. Seeman P., Lee T., Chau-Wong M., et al. Antipsychotic drug doses and neuroleptic-dopamine receptors. Nature 1976; 261: 717-719.

22. Post R. M., Fink E., Carpenter W. I. Cerebrospinal fluid amine metabolites in acute schizophrenia. Arch Gen Psychiatry, 1975; 32: 1063.

23. Seeman P. Brain dopamine receptors. Pharmacol Rev, 1980; 32: 229.

24. Zeeberg B. R., Gibson R. E., Reba R. C., et al. Elevated D-2 dopamine receptors in drug-naive schizophrenics. Science, 1988; 239: 789-791.

25. Waddington J. L. Implications of recent research on dopamine D-1 and D-2 receptor subtypes in relation to schizophrenia and neuroleptic drug action. Current Opinion in Psychiatry, 1989; 2: 89-92.

26. Seeman P. Oral communication. National Workshop on Schizophrenia Research[a]. Health and Welfare Canada and the Medical Research Council, Ottawa, October 1989.

27. Carlsson A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988; 1: 179-186.

28. Pickar D., Breier A., Kelso J. Plasma homovanillic acid as an index of central dopaminergic activity: studies in schizophrenic patients. Ann NY Acad Sci 1988; 537: 339-346.

29. Gariano R. F., Groves P. M. A mechanism for the involvement of colocalized neuropeptides in the actions of antipsychotic drugs. Biol Psychiatry 1989; 26: 303-314.

30. Albus M. Cholecystokinin. Prog Neuropsychopharmacol Biol Psychiatry 1988; 12 (Suppl.): S5-S21.

31. Van Kammen D. P., Yao J. K., Goetz K. Polyunsaturated fatty acids, prostaglandins, and schizophrenia. Ann NY Acad Sci 1989; 559: 411-423.

32. Takeuchi K., Uematsu M., Ofuji M., et al. Substance P involved in mental disorders. Prog Neuropsychopharmacol Biol Psychiatry 1988; 12 (Suppl.): S157-S164.

33. Kalivas P. W. Peptide modulation of dopamine neurons: implications for schizophrenia. Current Opinion in Psychiatry 1990; 3: 113-116.

34. Meltzer H. Y., Bastani B., Ramirez L., et al. Clozapine: new research on efficacy and mechanism of action. Eur Arch Psychiatry Neurol Sci 1989; 238: 332-339.

35. Meltzer H. Y., Shigehiro M., Jar-Chi Lee M. S. The ratios of Serotonin$_2$ and Dopamine$_2$ affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull 1989; 25(3): 390-392.

---

[a] The candidate acted as Science Writer for the National Workshop on Schizophrenia Research, Health and Welfare Canada and the Medical Research Council, October 1989, Ottawa.

36. Sharma R. Atypical antipsychotics. Current Opinion in Psychiatry 1989; 2: 49-53.

37. Meltzer H. Y. Clozapine: clinical advantages and biologic mechanisms. In: Schizophrenia: Scientific Progress 1989; Chap. 28: 302-307; Schulz S. C., Tamminga C. A. Eds., Oxford University Press.

38. Tamminga C. A., Gerlach J. New neuroleptics and experimental antipsychotics in schizophrenia. In: Psychopharmacology: The Third Generation of Progress 1987; Chap. 116: 1129-1140; H. Y. Meltzer Ed., Raven Press, New York.

39. Weissman M. M., Kidd K. K., Prusoff B. A. Variability in rates of affective disorders in relatives of depressed and normal probands. Arch Gen Psychiatry, 1982; 39: 1397-1403.

40. Zajecka J. M., Fawcett J., Easton M. S. Treatment of psychotic affective disorders. Current Opinion in Psychiatry 1990; 3: 43-47.

41. Pope H. G., Lipinski J. F. Diagnosis in schizophrenia and manic depressive illness. A reassessment of the specificity of " schizophrenic " symptoms in the light of current research. Arch Gen Psychiatry, 1978; 35: 811-828.

42. Schildkraut J. J. Catecholamine hypothesis of affective disorders. Am J Psychiatry, 1965; 122: 509-522.

43. Baldessarini R. J. The basis for amine hypothesis in affective disorders. A critical evaluation. Arch Gen Psychiatry, 1975; 32: 1087-1093.

44. Heninger G. R., Charney D. S. Mechanism of action of antidepressant treatments: Implications for the etiology and treatment of depressive disorders. In: Psychopharmacology: The third generation of progress, 1987; Chap. 54: 535-544, H. Y. Meltzer Ed., Raven Press, New York.

45. Murphy D. L., Aulakh C. S., Garrick N. A., et al. Monoamine oxidase inhibitors as antidepressants: Implications for the mechanism of action of antidepressants and the psychobiology of the affective disorders and some related disorders. In: Psychopharmacology: The third generation of progress, 1987; Chap. 55: 545-552, H. Y. Meltzer Ed., Raven Press, New York.

46. Siever L. J. Role of noradrenergic mechanisms in the etiology of the affective disorders. In: Psychopharmacology : The third generation of progress, 1987; Chap. 50: 493-504, H. Y. Meltzer Ed., Raven Press, New York.

47. Meltzer H. Y., Lowy M. T. The serotonin hypothesis of depression. In: Psychopharmacology: The third generation of progress, 1987; Chap. 52: 513-526, H. Y. Meltzer Ed., Raven Press, New York.

48. Jimerson D. C. Role of dopamine mechanisms in the affective disorders. In: Psychopharmacology: The third generation of progress, 1987; Chap. 51: 505-511, H. Y. Meltzer Ed., Raven Press, New York.

49. Kane J. M. Treatment of schizophrenia. Schiz Bull 1987; 13: 133-156.

50. Davis J. M. Drug treatment of schizophrenia. Current Opinion inPsychiatry 1990; 3: 29-34.

51. Klein D. F., Gittelman R., Quitkin R., et al. Review of the literature on mood stabilizing drugs. In: Diagnosis and treatment of psychiatric disorders: Adult and children 1980; 335-339, Williams & Wilkins, Baltimore.

52. Kocsis J. H. Lithium in the acute treatment of mania. In: Handbook of lithium therapy 1980; F. N. Johnson Ed., Lancaster, England.

53. Goodwin F. K., Zis A. P. Lithium in the treatment of acute mania: Comparison with neuroleptics. Arch Gen Psychiatry 1979; 36: 840-844.

54. Garfinkel P. E., Stancer H. C., Persad E. A. Comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. J Affective Disorders 1980; 2: 279-288.

55. Bradwejn J., Shriqui C., Koszycki D., et al (in press). Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. J Clin Psychopharmacol.

56. Chouinard G., Young S. N., Annable L. Antimanic effect of clonazepam. Biol Psychiatry 1983; 18: 451-466.

57. Modell J. G., Lenox R. H., Weiner S. Inpatient clinical trial of lorazepam for the management of manic agitation. J Clin Psychopharmacol 1985; 5: 109-113.

58. Jobling M., Stein G. Lorazepam in resistant mania (letter). Lancet 1986; 1: 5-10.

59. Lenox R. H., Modell J. G., Weiner S. Acute treatment of manic agitation with lorazepam. Psychosomatics 1986; 27: 28-32.

60. Shriqui C. L. Dyskinésie tardive: mise à jour. Revue Can. de Psychiatrie, 1988; 33: 637-644.

61. Shriqui C., Bradwejn J., Jones B. (in press). Tardive dyskinesia: Legal and preventive aspects. Can J Psychiatry

62. Casey D. E. Tardive dyskinesia. In: Psychopharmacology:The third generation of progress, 1987; Chap. 148, 1411-1419, HY Meltzer Ed., Raven Press, New York

63. Casey D. E. Tardive dyskinesia: epidemiologic factors as guide for prevention and management. Advances in Biochemical Psychopharmacology, 1985; 40: 15-2.

64. Kane J. M., Smith J. M. Tardive dyskinesia prevalence and risk factors: 1959 to 1979. Arch Gen Psychiatry 1982; 39: 473
-481.

65. Yassa R., Ghadirian A. M., Schwartz G. Prevalence of tardive dyskinesia in affective disorder patients. J Clin Psychiatry, 1983: 44(11):410-412.

66. Parepally H., Mukhervee S., Schnur D. B., et al. Tardive dyskinesia in bipolar patients. Biol Psychiatry 1989; 25: 163A.

67. Rifkin A., Siris S. Drug treatment of acute schizophrenia.
In: Psychopharmacology: The Third Generation of Progress 1987; Chap. 112: 1095-1101, H. Y. Meltzer Ed., Raven Press, New York.

68. Ayd F. J. A survey of drug-induced extrapyramidal reactions. JAMA 1961; 175: 1054.

69. Kane J., Honigfeld G., Singer J., et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45: 789-796.

70. Marder S. R., Van Putten T. Who should receive clozapine ? Arch Gen Psychiatry 1988; 45: 865-867.

71. Tardive dyskinesia: Report of the American Psychiatric Association Task Force on late neurological effects of antipsychotic drugs. APA Task Force Report 18, 1979; Washington, DC: American Psychiatric Association.

72. Tarsy D., Baldessarini R. J. Tardive Dyskinesia. Ann Rev Med 1984; 35: 605-623.

73. Baldessarini R. J. Clinical and epidemiologic aspects of tardive dyskinesia. J Clin Psychiatry 1985; 46: 4(2):8-13.

74. Sakkas P. N. Neuroleptic malignant syndrome. Current Opinion in Psychiatry 1989; 2: 17-19.

75. Kaufmann C. A., Wyatt R. J. Neuroleptic malignant syndrome. In: Psychopharmacology: The Third Generation of Progress 1987; Chap. 149: 1421-1430, H. Y. Meltzer Ed., Raven Press, New York.

76. Remington G. Pharmacotherapy of schizophrenia. Can J Psychiatry 1989; 34: 211-220.

77. Michalon M. Staying alert to neuroleptic side effects. The Can J of Diagnosis 1989: 121-130.

78. Kim A., Adler L., Angrist B., et al. Efficacy of low-dose metoprolol in neuroleptic-induced akathisia. J Clin Psychopharmacology 1989; 9: 294-296.

79. Rosebush P., Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 1989; 146: 717-725.

80. Schonecker M. Ein eigentumliches syndrom im oralen beriech bei megaphenapplikation. Nervanartz, 1957; 28: 35.

81. Chiang E., Pitts W. M., Rodriguez-Garcia M. Respiratory dyskinesia: review and case reports. J Clin Psychiatry, 1985; 46(6): 232-234.

82. Ruffieux A., Regli F. Les dyskinésies tardives. Rev Méd Suisse Romande, 1985; 105: 339-347.

83. Chouinard G., Annable L., Ross-Chouinard A., et al. A 5-Year Prospective Longitudinal Study of Tardive Dyskinesia: Factors Predicting Appearance of New Cases. J Clin Psychopharmacol, 1988; 8(4)[Suppl.]: S21-S26.

84. Gardos G., Cole J. O., Tarsy D. Withdrawal syndromes associated with antipsychotic drugs. Am J Psychiatry 1978; 135(11): 1321-1324.

85. Schooler N. R., Kane J. M. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry, 1982; 39: 486-487.

86. Casey D. E., Gerlach J. Tardive Dyskinesia: What is the long-term outcome ? In: Tardive dyskinesia and neuroleptics: From dogma to reason, 1986; Chap. 5, 75-97; Casey D. E., Gardos G. Eds., Clinical insights series, American

Psychiatric Press, Inc.

87. Tardive Dyskinesia: Biological mechanisms and clinical aspects, 1988; Wolf ME, Mosnaim AD, Eds. Progress in Psychiatry series, American Psychiatric Press, Inc.

88. Gardos G., Cole J. O., Haskell D., et al. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988; 8 (Suppl.): S31-S37.

89. Fornazzari X., Grossman H., Thornton J., et al. Tardive dyskinesia: A five year follow-up. Can J Psychiatry 1989; 34: 700-703.

90. Casey D. E. Tardive dyskinesia: reversible and irreversible. Psychopharmacology, 1985; 2: (Suppl.) 88-97.

91. Kane J. M., Woerner M., Lieberman J., et al. Tardive dyskinesia. In: Neuropsychiatric movement disorders, 1984; Chap. 5, 97-118; Jeste D. V., Wyatt R. J. Eds., Clinical insights series, American Psychiatric Press, Inc.

92. Kane J. M., Woerner M., Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. J Clin Psychopharmacol, 1988; 8(4)[Suppl.]: 52-56.

93. Robertson M. M. The psychiatric aspects of movement disorders. Current Opinion in Psychiatry 1990; 3: 83-89.

94. Grimes J. D., Hassan M. N., Preston D. N. Adverse neurologic effects of metoclopramide. CMA Journal 1982; 126: 23-25.

95. Mahler J. C., Brown R. P. More on metoclopramide and tardive dyskinesia (letter). N Engl J Med 1987; 316(7): 412-413.

96. Casey D. E. Spontaneous and tardive dyskinesias: clinical and laboratory studies. J Clin Psychiatry 1985; 46(4): 42-47.

97. Saltz B. L., Kane J. M., Woerner M. G., et al. Prospective study of tardive dyskinesia in the elderly. Movement Disorders, 1990; 5 (Suppl. 1): 56.

98. Fleischauer J., Kocher R., Hobi V., et al. Prevalence of tardive dyskinesia in a clinic population. Psychopharmacology Supplementum 1985; 2: 162-172.

99. Yassa R., Ananth J., Cordozo S., et al. Tardive dyskinesia in an outpatient population: prevalence and predisposing factors. Can J Psychiatry 1983; 28(5): 391-394.

100. Toenniessen L. M., Casy D. E., McFarland B. H. Tardive dyskinesia in the aged-duration of treatment relationships. Arch Gen Psychiatry 1985; 42: 278-284.

101. Yassa R., Iskandar H., Ally J. The prevalence of tardive dyskinesia in fluphenazine-treated patients. J Clin Psychopharmacol 1988; 8(4) (Suppl.): 17S-20S.

102. Chorfi M., Moussaoui D. Lack of dyskinesia in unmedicated schizophrenics. Pharmacology 1989; 97: 423.

103. Chouinard G., Annable L., Ross-Chouinard A., et al. A Ten-Year Follow-Up Study of Tardive Dyskinesia (Abstract), Canadian Psychiatric Association, 1989: 62-63, 39th Annual Meeting, St. John's Newfoundland.

104. Kane J., Lieberman J., Woerner M., et al. Tardive Dyskinesia: New Research. In: Schizophrenia: Scientific Progress, 1989; Chap. 37: 381-386; Schulz S. C., Tamminga C. A. Eds., Oxford University Press.

105. Jeste D. V., Wyatt R. J. Understanding and treating tardive dyskinesia 1982; New York, Guilford Press.

106. Jeste D. V., Lohr J. B., Kaufmann C. A., et al. Tardive dyskinesia and neuroleptics: From dogma to reason 1986; Chap. 2: Pathophysiology of tardive dyskinesia: Evaluation of supersensitivity theory and alternative hypothesis, 15-32, Clinical Insights Series, American Psychiatric Press.

107. Jeste D. V., Wyatt R. J. Dogma disputed: Is tardive dyskinesia due to postsynaptic dopamine receptor supersensitivity ? Journal of Clinical Psychiatry, 1981; 42(12): 455-457.

108. Waddington J. L. Further anomalies in the dopamine receptor supersensitivity hypothesis of tardive dyskinesia. TINS, 1985; (May): 200.

109. Jenner P., Marsden C. D. Is the dopamine hypothesis of tardive dyskinesia completely wrong ? TINS, 1986; June, 259-261 [with replies from Fibiger & Lloyd & Waddington].

110. Sandyk R., Fisher H. Serotonin in involuntary movement disorders. Intern. J. Neuroscience, 1988; 42: 185-205.

111. Thaker G. K., Tamminga C. A., Alphs L. D., et al. Brain gamma-aminobutyric acid abnormality in tardive dyskinesia. Arch Gen Psychiatry, 1987; 44: 522-529.

112. Thaker G. K., Nguyen J. A., Strauss M. E., et al.

Clonazepam treatment of tardive dyskinesia: A practical GABAmimetic strategy. Am J Psychiatry 1990; 147: 445-451.

113. Scheel-Kruger J. Dopamine-GABA interactions: evidence that GABA transmits, modulates, and mediates dopaminergic functions in the basal ganglia and the limbic system. Acta Neurol Scand Suppl 1986; 107: 1-54.

114. Arnt T., Scheel-Kruger J. Intranigral GABA antagonists produce dopamine-independent biting in rats. Eur J Pharmacol 1980; 62: 51-61.

115. Gunne L. M., Haggstrom J. E. Experimental tardive dyskinesia. J Clin Psychiatry, 1985; 46(4)(sec 2): 48-50.

116. Tamminga C. A., Crayton J. W., Chase T. N. Improvement in tardive dyskinesia after muscimol therapy. Arch Gen Psychiatry, 1979; 36: 595-598.

117. Fibiger H. C., Lloyd K. G. Neurobiological substrates of tardive dyskinesia: the GABA hypothesis. Trends Neurosci, 1984; 7: 462-64.

118. Gunne L. M., Haggstrom J. E., Sjokvist B. Association with persistent neuroleptic-induced dyskinesia of regional changes in the brain GABA synthesis. Nature, 1984; 309: 347-49.

119. Christensen E., Moller J., Faurbye A. Neuropathological investigation of 28 brains from patients with dyskinesia. Acta Psychiatr Scand, 1970; 46: 14-23.

120. Cadet J. L., Lohr J. B., Jeste D. V. Free radicals and tardive dyskinesia. TINS, 1986; 9: 107-108.

121. Cadet J. L. A unifying theory of movement and madness: involvement of free radicals in disorders of the isodendritic core of the brainstem. Medical Hypotheses, 1988; 27: 59-63.

122. Cadet J. L., Lohr J. B., Jeste D. V. Tardive dyskinesia and schizophrenic burnout: The possible involvement of cytotoxic free radicals. Handbook of schizophrenia, Vol. 2: Neurochemistry and neuropharmacology of schizophrenia, 1987; Chap. 15: 425-438, Elsevier Science Publishers.

123. Lohr J.B., Cadet J.L., Lohr M.A., et al. Vitamin E in the treatment of tardive dyskinesia: The possible involvement of free radical mechanisms. Schizophrenia Bulletin, 1988; 14(2): 291-296.

124. Shriqui C., Jones B. Free radicals and tardive dyskinesia. Can J Psychiatry, 1990; 35(3): 282-284.

125. Shriqui C., Jones B. Free radical involvement in schizophrenia and tardive dyskinesia. Schizophrenia Research, 1990; 3(1): 81.

126. Cadet J. L. Free radical mechanisms in the central nervous system: an overview. Intern. J. Neuroscience, 1988; 40: 13-18.

127. Fojtikova I., Binkova B., Topinka J., et al. The effects of alpha-tocopherol in schizophrenic patients treated with neuroleptics. Schizophrenia Research, 1990; 3(1): 93.

128. Barbeau A. Etiology of Parkinson's disease: a research strategy. Can J Neurol Sci, 1984; 11: 24-28.

129. Wolf M. A., Wertenschlag N. Facteurs de risque et prévention des dyskinésies tardives. Revue Can de psychiatrie, 1989; 34: 177-181.

130. Guy W. ECDEU Assessment Manual for Psychopharmacology, 1976; Washington D.C., US Dept. of Health, Education and Welfare.

131. Chouinard G., Ross-Chouinard A., Annable L., et al. Extrapyramidal symptom rating scale. Can J Neurol Sci, 1980; 7: 233.

132. Jeste D. V. , Lohr J. B., Clark K., et al. Pharmacological treatments of tardive dyskinesia in the 1980s. J Clin Psychopharmacol, 1988; 8: 38S-48S.

133. Naber D., Leppig M., Grohmann R., et al. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia- a retrospective study of 387 patients. Psychopharmacology 1989; 99: S73-S76.

134. Leppig M.,Bosch B., Naber D., et al. Clozapine in the treatment of 121 out-patients. Psychopharmacology 1989; 99: S77-S79.

135. Owen R. R., Beake B. J., Marby D., et al. Response to clozapine in chronic psychotic patients. Psychopharmacology 1989; 25: 253-256.

136. Lieberman J., Johns C., Cooper T., et al. Clozapine pharmacology and tardive dyskinesia. Psychopharmacology 1989; 99: S54-S59.

137. Yadalam K. G., Simpson G. M. Dopamine receptor sensitivity and tardive dyskinesia. Schizophrenia Research 1990; 3(1): 80.

138. Tarsy D. Movement disorders with neuroleptic drug treatment. Psychiatr Clin North Amer 1984; 3: 453-471.

139. Tanner C. M. Treatment of tardive dyskinesia: other therapies. Clin Neuropharm 1983; 6(2): 159-167.

140. Haefely W. Benzodiazepine interactions with GABA receptors. Neurosci Lett 1984; 47: 201-206.

141. Dinan T. G., Capstick C. A pilot study of verapamil in the treatment of tardive dyskinesia. Human Psychopharmacology, 1989; 4: 55-58.

142. Elkashef A. M., Ruskin P. E., Bacher N., et al. Vitamin E in the treatment of tardive dyskinesia. Am J Psychiatry, 1990; 147: 505-506.

143. Grimes J.D., Hassan M.N., Thakar J.H. Prevention of progression of Parkinson's disease with antioxidative therapy. Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 1988; 12: 165-172.

144. Cadet J. L. The potential use of vitamin E and selenium in parkinsonism. Medical Hypotheses, 1986; 20: 87-94.

145. Parkinson Study Group. DATATOP: A Multicenter Controlled Clinical Trial in Early Parkinson's Disease. Arch Neurol., 1989; 46: 1052-1060.

146. The Parkinson Study Group. Effect of Deprenyl on the Progression of Disability in Early Parkinson's Disease. N Engl J Med, 1989; 321: 1364-71.

147. Tappel A. L. Will antioxidant nutrients slow aging processes ? Geriatrics, 1968; 23: 97-105.

148. Cohen G. Oxy-radical toxicity in catecholamine neurons. NeuroToxicology, 1984; 5(1): 77-82.

149. Fridovich I. Superoxide radical: an endogenous toxicant. Ann. Rev. Pharmacol. Toxicol., 1983; 23: 239-257.

150. Poirier J., Donaldson J., Barbeau A. The specific vulnerability of substantia nigra to MPTP is related to the presence of transition metals. Biochem Biophys Res Commun, 1985; 128(1): 25-33.

151. Barbeau A. Manganese and extrapyramidal disorders. NeuroToxicology, 1984; 5(1):13-36.

152. Gutteridge J. M. C. Thiobarbituric acid-reactivity following iron-dependent free-radical damage to amino acids and carbohydrates. FEBS Letters, 1981; 128(2): 343-346.

153. Gutteridge J. M. C. Free-radical damage to lipids, amino acids, carbohydrates and nucleic acids determined by thiobarbituric acid reactivity. Int. J. Biochem., 1982; 14: 649-653.

154. Satoh K. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. Clinica Chimica Acta, 1978; 90: 37-43.

155. Wilson R. L. Free radical protection: Why vitamin E, not vitamin C, beta-carotene or glutathione? Ciba Foundation Symposium 101, 1983: 19-44, London, Pitman.

156. Burton G. W., Cheeseman K. H., Doba T., et al. Vitamin E as an antioxidant in vitro and in vivo. Ciba Foundation Symposium 101, Biology of Vitamin E, 5-18, 1983, London, Pitman.

157. Riederer P., Sofic E., Rausch W. D., et al. Transition Metals, Ferritin, Glutathione, and Ascorbic Acid in Parkinsonian Brains. J. Neurochem., 1989; 52: 515-520.

158. Korpi E. R., Wyatt R. J. Reduced haloperidol: effects on striatal dopamine metabolism and conversion to haloperidol in the rat. Psychopharmacology, 1984; 83: 34.

159. Cadet J. L., Katz M., Jackson-Lewis V., et al. Vitamin E attenuates the toxic effects of intrastriatal injection of 6-hydroxydopamine (6-OHDA) in rats: behavioral and biochemical evidence. Brain Research, 1989; 476: 10-15.

160. Fojtikova I. Personal communication, Badgastein, Austria, February 1990.

161. Medley I. Free radicals, neuroleptic drugs and tardive dyskinesia. Schizophrenia Research, 1990; 3(1): 81.

162. Medley I. Personal communication, Badgastein, Austria, February, 1990.

163. Pall H. S., Williams A. C., Blake D. R., et al. Evidence of enhanced lipid peroxidation in the cerebrospinal fluid of patients taking phenothiazines. Lancet, 1987; ii: 596-599.

164. Lohr J. B., Underhill S., Moir M., et al. Lipid peroxidation in CSF: Relationship to catecholamines and tardive dyskinesia. Biol Psychiatry, 1989; 25: 71A.

165. Lohr J. B., Cadet J. L., Wyatt R. J., et al. Partial reversal of the iminodipropionitrile-induced hyperkinetic syndrome in rats by alpha-tocopherol (Vitamin E). Neuropsychopharmacology, 1988; 1 (4): 305-309.

166. Bieri J. G., Corash L., Hubbard V. S. Medical uses of vitamin E, New Engl J Med, 1983; 308(18): 1063-1071.

167. Vitale J. J. Vitamins - Vitamin E, 1976; 25-27, The Upjohn Company.

168. Diplock A. T., The Role of Vitamin E in Biological Membranes. Ciba Foundation Symposium 101, Biology of Vitamin E, 1983: 45-55, London, Pitman.

169. Compendium of Pharmaceuticals and Specialties. Canadian Pharmaceutical Association, Vitamin E (monograph), Twenty-Third Edition, 1988: 1003.

170. Burton G. W., Ingold K. U. Vitamin E as an in vitro and in vivo antioxidant (Abstract), The New York Academy of Sciences, Symposium on: Vitamin E: Biochemistry and Health Implications, New York, November 1988.

171. Kayden H. J., Traber M. G. Vitamin E deficiency neuropathies in adults with or without fat malabsorption, (Abstract), The New York Academy of Sciences, Symposium on: Vitamin E: Biochemistry and Health Implication, New York, November 1988.

172. Muller D. P. R., Lloyd J. K., Wolff O. H. Vitamin E and neurological function: Abetalipoproteinaemia and other disorders of fat absorption. Ciba Foundation Symposium 101, Biology of Vitamin E, 1983: 106-121, London, Pitman.

173. Weder B., Meienberg O., Wildi E., Meier C. Neurologic disorder of vitamin E deficiency in acquired intestinal malabsorption, Neurology, 1984; 34: 1561-1565.

174. Haller J. Personal communication, Clinical Nutrition, Pharma Industry Unit, Department of Human Nutrition and Health, F. Hoffmann-La Roche & Co. Ltd, Basle, Switzerland, February, 1990.

175. Kitagawa M., Mino M. Effects of elevated d-Alpha (RRR) Tocopherol Dosage in Man. J. Nutr. Sci. Vitaminol., 1989; 35: 133-142.

176. Horwitt M. K. Supplementation with vitamin E. The American Journal of Clinical Nutrition, 1988; 47: 1088-1089.

177. Overall J. E., Gorham D. R. The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10: 799-812.

178. Endicott J., Spitzer R. L., Fleiss J. L., et al. The global assessment scale. Arch Gen Psychiatry, 1976; 33: 766-771.

179. Fleiss J. L. The crossover study. In: The Design and Analysis of Clinical Experiments 1986; Chap. 10: 263-290, John Wiley & Sons, New York.

180. Lachin J. M. An introduction to sample size determination and power analysis. In: Controlled Clinical Trials 1981; 2: 93-113.

181. Shriqui C., Bradwejn J., Jones B. Alpha-tocopherol in the treatment of tardive dyskinesia (submitted). Am J Psychiatry.

182. Ambani L. M., van Woert M. H., Murphy S. Brain peroxidase and catalase in Parkinson's disease. Archives of Neurology, 1975; 32: 114-118.

13.0 ACKNOWLEDGEMENTS

The candidate is grateful to:

Dr. Jacques Bradwejn Associate Professor, Department of Psychiatry, McGill University, as Thesis Supervisor; and to the remaining Members of the Thesis Supervisory Committee, McGill University: **Dr. Laurence Annable; Dr. Brian Collier; and Dr. Serge Gauthier.**

The candidate also wishes to acknowledge the contributions made by:

Dr. Barry Jones, Associate Professor, Department of Psychiatry, University of Ottawa; Dr. Ian Medley, Senior Psychiatry Registrar, University of Nottingham, England;

Dr. Ilena Fojtikova, Charles University, Prague, Czechoslovakia; Dr. Jean Lud Cadet, Professor of Psychiatry and Neurology, Columbia University, New York; Dr. Jurg Haller, Clinical Nutrition Unit, F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland; **Mrs. Kim Anderson and Mr. André Blanchard for invaluable Research Assistance;** Ms. Gabriella Boiardi for initial secretarial support; Novopharm Ltd., Toronto, for preparation of vitamin E and Placebo capsules; Clinical Nutrition, Pharma Industry Unit, Department of Human Nutrition and Health, F. Hoffmann-La Roche & Co. Ltd for Tocopherol Plasma Levels.

As a final acknowledgement, the candidate is grateful to the reviewers of this manuscript.

14.0 APPENDICES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE OF MENTAL HEALTH

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

STUDY	PATIENT	FORM	PERIOD	RATER	HOSPITAL
		117			
(1-6)	(7-9)	(10-12)	(13-15)	(16-17)	(79-80)

PATIENT'S NAME

RATER

DATE

INSTRUCTIONS: Complete Examination Procedure (reverse side) before making ratings.
MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one *less* than those observed spontaneously.

Code: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

		(Circle One)	CARD 01 (18-19)
FACIAL AND ORAL MOVEMENTS:	1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	0 1 2 3 4	(20)
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	(21)
	3. Jaw e.g., biting, clenching, chewing; mouth opening, lateral movement	0 1 2 3 4	(22)
	4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0 1 2 3 4	(23)
EXTREMITY MOVEMENTS:	5. Upper *(arms, wrists, hands, fingers)* Include choreic movements, (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex; serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	(24)
	6. Lower *(legs, knees, ankles, toes)* e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	(25)
TRUNK MOVEMENTS:	7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	(26)
GLOBAL JUDGMENTS:	8. Severity of abnormal movements	None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4	(27)
	9. Incapacitation due to abnormal movements	None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4	(28)
	10. Patient's awareness of abnormal movements Rate only patient's report	No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	(29)
DENTAL STATUS:	11. Current problems with teeth and/or dentures	No 0 Yes 1	(30)
	12. Does patient usually wear dentures?	No 0 Yes 1	(31)

EXTRAPYRAMIDAL SYMPTOM RATING SCALE
(CHOUINARD & ROSS-CHOUINARD)

STUDY

- ☐ Admission
- ☐ Baseline
- ☐ Day 4
- ☐ Day 7
- ☐ Day 14
- ☐ Week 1 (Ext)
- ☐ Week 2 (Ext)
- ☐ Week 3 (Ext)
- ☐ Week 4 (Ext)
- ☐ Week 5 (Ext)
- ☐ Week 6 (Ext)
- ☐ Other .....

Date of assessment

..... Year Month Day

Pt. No. .....

Initials .....

E:

I. PARKINSONISM, DYSTONIA AND DYSKINESIA: QUESTIONNAIRE AND BEHAVIORAL SCALE (PHYSICIAN OR NURSE)

Enquire into the status of each symptom and rate accordingly. For nurses, rate also the behavior observed

	Absent	Mild	Moderate	Severe
1. Impression of slowness or weakness, difficulty in carrying out routine tasks	0	1	2	3
2. Difficulty walking or with balance	0	1	2	3
3. Difficulty swallowing or talking	0	1	2	3
4. Stiffness, stiff posture	0	1	2	3
5. Cramps or pains in limbs, back or neck	0	1	2	3
6. Restless, nervous, unable to keep still	0	1	2	3
7. Tremors, shaking	0	1	2	3
8. Oculogyric crisis, abnormal sustained posture	0	1	2	3
9. Increased salivation	0	1	2	3
10. Abnormal involuntary movements (dyskinesia) of extremities or trunk	0	1	2	3
11. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips or face	0	1	2	3
12. Dizziness when standing up (especially in the morning)	0	1	2	3

II. PARKINSONISM: PHYSICIAN'S EXAMINATION

1. Expressive automatic movements (facial mask/ speech)
- 0 : normal
- 1 : very mild decrease in facial expressiveness
- 2 : mild decrease in facial expressiveness
- 3 : rare spontaneous smile, decrease blinking, voice slightly monotonous
- 4 : no spontaneous smile, staring gaze, low monotonous speech, mumbling
- 5 : marked facial mask, unable to frown, slurred speech
- 6 : extremely severe facial mask with unintelligible speech

2. Bradykinesia
- 0 : normal
- 1 : global impression of slowness in movements
- 2 : definite slowness in movements
- 3 : very mild difficulty in initiating movements
- 4 : mild to moderate difficulty in initiating movements
- 5 : difficulty in starting or stopping any movement, or freezing on initiating voluntary act
- 6 : rare voluntary movement, almost completely immobile

3. Rigidity Total _____
- right arm _____
- left arm _____
- right leg _____
- left leg _____

- 0 : normal muscle tone
- 1 : very mild, barely perceptible
- 2 : mild (some resistance to passive movements)
- 3 : moderate (definite resistance to passive movements)
- 4 : moderately severe (moderate resistance but still easy to move the limb)
- 5 : severe (marked resistance with definite difficulty to move the limb)
- 6 : extremely severe (nearly frozen)

4. Gait & posture
- 0 : normal
- 1 : mild decrease of pendular arm movement
- 2 : moderate decrease of pendular arm movement, normal steps
- 3 : no pendular arm movement, head flexed, steps more or less normal
- 4 : stiff posture (neck, back), small step (shuffling gait)
- 5 : more marked, festination or freezing on turning
- 6 : triple flexion, barely able to walk

5. Tremor Total _____
- right arm _____ head _____
- left arm _____ jaw/chin _____
- right leg _____ tongue _____
- left leg _____ lips _____

		OCCASIONNEL	FREQUENT	CONSTANT ALMOST
none	: 0			
borderline	: 1			
small aptitude	:	2	3	4
moderate amplitude	:	3	4	5
large amplitude	:	4	5	6

6. Akathisia
- 0 : none
- 1 : looks restless, nervous, impatient, uncomfortable
- 2 : needs to move at least one extremity
- 3 : often needs to move one extremity or to change position
- 4 : moves one extremity almost constantly if sitting, or stamps feet while standing
- 5 : unable to sit down for more than a short period of time
- 6 : moves or walks constantly

7. Sialorrhea
- 0 : absent
- 1 : very mild
- 2 : mild
- 3 : moderate: impairs speech
- 4 : moderately severe
- 5 : severe
- 6 : extremely severe: drooling

8. Postural stability
- 0 : normal
- 1 : hesitation when pushed but no retropulsion
- 2 : retropulsion but recovers unaided
- 3 : exaggerated retropulsion without falling
- 4 : absence of postural response, would fall if not caught by examiner
- 5 : unstable while standing, even without pushing
- 6 : unable to stand without assistance

STUDY

EXTRAPYRAMIDAL SYMPTOM RATING SCALE (CHOUINARD & ROSS-CHOUINARD)

ESRS

Date of assessment

Year Month Day

Pt. No. .....

Initials .....

III. DYSTONIA: PHYSICIAN'S EXAMINATION

1. Acute torsion dystonia — Total _____
   right arm ___ head ___
   left arm ___ jaw ___
   right leg ___ tongue ___
   left leg ___ lips ___
   0 : absent
   1 : very mild
   2 : mild
   3 : moderate
   4 : moderately severe
   5 : severe
   6 : extremely severe

2. Non acute or chronic or tardive dystonia — Total _____
   right arm ___ head ___
   left arm ___ jaw ___
   right leg ___ tongue ___
   left leg ___ lips ___
   0 : absent
   1 : very mild
   2 : mild
   3 : moderate
   4 : moderately severe
   5 : severe
   6 : extremely severe

IV. DYSKINETIC MOVEMENTS : PHYSICIAN'S EXAMINATION

		OCCASIONAL*	FREQUENT**	CONSTANT OR ALMOST SO
1. Lingual movements (slow lateral or torsion movement of tongue)				
none	0			
borderline	1			
clearly present, within oral cavity		2	3	4
with occasional partial protrusion		3	4	5
with complete protrusion		4	5	6
2. Jaw movements (lateral movement, chewing, biting, clenching)				
none	0			
borderline	1			
clearly present, small amplitude		2	3	4
moderate amplitude, but without mouth opening		3	4	5
large amplitude, with mouth opening		4	5	6
3. Buccolateral movements (puckering, pouting, smacking, etc)				
none	0			
borderline	1			
clearly present, small amplitude		2	3	4
moderate amplitude, forward movement of lips		3	4	5
large amplitude; marked, noisy smacking of lips		4	5	6
4. Truncal movements (rocking, twisting, pelvic gyrations)				
none	0			
borderline	1			
clearly present, small amplitude		2	3	4
moderate amplitude		3	4	5
greater amplitude		4	5	6
5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)				
none	0			
borderline	1			
clearly present, small amplitude, movements of one limb		2	3	4
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs		3	4	5
greater amplitude, movement involving two limbs		4	5	6
6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)				
none	0			
borderline	1			
clearly present, small amplitude, movements of one limb		2	3	4
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs		3	4	5
greater amplitude, movement involving two limbs		4	5	6
7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc)				
none	0			
borderline	1			
clearly present, small amplitude		2	3	4
moderate amplitude		3	4	5
greater amplitude		4	5	6

SPECIFY .....

* when activated or rarely spontaneous ** frequently spontaneous and present when activated

EXTRAPYRAMIDAL SYMPTOM RATING SCALE
(CHOUINARD & ROSS-CHOUINARD)

Study No.

ESRS

Date of assessment _____ Pt. No. _____
Year Month Day

Initials _____

V. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA
Considering your clinical experience, how severe is the dyskinesia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately severe	8: extremely severe

VI. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF PARKINSONISM
Considering your clinical experience, how severe is the parkinsonism at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately severe	8: extremely severe

VII. STAGE OF PARKINSONISM (Hoehn & Yahr)

0: normal
1: unilateral involvement only, minimal or no functional impairment (stage I)
2: bilateral or midline involvement, without impairment of balance (stage II)
3: mildly to moderately disabling: first signs of impaired righting or postural reflex (unsteadiness as the patient turns or when he is pushed from standing equilibrium with the feet together and eyes closed), patient is physically capable of leading independent life (stage III)
4: severely disabling: patient is still able to walk and stand unassisted but is markedly incapacitated (stave IV)
5: confinement to bed or wheelchair (stage V)

Investigator's signature _____ Date _____

MH-9—47
6-73

BRIEF PSYCHIATRIC RATING SCALE (Overall and Gorham)

BPRS

INSTRUCTIONS: *Insert General Scoring Sheet and Code 01 Under Sheet Number.*

This form consists of 18 symptom constructs, each to be rated on a 7—point scale of severity ranging from "not present" to "extremely severe". If a specific symptom is not rated, mark "0" = Not Assessed.

Mark the column headed by the term which best describes the patient's present condition.

USE A NO. 2 LEAD PENCIL. BE SURE TO MAKE MARKS HEAVY AND DARK. ERASE COMPLETELY ANY MARKS YOU WISH TO CHANGE.

NOT ASSESSED	NOT PRESENT	VERY MILD	MILD	MODERATE	MODERATELY SEVERE	SEVERE	EXTREMELY SEVERE
0	1	2	3	4	5	6	7

Mark on right half of scoring sheet on row specified			ROW NO.
1.	SOMATIC CONCERN	Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	1
2.	ANXIETY	Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	2
3.	EMOTIONAL WITHDRAWAL	Deficiency in relating to the interviewer and to the interview-er situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.	3
4.	CONCEPTUAL DISORGANI-ZATION	Degree to which the thought processes are confused, dis-connected or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	4
5.	GUILT FEELINGS	Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	5
6.	TENSION	Physical and motor manifestations of tension, "nervousness," and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	6
7.	MANNERISMS AND POSTURING	Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	7
8.	GRANDIOSITY	Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	8
9.	DEPRESSIVE MOOD	Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences con-cerning depression based upon general retardation and somatic complaints.	9
10.	HOSTILITY	Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety nor somatic complaints. *(Rate attitude toward interviewer under "uncooperativeness".)*	10
11.	SUSPICIOUS-NESS	Belief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.	11

Continue marking on right half of scoring sheet on row specified			ROW NO.
12.	HALLUCINA-TORY BEHAVIOR	Perceptions without normal external stimulus corre-spondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.	12
13.	MOTOR RETARDA-TION	Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on basis of patient's subjective impression of own energy level	13
14.	UNCO-OPERATIVE-NESS	Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.	14
15.	UNUSUAL THOUGHT CONTENT	Unusual, odd, strange, or bizarre thought content. Rate here the degree of unusualness, not the degree of disorgan-ization of thought processes.	15
16.	BLUNTED AFFECT	Reduced emotional tone, apparent lack of normal feeling or involvement.	16
17.	EXCITEMENT	Heightened emotional tone, agitation, increased reactivity.	17
18.	DISORIENT-ATION	Confusion or lack of proper association for person, place or time.	18

GLOBAL ASSESSMENT SCALE (241-GAS)
R. L. Spitzer, M. Gibbon and J. Endicott

Rate the subject's lowest level of functioning in the last week by selecting the lowest range which describes his functioning on a hypothetical continuum of mental health-illness. For example, a subject whose "behavior is considerably influenced by delusions" (range 21-30) should be given a rating in that range even though he has "major impairment in several areas" (range 31-40). Use intermediary levels when appropriate (e.g., 35, 58, 63). Rate actual functioning independent of whether or not subject is receiving and may be helped by medication or some other form of treatment.

100 | 91 — No symptoms, superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his warmth and integrity.

90 | 81 — Transient symptoms may occur, but good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, "everyday" worries that only occasionally get out of hand.

80 | 71 — Minimal symptoms may be present but no more than slight impairment in functioning, varying degrees of "everyday" worries and problems that sometimes get out of hand.

70 | 61 — Some mild symptoms (e.g., depressive mood and mild insomnia) OR some difficulty in several areas of functioning, but generally functioning pretty well, has some meaningful interpersonal relationships and most untrained people would not consider him "sick".

60 | 51 — Moderate symptoms OR generally functioning with some difficulty (e.g., few friends and flat affect, depressed mood, and pathological self-doubt, euphoric mood and pressure of speech, moderately severe antisocial behavior).

50 | 41 — Any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention (e.g., suicidal preoccupation or gesture, severe obsessional rituals, frequent anxiety attacks, serious antisocial behavior, compulsive drinking).

40 | 31 — Major impairment in several areas, such as work, family relations, judgment, thinking, or mood (e.g., depressed woman avoids friends, neglects family, unable to do housework), OR some impairment in reality testing or communication (e.g., speech is at times obscure, illogical, or irrelevant), OR single serious suicide attempt.

30 | 21 — Unable to function in almost all areas (e.g., stays in bed all day), OR behavior is considerably influenced by either delusions or hallucinations, OR serious impairment in communication (e.g., sometimes incoherent or unresponsive) or judgment (e.g., acts grossly inappropriately).

20 | 11 — Needs some supervision to prevent hurting self or others, or to maintain minimal personal hygiene (e.g., repeated suicide attempts, frequently violent, manic excitement, smears feces), OR gross impairment in communication (e.g., largely incoherent or mute).

10 | 01 — Needs constant supervision for several days to prevent hurting self or others, or makes no attempt to maintain minimal personal hygiene.

PATIENT INITIALS: ____ ____ ____

PATIENT #: _____

DATE: ____/____/____

SIDE EFFECT SHEET

	ABSENCE
NAUSEA _____	
DIARRHEA _____	
INTESTINAL CRAMPS _____	
FATIGUE _____	
WEAKNESS _____	
HEADACHE _____	
BLURRED VISION _____	
RASH _____	

OTHER _____

_____

_____

_____

NOTE: CHECK ONLY THOSE PRESENT

Differential Diagnosis of Tardive Dyskinesia

- Neuroleptic withdrawal-emergent dyskinesias
- Stereotyped movements and mannerisms associated with schizophrenia
- Spontaneous oral dyskinesias of advanced age or senility
- Oral dyskinesias related to dental conditions or prostheses
- Huntington's disease, Wilson's disease, Tourette's syndrome
- Rheumatic (Sydenham's) chorea; Postanoxic, postencephalitic extrapyramidal syndromes
- Drug intoxication's (L-dopa, amphetamines, anticholinergics, antidepressants, lithium, phenytoin)
- CNS complications of systemic metabolic disorders (e.g., hepatic or renal failure, hyperthyroidism, hypoparathyroidism, hypoglycemia)
- Brain neoplasm (thalamic, basal ganglia)
- Fahr's syndrome (familial calcification of the basal ganglia)
- Focal dystonias (Meige syndrome, spasmodic torticollis)

Table I

Table II Breakdown of sum of squares in the analysis of variance table

VARIABLE	DEGREES OF FREEDOM (df)
Between patients	26
Between drugs	1
Between periods	1
Residual Error	25
Total	53

Table III Scores for ESRS and AIMS total score at baseline and at the end of the placebo washout: means and standard error of the mean (SEM)

$\bar{X}$ (SEM) n= 27	BASELINE	WEEK 8-9 PLACEBO WASH-OUT
ESRS I	3.296 (0.557)	2.462 (0.423)
ESRS II	7.852 (0.954)	5.692 (0.908)
ESRS III	1.074 (0.306)	0.923 (0.254)
ESRS IV	13.889 (0.878)	10.154 (1.172)
ESRS V	3.407 (0.215)	2.731 (0.189)
ESRS VI	0.963 (0.242)	1.000 (0.192)
ESRS TOTAL	30.481 (1.928)	22.962 (1.867)
AIMS TOTAL	8.519 (0.707)	5.960 (0.871)

Table IV Scores for ESRS ans AIMS total score in patients first treated with Vitamin E: means and standard error of the mean (SEM)

VITAMIN E FIRST GROUP

$\bar{X}$ (SEM) n= 12	Vitamin E		Placebo	
	Wk 2-3	Wk 6	Wk 12	Wk 14-15
ESRS I	4.167 (0.860)	2.000 (0.522)	2.333 (0.396)	2.500 (0.337)
ESRS II	5.750 (1.088)	4.333 (0.924)	6.083 (1.234)	7.667 (1.322)
ESRS III	1.833 (0.562)	1.000 (0.400)	0.500 (0.230)	0.917 (0.260)
ESRS IV	13.333 (1.616)	11.000 (1.805)	11.083 (1.712)	11.083 (1.443)
ESRS V	3.417 (0.336)	2.833 (0.241)	3.250 (0.329)	3.000 (0.246)
ESRS VI	1.417 (0.313)	0.667 (0.284)	1.083 (0.313)	1.417 (0.260)
ESRS TOTAL	29.917 (2.980)	21.833 (2.489)	24.333 (2.530)	26.583 (2.043)
AIMS TOTAL	8.667 (1.176)	6.000 (1.267)	6.455 (1.358)	6.667 (0.980)

Table V Scores for ESRS and AIMS total score in patients first treated with placebo: means and standard error of the mean (SEM)

PLACEBO FIRST GROUP

$\bar{X}$ (SEM) n= 15	Placebo		Vitamin E	
	Wk 2-3	Wk 6	Wk 12	Wk 14-15
ESRS I	1.500 (0.374)	1.851 (0.376)	1.530 (0.256)	2.214 (0.434)
ESRS II	6.400 (1.588)	5.800 (1.562)	5.600 (1.344)	6.571 (1.926)
ESRS III	1.571 (0.532)	0.333 (0.126)	0.667 (0.232)	0.929 (0.305)
ESRS IV	8.800 (1.239)	9.467 (1.138)	9.667 (1.504)	8.929 (1.458)
ESRS V	2.533 (0.236)	2.600 (0.235)	2.667 (0.232)	2.500 (0.228)
ESRS VI	1.133 (0.322)	0.733 (0.284)	1.067 (0.267)	1.214 (0.318)
ESRS TOTAL	22.786 (3.389)	21.500 (2.460)	21.200 (1.981)	22.357 (2.376)
AIMS TOTAL	5.400 (0.779)	4.800 (0.670)	4.800 (0.846)	5.214 (0.956)

Table VI Scores for Extrapyramidal Symptom Rating Scale (ESRS) and AIMS at termination of Vitamin E and Placebo treatment: means and standard deviations (SD), mean differences and standard errors (SE), t values and statistical significance of differences from analysis of variance for two-period cross-over design.

	Vitamin E		Placebo		Difference			
	Mean	SD	Mean	SD	LS * Mean	SEM	t	p
ESRS I	2.07	1.66	2.19	1.30	-0.15	0.30	0.50	0.62
ESRS II	5.70	5.68	6.63	5.43	-1.17	1.07	1.09	0.29
ESRS III	0.93	1.30	0.59	0.75	0.31	0.24	1.28	0.21
ESRS IV	9.85	5.70	10.19	4.60	-0.31	1.00	0.31	0.76
ESRS V	2.63	0.84	2.78	0.89	-0.15	0.13	1.15	0.26
ESRS VI	0.93	1.11	1.04	1.06	-0.18	0.24	0.72	0.48
AIMS	7.11	4.27	7.11	3.61	-0.05	0.55	0.09	0.93

* Least squares estimate from analysis of variance for two-period cross-over design. Note that the least squares estimate is adjusted for the fact that the number of patients beginning treatment with Vitamin E differed from the number beginning treatment with Placebo.

Table VII Period effect analysis, irrespective of drug treatment: means and standard deviations (SD), and statistical significance of differences from analysis of variance for the two-period crossover design

	First 6 weeks PERIOD I		Last 6 weeks PERIOD 2		p
	Mean	SD	Mean	SD	
ESRS I	1.96	1.56	2.30	1.41	0.252
ESRS II	5.15	4.96	7.19	5.96	0.054 *
ESRS III	0.63	1.11	0.89	1.01	0.359
ESRS IV	10.15	5.25	9.89	5.16	0.824
ESRS V	2.70	0.87	2.70	0.87	0.900
ESRS VI	0.70	1.03	1.26	1.06	0.027 *
AIMS TOT.	6.89	4.01	7.33	3.88	0.422

Table VIII Side effects reported with Vitamin E or Placebo (n=27)

NUMBER OF PATIENTS REPORTING SIDE EFFECTS

	VITAMIN E	PLACEBO
Nausea	2	0
Diarrhea	2	9
Intestinal cramps	3	3
Fatigue	3	0
Weakness	0	1
Headache	1	0
Blurred Vision	1	0
Rash	2	1
Other	5	2

Table IX Statistical Power Analysis: Minimum Detectable Treatment Differences with 80% and 90% Power and N=27 (two-tailed tests at p=0.05).

Scale	Placebo Mean Value	S.D. (Difference)	Minimum Detectable Difference		Minimum Detectable Difference as % of Placebo Response	
			80% Power	90% Power	80% Power	90% Power
ESRS I	2.07	1.56	0.87	1.01	42.0	48.8
ESRS II	5.70	5.56	3.11	3.60	54.6	63.2
ESRS III	0.93	1.25	0.70	0.81	75.3	87.1
ESRS IV	9.85	5.20	2.91	3.37	29.5	34.2
ESRS V	2.63	0.68	0.38	0.44	14.5	16.7
ESRS VI	0.93	1.25	0.70	0.81	75.3	87.1
AIMS	7.11	2.86	1.60	1.85	22.5	26.0

Figure 1

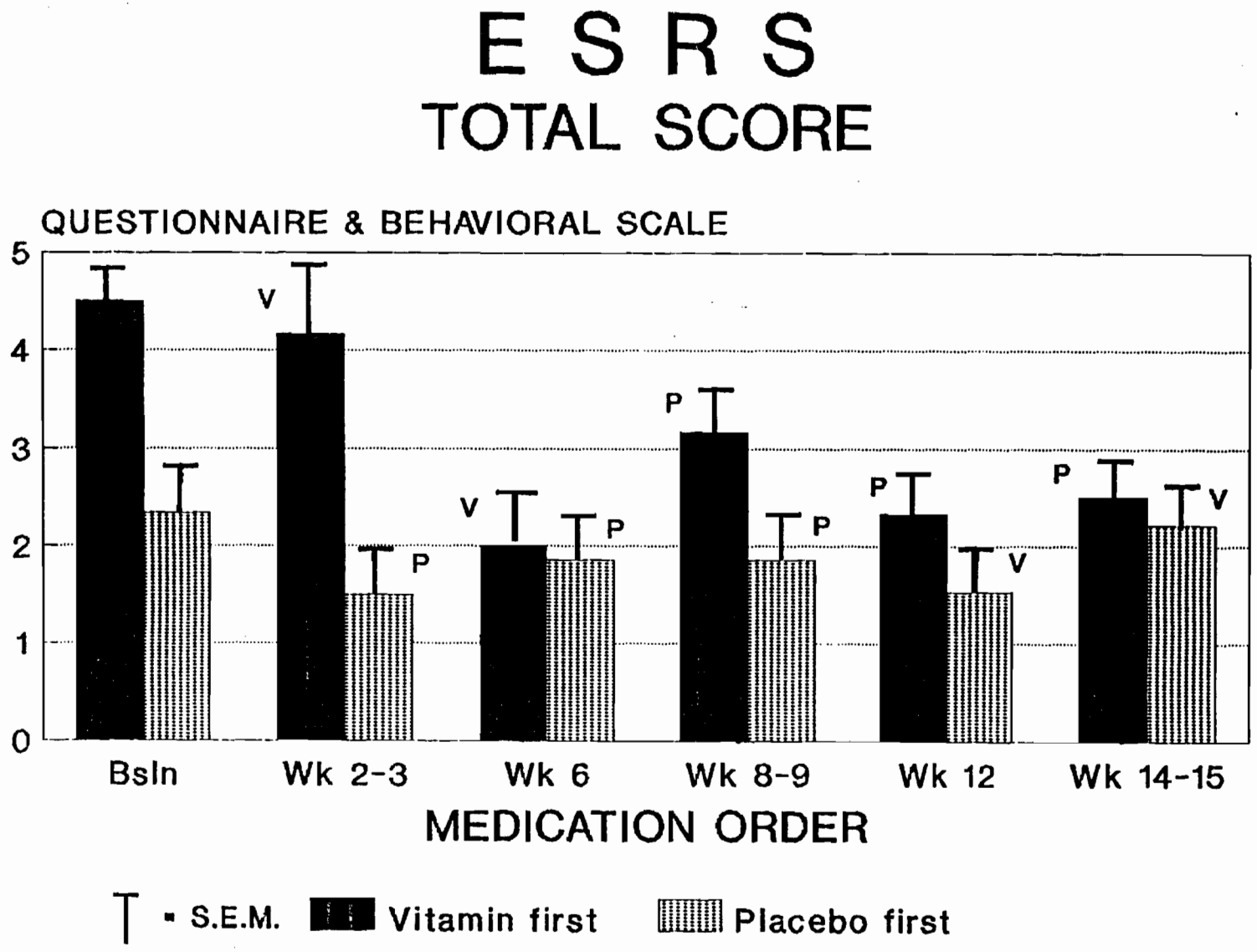

E S R S
TOTAL SCORE
QUESTIONNAIRE & BEHAVIORAL SCALE
5
4
3
2
1
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
S.E.M.
Vitamin first
Placebo first

Figure 2

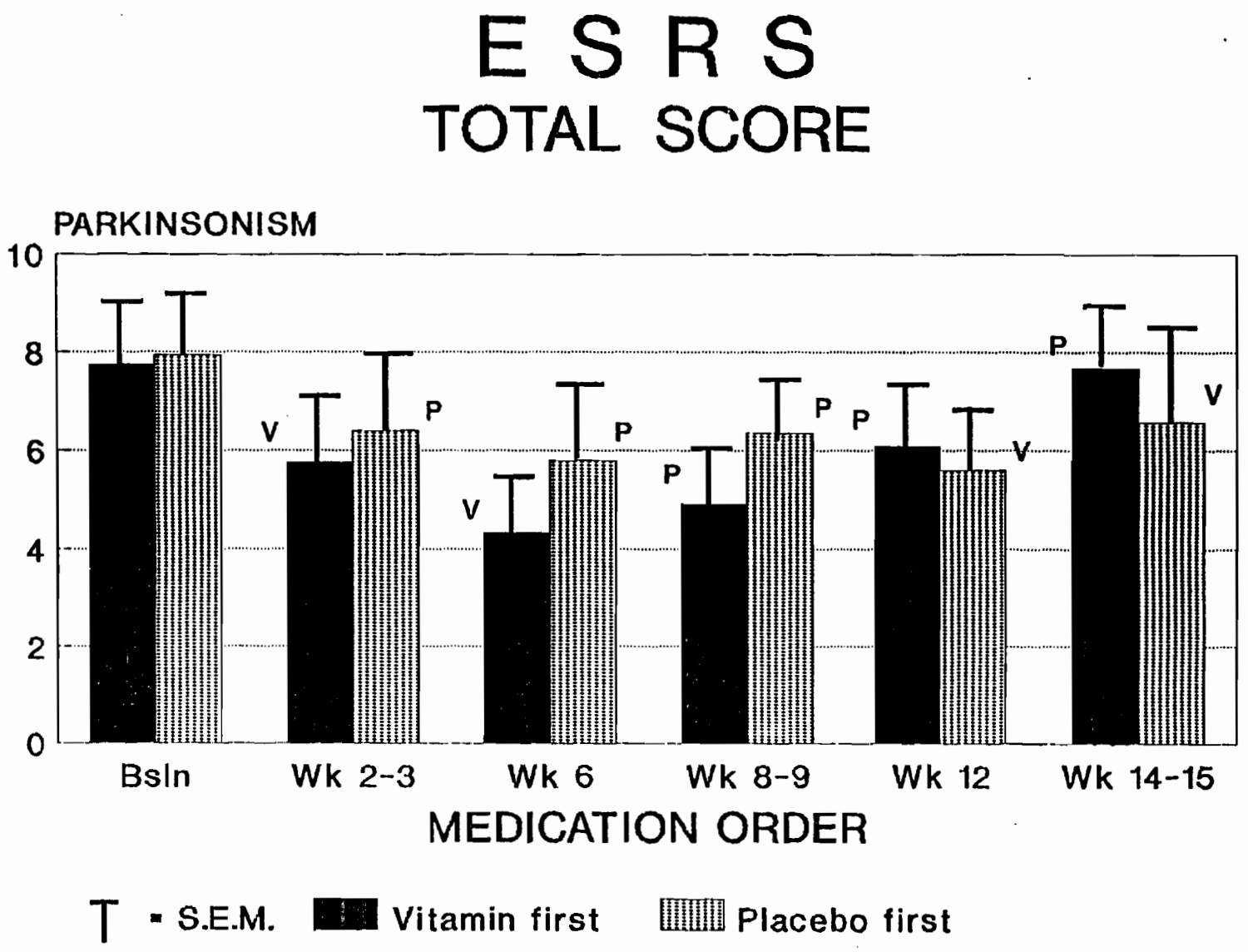

E S R S
TOTAL SCORE
PARKINSONISM
10
8
6
4
2
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
T = S.E.M.
Vitamin first
Placebo first

Figure 3

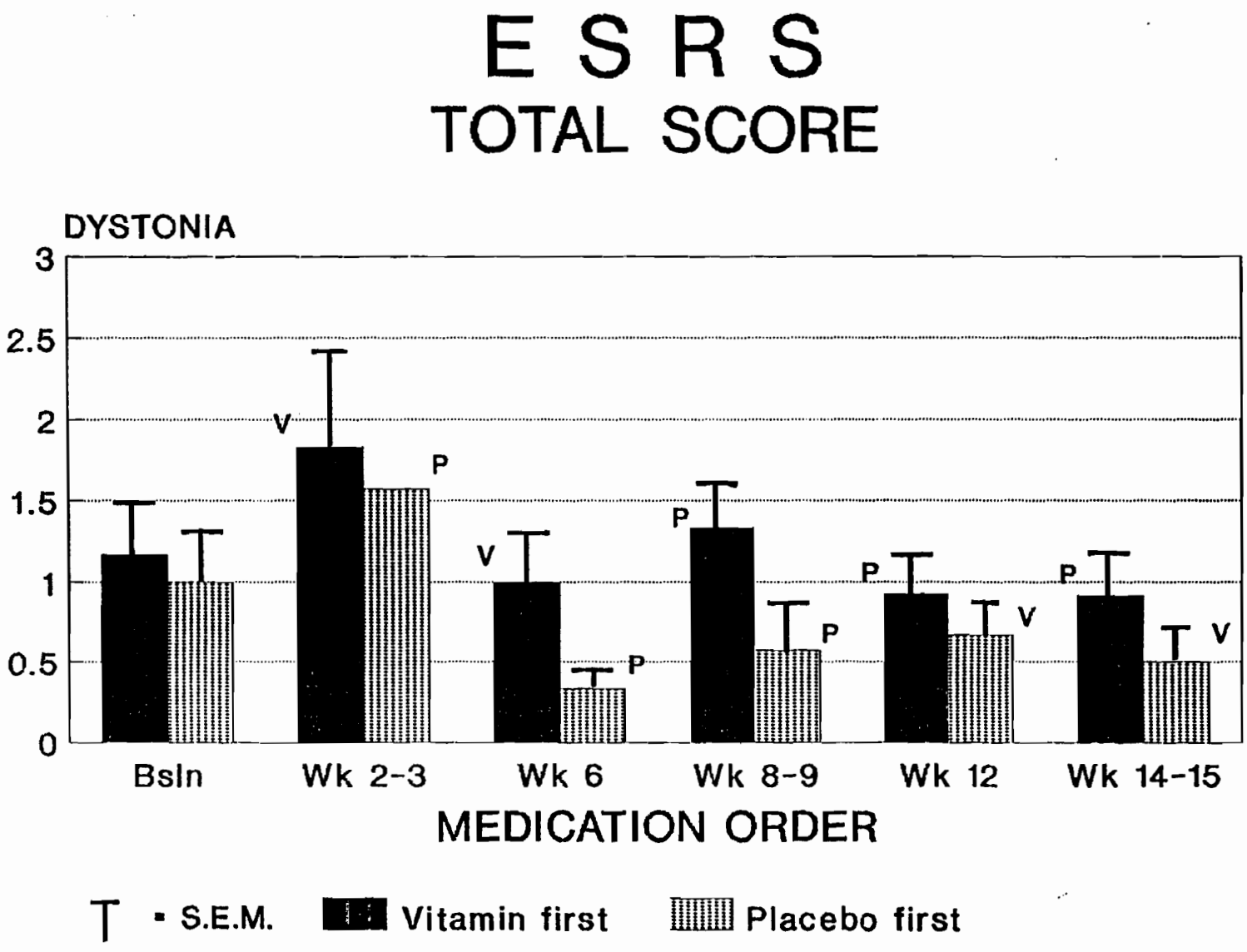

E S R S
TOTAL SCORE
DYSTONIA
3
2.5
2
1.5
1
0.5
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
T = S.E.M.
Vitamin first
Placebo first

Figure 4

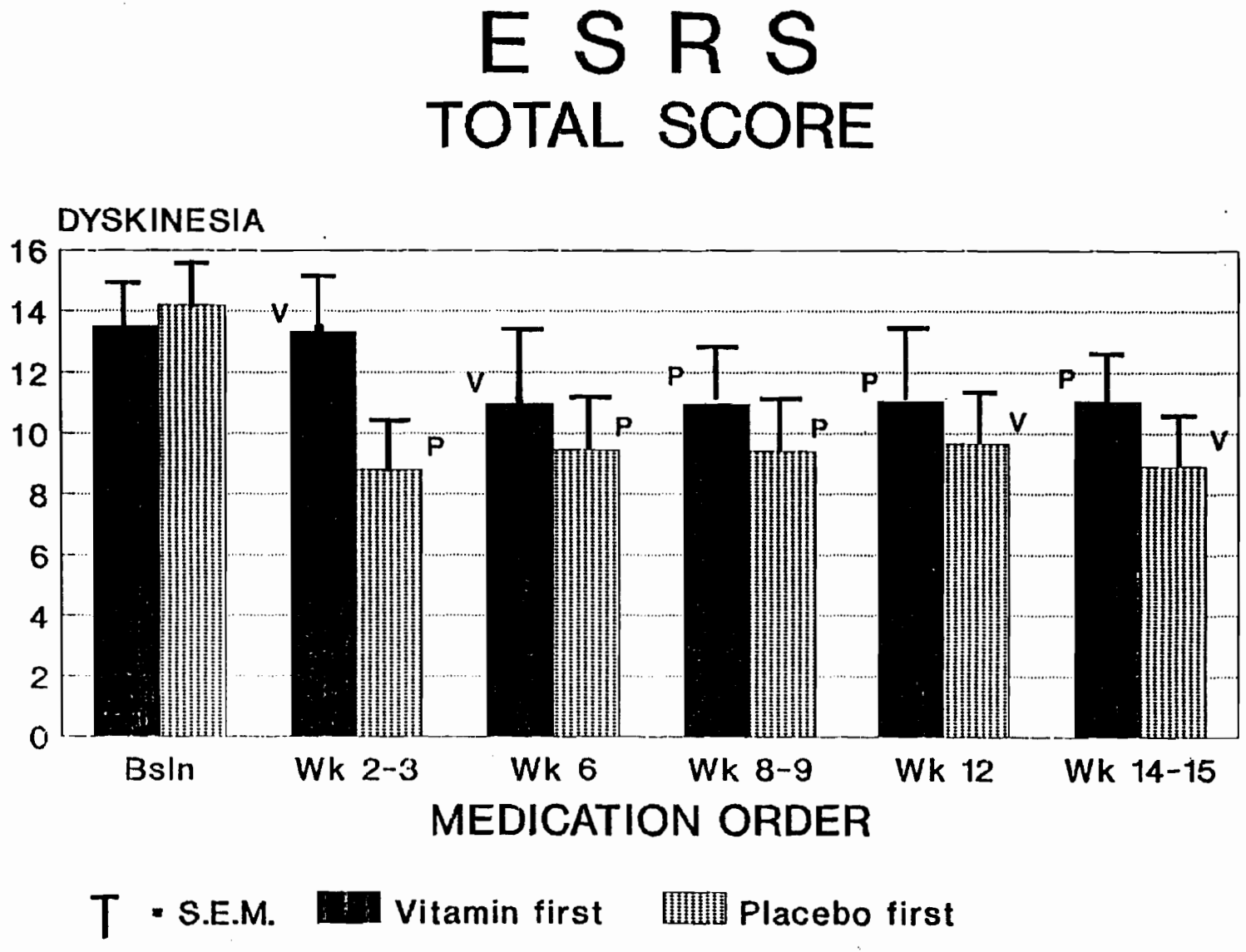

E S R S
TOTAL SCORE
DYSKINESIA
16
14
12
10
8
6
4
2
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
T = S.E.M.
Vitamin first
Placebo first

Figure 5

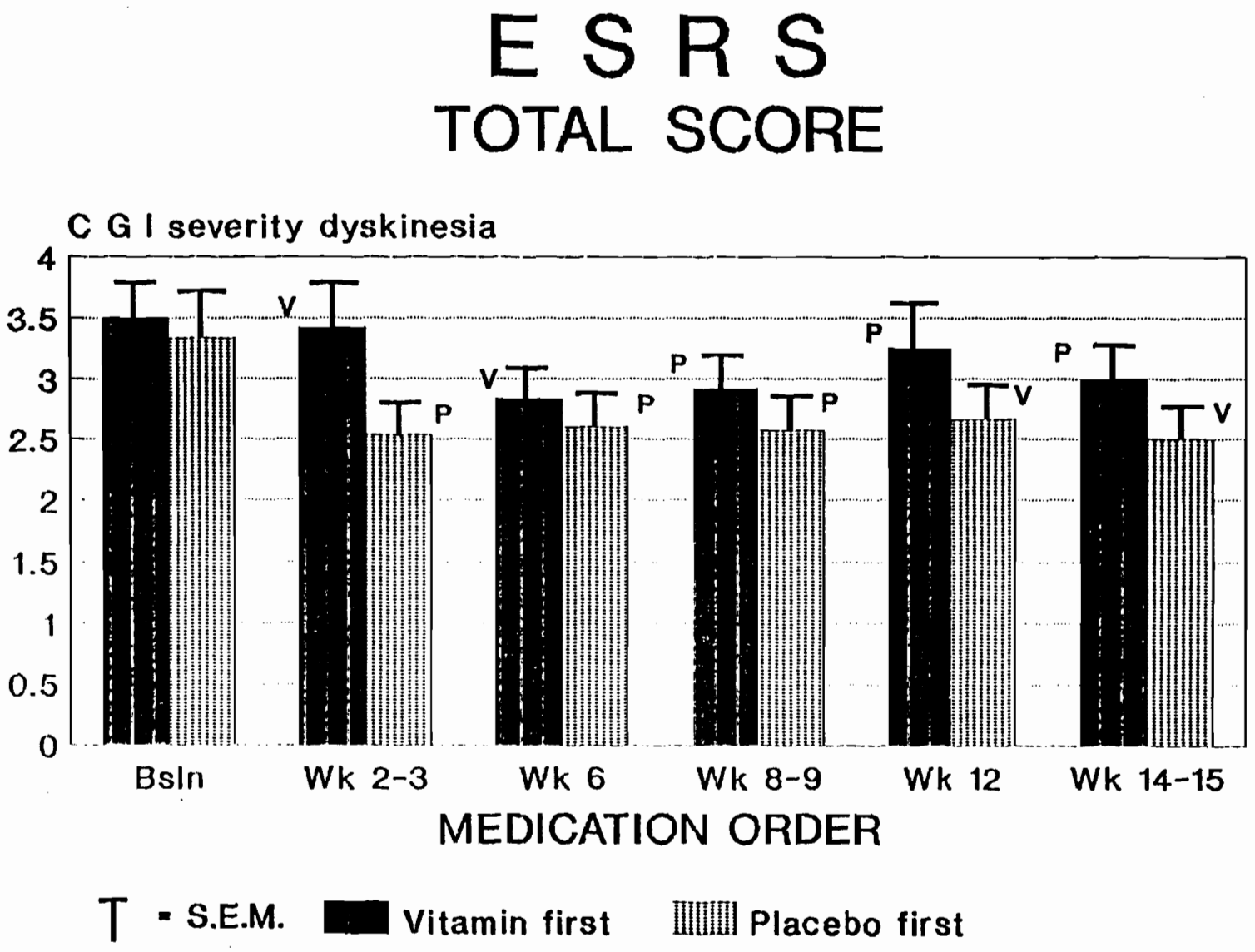

E S R S
TOTAL SCORE
C G I severity dyskinesia
4
3.5
3
2.5
2
1.5
1
0.5
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
T - S.E.M.
Vitamin first
Placebo first

Figure 6

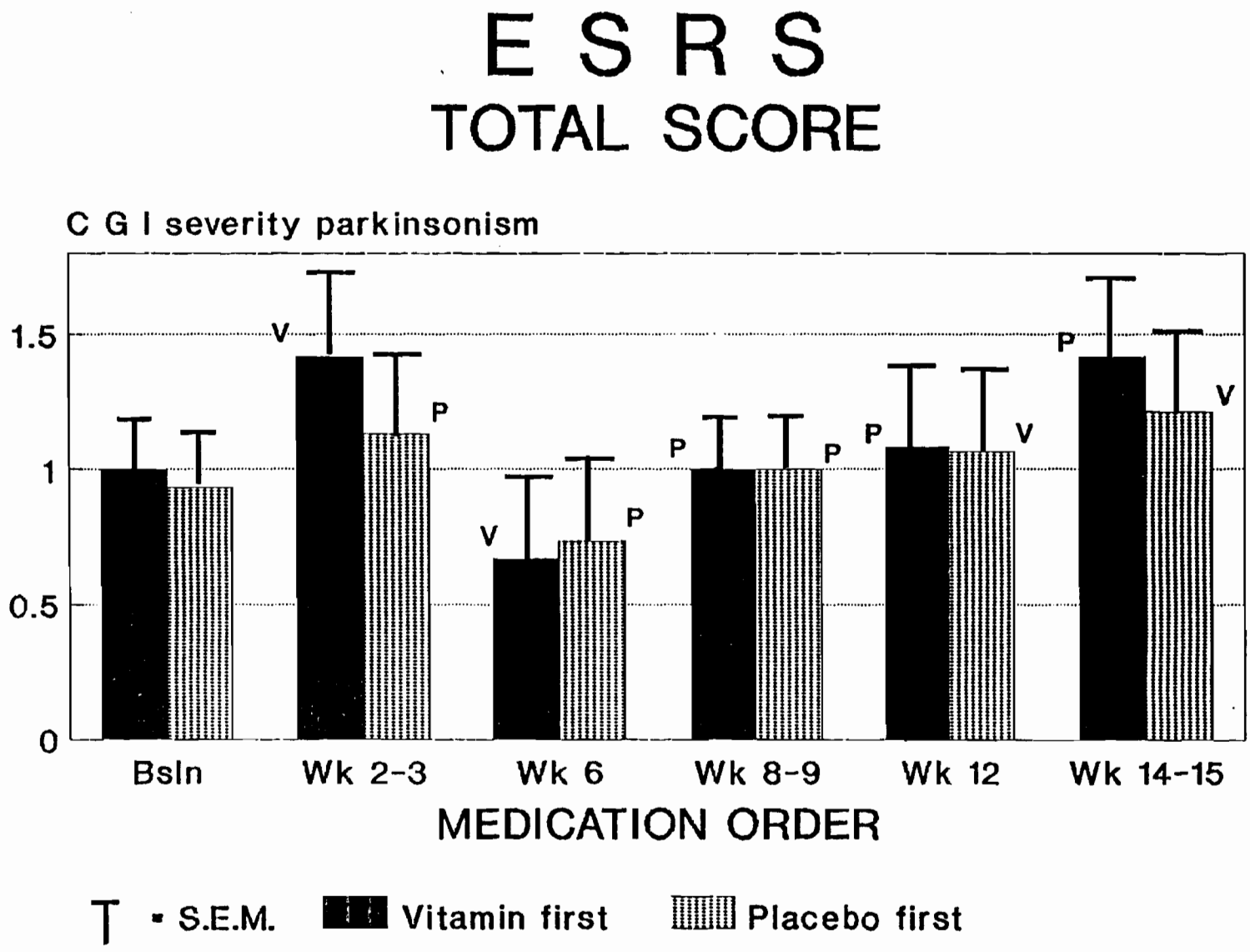

E S R S
TOTAL SCORE
C G I severity parkinsonism
1.5
1
0.5
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
T = S.E.M.
Vitamin first
Placebo first

Figure 7

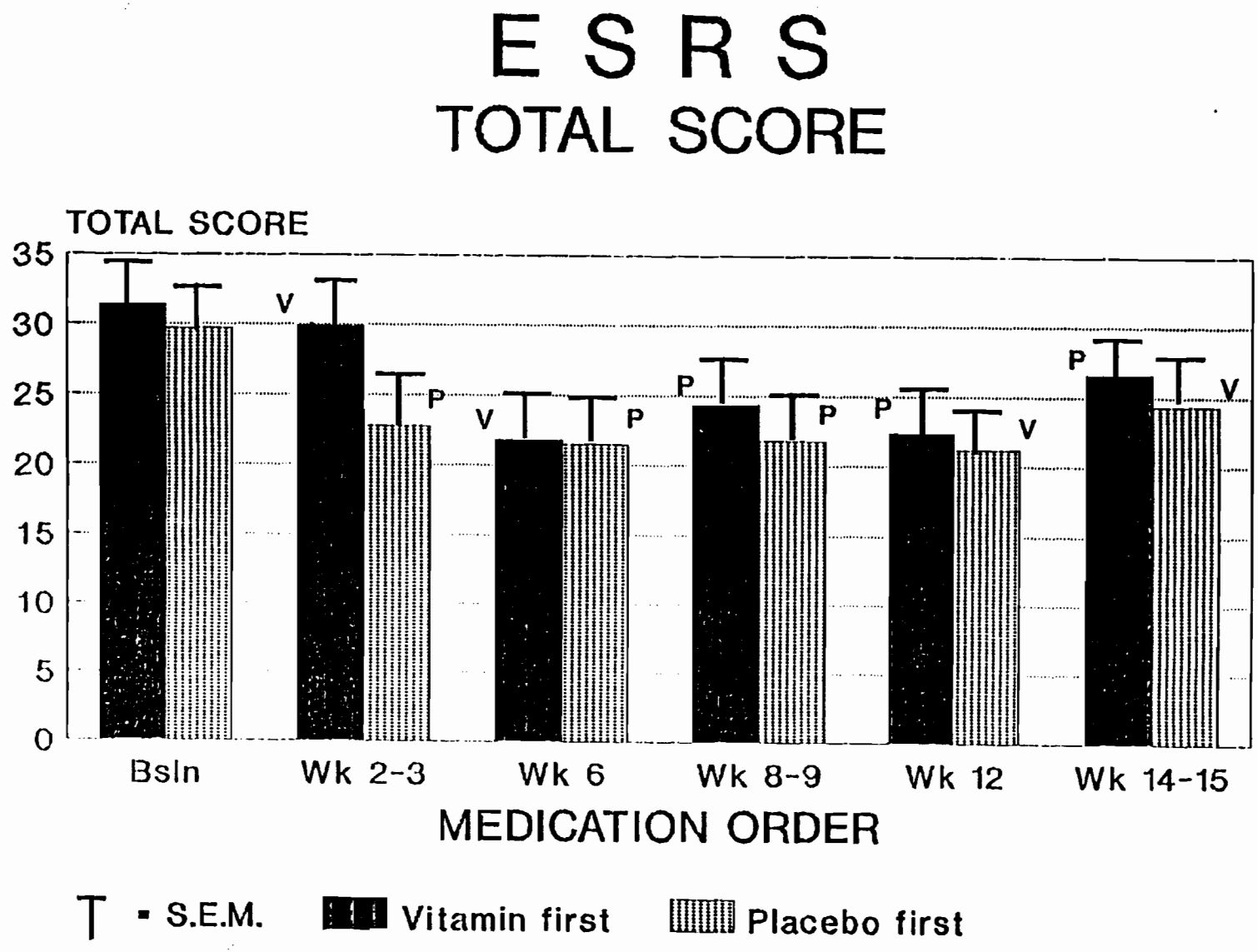

E S R S
TOTAL SCORE
TOTAL SCORE
35
30
25
20
15
10
5
0
V
P
V
P
P
P
P
V
P
V
Bsln
Wk 2-3
Wk 6
Wk 8-9
Wk 12
Wk 14-15
MEDICATION ORDER
T = S.E.M.
Vitamin first
Placebo first

Figure 8

A I M S
TOTAL SCORE

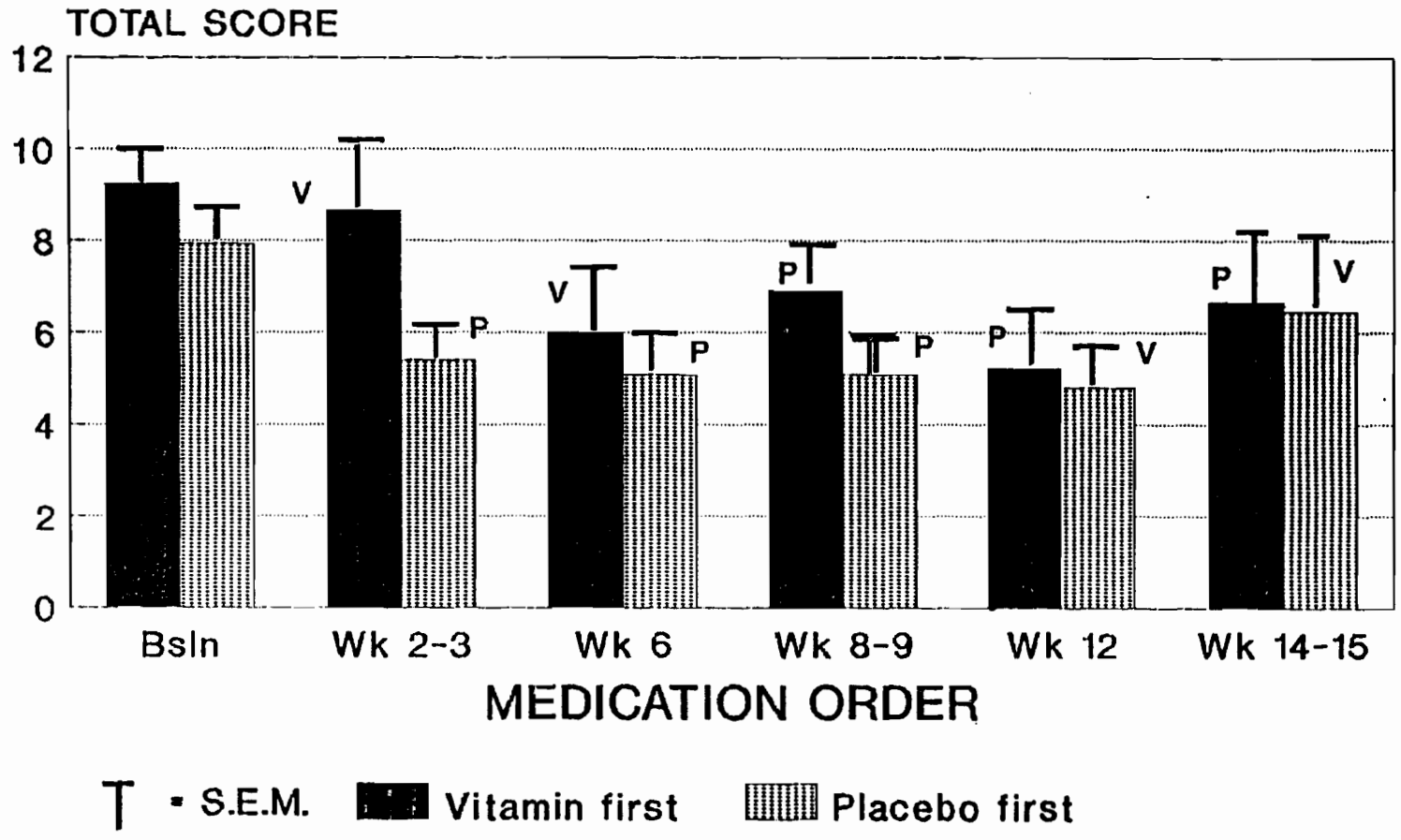
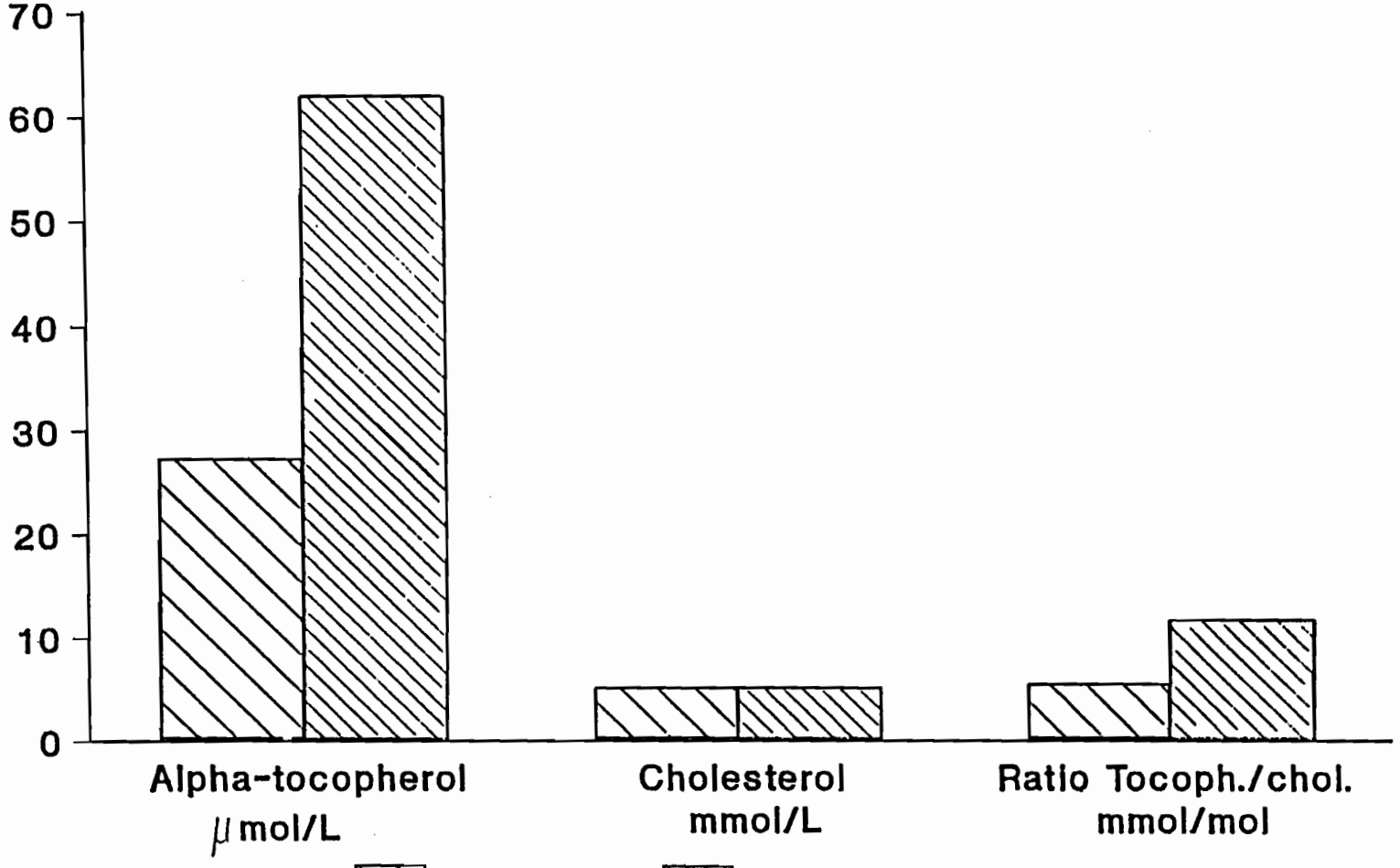


Figure 9

PLASMA LEVELS



Paired t-test= -6.41, p<0.001

Paired t-test= -6.98, p<0.001

Diagnostic criteria for Schizophrenia

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

   (1) two of the following:

      (*a*) delusions
      (*b*) prominent hallucinations (throughout the day for several days or several times a week for several weeks, each hallucinatory experience not being limited to a few brief moments)
      (*c*) incoherence or marked loosening of associations
      (*d*) catatonic behavior
      (*e*) flat or grossly inappropriate affect

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

   (3) prominent hallucinations [as defined in (1)(*b*) above] of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other

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

C. Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out, i.e., if a Major Depressive or Manic Syndrome has ever been present during an active phase of the disturbance, the total duration of all episodes of a mood syndrome has been brief relative to the total duration of the active and residual phases of the disturbance.

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

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

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

   Prodromal or Residual Symptoms:

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

Diagnostic criteria for Schizophrenia continued

(3) markedly peculiar behavior (e.g., collecting garbage, talking to self in public, hoarding food)
(4) marked impairment in personal hygiene and grooming
(5) blunted or inappropriate affect
(6) digressive, vague, overelaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech
(7) odd beliefs or magical thinking, influencing behavior and inconsistent with cultural norms, e.g., superstitiousness, belief in clairvoyance, telepathy, "sixth sense," "others can feel my feelings," overvalued ideas, ideas of reference
(8) unusual perceptual experiences, e.g., recurrent illusions, sensing the presence of a force or person not actually present
(9) marked lack of initiative, interests, or energy

Examples: Six months of prodromal symptoms with one week of symptoms from A; no prodromal symptoms with six months of symptoms from A; no prodromal symptoms with one week of symptoms from A and six months of residual symptoms.

E. It cannot be established that an organic factor initiated and maintained the disturbance.

F. If there is a history of Autistic Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present.

Classification of course. The course of the disturbance is coded in the fifth digit:

1-Subchronic. The time from the beginning of the disturbance, when the person first began to show signs of the disturbance (including prodromal, active, and residual phases) more or less continuously, is less than two years, but at least six months.

2-Chronic. Same as above, but more than two years.

3-Subchronic with Acute Exacerbation. Reemergence of prominent psychotic symptoms in a person with a subchronic course who has been in the residual phase of the disturbance.

4-Chronic with Acute Exacerbation. Reemergence of prominent psychotic symptoms in a person with a chronic course who has been in the residual phase of the disturbance.

5-In Remission. When a person with a history of Schizophrenia is free of all signs of the disturbance (whether or not on medication), "in Remission" should be coded. Differentiating Schizophrenia in Remission from No Mental Disorder requires consideration of overall level of functioning, length of time since the last episode of disturbance, total duration of the disturbance, and whether prophylactic treatment is being given.

0-Unspecified.

Diagnostic criteria for Bipolar Disorders

296.6x Bipolar Disorder, Mixed

For fifth digit, use the Manic Episode codes (p. 218) to describe current state.

A. Current (or most recent) episode involves the full symptomatic picture of both Manic and Major Depressive Episodes (except for the duration requirement of two weeks for depressive symptoms) (p. 217 and p. 222), intermixed or rapidly alternating every few days.

B. Prominent depressive symptoms lasting at least a full day.

Specify if seasonal pattern

296.4x Bipolar Disorder, Manic

For fifth digit, use the Manic Episode codes (p. 218) to describe current state.

Currently (or most recently) in a Manic Episode (p. 217). (If there has been a previous Manic Episode, the current episode need not meet the full criteria for a Manic Episode.)

Specify if seasonal pattern

296.5x Bipolar Disorder, Depressed

For fifth digit, use the Major Depressive Episode codes (p. 223) to describe current state.

A. Has had one or more Manic Episodes

B. Currently (or most recently) in a Major Depressive Episode (p. 222). (If there has been a previous Major Depressive Episode, the current episode need not meet the full criteria for a Major Depressive Episode.)

Specify if seasonal pattern

Diagnostic criteria for Manic Episode

Note: A "Manic Syndrome" is defined as including criteria A, B, and C below. A "Hypomanic Syndrome" is defined as including criteria A and B, but not C, i.e., no marked impairment.

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood.

B. During the period of mood disturbance, at least three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity
(2) decreased need for sleep, e.g., feels rested after only three hours of sleep
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility, i.e., attention too easily drawn to unimportant or irrelevant external stimuli
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities which have a high potential for painful consequences, e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments

C. Mood disturbance sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others.

D. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e., before the mood symptoms developed or after they have remitted).

E. Not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS.

F. It cannot be established that an organic factor initiated and maintained the disturbance. **Note:** Somatic antidepressant treatment (e.g., drugs, ECT) that apparently precipitates a mood disturbance should not be considered an etiologic organic factor.

(continued)

Diagnostic criteria for Manic Episode continued

Manic Episode codes: fifth-digit code numbers and criteria for severity of current state of Bipolar Disorder, Manic or Mixed:

1-Mild: Meets minimum symptom criteria for a Manic Episode (or almost meets symptom criteria if there has been a previous Manic Episode).

2-Moderate: Extreme increase in activity or impairment in judgment.

3-Severe, without Psychotic Features: Almost continual supervision required in order to prevent physical harm to self or others.

4-With Psychotic Features: Delusions, hallucinations, or catatonic symptoms. If possible, specify whether the psychotic features are *mood-congruent* or *mood-incongruent.*

Mood-congruent psychotic features: Delusions or hallucinations whose content is entirely consistent with the typical manic themes of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person.

Mood-incongruent psychotic features: Either (*a*) or (*b*):

(a) Delusions or hallucinations whose content does *not* involve the typical manic themes of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person. Included are such symptoms as persecutory delusions (not directly related to grandiose ideas or themes), thought insertion, and delusions of being controlled.

(*b*) Catatonic symptoms, e.g., stupor, mutism, negativism, posturing.

5-In Partial Remission: Full criteria were previously, but are not currently, met; some signs or symptoms of the disturbance have persisted.

6-In Full Remission: Full criteria were previously met, but there have been no significant signs or symptoms of the disturbance for at least six months.

0-Unspecified.

Diagnostic criteria for Major Depressive Episode

Note: A "Major Depressive Syndrome" is defined as criterion A below.

A. At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucinations, incoherence, or marked loosening of associations.)

(1) depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day, as indicated either by subjective account or observation by others
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time)
(3) significant weight loss or weight gain when not dieting (e.g., more than 5% of body weight in a month), or decrease or increase in appetite nearly every day (in children, consider failure to make expected weight gains)
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Diagnostic criteria for Major Depressive Episode continued:

B. (1) It cannot be established that an organic factor initiated and maintained the disturbance
(2) The disturbance is not a normal reaction to the death of a loved one (Uncomplicated Bereavement)

Note: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by Major Depression.

C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e., before the mood symptoms developed or after they have remitted).

D. Not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS.

Major Depressive Episode codes: fifth-digit code numbers and criteria for severity of current state of Bipolar Disorder, Depressed, or Major Depression:

1-Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others.

2-Moderate: Symptoms or functional impairment between "mild" and "severe."

3-Severe, without Psychotic Features: Several symptoms in excess of those required to make the diagnosis, and symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

4-With Psychotic Features: Delusions or hallucinations. If possible, specify whether the psychotic features are *mood-congruent* or *mood-incongruent.*

Mood-congruent psychotic features: Delusions or hallucinations whose content is entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment.

Mood-incongruent psychotic features: Delusions or hallucinations whose content does *not* involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Included here are such symptoms as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting, and delusions of control.

5-In Partial Remission: Intermediate between "In Full Remission" and "Mild," and no previous Dysthymia. (If Major Depressive Episode was superimposed on Dysthymia, the diagnosis of Dysthymia alone is given once the full criteria for a Major Depressive Episode are no longer met.)

6-In Full Remission: During the past six months no significant signs or symptoms of the disturbance.

0-Unspecified.

(continued)

Diagnostic criteria for Major Depressive Episode continued

Specify chronic if current episode has lasted two consecutive years without a period of two months or longer during which there were no significant depressive symptoms.

Specify if current episode is **Melancholic Type**.

Diagnostic criteria for Melancholic Type

The presence of at least five of the following:

(1) loss of interest or pleasure in all, or almost all, activities
(2) lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)
(3) depression regularly worse in the morning
(4) early morning awakening (at least two hours before usual time of awakening)
(5) psychomotor retardation or agitation (not merely subjective complaints)
(6) significant anorexia or weight loss (e.g., more than 5% of body weight in a month)
(7) no significant personality disturbance before first Major Depressive Episode
(8) one or more previous Major Depressive Episodes followed by complete, or nearly complete, recovery
(9) previous good response to specific and adequate somatic antidepressant therapy, e.g., tricyclics, ECT, MAOI, lithium

INFORMED CONSENT AGREEMENT

PATIENT NAME: _____

DATE OF BIRTH: ___/___/___

You are being asked to participate in a drug research project. However, before you give your consent to be a volunteer, we want you to read the following and ask as many questions as necessary to be sure that you understand what your participation would involve.

NATURE OF THE STUDY

You are being asked to take part in a drug study which involves your receiving and taking, in a random order, Vitamin E (Alpha-Tocopherol) and placebo (inactive substance) separately, in capsule form, for a six week period each. Since Vitamin E (Alpha-Tocopherol) is experimental in the treatment of Tardive Dyskinesia it has not yet been approved for this purpose in Canada by the Health Protection Branch (HPB). This research project has been reviewed by an institutional review committee, and the committee has given permission to your psychiatrist to allow people such as yourself to volunteer to participate in the study.

PURPOSE AND DESIGN OF THE STUDY

The objective of this study is to evaluate the effectiveness of Vitamin E (Alpha-Tocopherol) in the treatment of Tardive Dyskinesia. Tardive Dyskinesia is a movement disorder which is an undesirable side effect which occurs in certain patients receiving long term antipsychotic drug treatment. There is still as yet no clear effective treatment for tardive dyskinesia. The design of this study is double-blind which means that neither you, nor your psychiatrist will know which medication you are taking(placebo or Vitamin E) during the 12 week total study period (except in case of emergency). Throughout the study you will have received for a six week period each both the Vitamin E treatment and the placebo individually. This is done in order to assess the true efficacy of Vitamin E in the treatment of Tardive Dyskinesia, more precisely, the efficacy of Vitamin E in decreasing your movement disorder.

PROCEDURES TO BE FOLLOWED DURING THE STUDY

At the beginning of the study you will be seen at least once weekly for the first two weeks and then at two to three week intervals which would correspond to the scheduled day of your intramuscular injection of depot antipsychotic medication if you are receiving such medication. You will be interviewed and assessed by the same psychiatrist throughout the study period. There will be a neurological examination performed before entrance to the study and also some blood tests done. There may be some pain or bruising associated with the blood drawing. The purpose of these periodic evaluations will be to determine

whether the treatment you are receiving is helpful in decreasing the movement disorder associated with Tardive Dyskinesia and to be sure that it is not causing you any harm. Your reactions to the medication you will be taking during this study will be carefully monitored. You will be asked to tell your psychiatrist of all other drugs which you take, in addition to the study drug, while you are participating in the study. It will also be important that you discuss with the psychiatrist any unpleasant or unusual as well as positive symptoms which you might experience during the study. Your participation in the study is voluntary. It will involve your participation at regularly scheduled visits. At each visit, except the last, you will be given medication to take orally everyday until your next visit.

FORESEEABLE RISKS

Adverse reactions have rarely been reported with large doses of Vitamin E. Such rare adverse reactions include: nausea, diarrhea, intestinal cramps, fatigue, weakness, headache, blurred vision, rash, gonadal dysfunction, decreased thyroid laboratory measurements (serum thyroxine and triiodothyronine). These effects are known to disappear after discontinuing the medication. You should realize that the side effects which have been listed represent a wide range of side effects. You may experience some of these side effects but it is most unlikely that you would experience all of them. It is important for you to know that the drug could have no beneficial effects for your movement disorder.

POTENTIAL BENEFITS OF THE STUDY

There is one study in the literature which has reported some beneficial effects of Vitamin E (Alpha-Tocopherol) in the treatment of Tardive Dyskinesia. Therefore, patients receiving this drug may experience a decrease of their movement disorder. All patients in this study will receive the benefit of periodic evaluation of symptoms and general health discussions with the doctor, the health information derived from laboratory tests, and finally the chance to contribute to a scientific investigation.

CONFIDENTIALITY

Every reasonable effort will be made to keep your medical records confidential. By signing this consent form, you give permission to your physician to release the information regarding or obtained as a result of your participation in this study to the Canadian Health Protection Branch and other government agencies which, if needed, would allow them to inspect all your medical records. Your identity will remain confidential, except that it will be provided as noted above or as may be required by law.

GENERAL

Your participation in this study is purely voluntary, and you may withdraw your consent and discontinue your participation in the study at any time. Should you wish to withdraw your consent, you would be asked to notify your

study psychiatrist. Such a decision on your part will not influence your further medical care or result in loss of benefits to which you are otherwise entitled.

Your participation in the study may be discontinued without your consent if, in your psychiatrist's clinical judgement, discontinuance is in your best interest; and if you fail to comply with study procedures. If you have an adverse reaction as a result of the study; or you have any questions about the study; or any additional concerns, please contact:

Dr. Jacques Bradwejn or Dr. Christian Shriqui at 344-3584.

We have tried to explain all the important details about the drug and the study to you. If you have any questions that are not answered here, your psychiatrist will be happy to give you further information.

INFORMED CONSENT AGREEMENT

I have read the preceding information and I have had an opportunity to ask questions to help me understand what my participation will involve. I freely give my consent to participate in the study.

My signature below indicates that the study and related procedures have been explained to me in terms I can understand. I agree to participate in the study until I decide otherwise. I acknowledge having received a copy of this agreement.

_____ ___/___/___

Signature of Patient or Legally Authorized Representative — Date

_____ ___/___/___

Signature of Witness — Date

_____ ___/___/___

Signature of Investigator — Date

FORMULE DE CONSENTEMENT ECLAIRE

NOM DU PATIENT: _____

DATE DE NAISSANCE: ___/___/___/

On vous propose de participer à un projet de recherche sur un médicament. Avant d'accorder votre consentement, nous vous demandons de lire ce document attentivement et de poser toutes les questions que vous jugez utiles pour vous assurer de comprendre ce à quoi vous vous engagez.

NATURE DE L'ETUDE

On vous propose de participer à une étude sur un médicament qui implique la prise de vitamine E (Alpha-Tocophérol) et d'un placebo (substance inactive) séparément pour une période de six semaines pour chaque substance. Vu que la vitamine E (Alpha-Tocophérol) est expérimental dans le traitement de la dyskinésie tardive, son usage n'est pas approuvé à cette fin au Canada par la Direction Générale de la Protection de la Santé (Health Protection Branch). Cette étude a été révisée par le comité de déontologie de l'hôpital St. Mary's qui a autorisé votre psychiatre à permettre la participation de personnes comme vous.

L'OBJECTIF ET MODALITE DE L'ETUDE

L'objectif de cette étude est d'évaluer l'efficacité de la vitamine E (Alpha-Tocophérol) dans le traitement de la dyskinésie tardive. La dyskinésie tardive est un désordre du mouvement survenant comme effet secondaire indésirable chez certains patients recevant une médication antipsychotique à long terme. Il n'existe aucun traitement démontré clairement éfficace pour la dyskinésie tardive. Cette etude est à double insue: ni vous ni votre psychiatre ne saurez lequel des deux médicaments (placebo ou vitamine E) vous sera administré durant les 12 semaines de l'etude (sauf dans un cas d'urgence). Au cours de l'etude vous recevrez la vitamine E et le placebo séparément pour une période de six semaines chaque. Ceci est fait afin de déterminer l'efficacité véritable de la vitamine E dans le traitement de la dyskinésie tardive soit son efficacité à pouvoir diminuer l'intensité de vos mouvements involontaires.

DEMARCHE A SUIVRE DURANT L'ETUDE

Pour les premières deux semaines de l'etude vous serez évalué par votre psychiatre au moins une fois par semaine à des intervales de deux à trois semaines dépendant du calendrier d'injection de votre médication antipsychotique à longue action (si vous recevez une telle médication). Un examen neurologique sera fait ainsi que des prises de sang avant votre entrée dans l'étude. Il se peut que qu'une douleur ou la formation d'une ecchymose survienne avec les prise de sang. Le but des évaluations périodiques sera de déterminer l'efficacité de la médication que vous recevrez a diminuer l'intensité de vos mouvements involontaires et aussi pour s'assurer que cet agent ne vous cause aucun problème. On surveillera attentivement vos

réactions au médicament. Il est important que vous mentionniez au psychiatre à chaqu'une des entrevues le nom de tout autre médicament que vous prenez pendant que vous participez à l'etude. Il est important que vous discutez avec le psychiatre de tout symptômes désagréables ou inhabituels ainsi que d'éffets positifs pouvant survenir durant l'étude. Votre participation à cette étude est sur une base toute à fait volontaire. Celle-ci implique votre participation à des visites régulières et à chaque visite, sauf la dernière, vous recevrez une médication à prendre par la bouche chaque jour jusqu'à la visite subséquente.

RISQUES POSSIBLES

Des réactions adverses ont rarement été rapportées avec l'utilisation de hautes doses de vitamine E. De telles réactions adverses peuvent inclure: nausées, diarrhées, crampes intestinales, fatigue, sensation de faiblesse, maux de tête, vision embrouillée, éruption cutanée, troubles de la fonction gonadique, une baisse des mesures de laboratoires de fonction thyroïdienne (thyroxine et triiodothyronine sérique). De tels réactions adverses disparaissent après l'interruption du médicament. Vous devez comprendre que les éffets indésirables enumerés représentent une large gamme de réactions. Il est possible que vous présentiez certaines de ces réactions mais il est peut probable que vous les présentiez toutes. Il est important que vous sachiez qu'il n'est pas garantie que le médicament améliore l'intensité de vos mouvements involontaires.

AVANTAGES POSSIBLES DE L'ETUDE

Il y a une etude dans la littérature qui a rapportée des effets bénéfiques de la vitamine E (Alpha-Tocophérol) dans le traitement de la dyskinésie tardive. Ainsi, il est raisonnable de penser que les patients qui recevront cette médication pourraient voir l'intensité de leur mouvements involontaires diminuer. Tous les patients participant à cette étude vont bénéficier d'une évaluation régulière de leur symptômes et de discussions avec un psychiatre sur les résultats des tests de laboratoire entrepris et leur état de santé général. De plus, les patients participant à l'étude auront la satisfaction de contribuer à une investigation clinique.

CARACTERE CONFIDENTIEL

Tous les efforts possibles seront fait pour que l'information contenue dans vos dossiers médicaux demeure confidentielle. En signant cette formule de consentement, vous autorisez votre psychiatre à transmettre des renseignements obtenus durant votre participation à cette étude à la Direction générale de la

protection de la santé, à d'autres divisions de Santé Canada, ou à d'autres gouvernements, et vous consentez à ce qu'ils inspectent, au besoin, tous vos dossiers médicaux. Votre identité demeurera confidentielle sauf en dehors des clauses mentionées ci-haut ou tel que requis par la loi.

GENERALITES

Votre participation a cette étude se fait sur un base tout à fait volontaire. Vous pouvez retirer votre consentement ou interrompre votre participation à cette étude à n'importe quel moment. Si vous désirez retirer votre consentement, veuillez en aviser votre psychiatre. Une telle décision de votre part n'influencera en rien les soins médicaux qui vous seront prodigués ultérieurement et n'entraineront pas la perte des avantages auxquels vous avez droit. Votre participation à cette etude pourra être interrompue sans votre consentement si votre psychiatre juge que c'est mieux pour vous, et si vous ne respectez pas les modalités de l'étude. Si vous présentez une réaction adverse suite à cette étude, ou si vous avez des questions au sujet de l'étude ou toute autre question, n'hésitez pas à communiquer avec le Dr. Jacques Bradwejn ou le Dr. Christian Shriqui en composant le 344-3584. Nous avons tenté de vous expliquer tous les détails importants relatifs au médicament et à l'étude. Si vous avez d'autres questions, votre psychiatre sera heureux de vous donner de plus amples renseignements.

ENTENTE DE CONSENTEMENT ECLAIRE

J'ai lu l'information précédente et j'ai eu l'opportunité de poser toutes questions afin de m'aider à comprendre les implications de ma participation. Je consens librement à participer à cette étude.

Ma signature ci-dessous indique que l'étude et la démarche relative à celle-ci mon été expliquées en des termes accessibles à mon niveau de compréhension. J'accepte de participer à cette etude mais je peux retirer mon consentement en tout temps. J'acquiesse avoir reçu une copie de cette entente.

_____ ___/___/___

Signature du patient ou du représentant légalement autorisé — Date

_____ ___/___/___

Signature du témoin — Date

_____ ___/___/___

Signature du chercheur — Date

THE REVIEWS

Dyskinésie tardive: mise a jour*

CHRISTIAN L. SHRIQUI, m.d.[1]

La Dyskinésie tardive (DT) est un syndrome neurologique lié à l'utilisation à long terme de médication antipsychotique. Sa prévalence significative (estimée à 15-20%), son irréversibilité potentielle en font un problème d'intérêt majeur en psychiatrie.

Le tableau clinique se caractérise par la combinaison variable de mouvements involontaires répétitifs de type choréiforme, athétosique ou dystonique; d'intensité et de localisation variables. L'évolution individuelle du syndrome est imprévisible mais des études longitudinales récentes sur son évolution donnent lieu à un optimisme prudent.

Tous les neuroleptiques sont impliqués dans l'apparition du syndrome et plusieurs facteurs de risque on été invoqués. Seul l'âge avancé joue un rôle clairement prédisposant.

Bien que plusieurs hypothèses aient été invoquées, la physiopathologie du syndrome demeure un mystère.

La question du consentement informé est abordée en raison des implications médico-légales du syndrome.

La prévention du syndrome, qui ne dispose d'aucun traitement démontré clairement efficace, est une considération essentielle. Seule la baisse graduelle (et idéalement l'arrêt complet) de la médication antipsychotique, lorsque l'état mental du patient le permet, constitue le traitement de choix à l'heure actuelle.

En 1952, l'introduction des neuroleptiques en thérapeutique amena une véritable révolution propulsant la psychiatrie dans une ère nouvelle. L'espoir qu'a suscité cette découverte demeure inégalé jusqu'à présent. Toutefois ces agents thérapeutiques ont plusieurs limitations: ils ne guérissent pas la schizophrénie, sont de faible efficacité face aux symptômes négatifs de cette maladie, et entraînent des effets secondaires variés, essentiellement moteurs, souvent gênants pour les patients, parfois irréversibles.

La dyskinésie tardive peut se définir comme un syndrome neurologique de mouvements involontaires hétérogènes, répétitifs et anormaux, d'intensité et de sévérité variables, qui survient chez certains individus exposés à un traitement neuroleptique à long terme (arbitrairement défini dans la littérature comme une période minimale de 3 à 6 mois), et qui n'est pas attribuable à d'autres causes (1-6). Ce syndrome fut rapporté pour la première fois dans la littérature par Schönecker en 1957 (7). Sigwald et al en 1959 furent les premiers à introduire la description des dyskinésies "facio-bucco-linguo-masticatrice", mais le syndrome ne reçut le terme de dyskinésie tardive (DT) proprement dit qu'avec Faurbye et al en 1964 pour le distinguer des dyskinésies aiguës qui surviennent plus tôt en cours de traitement (8,9).

La nature réversible du syndrome fut soulignée dès ses premières publications (7,9,10) mais ceci est peu connu et cède à la croyance plus générale de son irréversibilité (11). Bien que sa nature parfois irréversible soit documentée (1), *une dyskinésie tardive n'est pas synonyme d'irréversibilité* (3).

Sa prévalence significative, son irréversibilité potentielle, ses implications médico-légales récentes (aux États-Unis particulièrement), font de ce syndrome un problème d'intérêt majeur en psychiatrie.

Tableau clinique et évolution

La dyskinésie tardive, trouble hyperkinétique de nature extrapyramidale, est caractérisée par la combinaison variable de mouvements involontaires répétitifs, non rythmiques et sans but, de type choréique, athétosique et dystonique affectant le plus souvent la bouche, les lèvres, la langue, la mâchoire (triade bucco-linguo-masticatrice) mais aussi les extrémités, le cou, le tronc ainsi que n'importe quel autre groupe musculaire (1,2,12-14).

Les dyskinésies linguales et orofaciales, plus fréquemment retrouvées chez des patients âgés, sont les plus caractéristiques du syndrome (2-4,15). Les mouvements de la langue insidieux au début, des mouvements "tic-like" du visage ou un clignotement fréquent des yeux sont des signes précoces. D'autres mouvements tels le "piano-playing" des doigts et des orteils, des grimaces, du blépharospasme peuvent survenir (1-4,16).

Comme le suggèrent Chiang et al (17), la dyskinésie respiratoire n'est peut-être pas aussi rare qu'on le croit, celle-ci étant difficile à diagnostiquer. Un cas de dysfonction sexuelle comme complication d'une DT vient d'être récemment rapporté dans la littérature (18).

*Texte reçu octobre 1986.

[1]Résident en psychiatrie, Département de psychiatrie, Université de Montréal.

Demandes de tirés à part: Dr. C.L. Shriqui, Division de psychopharmacologie, Département de psychiatrie, Centre Hospitalier de St. Mary, 3830 Avenue Lacombe, Montréal, Québec H3T 1M5.

Les mouvements dyskinétiques sont habituellement exacerbés par la tension émotionnelle, une concentration soutenue lors de tâches fines, et le mouvement volontaire d'autres groupes musculaires; par contre, ils sont atténués par la sédation ou la somnolence et disparaissent pendant le sommeil (3,4,13), mais ces indices ne sont pas fiables pour poser un diagnostic (19).

Un syndrome ressemblant à la DT a été rapporté chez l'enfant, se manifestant par de la chorée, athétose, myoclonie et hémiballisme (3,4).

L'anosognosie des patients face à leurs symptômes dyskinétiques serait plus fréquente auprès de patients institutionnalisés chroniques, qu'auprès de jeunes patients atteints moins sévèrement (4).

Les manifestations hétérogènes de la DT peuvent refléter l'existence de divers sous-groupes du syndrome, ayant chacun une physiopathologie, une symptomatologie et une réponse au traitement distinctes.

Bien que 7 variantes de DT aient été identifiées dans la littérature (20), on peut distinguer la DT en 2 sous-groupes principaux: une forme classique choréoathétoïde et la dystonie tardive. Chacun de ces 2 sous-types serait redivisé en 3 sous-classes: orofaciale, tronculaire et des extrémités (6).

Il est important de souligner qu'une DT peut coexister avec d'autres troubles moteurs tels une akathisie ou des symptômes parkinsoniens (14).

Trois types de dyskinésies, en rapport avec leur apparition en cours de traitement, ont été décrites: la dyskinésie tardive manifeste (overt), masquée (covert) et de retrait (withdrawal) (16, 21). La dyskinésie de retrait est définie comme une forme généralement circonscrite de DT, ayant le meilleur pronostic et disparaissant spontanément dans les 12 semaines après l'arrêt de la médication. La forme masquée se manifeste avec l'arrêt ou la baisse de la médication neuroleptique sans résolution spontanée.

Bien que d'intérêt théorique, la distinction entre ces 3 types de dyskinésies est loin d'être aussi clairement délimitée en pratique courante. Il est peut-être plus prudent d'énoncer que ces divers types de DT, qui figurent dans les critères diagnostics de recherche de Schooler et Kane (22), ont leur plus grand intérêt dans ce domaine.

L'évolution spontanée des DT est imprévisible et il est clair que son pronostic à long terme n'a pas encore été suffisamment étudié. Les effets bénéfiques de l'arrêt de la médication neuroleptique sur l'évolution à long terme de la DT semblent de plus en plus établis (1-4,23,24). Les études longitudinales récentes sur l'évolution à long terme de la DT, et les duplications futures de telles études vont certainement entraîner une réévaluation de la distinction entre DT irréversibles et DT persistantes, car comme le démontrent plusieurs de ces études, il n'est pas rare d'observer des rémissions spontanées après plusieurs années.

Gardos et al, dans leur étude longitudinale sur 5 ans de 85 patients schizophrènes externes, tous traités aux neuroleptiques de façon uniforme, montraient la tendance à long terme de la DT à atteindre un plateau une fois que la dyskinésie atteignait une sévérité légère, alors que chez seulement une minorité de patients la dyskinésie avait tendance à s'aggraver (25).

Dans une étude récente, Casey (11) a fait un suivi de 27 patients dyskinétiques pendant 5 ans. Au terme de l'étude, la DT avait disparu chez 8 des 27 patients (29,6%) et s'était améliorée de plus de 50% chez la majorité des patients sevrés en totalité ou partiellement de leurs neuroleptiques. Cette étude longitudinale conduit à diverses observations :

- La poursuite du traitement neuroleptique, lorsque les bénéfices sont évidents pour le patient, n'entraîne pas invariablement une aggravation de la symptomatologie dyskinétique
- Chez certains patients, la DT s'améliore avec ou sans l'arrêt de la médication
- L'âge est en corrélation inverse avec le degré d'amélioration de la DT; les patients plus jeunes s'améliorent davantage que les patients âgés
- L'utilisation de la dose minimale efficace, ou l'arrêt de la médication lorsque possible, est une approche rationnelle et bénéfique.

Diagnostic différentiel

Tous les antipsychotiques actuellement disponibles sur le marché produisent des effets secondaires neurologiques indésirables. La DT doit être distinguée d'autres symptômes extrapyramidaux induits par les neuroleptiques qui incluent: le parkinsonisme, l'akathisie, la dystonie aiguë, le syndrome malin aux neuroleptiques, qui surviennent souvent tôt en cours de traitement et réversibles pour la plupart après la baisse ou l'arrêt de la médication (Tableau I).

Bien que des DT soient survenues lors de durées de traitement plus courtes, il n'est pas courant qu'elles surviennent avant au moins 3 à 6 mois de traitement; en fait, elles surviendraient généralement après 1 à 2 ans de traitement neuroleptique continu (1,3,4).

Schooler et Kane ont proposé des critères diagnostiques de recherche de DT qui sont souvent employés dans la littérature (22). Malgré le caractère arbitraire de certains de ces critères, ces auteurs ont eu le mérite de mettre de l'ordre dans la classification nosographique des DT, offrant ainsi à la communauté scientifique un repère commun pour l'étude de l'épidémiologie, de la physiopathologie et du traitement des DT (5).

L'intérêt accru de la DT entraîne une plus grande attention des cliniciens vis-à-vis de mouvements suspects décelables à l'examen clinique. Il est important néanmoins de ne pas surdiagnostiquer le syndrome dyskinétique tardif qui peut imiter divers troubles et qui connaît un diagnostic différentiel étendu (Tableau II) (1,3,4,16,26).

La production de mouvements involontaires persistants d'origine médicamenteuse est virtuellement exclusive à la médication antipsychotique et le terme

Tableau I
Effets secondaires neurologiques aigus des antipsychotiques

RÉACTION	MANIFESTATIONS CLINIQUES	PÉRIODE D'APPARITION*	TRAITEMENT
Dyskinésie aiguë (dystonie aiguë)	Spasme, muscles médians (cou, visage, langue, yeux, gorge, dos), peut mimer convulsions	1-5 jours	Agents antiparkinsoniens anticholinergiques: valeur diagnostic et curative (I.M. puis P.O.)
Parkinsonisme	Bradykinésie (masque facial, perte de balancement bras), rigidité, posture et démarche anormales, tremblements, syndrome du lapin	5-90 jours	Agents antiparkinsoniens (anticholinergiques, amantadine)
Syndrome malin aux neuroleptiques	Rigidité, tremblements, dystonie, mutisme, stupeur, hyperactivité autonomique (hyperthermie, diaphorèse, tachycardie, hyper/hypotension, incontinence urinaire)	Variable	Arrêt immédiat des antipsychotiques, soins intensifs, Bromocriptine, Dantrolène (mortalité environ 20%)
Akathisie	Agitation motrice, sensation subjective de tension, "pacing", "restless legs", compulsion d'être en mouvement à distinguer d'une aggravation psychotique	6-60 jours (parfois plus tard)	Baisse ou changement d'antipsychotique?, Propranolol?, anticholinergiques, benzodiazépines

*À partir du début du traitement antipsychotique

"dyskinésie tardive" doit d'ailleurs être réservé aux seules dyskinésies induites par ces agents (4,5).

La L-DOPA et les amphétamines produisent des dyskinésies disparaissant rapidement avec l'arrêt de la médication. Les antidépresseurs tricycliques, rarement associés à des DT persistantes, l'ont été presque toujours auprès de patients qui avaient une histoire de traitements aux antipsychotiques. L'arrivée de l'Amoxapine, un antidépresseur hétérocyclique ayant une structure chimique similaire à la Loxapine, qui peut induire des réactions extrapyramidales (REP), devrait être utilisée avec prudence à cause de son potentiel à entraîner une DT (19). L'observation que le Métoclopramide peut induire des DT chez des patients non psychiatriques, semble être liée à ses propriétés antagonistes auprès des récepteurs dopaminergiques (DA) (4,16).

Le *Syndrome du Lapin*, apparaissant souvent tard en cours de traitement, serait une forme localisée (bouche, mâchoire) de tremblements parkinsoniens, réversible, qui répond habituellement aux anticholinergiques antiparkinsoniens.

Les *maniérismes* et *stéréotypies* rencontrés chez des schizophrènes chroniques ont une valeur symbolique et sont habituellement conscients pour le patient (3,4,27).

Les *dyskinésies spontanées* (dont la prévalence est estimée autour de 4 à 7%), habituellement orofaciales, rencontrées leplus souvent chez des patients âgés séniles, ont une prévalence nettement inférieure à la DT évaluée à 15% (lorsque corrigée pour le taux de dyskinésies spontanées) (4,27,28).

La présence d'affections du système extrapyramidal génétiquement déterminées telles la chorée de Huntington et la maladie de Wilson doit être envisagée.

L'examen neurologique d'une DT, en plus de révéler la présence de mouvements involontaires suggestifs du syndrome, ne devrait pas révéler la présence de signes neurologiques cérébelleux, sensitifs ou pyramidaux (à moins que la DT ne soit concomitante d'un autre trouble neurologique) (19).

Plusieurs examens paracliniques de laboratoire (cuivre et céruléoplasmine sériques, SGOT/SGPT, bilirubine, albumine, créatinine sérique et clearance créatinine, T_3, T_4, TSH,calcium et glucose sériques . . .) et radiologiques (tomographie axiale dans la chorée de Huntington, néoplasies cérébrales . . .) peuvent être utiles au diagnostic différentiel pour éliminer des causes autres qu'une DT.

Bien que l'EEG soit utile dans le diagnostic différentiel, la DT ne serait pas associée à des changements spécifiques à l'EEG (29). Selon une étude récente, l'EMG peut mettre en évidence des caractéristiques différentes entre des patients atteints de tremblements et de DT (30).

Épidémiologie

1. *Taux de prévalence*

Le Task Force Report de l'American Psychiatric Association soulignait la grande variabilité des taux de prévalence de la DT rapportés dans la littérature, oscillant entre 0,5 et 65% (moyenne évaluée autour de 20%). Cette variation relevait de divers facteurs: l'inhomogénéité des populations de patients étudiés, les critères diagnostics et méthodes d'évaluation différentes employés (1).

Bien que rapportée à des taux plus élevés (31-33), le taux de prévalence des DT se situerait autour de 15-20% et la prévalence du syndrome irait même en augmentant

Tableau II
Diagnostic Différentiel des DT

- Autres syndromes extrapyramidaux induits par les neuroleptiques (Tableau I)
- Mouvements stéréotypés et maniérismes de la schizophrénie
- Dyskinésies orales spontanées associées à l'âge avancé ou à la démence
- Dystonies focales (syndrome de Meige, torticolis spasmodique)
- Maladie de Huntington
- Maladie de Wilson
- Maladie de Gilles de la Tourette
- Syndromes extrapyramidaux postanoxiques, postencéphalitiques
- Intoxication chronique au manganèse ou autres métaux lourds
- Chorée rhumatismale (Sydenham)
- Syndrome de Fahr (calcification familiale des ganglions de la base)
- Intoxications médicamenteuses (L-DOPA, amphétamines, anticholinergiques, antidépresseurs, lithium, phénytoin)
- Complications neurologiques de troubles métaboliques systémiques (e.g. insuffisance hépatique ou rénale, hyperthyroïdie, hypoparathyroïdie, hypoglycémie)
- Tumeur cérébrale ou autre anomalie structurale impliquant le thalamus ou les ganglions de la base

(2-4,11,15,27,28). L'importante étude de Kane et Smith (1982), regroupant 34 555 patients de 56 études publiées de 1959 à 1979, évaluait à 20% le taux de prévalence moyen de la DT (28).

L'incidence de nouveaux cas de DT serait de 3-4% par année d'exposition aux neuroleptiques (34).

Le rôle étiologique des neuroleptiques sur les DT, basé largement sur les preuves épidémiologiques, est assez clairement affirmé dans la littérature (1,4,14, 16,28,35,36). Toutefois, certains auteurs s'opposent à une telle affirmation et invoquent le rôle que joue la maladie (schizophrénie) dans l'apparition de ces mouvements involontaires (37,38). De plus, il est probable que d'autres facteurs tels une susceptibilité individuelle puissent jouer un rôle important dans l'apparition du syndrome (1).

2. *Facteurs de risque*

De nombreux facteurs de risque ont été suggérés. Que l'exposition aux antipsychotiques joue un rôle dans le développement d'une DT est inhérent à la définition même du syndrome. La majorité des DT apparaissant dans les 3 premières années de traitement, et le fait que plusieurs patients traités aux neuroleptiques pendant des années ne développent jamais le syndrome, suggère l'existence d'un certain seuil où l'exposition continue et la durée de traitement cessent d'être un facteur de risque déterminant (2,9,14,28).

La grande majorité des études n'ont pu établir de façon certaine un risque accru de DT avec la dose totale cumulative et la durée de traitement aux antipsychotiques (1,2,14,15,28,38).

Dans une étude récente entre la durée de traitement aux neuroleptiques et la prévalence de la DT auprès de 57 patients psychiatriques âgés et hospitalisés, Toenniessen et Casey ont trouvé que la prévalence de la DT, dans ce groupe d'âge, augmentait avec une plus longue durée de traitement (dans l'étude, le taux de prévalence des DT était de 49%). Leur analyse révélait que le risque maximal de DT dans cette population de patients âgés survenait au cours des 2 premières années de traitement (39). Cette étude souleva deux questions non encore résolues dans la littérature:

1) la présence d'un syndrome cérébral organique (SCO) jouerait-elle un rôle dans le niveau de susceptibilité des patients à développer une DT? (2,14,28,31).
2) instituer pour la première fois un traitement neuroleptique de maintien chez un patient âgé augmente-t-il davantage le risque de DT persistente? (40).

Certains agents, tels la Thioridazine entraînant moins de réactions extrapyramidales aiguës, seraient moins susceptibles d'induire des DT (14,36,41). En dépit de cet effet protecteur suggéré de la Thioridazine, tous les neuroleptiques sont susceptibles de provoquer une DT et il n'a pas été possible, à cause de difficultés méthodologiques (entre autres facteurs la polypharmacologie neuroleptique), de distinguer une classe ou type particulier de neuroleptique qui serait clairement susceptible, à plus haut ou faible risque, d'induire une DT (1,2,14,15,28).

Seul l'âge avancé est clairement impliqué dans la littérature (1-4,11,13,15,16,19,27,31,39,42); les DT ayant une prévalence accrue chez les personnes âgées. La vieillesse a aussi été associée à une sévérité et une persistance plus grande des DT et certaines études ont noté une augmentation progressive des DT jusqu'à l'âge de 70 ans, après quoi l'âge serait une variable moins discriminante (15,40).

Bien que la prépondérance du sexe féminin soit rapportée dans la littérature, certaines études ne l'ont pas démontré (1,28). Chouinard et al ont même rapporté que les patients de sexe masculin semblaient plus susceptibles de développer des formes sévères de DT (12).

La présence d'une sensibilité individuelle génétique dans l'apparition des DT reste à définir.

À l'heure actuelle, aucun consensus n'existe quant au rôle des anticholinergiques et des réactions extrapyramidales aiguës dans l'apparition du syndrome (1,2,14,15,28).

Les "drug holidays" dans le traitement de maintien neuroleptique, que Ayd fut le premier à prôner dès 1965 afin de diminuer l'incidence ou la sévérité des DT, ont été au contraire impliqués à un accroissement du risque de DT (2,15,43,44).

Quant à la question du diagnostic, la DT n'est pas spécifique aux patients schizophrènes et survient entre autres chez des patients traités aux neuroleptiques pour des troubles gastrointestinaux, des syndromes douloureux chroniques, des troubles de la personnalité (1). Les patients ayant un trouble affectif seraient, d'après certaines études, à plus hauts risques de DT (2,15,24,32).

De plus, des facteurs tels une longue durée des hospitalisations antérieures, une mauvaise réponse à la médication antipsychotique ont été suggérés comme favorisant l'apparition des DT (12,35).

Physiopathologie

Plusieurs hypothèses concernant la physiopathologie des DT ont été suggérées. Ses différentes manifestations cliniques et réponses variéees au traitement laissent entrevoir plus qu'un seul mécanisme physiopathologique.

Il est suggéré que la DT est caractérisée par un état d'hyperdopaminergie fonctionnelle relative du système nigro-strié. Plusieurs mécanismes conduisant à cet état d'hyperdopaminergie relative ont été suggérés:

- la perte de contrôle de la synthèse et/ou de libération de dopamine au niveau pré-synaptique;
- l'augmentation du nombre ou de l'efficacité des récepteurs DA post-synaptiques dûs à une hypersensibilité de dénervation;
- une diminution de la disponibilité d'autres systèmes de modulation impliquant le GABA, l'acétylcholine, la sérotonine,substance P, endorphines ou autres peptides (1,3,4,14,16,36,41,42,45).

Jeste et Wyatt (46) ont critiqué l'hypothèse de supersensibilité des récepteurs DA post-synaptiques. Leur analyse les amène à diverses conclusions dont la plus rigoureuse est la suivante: la supersensibilité des récepteurs DA post-synaptiques serait une conséquence normale de l'administration de neuroleptiques. Ils admettront que cette supersensibilité DA post-synaptique puisse être responsable de dyskinésies de retrait, mais que les études cliniques n'appuient pas cette hypothèse chez la plupart des patients ayant une DT persistante.

L'implication d'autres systèmes de modulation est illustrée dans un modèle expérimental de DT où Gunne et Häggström ont rapporté une diminution de l'activité de l'acide glutamique décarboxylase (un enzyme synthétiseur du GABA) chez des singes traités aux antipsychotiques ayant développé des mouvements dyskinétiques (47).

Alors qu'il eut été raisonnable de s'attendre à des altérations structurales du cerveau dans la DT, les études postmortem chez l'animal et l'humain n'ont été que peu concluantes jusqu'à présent (4,14).

L'activité plasmatique de la dopamine-bêta-hydroxylase (DBH) a été rapportée comme significativement élevée chez des patients schizophrènes atteints de DT (24). Dans ce groupe, ceux ayant des taux de DBH moins élevés avaient des ventricules plus grands. On a observé, chez certains patients schizophrènes du type 2 (Crow), une relation possible entre l'élargissement ventriculaire, l'exposition prolongée aux neuroleptiques (ces deux facteurs étant non liés entre eux), avec une tendance accrue à développer des mouvements dyskinétiques sévères et persistants (38,48).

Le consentement: mythe ou réalité?

Bien que la DT fut décrite 5 années après l'introduction des neuroleptiques, des poursuites légales liées au développement du syndrome ne sont que d'apparition récente. Les deux premiers cas jugés aux États-Unis (1982/1983) l'ont été en faveur des patients, qui se sont vus octroyer des sommes considérables (760 000 $ et plus de 1 500 000 $ respectivement) (49). Selon Gualtieri et Sprague, la gravité actuelle des répercussions médico-légales des DT repose sur le fait que les points principaux dans de tels cas litigieux, qui auraient pu prévenir une poursuite ou un jugement défavorable envers le thérapeute, ne sont pas systématiquement mis en pratique. Ces derniers consistent en la prescription conservatrice de neuroleptiques, le consentement informé, la surveillance attentive des signes précoces de DT, la documentation des effets bénéfiques du traitement ainsi que la baisse ou l'arrêt de la médication lorsque l'état mental du patient le permet.

La situation actuelle au Québec et au Canada n'est certainement pas superposable à celle de nos voisins américains, mais nous laisse entrevoir une tendance qui ne tardera pas à rejoindre nos frontières. En août 1983, ceci faisait l'objet d'un Avis du secrétaire général de la Corporation professionnelle des médecins du Québec; en plus de suggérer diverses mesures de prudence semblables à celles énumérées plus haut, l'article affirmait: "Le patient doit en être informé (avantages et inconvénients de la thérapie) et on doit lui expliquer les complications les plus sérieuses pouvant être encourues." (50)

En 1979, le Task Force Report de l'APA sur la DT suggérait la tenue d'une discussion informelle entre le thérapeute, le patient et sa famille pour discuter les risques et bénéfices du traitement antipsychotique lorsque celui-ci est envisagé sur une base de maintien; décision qui serait inscrite dans le dossier médical.

Dans un article récent, Munetz (51) a souligné la résistance qui existe à discuter du risque de DT avec les patients, en détaillant 3 barrières principales: la résistance institutionnelle, du thérapeute, et du patient. La crainte que les patients réagissent à l'information en arrêtant le traitement n'est pas fondée, d'après l'étude contrôlée de Munetz (52). De plus, le résultat de cette étude permet de conclure à la plus grande efficacité du consentement informé sous la forme d'une discussion informelle par rapport au consentement formel écrit.

Prévention et traitement

Lors du dernier congrès mondial de psychiatrie biologique en septembre 1985, Pierre Deniker a prononcé une conférence étonnante intitulée: "Doit-on retirer les antipsychotiques du marché?", en réponse à certains articles parus dans les médias français et aux avertissements que le Food and Drug Administration américain a émis concernant l'utilisation des neuroleptiques. Ce pionnier de la recherche psychiatrique répondra très clairement à cette question qui me paraîtra

la plus fondamentale de tout le congrès: un retrait des neuroleptiques provoquerait rapidement la réapparition des psychoses caricaturales des anciens manuels de psychiatrie et les milieux psychiatriques asilaires en seraient davantage inondés. Il ajoutera avec fermeté: "Si la maladie mentale fait moins peur aujourd'hui, c'est grâce à l'avènement de la chimiothérapie". Il n'est donc pas question de répéter l'histoire du grand bond en avant, deux pas en arrière.

Parce qu'il n'existe pas de traitement clairement efficace, la prévention primaire de la DT est d'une importance primordiale évidente.

Les indications à court et long terme d'un traitement neuroleptique ont été amplement revisées dans la littérature et les preuves appuyant un traitement prolongé de maintien n'existent que pour la schizophrénie (1,43). L'utilisation d'antipsychotiques pour des conditions pouvant être traitées par d'autres agents, telles que l'anxiété, la dépression non psychotique, l'insomnie, doit être évitée autant que possible. Devant l'indication d'un traitement neuroleptique, la dose minimale efficace (DME) et la durée de traitment le plus court possible sont indiqués.

Après la rémission d'un premier épisode psychotique, la médication devrait être baissée et même interrompue au bout de 6 à 12 mois. L'intention de poursuivre le traitment au-delà de 6 mois nécessite des discussions entre le médecin, le patient et parfois aussi sa famille, afin de bien évaluer les risques/bénéfices d'un traitement prolongé (43).

La détection précoce pouvant limiter ou accroître la réversibilité du syndrome constitue la prévention secondaire des DT (19,36). L'utilisation de plus en plus grande en clinique d'échelles d'évaluation telles le Abnormal Involuntary Movement Scale (AIMS) (53) ou l'échelle détaillée de symptômes extrapyramidaux de Chouinard et Ross-Chouinard (54) va certainement accroître la détection précoce des DT.

L'usage de médication antiparkinsonienne pour démasquer une DT est controversé (55,56). De plus, l'administration concomitante de neuroleptiques et d'anticholinergiques antiparkinsoniens a été suggérée comme pouvant prédisposer à une DT. Jusqu'à ce que cette association soit clarifiée, l'utilisation routinière de ces agents devrait être limitée à la plus courte durée possible.

Une étude contrôlée récente sur l'analyse de la voix de patients dyskinétiques suggère l'utilité de cette technique comme moyen objectif de diagnostic précoce de DT (57).

L'absence de traitement établi se reflète par les multiples agents ayant fait l'objet d'essais thérapeutiques (1,3,4,36). Cette mise à jour ne vise pas à détailler les stratégies thérapeutiques employées dans la DT. Un aperçu de ces stratégies est présenté que l'on peut distinguer en 4 groupes:

1. *Substances réduisant l'activité dopaminergique*

Bien que la réintroduction ou l'augmentation du dosage des antipsychotiques réduisent souvent l'intensité des dyskinésies, ceci est habituellement transitoire et n'est pas recommandé dans la littérature, pouvant aggraver ultimement la pathogénèse du syndrome.

L'utilisation potentiellement bénéfique d'antipsychotiques atypiques, tels la Thioridazine ou la Clozapine (retirée du marché nord-américain à cause de son risque d'agranulocytose), chez un patient dyskinétique nécessitant un traitement, a été suggérée à cause de la spécificité d'action de ces composés sur le système dopaminergique mésolimbique, pouvant ainsi éviter la progression de l'hypersensibilité des récepteurs striataux (14,36,41,45).

Des agents antipsychotiques, bloquant préférentiellement les récepteurs dopaminergiques D2, et même sans activité antipsychotique tels le métoclopramide ont été invoqués dans le traitement des DT. Bien que dans de courts essais cet agent ait diminué la sévérité de DT, celui-ci a été démontré comme pouvant induire une DT, suggérant que le blocage prolongé des récepteurs D2 entraîne un état d'hypersensibilité semblable au blocage des deux récepteurs D1 et D2 (36).

L'utilisation d'agents empêchant le "stockage" des cathécolamines, tels la réserpine ou la tétrabénazine, peuvent parfois aider mais sont d'usage limité à cause de la fréquence de leurs effets secondaires.

2. *Substances augmentant l'activité cholinergique*

La DT se trouvant sous plusieurs aspects à l'opposé du syndrome parkinsonien: la DT reflétant une hyperdopaminergie relative fonctionnelle (et une sous-activité cholinergique relative); le parkinsonisme, par une faible neurotransmission de dopamine (et un excès cholinergique relatif); l'utilisation d'agents cholinomimétiques dans la DT est née.

Le Déanol et la phosphatidyl choline qui se trouve naturellement dans la lécithine ont été employés avec des résultats variables.

3. *Substances augmentant l'activité gabaergique*

Des benzodiazépines telles le diazépam et le clonazépam sont bénéfiques chez certains patients soit par leurs propriétés sédatives ou myo-relaxantes ou possiblement via leur rôle à accroître l'activité gabaergique. La baclofen a été utilisé avec des succès mitigés.

4. *Autres substances*

Une stratégie paradoxale utilisant un agoniste dopaminergique tel la L-DOPA dans le but de désensibiliser les récepteurs post-synaptiques a été suggérée. Cette approche demeure toujours expérimentale. Le Propranolol a été utilisé de façon expérimentale sans aucun consensus vis-à-vis son efficacité.

Ce survol thérapeutique permet de constater que la baisse graduelle, et idéalement l'arrêt de la médication antipsychotique, constitue à l'heure actuelle le traitement de choix des DT lorsque l'état mental du patient le permet. Un algorithme pour le diagnostic et la conduite à tenir face à une DT est présenté dans la Figure 1.

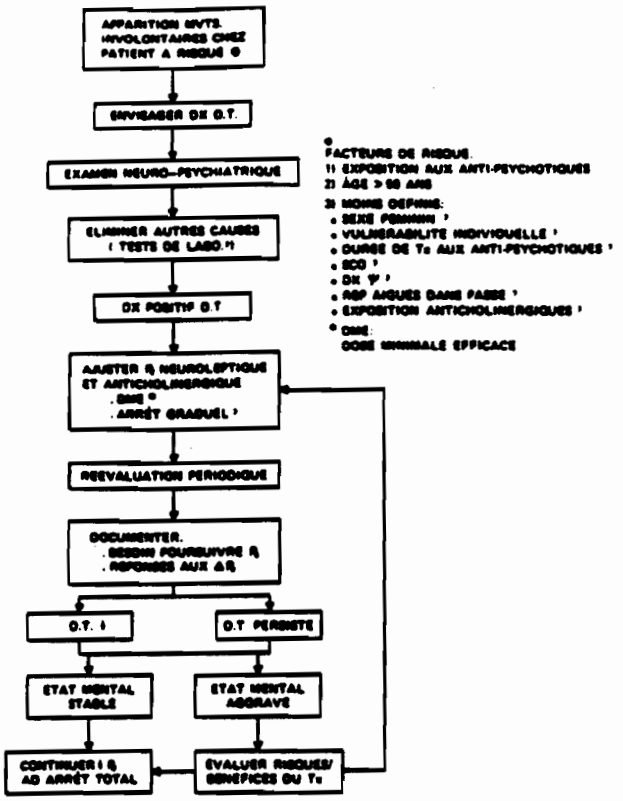


Figure 1. Algorithme pour le diagnostic et conduite à tenir face à une dyskinesie tardive.

Conclusion

Les résultats d'études longitudinales récentes sur l'évolution à long terme des DT, traitées ou non, donnent lieu à un optimisme prudent. Une association entre ce syndrome et l'utilisation plus ou moins prolongée de médication antipsychotique ne fait pas de doute mais ne sous-estime en rien l'implication d'autres facteurs potentiels tels une vulnérabilité individuelle.

Les mesures suivantes:

- une réévaluation périodique de la nécessité à poursuivre le traitement neuroleptique
- l'utilisation de doses minimales efficaces
- informer le patient des risques possibles du traitement à long terme
- examiner le patient à intervalles réguliers pour la détection de signes précoces de DT
- documenter ces étapes

aideront à l'évaluation des risques/bénéfices du traitement.

La prévention et l'issue souvent favorable du syndrome reposent sur ces quelques considérations thérapeutiques.

Le modèle de spécificité d'action des récepteurs aidera certainement à la recherche de nouveaux neuroleptiques dénués d'effets secondaires moteurs.

Remerciements

L'auteur désire remercier le centre de documentation de l'Hôtel-Dieu de Montréal pour son aide dans la recherche bibliographique; M. André Béerens, illustrateur médical et le service de photographie médicale de l'Hôtel-Dieu de Montréal; le Dr Jean Cuthill, psychiatre à l'Hôtel-Dieu de Montréal, pour ses commentaires sur la physiopathologie du syndrome; Raymonde Thibeault pour l'excellence du traitement de texte.

Références

1. Tardive dyskinesia: report of the American Psychiatric Association Task Force on late neurological effects of antipsychotic drugs, APA Task Force Report 18. Washington DC: American Psychiatric Association, 1979.
2. Casey DE. Tardive dyskinesia: epidemiologic factors as a guide for prevention and management, advances in biochemical psychopharmacology. 1985; 40: 15-24.
3. Tarsy D. Movement disorders with neuroleptic drug treatment. Psychiatr Clin North Amer 1984; (3): 453-471.
4. Tarsy D, Baldessarini RJ. Tardive dyskinesia. Ann Rev Med 1984; 35: 605-623.
5. Tarsy D. History and definition of tardive dyskinesia. Clin Neuropharmacol 1983; 6(2): 91-99.
6. Wolf ME, Mosnaim AD. Identifying subtypes of tardive dyskinesia. Hosp Community Psychiatry 1984; 35(8): 828-830.
7. Schönecker M. Ein eigentumliches syndrom im oralen beriech bei megaphenapplikation. Nervanartz 1957; 28: 35.
8. Sigwald J, Bouttier D, et al. Quatre cas de dyskinésie facio-bucco-linguo-masticatrice à évolution prolongée secondaire à un traitement par les neuroleptiques. Rev Neurol (Paris) 1959; 100: 751-755.
9. Faurbye A, Rasch PJ, Peterson PB, et al. Neurological symptoms in pharmacotherapy of psychoses. Acta Psychiatr Scand 1964; 40: 10-27.
10. Uhrbrand L, Faurbye A. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine, and electroconvulsive therapy. Psychopharmacologia 1960; 1: 408-418.
11. Casey DE. Tardive dyskinesia: reversible and irreversible. Psychopharmacology 1985; 2: (Suppl.) 88-97.
12. Chouinard G, Annable L, Ross-Chouinard A, et al. Factors related to tardive dyskinesia. Am J Psychiatry 1979; 136(1): 79-83.
13. Engle VF, Whall A, Dimond C, et al. Tardive dyskinesia: are your older clients at risk? J Gerontol Nurs, 1985; 11(9): 25-27.
14. Ruffieux A, Regli F. Les dyskinésies tardives. Rev Méd Suisse Romande 1985; 105: 339-347.
15. Baldessarini RJ. Clinical and epidemiologic aspects of tardive dyskinesia. J Clin Psychiatry 1985; 46: 4(2): 8-13.
16. Goetz CG, Klawans HL. Tardive dyskinesia. Neurol Clin 1984; 2(3): 605-614.
17. Chiang E, Pitts WM, Rodriguez-Garcia M. Respiratory dyskinesia: review and case reports. J Clin Psychiatry 1985; 46(6): 232-234.
18. Yassa R, Lal S. Impaired sexual intercourse as a complication of tardive dyskinesia. Am J Psychiatry 1985; 142(12): 1514-1515.
19. Bassuk EL, Schoonover SC, Gelenberg AJ. The practitioner's guide to psychoactive drugs, second edition. New York: Plenum Medical Book Company, 1984: 115-165.

20. Stahl SM. Akathisia and tardive dyskinesia. Arch Gen Psychiatry 1985; 42: 915-917.
21. Gardos G, Cole JO, Tarsy D. Withdrawal syndromes associated with antipsychotic drugs. Am J Psychiatry 1978; 135(11): 1321-1324.
22. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry 1982; 39: 486-487.
23. Fahn S. A therapeutic approach to tardive dyskinesia. J Clin Psychiatry 1985; 46(2): 19-24.
24. Jeste DV, Wyatt RJ. Prevention and management of tardive dyskinesia. J Clin Psychiatry 1985; 46(4); (2): 14-18.
25. Gardos G, Cole JO, Perenyi A, et al. Five-year follow-up study of tardive dyskinesia. Advances in biochemical psychopharmacology 1985; 40: 37-41.
26. Klawans HL. Recognition and diagnosis of tardive dyskinesia, J Clin Psychiatry 1985; 46(4) (Sec. 2): 3-7
27. Casey DE. Spontaneous and tardive dyskinesias: clinical and laboratory studies. J Clin Psychiatry 1985; 46(4): (2): 42-47.
28. Kane JM, Smith JM. Tardive dyskinesia prevalence and risk factors. 1959 to 1979. Arch Gen Psychiatry 1982; 39: 473-481.
29. Wolf ME, Koller WC, Mosnaim AD. Electroencephalogram in tardive dyskinesia, clinical electroencephalography. 1984; 15(4): 222-225.
30. Bathien N, Koutlidis RM, Rondot P. EMG patterns in abnormal involuntary movements induced by neuroleptics. J Neurol Neurosurg Psychiatry 1984; 47: 1002-1008.
31. Fleischhauer J, Kocher R, Hobi V, et al. Prevalence of tardive dyskinesia in a clinic population. Psychopharmacology Supplementum 1985; 2: 162-172.
32. Yassa R, Ghadirian AM, Schwartz G. Prevalence of tardive dyskinesia in affective disorder patients. J Clin Psychiatry 1983; 44(11): 410-412.
33. Yassa R, Ananth J, Cordozo S, et al. Tardive dyskinesia in an outpatient population: prevalence and predisposing factors. Can J Psychiatry 1983; 28(5): 391-394.
34. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: incidence prevalence and risk factors. Abstract du IVième congrès mondial de psychiatrie biologique. Philadelphie, PA, 1985.
35. Kane JM, Woerner M, Weinhold P, et al. Epidemiology of tardive dyskinesia. Clin Neuropharm, 1983; 6(2): 109-115.
36. Tanner CM. Treatment of tardive dyskinesia: other therapies. Clin Neuropharm 1983; 6(2): 159-167.
37. Marsden CD. Is tardive dyskinesia a unique disorder? Psychopharmacol 1985; 2(Suppl.) 64-71.
38. Owens DG. Involuntary disorders of movement in chronic schizophrenia — the role of the illness and its treatment. Psychopharmacol 1985; 2(Suppl.): 79-87.
39. Toenniessen LM, Casey DE, McFarland BH. Tardive dyskinesia in the aged-duration of treatment relationships. Arch Gen Psychiatry 1985; 42: 278-284.
40. Smith JM, Baldessarini RJ. Changes in prevalence, severity and recovery in tardive dyskinesia with age. Arch Gen Psychiatry 1980; 37: 1368-1373.
41. Borison RL, Hitri A, Blowers AJ, et al. Antipsychotic drug action: clinical, biochemical, and pharmacological evidence for site specificity of action. Clin Neuropharmacol 1983; 6(2): 137-150.
42. Black JL, Richelson E, Richardson JW. Antipsychotic agents: a clinical update. Mayo Clin Proc 1985; 60: 777-789.
43. Davis JM, Schyve PM, Pavkovic I. Clinical and legal issues in neuroleptic use. Clin Neuropharmacol 1983; 6(2): 117-128.
44. Goldman MB, Luchins DJ. Intermittent neuroleptic therapy and tardive dyskinesia: a literature review. Hosp Community Psychiatry 1984; 35(12): 1215-1219.
45. Klawans HL, Carvey P, Tanner CM, et al. The pathophysiology of tardive dyskinesia 1985; 46(4): (2): 38-41.
46. Jeste DV, Wyatt RJ. Dogma disputed: is tardive dyskinesia due to postsynaptic dopamine receptor supersensitivity? J Clin Psychiatry 1981; 42(12): 455-457.
47. Gunne LM, Häggström JE. Experimental tardive dyskinesia. J Clin Psychiatry 1985; 46(4) (sec 2): 48-50.
48. Waddington JL, Youssef HA, Molloy AG, et al. Association of intellectual impairment, negative symptoms and aging with tardive dyskinesia: clinical and animal studies. J Clin Psychiatry 1985; 46(4): (2): 29-33.
49. Gualtieri CT, Sprague RL. Preventing tardive dyskinesia and preventing tardive dyskinesia litigation. Psychopharmacol Bull 1984; 20(3): 346-348.
50. Corporation professionnelle des médecins du Québec. Avis du secrétaire général. Médication antipsychotique et dyskinésie tardive, Bulletin 1983; Volume 13(2).
51. Munetz MR. Overcoming resistance to talking to patients about tardive dyskinesia. Hosp Community Psychiatry 1985; 36(3): 283-287.
52. Munetz MR, Roth LH. Informing patients about tardive dyskinesia. Arch Gen Psychiatry 1985; 42: 866-871.
53. Guy W. ECDEU assessment manual for psychopharmacology. Washington DC: US Department of Health, Education and Welfare, 1976.
54. Chouinard G, Ross-Chouinard A, Annable L, et al. Extrapyramidal symptom rating scale. Can J Neurol Sci 1980; 7: 233.
55. Chouinard G, De Montigny C, Annable L. Tardive dyskinesia and antiparkinsonian medication. Am J Psychiatry 1979; 136(2): 228- 229.
56. Gardos G, Cole JO, Rapkin RM, et al. Anticholinergic challenge and neuroleptic withdrawal. Arch Gen Psychiatry 1984; 41: 1030-1035.
57. Denber HCB, Denber M. Preliminary report: voiceprint analysis in tardive dyskinesia. Rev de psychiatrie de l'Univ d'Ottawa 1985; 10(1): 17-20.

Summary

Tardive Dyskinesia (TD) is a neurological syndrome associated with long-term use of antipsychotic drug treatment (APD). Its significant prevalence (estimated 15-20%) and potential irreversibility are a major concern in psychiatry.

The clinical picture is characterized by involuntary repetitive movements of choreoathetotic and dystonic nature varying in location and intensity. The individual outcome of TD is unpredictable but recent long-term studies give reason for prudent optimism.

All neuroleptics are involved in the disorder, numerous risk factors have been suggested; advancing age is the only one which has a clearly definite role.

Even though several hypotheses have been suggested, the pathophysiology of the disorder remains a mystery.

Informed consent is discussed in this update with regard to the legal implications of the disorder.

Because of lack of effective treatment, prevention of TD is essential. The present treatment of choice is gradual reduction (and ideally discontinuance) of APD treatment when possible.