LECITHIN THERAPY FOR TARDIVE DYSKINESIA

Dissertation

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By

Barbara Beckham, M.A.
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Drug-induced tardive dyskinesia, an irreversible involuntary movement disorder caused by neuroleptic drugs, may reflect cholinergic hypofunction in the corpus striatum. Therapeutic results have been reported in trials of choline and lecithin, nutritional substrates which may enhance cholinergic neurotransmission.

Lecithin's effects on dyskinetic symptoms were examined in 50 male patients in a double-blind, placebo-controlled trial. Patients were randomly assigned to treatment or control groups; 31 patients were retained in the analytic cohort. Experimental patients were treated with 60 gm/day lecithin (55% phosphatidyl choline) for 11 days. Symptom frequency was rated from videotapes made at baseline, 3 and 11 days of treatment, and 1 week follow-up.

Lecithin significantly suppressed symptoms; 93% of the treated patients exhibited a therapeutic response. Previous reports of choline and lecithin treatment were reviewed and critiqued.
ACKNOWLEDGMENT

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LECITHIN THERAPY FOR TARDIVE DYSKINESIA

Tardive dyskinesia is a hyperkinetic movement disorder associated with neuroleptic drugs. It is characterized by involuntary orofacial movements which may be accompanied by limb and trunkal choreoathetosis (Tarsy & Baldessarini, 1976). The syndrome is strikingly prevalent among long-term psychiatric patients, and its incidence has increased with the increased and prolonged use of neuroleptics (Jeste & Wyatt, 1981).

Twenty-five years into the neuroleptic era, drug-induced tardive dyskinesia has emerged as a significant public health problem (Gardos & Cole, 1980a). The tics and choreatic movements of tardive dyskinesia are grotesque and often socially objectionable, and thus are a source of considerable embarrassment to the patient and his family (Crane, 1968). When more advanced, the syndrome can impair speaking, eating, breathing, and in some cases may reduce life expectancy (Mehta, Mallya, & Volavka, 1980). Tardive dyskinesia’s most distinctive feature is that symptoms persist even after withdrawal of antipsychotic drugs.

Although there is no established therapy for tardive dyskinesia, researchers have recently reported therapeutic results in trials using choline and lecithin. Side effects
of diarrhea, sweating, and a "fishy" body odor limit patient acceptance of choline, however (Casey & Tepper, 1979).

Oral doses of lecithin, the major dietary source of choline, may represent an alternative treatment. Recent non-blind trials have demonstrated that lecithin is more effective than choline in reducing dyskinetic symptoms with fewer adverse side effects. More extensive trials of lecithin therapy appear justified on the basis of these first reports.

This study investigated the effects of lecithin therapy in patients with tardive dyskinesia under double-blind placebo-controlled conditions. A familiarity with the syndrome's clinical manifestations, pathophysiology, assessment, and pharmacotherapy is essential for understanding current treatment strategies. Each of these topics is briefly discussed preceding a review of current treatment research.

Extrapyramidal Syndromes

Extrapyramidal motor disorders associated with neuroleptic therapy have been widely recognized and investigated since the introduction of the phenothiazines in the early 1950's (Kazamatsuri, Chien, & Cole, 1972). Tardive dyskinesia is considered to be an extrapyramidal disorder and as such has several features in common with the other extrapyramidal syndromes: (a) It fluctuates in severity over time; (b) it disappears during sleep; and
(c) it increases with emotional arousal. It differs from them in that it cannot be relieved by discontinuation of causative neuroleptic drugs or by concurrent administration of conventional antiparkinson agents (Kazamatsuri et al., 1972).

The extrapyramidal system is the complex of multisynaptic upper motor neurons that interconnect the basal ganglia, thalamic and subthalamic nuclei, and substantia nigra with one another and with parts of the reticular formation, cerebellum, and cerebrum. The system modulates and integrates motor impulses that originate in the cortex. Thus, extrapyramidal disorders are characterized by involuntary movements, impairments of voluntary movement, and changes in muscle tone or posture.

The system's chemical mediators are dopamine, serotonin, and acetylcholine. Pathogenesis in the extrapyramidal system often has a significant chemical component (Berkow, 1977).

Tardive Dyskinesia: Clinical Features

First described in two brief reports from Europe in the late 1950's, tardive dyskinesia has been characterized (Crane, 1968) as follows: (a) Choreiform or athetoid involuntary movements; (b) late occurrence in the course of neuroleptic drug treatment, sometimes appearing after discontinuation or decrease of drug administration; and (c) irreversibility. The involuntary movements persist for
months to years after neuroleptic treatment is discontinued, and response to any type of therapy is poor (Crane, 1968; Faurbye, 1970).

The syndrome's most frequent and marked symptoms, as described by Cole & Gardos (1980b), are choreoathetoid movements, tics, grimaces, and dystonia. Typical symptoms are in the tongue, jaw, and lips. Movements include slow repetitive chewing movements, sucking and smacking movements of the lips, chewing and lateral jaw movements, facial grimacing, furrowing of the brow, blinking, and tongue protrusion against the cheek and outside the mouth. Choreiform finger movements, finger counting, and hand clinching movements are also common. Similar movements occur in the ankles and toes. Head nodding, body rocking, and twisting movements of the head and neck also occur.

The type of movement varies widely from patient to patient; patient age appears to influence the topographic distribution of symptoms (Task Force on Late Neurological Effects of Antipsychotic Drugs, 1980). Orofacial dyskinesia is more common in older patients. Abnormal movements of the extremities and trunk are more common in younger dyskinetics (Degkwitz, 1969; Marsden & Jenner, 1980). Jeste and Wyatt (1980) have prepared an excellent review of the syndrome's clinical features.

Severity can range from virtually undetectable to severe and incapacitating. The patient often seems unaware
of, and may deny, movements, unless symptoms interfere with drinking or eating (Wojcik, Gelenberg, LaBrie, & Mieske, 1980). However, Smith, Kucharski, Oswald, and Waterman (1979) found that although patients deny awareness of symptoms, they will attempt to conceal their movements when asked about them and can describe symptoms in other patients in great detail.

Clinical manifestation of the disorder may also vary in severity in different areas of the body in the same patient. Most patients can voluntarily inhibit movements for brief periods with attention; movements resume when the patient is distracted. Symptoms are increased by movements in distant parts of the body and by stress. They disappear during sleep (Jeste & Wyatt, 1979).

Dyskinesias may appear at any time during drug treatment but are especially frequent after antipsychotic medication is stopped or after more than 2 years of treatment (Crane, 1973). Risk rises to 25% by the third year of neuroleptic treatment (Fawcett, 1981). Older patients and women may be at higher risk and have a poorer prognosis for recovery (Task Force on Late Neurological Effects of Antipsychotic Drugs, 1980). Recent reports have placed the prevalence of tardive dyskinesia close to 50% in both in- and outpatient populations (Gardos & Cole, 1980).

The syndrome is not associated with any particular neuroleptic drug or class of neuroleptics (Cole & Gardos,
1980) and is not related to duration or quantity of exposure. Equivalent exposure to neuroleptics does not produce tardive dyskinesia in all patients (Task Force on Late Neurological Effects of Antipsychotic Drugs, 1980). However, treatment with any antipsychotic drug involves the risk of tardive dyskinesia, regardless of the dosage, duration of treatment, the patient's age, or diagnosis.

Onset of the disorder is insidious and is heralded by vermicular, i.e., worm-like, movements of the tongue (American College of Neuropsychopharmacology/Food and Drug Administration, 1973). Early symptoms are subtle but gradually worsen until they become significant enough to be recognized by the casual observer.

The syndrome frequently resolves if it is detected very early and neuroleptic medication is discontinued immediately (Quitkin, Rifkin, Gochfeld, & Klein, 1977). In practice, however, psychosis is still treated with neuroleptics, even when tardive dyskinesia is present (Opler, Katz, Kobayashi, & Ruiz, 1980). Continued or increased neuroleptic treatment can mask symptoms but also causes a gradual worsening of the disorder (Fann, 1980). Once the syndrome is established, the involuntary movements persist for months to years after neuroleptic treatment is discontinued and are apparently irreversible (Crane, 1968).

Pathophysiology. The pathogenesis and pathophysiology underlying tardive dyskinesia are not completely understood.
However, there is evidence which suggests that dopamine acting at striatal dopaminergic receptor sites may be closely related to the initiation of choreiform movements (Klawans & Rubovits, 1974). The antipsychotic agents responsible for the production of tardive dyskinesia block the access of dopamine at postsynaptic dopaminergic receptor sites (Snyder, 1976). Moreover, drugs which modify the central availability of dopamine alter choreiform symptomatology in other movement disorders, e.g., Parkinson's disease, Huntington's chorea (Klawans & Rubovits, 1974).

Observations of these drug interactions led Klawans and Rubovits (1972) and Carlsson (1970) to propose dopamine receptor hypersensitivity in the basal ganglia as a likely basis for the development of tardive dyskinesia (Kazamatsuri et al., 1972). Both theorized that the blocking of dopamine receptors in the course of antipsychotic therapy triggers an adaptive response in the postsynaptic dopamine receptors. The adaptation probably includes the development of an increased number of receptor binding sites for dopamine, as well as a hypersensitivity to local dopamine. It was further hypothesized that, when the neuroleptic blockade is removed or diminished, the striatal neurons respond abnormally to the restored dopamine. This results in the symptoms of tardive dyskinesia (Klawans & Rubovits, 1974).
The dopamine-hypersensitivity model of tardive dyskinesia accounted for the fact that symptoms often appear after neuroleptic dose reduction or withdrawal: A decrease at the striatal level of the neuroleptic would permit more dopamine to reach the sensitized dopamine receptors (Crane, 1973). That dyskinesia can emerge during neuroleptic therapy suggested that the competitive blockade can be overcome by endogenous dopamine (Klawans, 1973).

Although the pathophysiology of tardive dyskinesia seems to be most closely related to dopaminergic mechanisms, other neuronal systems, particularly cholinergic pathways, also influence striatal function (Klawans & Rubovits, 1973). An expansion of the dopamine-hypersensitivity theory implicates the relative hypofunctioning of the reciprocal cholinergic influences in the striatum (Gerlach, Reisby, & Randrup, 1974). Acetylcholine has been shown to exert an influence on the striatum opposite to that of dopamine, and a balance of influence of the two neurotransmitters is thought to be necessary for normal function (Klawans, 1968; Klawans & Rubovits, 1973).

In 1973, Klawans proposed that tardive dyskinesia may involve an imbalance in the postulated reciprocal inhibitory relation between dopaminergic and cholinergic neurons in the basal ganglia. The hypocholinergic hypothesis was supported by reports that anticholinergic drug treatment aggravated tardive dyskinesia (Gerlach et al., 1974). Hence, a logical
treatment strategy involves re-establishing the dopamine/acetylcholine balance, either by lowering the high- or raising the low-transmitter system.

**Treatment**

Since continuation or increase of dopamine blockade can cause a gradual worsening of the disorder (Crane, 1973), recent treatment research has involved pharmacologic precursor strategies aimed at enhancing central cholinergic activity in an attempt to restore the cholinergic-dopaminergic balance (Carpenter & Rudo, 1979). If the involuntary movements of tardive dyskinesia are caused by an imbalance between the dopaminergic and cholinergic systems, drugs which increase acetylcholine activity in the striatum, either by increasing acetylcholine synthesis through increased availability of its rate-limiting precursor or by preventing its degradation, should restore balance and thereby control tardive dyskinesia (Fann, 1980).

Efforts to identify a cholinergic therapy for tardive dyskinesia have generated data which tentatively support two of the four agents investigated thus far. Deanol, the first putative acetylcholine precursor to be examined (Casey & Denny, 1974; Miller, 1974), benefited many patients under open or single-blind conditions. Of 50 patients treated with 20-2,000 mg per day for 1-16 weeks in 15 studies, 26 improved, 23 were unchanged, and 1 worsened (Casey, 1977).
However, when treated under double-blind conditions, only 10 of 74 patients in 7 studies improved (Casey & Tepper, 1979).

The negative deanol trials do not constitute a strong argument against the cholinergic treatment strategy, however. Recent reports have demonstrated that although deanol increases plasma choline, it also competes with choline for transport across the blood-brain barrier (Millington, McCall, & Wurtman, 1978) and impedes choline uptake by synaptosomes.

Studies of physostigmine, an anticholinesterase inhibitor which increases brain acetylcholine, were more positive. Intravenous administration of physostigmine suppressed tardive dyskinesia under double-blind conditions (Fann, Lake, Gerber, & McKenzie, 1974; Gerlach et al., 1974). However, physostigmine's short duration of action, route of administration, as well as many unpleasant side effects including nausea, vomiting, and mental dullness, made it impractical as a treatment (Davis, Hollister, Barchas, & Berger, 1976).

A third, more promising strategy for increasing central cholinergic tone involves the administration of the acetylcholine precursor choline in the form of choline chloride (ChCl) or phosphatidylcholine (lecithin) (Gelenberg, Doller-Wojcik, & Growdon, 1970). The brain is unable to synthesize choline and extracts it instead from the systemic circulation both as plasma-free choline and in
phospholipid form as phosphatidylcholine (Aquilonius & Eckernas, 1975). It was suggested that large doses of choline, acting as a precursor, would accelerate acetylcholine synthesis (Cohen & Wurtman, 1975), and, in turn, increase acetylcholine release (Wurtman, 1979). Plasma choline enters the brain either by free diffusion or a carrier-mediated transport system (Aquilonius & Eckernas, 1975). Uptake is not saturated even at very high concentrations of choline in plasma (Cohen & Wurtman, 1975).

Choline in blood derives from two sources: dietary consumption, primarily as lecithin in food (Cohen & Wurtman, 1976), and from synthesis in the liver (Gelenberg et al., 1970). ChCl, equivalent to 86.8% choline, is the nitrogenous base component of the lecithin-type phosphatides. ChCl is well tolerated when given orally in doses as large as 30 g daily, except for the unpleasant odor of trimethylamine, its metabolic product, which appears in the breath, perspiration, and urine. Diarrhea, nausea, or vomiting may also develop in some patients.

The possibility of using choline as a precursor for brain acetylcholine was suggested by numerous studies indicating that both intravenous and oral administration of choline increased brain acetylcholine levels in rats and increased plasma concentration of choline in humans (Cohen & Wurtman, 1975, 1976). Researchers explored the possibility that choline administration might increase central
cholinergic tone in humans (Davis, Berger, & Hollister, 1979).

Following publication of the animal studies, Davis et al. (1975) described a patient in whom choline treatment decreased tardive dyskinesia symptoms. Davis and associates administered ChCl to a male patient who had previously demonstrated a therapeutic response to physostigmine. Only slight changes in symptoms were noted, until a dose of 16 g was reached after 8 days of treatment. At this point, abnormal movements decreased to approximately 20% of baseline frequency.

During treatment, cholinergic stimulation was manifested by increased sweating and salivation. When choline was discontinued, movements returned to baseline within 3 days.

In a further examination of the choline-precursor loading strategy, Tamminga, Smith, Ericksen, Chang, and Davis (1977) conducted a nonblind trial of oral choline in four patients with moderate to severe tardive dyskinesia. Subjects were withdrawn from all medications on admission to the study and allowed to be drug-free for 2 weeks. Symptom severity was rated three times a week with an observational scale on which movements of specific body parts were rated from 0 to 4.

Choline was given orally in doses beginning at 3 g per day and increasing to 18 g over a 3-week period. The form
of choline and the method of administration were not reported. Three of the patients had previously demonstrated a positive response to intravenous physostigmine; the fourth had not been challenged with physostigmine.

The results indicated some therapeutic effect. Two of the four patients showed a trend toward improvement at doses greater than 6 g per day. Symptoms decreased by about 60% when dosage reached 15 g daily. Choline administration was stopped in two patients who became depressed before a therapeutic dose was attained.

In a somewhat more sophisticated study, Davis et al. (1976) used oral doses of ChCl to treat four male inpatients with tardive dyskinesia. The disorder had been apparent in three of the patients for 1 to 2 years but in the fourth patient for only 3 months. All had a history of neuroleptic treatment and had responded positively to physostigmine challenge. Antipsychotic medication was discontinued during the study in all except one patient who received 3 mg haloperidol daily.

ChCl dissolved in water to a concentration of 1 g per 2 ml was given orally in strawberry syrup. Dosage was gradually increased over a 16 to 24 day period from 1 g ChCl four times a day to 16 g for one subject and to 20 g per day for the other three. The maximum dose was maintained for 3 to 8 weeks, after which placebo was substituted. Two
patients were given a second trial of ChCl at 20 g per day after the placebo period.

Five-minute videotapes were made of the patients three to five times per week during the study. The tapes were reviewed by blind raters who assessed symptom severity by counting the number of movements per 45-second epoch, using the most easily counted choreiform movement as the criterion. Treatment results were evaluated by analyzing movement frequencies before, during, and after treatment with the Mann-Whitney U.

Each patient experienced a significant improvement in symptoms during ChCl treatment. All four patients had significantly fewer involuntary movements, although the decrease in one patient's movements only reached significance when his predrug frequency was compared to that during high-dose treatment. Movement frequency decreased in three of the four patients as dosage increased from 4-8 g per day to 12-20 g.

Results during the placebo period following treatment were more complicated. One patient relapsed to a movement frequency slightly greater than pretreatment level. Although movement frequency tended to increase as the placebo period progressed, the other three patients did not return to their pretreatment frequencies.

In two patients, the frequency of movement was lower during the first 14 days of placebo than during treatment.
The delayed relapse suggests that choline may have a long duration of action unrelated to plasma choline levels which return to normal within 48 hours after treatment is discontinued.

Two patients were re-treated with ChCl after the placebo period. One patient who had responded to a maximum dose of 16 g during the first trial showed no decrease in symptoms until dosage was increased to 20 g. The second patient re-treated had not relapsed to predrug level during the placebo period, and his response to re-treatment was nonsignificant.

Three patients experienced side effects during treatment. Two patients complained of dizziness and nausea; another developed diarrhea and increased salivation. Symptoms improved when patients were treated with 45-75 mg of propantheline bromide daily. The "dead fish" body odor which develops in patients treated with choline does not respond to propantheline, however.

Growdon, Hirsch, Wurtman, and Wiener (1977) examined choline therapy in a double-blind crossover study of 20 patients with tardive dyskinesia. Patients were selected for stable chronic bucco-lingual-masticatory dyskinesia from a large, heterogeneous state hospital population. Each patient had received neuroleptics in the past. Anticholinergic medications were discontinued during the study; 13 patients continued their neuroleptic medication.
Symptom severity was measured by counting the number of eye blinks, tongue protrusions, slow tongue movements inside the mouth, jaw closures, or lip movements visible during a 30-second interval. Each patient was assessed while sitting in a quiet private room with a ward nurse and two investigators. The two investigators counted the movements independently on 2 separate days before the study began and made subsequent counts every 3 days thereafter. Symptom frequency during the control period, the second week of ChCl treatment, and the second week of placebo were analyzed for the percentage of change from baseline.

ChCl mixed with Kool-Aid (registered trademark of General Foods) was administered in divided daily doses equal to 150 mg/kg during the first week and 200 mg/kg during the second week. The placebo, sucrose octa acetate, was also dissolved in Kool-Aid. Both solutions tasted bitter. Half the patients received choline and the other half placebo, for 2 weeks: These schedules were reversed after a 10-day interval during which neither choline nor placebo was dispensed. The patients, nursing staff, and examiners were all blind to which doses contained choline. Blood samples for choline measurement were collected from patients several times during the study.

Abnormal movements improved in 9 of 20 patients during choline administration but were unaffected by the placebo. Symptoms were reduced by more than 75% in five patients and
by approximately 50% in four patients. Ten patients showed no response to choline, and one patient's symptoms were dramatically worsened with a temporary increase in abnormal movements of more than 500%. Patients who responded to choline did not differ significantly from the group as a whole with regard to age, sex, primary diagnosis, concurrent neuroleptic medication, or blood choline levels drawn before or during treatment.

No serious side effects were reported. Two patients were more withdrawn than usual and possibly depressed. Three patients experienced symptoms of mild cholinergic toxicity while taking 200 mg/kg daily. All adverse effects, including lacrimation, blurred vision, anorexia, and diarrhea, were dose-related and subsided when the dosage was reduced.

Growdon et al. noted that the variety of their patients' responses to choline, i.e., 9 better, 1 worse, 10 unchanged, suggests that the patient sample was indeed heterogeneous, at least with regard to a cholinergic mechanism. Thus, since the onset of tardive dyskinesia was documented in only one patient, and response to increased choline was not tested with physostigmine, it is possible that some patients in the series had senile chorea, stereotypy, or some other movement disorder rather than true drug-induced dyskinesia.
The prolonged duration of some dyskinesias following withdrawal of neuroleptics suggests that a more permanent, perhaps structural damage of the nigrostriatal system or a related pathway may occur (Tarsy & Baldessarini, 1974). Since most of the subjects in the Growdon et al. study were elderly women who had taken neuroleptics for many years, some may have already experienced structural damage which could not be overcome by the restored cholinergic balance. Neurohistopathological changes have been detected in the brains of animals (Pakkenberg, Fog, & Nilakantan, 1973) and humans (Christensen, Moller, & Faurbye, 1970) chronically exposed to neuroleptic agents.

An alternative explanation, however, might be that ChCl dosage did not reach a therapeutic level in patients who failed to respond. Therapeutic dosages ranged from 16-20 g per day in previous studies. A 150 lb. (68.04 kg) patient in the Growdon et al. study would have received a maximum dosage of only 13.6 g ChCl per day.

Taken together, the results of the choline trials suggest that ChCl may be beneficial for some patients with tardive dyskinesia. Beyond this, assuming choline's beneficial results are corroborated by other workers, the utility of choline treatment must be examined. For many patients, tardive dyskinesia's greatest impact is on social adjustment. Thus, for one patient whose movements decreased from 26 to 20 per 45-second epoch in the Davis et al. (1975)
study, symptom improvement may not be great enough to justify continued treatment, especially when it is accompanied by repugnant body odor. A useful therapy for tardive dyskinesia should provide social as well as statistically significant symptom relief.

In regard to this point, Berger (1981) has suggested that significant symptom reduction in tardive dyskinesia be defined as a 50% reduction from baseline in symptom frequency to distinguish clinically significant symptom changes from those which reach statistical significance. Jeste and Wyatt (1979) have also recommended that treatment data be analyzed both in terms of symptom change and the number of patients attaining 50% or more improvement.

In addition to providing significant symptom relief, a cholinergic drug treatment for tardive dyskinesia should be orally active and long-lasting. Oral doses of lecithin, the major dietary source of choline, may represent an alternative treatment. Lecithin consumption, like that of free choline, elevates the blood choline levels in humans (Wurtman, Hirsch, & Growdon, 1977). However, the effect of lecithin is considerably greater and more prolonged than that of an equimolar dose of ChCl.

In healthy subjects who took 3 g of ChCl (2.3 g free base), serum choline reached a peak of 86% above controls after 30 minutes but was not significantly higher than normal after 4 hours; in those who consumed 100 g of
lecithin (2.3 g free base), the first significant rise in serum choline occurred after 1 hour, but peak levels 265% above controls persisted for at least 12 hours (Wurtman et al., 1977). Since the effect of lecithin is greater and more prolonged than that of ChCl, lecithin may be a more effective therapeutic agent than ChCl for increasing cholinergic tone.

Growdon, Gelenberg, Doller, Hirsch, and Wurtman, (1978) tested the therapeutic potential of lecithin granuals (Sigma Chemical Company) for treating tardive dyskinesia in two patients whose movements had previously decreased during ChCl ingestion (Growdon et al., 1977) and partially purified lecithin (Phospholipon, American Lecithin Company) in one patient who had not previously taken ChCl. The first two patients continued neuroleptic medication but had discontinued ChCl at least 2 weeks before lecithin treatment began; the third patient was not taking any medication before the lecithin trial.

Symptom severity decreased to approximately 25% of baseline during treatment in all three patients. Two patients were measured at 2 months; the third was measured at 2 weeks. Serum choline levels rose significantly during treatment. Therapeutic dose ranged from 40-80 g daily.

Growdon et al. found lecithin to be as effective as ChCl in reducing dyskinetic symptoms. Lecithin's 2-month
duration of clinical benefits matched that of the longest ChCl trial.

In further non-blind trials, Gelenberg, Doller-Wojcik, and Growdon, (1979) compared the effects of choline with lecithin in five outpatients. Patients were treated with 150-200 mg/kg ChCl daily for 6-8 weeks. After a washout period that varied from 18 days to 5 weeks, patients began lecithin treatment with an initial daily dose of 21 g. Dosage was increased at weekly intervals to a maximum daily dosage of 105 g which was maintained for 8 weeks to 6 months.

Patients drank powdered ChCl mixed in fruit drink or soda. Lecithin, supplied as granules that contained 20% phosphatidyl choline, was mixed with or sprinkled on apple sauce, yogurt, or ice cream. Four of the five patients continued routine neuroleptic medications, with the exception of anticholinergic agents, throughout the study.

Symptom severity was rated weekly on three measures: (a) the Abnormal Involuntary Movement Scale (AIMS), (b) frequency of movements per 30-second epoch, and (c) videotape. Parkinsonian signs were rated on a scale devised by the investigators and the Simpson-Angus Scale. Mental status was evaluated with the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Index (CGI). Side effects and patients' subjective global assessments were also recorded.
Laboratory testing included electrocardiograms, complete blood count, urinalysis, serum enzyme, and lipid profiles. Serum choline levels were assayed before treatment, during choline therapy, and again during lecithin therapy.

The patients studied tended to be less severely affected, younger, and less chronic than those in earlier studies. However, stable signs of tardive dyskinesia had been present in the study subjects for 1-5 years; onset was well documented in all cases. Global severity of symptoms was rated from mild to severe by two raters.

Based on average weekly AIMS scores of body parts that showed at least mild abnormal movements at baseline, all of the patients improved on both treatments with a tendency toward greater improvement on lecithin. During the washout period, the patients' movements began to increase within several days, and most had returned to pretreatment levels within 1-2 weeks. Four of the five patients continued neuroleptic medications throughout the study.

The percentage of change in AIMS body part scores from baseline ranged from 36% worse to 91% better during choline therapy. Lecithin therapy change scores ranged from 50% worse to 82% better. Two patients experienced transient increases in symptoms during the study when their neuroleptic dosage was decreased.
All five patients objected to the bitter taste of ChCl and all developed the distinctive, unpleasant "fishy" body odor after several days on the higher dose of choline. Each patient also developed dose-limiting gastrointestinal irritation on choline.

Patients experienced no side effects during lecithin therapy. Lecithin did not produce a body odor, and patients found it palatable. Two patients discontinued lecithin because of increasing paranoia unrelated to treatment. At the time the study was reported, the other three patients had continued to receive 105 g daily doses of lecithin for 6 months without evidence of tolerance to therapeutic benefit.

Both treatments produced considerable increases in serum choline levels. No changes in the other laboratory test values occurred during either treatment. There was a mild and transient tendency toward the appearance of or an increase in Parkinsonian signs, e.g., bradykinesia, tremor, or rigidity, during both treatments.

There were no consistent changes in patients' mental status on either treatment. Two patients were noted to be slightly more depressed during the study, but two other patients showed a marked improvement in preexisting depression.

The data from this open trial supported earlier findings that ChCl can alleviate some of the symptoms of tardive dyskinesia. Further, the lecithin therapy appeared
to be at least as effective as choline, with fewer adverse side effects and greater patient acceptance. However, the precise degree of symptom improvement contributed by lecithin is difficult to determine. Of the 15 lecithin change scores reported, 5 represent improvement beyond that achieved with ChCl, and 2 represent improvement gained after symptoms had increased during ChCl treatment. The degree to which the remaining eight lecithin scores were contaminated by prior ChCl treatment is unknown.

Gelenberg et al.'s results provided further evidence that lecithin treatment might be useful for some tardive dyskinesia patients. However, only two of the four patients for whom lecithin treatment scores were reported attained a clinically significant reduction, i.e., at least 50%, in any symptom. Whether lecithin, at dosages greater than the 21 g phosphatidyl choline present in 105 g of 20% pure lecithin, could provide clinically useful symptom suppression remained to be examined.

In late 1979, Jackson, Nuttal, Ibe, and Perez-Cruet reported the results of a double-blind, placebo-controlled crossover study of lecithin in six patients. Several important details of the study, e.g., the dosage of lecithin used, were not reported until much later (Jackson, Davis, Cohen, & Nuttal, 1981), however.

The six patients involved in the Jackson et al. study were randomly assigned to either lecithin or control
treatment for 14 days. Following a 10-day washout period, assignment was reversed for 14 days. Patients were treated with a daily dose of 50 g of 70% pure lecithin (35 g phosphatidyl choline) in a mixture of milk and ice cream.

The investigators attempted to withdraw their patients from neuroleptic medications prior to participation in the study. Five of the six patients were returned to neuroleptic treatment because of worsening psychosis. Subsequently, a fixed dose of a single medication was maintained for 2 weeks before the study began and throughout the 7-week study period.

Treatment effects were assessed via AIMS ratings of videotapes made at baseline, on the 7th and 14th days of treatment, on the 10th day of washout, and on the 7th and 10th day of crossover control. Patient mental status was monitored with weekly administrations of the BPRS and the Missouri In-Patient Behavior Scale.

Group mean AIMS scores during lecithin treatment showed a statistically significant decrease compared to control at both 7 and 14 days of treatment. All six patients showed a decrease in symptoms. The amount of reduction in symptoms is not reported. AIMS scores appear to be approximately 25-30% reduced as estimated from figures. Serum choline increased to more than double the pretreatment level. However, there was no corresponding change in phosphatidyl choline. Dyskinesia symptoms and serum choline reverted to
original levels upon ceasing lecithin. There was some persistence of therapeutic effect on follow-up at 10 days.

Although the authors state that no side effects were encountered, one patient was withdrawn from the study because of nausea and vomiting—expected side effects of acetylcholine increase. Lecithin treatment was not associated with Parkinsonian symptoms, sedation, lethargy, depression, or change in body odor.

Jackson et al. state that their results represent a further example of clinical amelioration of tardive dyskinesia with lecithin. The degree of clinical efficacy is difficult to estimate from the data they report, however. Changes in symptom severity were reported only in terms of mean scores on the 4-point AIMS scale. At pretest, the group mean was approximately 3.25 (moderate); after 14 days of treatment, it was 2.2 (mild). Although each patient showed a therapeutic response, whether any patient attained a 50% decrease in symptoms cannot be determined.

In summary, the data derived from acetylcholine precursor loading in tardive dyskinesia patients via ChCl and lecithin are consistent with the hypothesis of relative central acetylcholine hypofunction and suggest that this strategy may be a useful treatment for some patients. Aside from their potential value as treatments, these early studies have demonstrated a role for ChCl and lecithin in
broadening understanding of tardive dyskinesia and its pathophysiology.

Further, double-blind, placebo-controlled research is needed to confirm lecithin's therapeutic potential. Prospective studies of larger samples of patients are needed to determine what proportion of patients is likely to respond to treatment and whether therapeutic benefits justify continued lecithin trials. Before describing the current study, some of the methodological problems, including assessment, patient, and treatment design issues, require discussion.

Methodological Issues

Assessment. Although a variety of techniques have been used to measure tardive dyskinesia, none has been widely accepted as a valid, reliable, sensitive, and comprehensive measure of the syndrome. Gardos and Cole have reviewed both the available assessment techniques for tardive dyskinesia (1977) and the problems encountered in its accurate assessment (1980b).

Tardive dyskinesia treatment assessment must accomodate the following clinical features of the syndrome: (a) involuntary movements occur in many different areas of the body and frequently involve several areas in the same patient; (b) no two patients have precisely the same symptom; (c) patients can usually suppress symptoms for a short while; (d) symptoms vary in severity in different
areas of the body, even in the same patient; (e) some symptoms are present only when the patient is standing; others occur only when seated; (f) predominant symptom expression may migrate from one area of the body to another over time; (g) involuntary movements are of several different types, including quick tic-like movements and slow, writhing, twisting movements of athetosis; and (h) some symptoms may closely resemble normal, nonsymptomatic movements.

Symptom assessment is made even more difficult by the variety of factors which may temporarily influence symptom expression. Symptom expression is influenced by all of the following: (a) simultaneous activity or movement in affected and nonaffected areas of the body; (b) medication changes and the dose schedule of concurrent neuroleptic medication; (c) physiological and emotional level of arousal; and (d) alcohol consumption. For example, oral dyskinesia will vanish when a patient speaks, while symptoms in the hands will increase. Vo...
The two most commonly used rating techniques in treatment research have been global or multi-item rating scales and movement frequency counts. Global scales such as the 7-point Clinical Global Impressions (CGI) (Guy, 1976) and the 4-point Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) have been widely used in early clinical drug trials. Rating scales of this type are generally reliable, but lack sensitivity. Severely affected patients who improve with treatment may still be rated as severe at the end of a drug trial.

Frequency counts, although reliable, valid, and sensitive to symptom changes, provide little information regarding a treatment's clinical efficacy unless frequency is dramatically increased or decreased. Further, it is possible for symptom frequency to remain unchanged as the intensity of the symptom is modified by treatment.

Symptom assessment via objective ratings of sequential videotapes made during treatment trials has been widely adopted and provides several advantages to the investigator. First, raters can easily be kept blind to treatment trial by presenting tapes for rating in random sequence. Tapes can be replayed as often as necessary or shown in slow motion for analysis of complex movements. Symptom recordings made days or weeks apart can be viewed simultaneously to detect treatment effect without the risk of rater drift. Both
frequency counts and multi-item or global ratings can be made from the videotapes.

Some movements, especially movements inside the mouth or facial movements in persons with dark skin, are sometimes inadequately documented on videotape. However, video recording is superior to "live" observation for certain types of small movements. A fixed camera with a telephoto lens can focus on particular areas of a patient's body for lengthy periods without the patient's awareness and probable embarrassment. Moreover, minor symptoms which might go unnoticed during "live" observation are preserved for later scrutiny and evaluation.

Whenever possible, two measurement techniques, one objective and one which relies on the rater's subjective clinical judgement should be used (Chien, Jung, & Ross-Townsend, 1980). Coupling a rating method with one of the objective techniques may yield optimal results in that the validity and clinical relevance of the former may be complemented by the precision and sensitivity of the latter (Gardos & Cole, 1980b). Multi-item scales are more useful in studies of prevalence and of etiological factors.

Patient variables. The variability of tardive dyskinesia patients' responses to treatments is notable: Treatments described as therapeutic in early reports are frequently found to have no effect or to aggravate symptoms in later studies. Beyond the fact that many early clinical
trials are poorly controlled, researchers studying tardive dyskinesia have offered some additional explanations for this phenomenon.

First, there is no specific diagnostic test, clinical or laboratory, that will definitely confirm or rule out the diagnosis of tardive dyskinesia (Jeste & Wyatt, 1980). Its symptoms overlap with other pathological conditions of the central nervous system. Undoubtedly many trials have included patients who did not have true drug-induced dyskinesia; ambiguity in diagnosis has resulted in inconsistent therapeutic response. At least 50% of the patients referred by ward physicians to this study as potential participants did not have tardive dyskinesia; most of these had Parkinsonian symptoms or schizophrenic mannerisms.

To diagnose tardive dyskinesia, it is necessary to distinguish the patient's symptoms from the numerous disorders of the extrapyramidal and pyramidal motor symptoms, brain stem, and cerebellum which may produce abnormal movements, and from the stereotypes frequently seen in schizophrenics and the developmentally disabled. Jeste and Wyatt (1980) have proposed the following diagnostic criteria which may be helpful in making the diagnosis: (a) involuntary, stereotyped movements characteristic of the disorder; (b) movements disappear during sleep; (c) volitional movement in affected areas can
temporarily suppress symptoms in that area; (d) stress and movement in distant parts of the body enhance symptom expression; (e) symptoms do not respond to antiparkinson drugs and may be worsened by them; (f) the patient has no other disorders that could fully explain the symptoms; and (g) the patient has a history of at least 3 months exposure to neuroleptics. Particular care must be taken to rule out anoxic damage, dyskinesias induced by other drugs (e.g., L-Dopa, antihistamines), post-paralytic dyskinesia, ill-fitting dentures, Tourette syndrome, Meige disease, and Huntington's chorea. The recent American Psychiatric Association Task Force Report on Late Neurological Effects of Antipsychotic Drugs (1980) is an excellent source of further information regarding differential diagnosis.

Assuming correct diagnosis, a variety of other patient variables may influence response to treatment. First, age of the patient may be an important variable in determining the outcome of cholinergic manipulations, as older patients were more sensitive to both cholinergic augmentation and inhibition in one study (Gerlach et al., 1974). Patients also probably have different response thresholds. At least some nonresponders may be patients for whom insufficient doses of therapeutic agents were used.

Patient response to cholinergic augmentation is also influenced by concurrent medication. Many investigators have not reported concurrent medications or have reported
only combined data from patients who continued centrally active medications with those who did not. Drug effects attributed to treatment may actually reflect an interaction between the experimental drug and concurrent medication. Moreover, impairment of cholinergic function may be so aggravated by the simultaneous use of anticholinergic or antihistaminic agents that new symptoms may be evoked, despite competing efforts to restore function via cholinergic augmentation.

Dyskinetic symptoms fluctuate with changes in neuroleptic and anticholinergic medications, e.g., Gelenberg et al., (1979). This phenomenon demonstrates the necessity of placing emphasis on the state of receptor responsiveness, rather than the absolute concentration of amines (Barbeau, 1974). Accordingly, whether or not concurrent medications are discontinued prior to clinical drug trials is much less important than maintaining a stable dose of all centrally active medications for at least 3 months before and throughout the study period (Jeste & Wyatt, 1979).

Duration and severity of symptoms may also influence treatment response. Because symptoms are especially variable in patients with mild forms of the disorder, severely affected patients are frequently considered the most suitable for research (Carroll, Curtis, & Kokmen, 1977). Chronic patients may be less responsive to treatment, however, than younger patients and those whose
symptom complex is less well developed (American College of Neuropsychopharmacology/Food & Drug Administration, 1973). In accordance with this point of view, Quitkin et al. (1977) argued that the most important variable for determining reversibility is the length of time symptoms persist prior to discontinuation of neuroleptics.

Treatment and design variables. The analysis of cholinergic augmentation research is complicated by a number of confounding treatment and design variables. First, it is very difficult to compare treatment dosages across studies. Some investigators report daily dosage; others report dosage in ratio to patient weight. The question of dosage is further confused by the fact that some investigators have not reported which choline salt was administered, i.e., choline chloride, 86.6% free-choline base, or choline bitartrate, 47.8% free-choline base.

Lecithin research presents a similar problem. The term "lecithin" refers to a mixture of phospholipids, including "true lecithin," i.e., phosphatidyl choline. Partially purified lecithin preparations are available in several concentrations which contain different amounts of phosphatidyl choline.

Second, investigators have not reported dose-response functions. Treatment effects during the first 2 weeks of choline or lecithin treatment have not been reported and cannot be determined from available reports. It is unclear
whether a therapeutic response is attained only after 2 weeks on incremental dosage or if initial assessments were first scheduled only after 2 weeks' treatment.

The present study was designed to test the hypothesis that lecithin will decrease tardive dyskinesia symptoms under double-blind, placebo-controlled conditions. It was also designed to determine the effects of lecithin in patients who were in continuing routine inpatient psychiatric treatment and who were typical of the type of patient affected by tardive dyskinesia.

**Method**

**Patients**

Patients at the Veterans Administration (VA) Medical Center, Waco, Texas, were screened for manifestations of tardive dyskinesia by the principal investigator and a neurologist experienced in diagnosing movement disorders. Patients identified in this preliminary survey were then evaluated more thoroughly to select cases which met study criteria. Clinical criteria for participation in the study included (a) at least moderate dyskinetic movements in at least one body area, (b) a minimum of 6 months exposure to neuroleptic drugs, (c) dyskinetic movements which could be seen and counted on videotape, (d) no medical contraindications to cholinergic medication, and (e) clinical impression that symptoms represented true tardive
dyskinesia, rather than other forms of movement disorders or schizophrenic stereotypies.

Patients with the following characteristics were excluded from the study: (a) current or recent history of alcohol abuse; (b) change in neuroleptic dosage within the last 4 months; (c) symptoms so severe that the patient might not be able to drink the study treatment "milkshake" or attend videotape assessments off his ward; or (d) history of recent refusals of medication or uncooperativeness. In addition to the above, no patient was included in the final sample whose dyskinesia did not increase under the stress of one of the symptom activation procedures described in the clinical assessment section below. Because estimates of the duration of tardive dyskinesia tend to be imprecise (Jeste & Wyatt, 1979), no minimum duration of symptoms was required. However, tardive dyskinesia symptoms had been present and stable in each patient for at least 6 months, and global severity of symptoms was at least mild as judged by the principal investigator and study neurologist.

Fifty male patients, including two outpatients, met study criteria and were enrolled in the study. Prior to participation, informed consent was obtained from each patient or his guardian according to the provisions of a protocol on tardive dyskinesia approved by the North Texas State University Use of Human Subjects Review Board and the
Thirty-eight patients completed the study. Table 1 summarizes sample attrition. Five patients were discharged before they had completed the study. Three patients withdrew from the study. One patient found the treatment mixture too unpalatable (control); another felt the treatment was making his psychiatric condition worse (control). The third complained of the inconvenience of the videotape assessments required by the study but wished to continue receiving the treatment mixture (lecithin).

Four other patients were dropped from the study because of events that interfered with accurate symptom assessment. One patient broke his dentures and suffered a mouth injury during a seizure; another had new and apparently painful dentures fitted during the study. A third patient was dropped because of medication changes which significantly modified his symptoms. The fourth patient was dropped when the investigator suspected he had been drinking alcohol prior to videotape assessment.

An additional five patients who completed the study were misdiagnosed and were dropped from the sample. One patient had a diagnosis of Alzheimer's disease with no verifiable history of neuroleptic treatment; another patient's choreoathetoid tongue protrusion was rediagnosed as postparalytic dyskinesia. Results of another patient's
Table 1
Sample Attrition

<table>
<thead>
<tr>
<th>Group</th>
<th>Lecithin</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients accepted into study</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Patients completing protocol</td>
<td>21</td>
<td>17</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for premature termination</th>
<th>Lecithin</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge from hospital</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Subject refusal</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Protocol violation--subject</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Protocol violation--staff</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

| Patients in analytic cohort        | 15       | 16      | 31    |

| Reason excluded:                  |          |         |       |
| Spoiled assessment tape           | 2        | 0       | 2     |

| Diagnosis changed to:             |          |         |       |
| Alzheimer's disease               | 1        | 0       | 1     |
| Meige disease                     | 2        | 0       | 2     |
| Post-paralytic dyskinesia         | 1        | 0       | 1     |
| Traumatic encephalopathy          | 1        | 0       | 1     |
brain scan, which became available after completion of the study, indicated traumatic encephalopathy. Two patients' diagnoses were changed to Meige syndrome (Tolosa, 1979). Two additional patients were dropped from the study because of spoiled assessment tapes.

The 31 patients retained in the analytic cohort ranged in age from 23 to 77. Patients had been treated for psychiatric disorders for an average of 17.26 years, with a range of 1 to 45 years. Table 2 summarizes the sample's demographic characteristics.

Sample mean daily dosage of neuroleptic medication was 427 mg in chlorpromazine equivalents (Davis & Cole, 1975). At the time of the study, four patients were not taking any neuroleptic medication. Concurrent medications are shown in Table 5 (Appendix B). Since records of past medication therapy in chronic psychiatric patients in public facilities are notoriously poor, length of neuroleptic exposure is not reported (Cole & Gardos, 1980).

**Procedure**

Patients were randomly assigned to lecithin or control treatment for a period of 1 month while continuing to receive their regular neuroleptic medication, if any. Only a member of the hospital pharmacy staff was aware of each patient's group assignment during the study. The investigator, patients, ward nurses, and physicians were all blind to patient status.
Table 2
Demographic Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>Race</th>
<th>Diagnosis</th>
<th>Treatment setting</th>
<th>Chron-icity</th>
<th>Dental Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Psych</td>
<td>Medical</td>
<td>Nursing Home Care</td>
</tr>
<tr>
<td>Lecithin</td>
<td>15</td>
<td>57.9</td>
<td>11</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Control</td>
<td>16</td>
<td>52.4</td>
<td>14</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>55.0</td>
<td>25</td>
<td>3</td>
<td>21</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>
Most patients were maintained at a stable neuroleptic dosage throughout the study. Medication changes that did occur, including PRN drug administrations, were recorded.

The first few patients who entered the study were required to have antiparkinson medications discontinued prior to participation, to avoid potential anticholinergic moderation of treatment response. This requirement was dropped when it became apparent that it was very upsetting to the patients in this sample. Chronic psychiatric patients are frequently reluctant to decrease their drug dosages and resist such changes, because they fear they will become more ill (Lesser & Friedmann, 1981). Consequently, seven patients were being treated with antiparkinson agents during the study; two of the seven were in the experimental group.

**Lecithin Treatment**

Lecithin (LKE-Granules), purchased from American Lecithin Company, Atlanta, Georgia, was supplied to the hospital pharmacy as granules containing 55% phosphatidyl choline. Individual doses of lecithin and the control substance were each emulsified in 8 oz. of milk and dispensed from the hospital pharmacy on a daily basis. The control substance was a mixture of crushed graham cracker and corn oil which, when mixed with milk, resembled the lecithin mixture in taste, appearance, and viscosity. The mixtures were further disguised and made more palatable by the addition of artificial sweetener and vanilla extract.
Experimental patients received a divided daily dose of 60 g LKE-Granules (33 g free-choline base) for 11 days. Control patients received the control mixture. Doses were administered by the ward nurse who was asked to observe the patient drink the mixture. All patients received the same fixed dose of lecithin, if any, throughout the study.

Clinical Assessment

Treatment effect was assessed by blind evaluation of randomly sequenced videotapes made during standard examinations before, during, and after treatment. Baseline symptom recordings were obtained for each patient 4 days before starting treatment and at weekly intervals for the next 3 weeks. Thus, patients were assessed before treatment, on the 3rd and 11th days of treatment, and 1 week posttreatment.

With a few exceptions, patients were videotaped at approximately the same time of day and on the same weekday each time they were evaluated. Each patient was evaluated within 8 hours of his last experimental dosage (Growdon et al., 1976). Recordings lasted approximately 5 minutes and were conducted in the investigator's office. Although patients had been informed they would be taped, the camera was screened from view.

Each patient was taped standing and sitting, with close-up views of each of the patient's individual symptom areas, including, for example, face, hands, or trunk area.
while seated. In addition, the patient was distracted by conversation and by a standard symptom activation task selected to require the patient's concentration and movement of nonaffected areas of the body, such as counting serial sevens, stringing wooden beads, or reciting a poem. Because dyskinetic movements increase with the psychological loading provided by a task that requires activity and attention (Narabayashi, Chida, & Kondo, 1979), the symptom activation task was included both as an aid in establishing correct diagnosis and to compensate for differences in the level of patient arousal from week to week.

The patient was briefly interviewed after each taping. Side effects and the patient's subjective global assessment of the treatment were recorded. Overall severity of illness was rated at baseline and at 11 days of treatment on the 7-point CGI (Appendix C; Guy, 1976).

Treatment effects were evaluated with respect to changes in symptom severity. Each patient's four videotapes were rerun in random sequence and scored by the investigator. Symptom severity was rated by selecting the most easily counted dyskinetic movement in up to four symptom areas for each patient and counting its frequency (Davis et al., 1976). The mean frequency of dyskinetic movements per minute was calculated for each evaluation. Scores were calculated before the drug code was broken.
The four symptom areas in which movement frequency was recorded were (a) upper face, e.g., blinking, wrinkling the brow; (b) bucco-lingual-masticatory area, i.e., jaw, tongue, lips; (c) upper and lower extremities; and (d) trunk or holokinetic movements.

Only one symptom was selected for scoring in each of the four areas in which a patient might have symptoms. Thus, each patient contributed at least one and as many as four symptom area scores for analysis. The number of patients rated in each of the four areas is shown in Table 3.

Table 3

Patient Symptom Distribution

<table>
<thead>
<tr>
<th>Group</th>
<th>Upper Face</th>
<th>BLM*</th>
<th>Extremities</th>
<th>Trunk</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin</td>
<td>4</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>(N = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>(N = 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>19</td>
<td>12</td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>(N = 31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bucco-lingual-masticatory
**Results**

Symptom frequency scores were analyzed for each body area separately, using a repeated-measures analysis of covariance with baseline scores used as the covariant. Raw score and adjusted treatment means for three of the symptom areas are presented in Table 6 (Appendix D). Too few trunk scores were available for statistical analysis.

Scores were also examined with regard to the percentage change from baseline at 3 and 11 days of treatment and at follow-up. Patient age, diagnosis, chronicity, concurrent neuroleptic medications, symptom severity, and duration and quantity of exposure to neuroleptic medications were counterbalanced via randomization.

**Symptom Frequency**

Lecithin treatment significantly suppressed symptom frequency in each of the three body areas analyzed. Symptom frequency decreased by at least 50% in at least one symptom in 11 of the 15 patients treated with lecithin (80% of the sample). Six patients experienced 100% symptom suppression in at least one symptom (40% of the sample); one patient experienced 100% suppression in four symptoms.

**Upper face.** The lecithin group included four patients who contributed scores in the upper-face category. Analysis of covariance demonstrated that treatment effect was statistically significant, $F(1, 5) = 18.22$, $p < .01$. 
On day 3 of treatment, mean decrease in symptoms was 53% compared to baseline. Three patients attained at least 50% decrease on day 11; mean decrease was 74.57%.

On follow-up, two patients maintained a 100% decrease in symptoms; the other two patients showed greater therapeutic response than at day 3 or 11. The mean decrease for the group was 84% compared to baseline, with all four patients attaining more than 50% decrease in symptoms. Thus, for upper-face symptoms, therapeutic response was greatest during follow-up after lecithin treatment had been discontinued.

**Bucco-lingual-masticatory symptoms.** Eleven patients treated with lecithin contributed scores for analysis in the category of bucco-lingual-masticatory symptoms. Analysis of covariance indicated that treatment effect was statistically significant, $F(1, 17) = 7.18, p < .02$.

One patient's score on day 3 of treatment was dropped from the analysis, because his videotape evaluation that day closely followed a lower-GI examination. The 10 remaining patients all demonstrated a therapeutic response on day 3, with a mean decrease in symptoms of 51% compared to baseline.

Six patients exhibited further reductions in symptoms on day 11 of treatment; three patients maintained the decreases they showed on day 3. Symptoms in one patient increased slightly compared to day 3 but remained 87% below
baseline. Another patient showed a 99% increase over baseline. The mean decrease for the group at 11 days was 60%.

Four patients maintained or increased therapeutic response at follow-up; therapeutic gains were partially maintained in an additional five patients whose symptoms had begun to increase but had not returned to baseline. Mean change from baseline was -40%. Symptoms in two patients increased to levels greater than baseline. Symptoms exceeded baseline by 74% in one patient and by 57% in the other.

**Extremity symptoms.** Five patients treated with lecithin had symptoms in the extremities which were scored for analysis. Analysis of covariance demonstrated that treatment effect was statistically significant, \( F(1, 10) = 8.43, p < .05 \). At 3 days of treatment, two of five patients attained a 50% decrease in symptoms compared to baseline. Mean decrease for the group was 40%. At 11 days of treatment, three of five patients attained at least a 50% decrease with a group mean decrease of 60%.

At follow-up, symptom suppression was maintained or increased in two patients. Symptoms returned to baseline in one patient and exceeded baseline by an average of 34% in the other two patients. Mean change from baseline at follow-up was -15%.
Trunkal symptoms. Only three patients were scored for trunkal symptoms; two were in the lecithin group. Both patients attained at least 50% decrease in symptoms on day 3; symptoms were completely suppressed in both on day 11. Mean decrease for day 3 and day 11 were 79% and 100%, respectively. One patient showed no increase in symptoms at follow-up; the other patient experienced a 62% increase in symptoms above baseline. The mean change from baseline at follow-up was -38%.

No statistical analysis was performed on trunkal scores, because of the low number of patients contributing symptom scores. Several other patients in the sample showed dyskinetic symptoms in the trunk, but the extreme variability of the symptoms made frequency estimation unfeasible.

Clinical Global Impressions (CGI)

The 7-point CGI evaluations for overall severity of tardive dyskinesia symptoms at baseline and 11 days of treatment (Table 4) reflect a milder treatment response than that suggested by the symptom frequency data. Patients in the lecithin group improved from a mean of 4.2 (moderately ill) at baseline to a mean of 3.2 (mildly ill) at 11 days. Symptom severity in the control group was slightly less than moderately ill at both assessments. Analysis of covariance of the CGI scores revealed that the treatment effect was significant at the .01 level ($F = 6.999$, $df = 1$).
Table 4
Clinical Global Impressions

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline</th>
<th>11 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin $\bar{X}$</td>
<td>4.2</td>
<td>3.2</td>
</tr>
<tr>
<td>SD</td>
<td>1.08</td>
<td>1.42</td>
</tr>
<tr>
<td>Control $\bar{X}$</td>
<td>3.75</td>
<td>3.63</td>
</tr>
<tr>
<td>SD</td>
<td>.68</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Side Effects

No serious side effects occurred during lecithin treatment. Adverse effects consisted primarily of GI complaints and Parkinsonian symptoms. Two-thirds of the lecithin group complained of nausea, mild vomiting, or abdominal pain, or exhibited Parkinsonian symptoms of tremor or mask-like faces. Twenty percent of the control group also had GI complaints. Most of the symptoms were mild and were controlled with antacid medications. One patient in the lecithin group complained of sleeplessness and irritability. At least 75% of the sample complained that they did not like the taste of the mixtures; three patients refused a dose because of objections to its taste.

Discussion

Results from this double-blind, placebo-controlled trial support earlier evidence of a therapeutic response to
lecithin in tardive dyskinetics. There was a rapid onset of treatment response during the study. Therapeutic changes were apparent after only 3 days of high dose treatment and suggest that response to treatment can be rapid, if dosage is within the therapeutic range. The delayed return to baseline symptom severity and occasional enhanced symptom suppression during follow-up exhibited in this trial are typical of the results obtained in previous choline loading treatment studies. This phenomenon may reflect corresponding increases in brain acetylcholine which also begin later and outlast accompanying rises in plasma and brain choline (McIntosh, 1979).

Individual degree of treatment response and severity of side effects varied from patient to patient. Treatment response may be related to intraindividual differences in drug metabolism, degree of neuronal deterioration, severity of symptoms, or patient weight. Since doses were not adjusted to pursue ideal, individually titrated dosage, even greater therapeutic response may be possible. Satisfactory symptom suppression might be attained in longer trials with doses below the threshold of adverse effects.

That 93% of the treatment sample exhibited a positive response to lecithin is in agreement with previous lecithin treatment research but not with earlier choline-loading investigations, which usually reported 50% responders. The uniformity of treatment response can probably be attributed
to the strict inclusion characteristics used in this study, especially that of including only those patients whose movements increased under stress.

Two of the three patients who exhibited less than 50% improvement in symptoms were the last patients treated in the study. It is possible that the lecithin granules, delivered in bulk at the beginning of the study, had deteriorated during the 6 months it took to complete the study and were no longer active when these last patients were treated. Because lecithin deteriorates upon exposure to oxygen, the study medication was stored in a closed container in a low-oxygen atmosphere. However, the lecithin was handled daily in a normal atmosphere and undoubtedly deteriorated to a certain degree.

The third patient, whose symptom frequency declined by less than 50%, was one in whom treatment appeared to affect symptom amplitude to a much greater degree than symptom frequency. Despite the fact that his symptom frequency was relatively stable across ratings, the patient was clinically much improved. Pretreatment symptom expression had been brisk and vigorous; during treatment, symptoms became milder and much less forceful. Although it may be more difficult to obtain interrater reliability for symptom severity, future research should include a separate dependent measure of symptom amplitude.
Although all but three of the treated patients exhibited the 50% decrease in symptom frequency, which has been adopted as a minimum for clinical utility, it would be premature to advocate lecithin as a treatment for tardive dyskinesia. Based on the small percentage of patients who experienced at least a temporary rebound increase in symptom severity following lecithin treatment, future research should be approached with some caution. The rebound above baseline symptom severity raises the concern that long-term use of lecithin may further aggravate the development of tardive dyskinesia (Davis et al., 1979).

The present study also demonstrates only the short-term effects of lecithin in tardive dyskinesia. Longer trials are necessary to determine lecithin's durability as a treatment. Moreover, the current study was restricted to male patients. Generalization to females should be cautious.

One obvious methodological limitation of this report is that the principal investigator was the only observer. The investigator originally intended to edit the assessment videotapes to exclude unscorable portions, so that other raters might perform the symptom frequency counts. However, since the tapes had been recorded without sound, and video editing equipment was not available, it would have been difficult for another rater to suspend symptom rating to exclude sections of the tapes which had been spoiled by
intercurrent events that may have distracted the patient or modified symptom expression, e.g., a door opening off camera, a telephone ringing, the patient conversing with the camera operator.

The fact that the sole rater was blind to patient treatment assignment offsets this limitation somewhat. Objectivity in scoring was obtained by (a) presenting the assessment tapes in random sequence, (b) the use of a quantitative measure, and (c) repeated ratings—up to half a dozen—of each assessment tape. Future studies should attempt to replicate these results with multiple raters, however.

Although originally proposed as a neurotransmitter replacement strategy, the mechanism of action involved in lecithin treatment remains to be elucidated. In 1980, Berger & Rexroth stressed that despite increases in brain acetylcholine following choline loading, it is not absolutely clear that ChCl or lecithin increase cholinergic activity. Lecithin's therapeutic effects could be due to the presence of essential fatty acids or other unknown constituents (Cole & Gardos, 1980).

Recently, Kilbinger & Kruel (1981) demonstrated that high concentrations of choline do not improve cholinergic synaptic transmission and that increases in acetylcholine following choline administration are probably due to a reduction in acetylcholine release rather than accelerated
synthesis. Whatever the biochemical consequences of lecithin, its beneficial effect in this and other clinical studies may be mediated by a mechanism other than increased neuronal release of acetylcholine.
Information About Lecithin Therapy for Tardive Dyskinesia

Tardive dyskinesia is a well recognized side-effect of a large number of medications used in psychiatric treatment. The disorder usually involves involuntary movements in the mouth, face, tongue, or hands. Movements often persist for months to years after the medication which causes the disorder has been discontinued.

There is no known treatment for the disorder. However, recent research has suggested that lecithin, a nutrient found in eggs and soybeans, may be a treatment for tardive dyskinesia. This study is being undertaken to investigate the effectiveness of lecithin as a treatment for tardive dyskinesia.

If you participate in this study, you would take an additional medication in the morning for two weeks. The medication, which will be mixed in a glass of milk, would either be lecithin or another substance which has no effect on tardive dyskinesia symptoms. Neither you, your doctor, nor the experimenter would know which substance you had taken until the experiment is over.

You would also be videotaped four times—once before and once after the study, as well as twice while you were taking the study medication. Each tape will last about 5 minutes. You would be taped here at the hospital and the tapes will be rated by people assisting in this research. Your identity as a participant would not be revealed in any published or oral presentation of the results of this study. The tapes will be destroyed after they are rated.

The experimental medication may make your tardive dyskinesia symptoms worse, better, or may have no effect at all. The effects of the experimental medication probably will not last after you are no longer taking it. No side effects are expected, but if any occur, you would notify your ward nurse or doctor immediately. All your other medications and therapies would continue as usual. You would be free to withdraw from the study at any time.

The experimenter is available to answer any questions you have about this study and you may also wish to consult your doctor. After the study is over, the experimenter will be available to tell you which substance you took and to explain the outcome of the study.
In the unlikely event you are injured as a result of participation in this study, the Waco VAMC will furnish medical care as provided by Federal statute. Compensation for such injury may be available to you under the provisions of Title 38, United States Code, Section 351, and/or the Federal Tort Claims Act. For further information, contact the VA District Legal Counsel at 756-6511 - Ext. 626.

I, ________________________________________________, certify that the above written summary was discussed and explained fully to me by Barbara Beckham on this date.
### Table 5
Concurrent Medications

<table>
<thead>
<tr>
<th>CPZ equivalents&lt;sup&gt;a&lt;/sup&gt; (mg/day)</th>
<th>Daily dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td>Mean</td>
</tr>
<tr>
<td>Lecithin</td>
<td>406</td>
</tr>
<tr>
<td>Control</td>
<td>448</td>
</tr>
<tr>
<td>Total</td>
<td>427</td>
</tr>
</tbody>
</table>

<sup>a</sup>CPZ equivalents computed in accordance with Davis and Cole (1975).
### Antipsychotic medication

<table>
<thead>
<tr>
<th>Haloperidol (Haldol)</th>
<th>Chlorpromazine (Thorazine)</th>
<th>Trifluoperazine (Stelazine)</th>
<th>Thioridazine (Mellaril)</th>
<th>Thiothixene (Navane)</th>
<th>Chlorpromazine + Fluphenazine C</th>
<th>Chlorpromazine + Fluphenazine D</th>
<th>Chlorpromazine + Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>None</td>
</tr>
</tbody>
</table>

Additional medications

<table>
<thead>
<tr>
<th>Haloperidol (Haldol)</th>
<th>Chlorpromazine (Thorazine)</th>
<th>Trifluoperazine (Stelazine)</th>
<th>Thioridazine (Mellaril)</th>
<th>Thiothixene (Navane)</th>
<th>Chlorpromazine + Fluphenazine C</th>
<th>Chlorpromazine + Fluphenazine D</th>
<th>Chlorpromazine + Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lithium</td>
<td>Antiparkinsonian</td>
<td>Antidepressant</td>
<td>Cholinergic</td>
<td>Hypnotic</td>
<td>Minor tranquilizer</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**b**Trade name is in parentheses.

**c**Fluphenazine was converted to CPZ units on the basis of a dose of 25 mg I.M. every 2 weeks to 300 mg chlorpromazine daily (Chouinard, Anrable, Ross-Chouinard, & Nestoros, 1979).
Appendix C

Clinical Global Impressions

Instructions to rater: Considering your total clinical experience with this particular population, how severely ill is the patient at this time?

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline
3 = Midly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients
## Appendix D

### Table 6

Raw Score ($\bar{X}$) and Adjusted ($\bar{Y}$) Mean Symptom Frequency per Minute

<table>
<thead>
<tr>
<th>Symptom Area</th>
<th>Assessment</th>
<th>Baseline</th>
<th>3 Days</th>
<th>11 Days</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper Face</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control $\bar{X}$</td>
<td>50.2</td>
<td>41.5</td>
<td>50.8</td>
<td>56.3</td>
<td></td>
</tr>
<tr>
<td>$\bar{Y}$</td>
<td>45.2</td>
<td>38.2</td>
<td>47.2</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>Lecithin $\bar{X}$</td>
<td>41.4</td>
<td>21.9</td>
<td>14.6</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>$\bar{Y}$</td>
<td>45.2</td>
<td>24.3</td>
<td>17.2</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td><strong>BLM</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control $\bar{X}$</td>
<td>47.5</td>
<td>42.1</td>
<td>39.5</td>
<td>41.4</td>
<td></td>
</tr>
<tr>
<td>$\bar{Y}$</td>
<td>36.4</td>
<td>33.5</td>
<td>32.4</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Lecithin $\bar{X}$</td>
<td>28.4</td>
<td>11.7</td>
<td>9.5</td>
<td>18.7</td>
<td></td>
</tr>
<tr>
<td>$\bar{Y}$</td>
<td>36.4</td>
<td>17.9</td>
<td>14.6</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td><strong>Extremity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control $\bar{X}$</td>
<td>42.7</td>
<td>43.0</td>
<td>34.9</td>
<td>37.7</td>
<td></td>
</tr>
<tr>
<td>$\bar{Y}$</td>
<td>49.1</td>
<td>48.4</td>
<td>38.9</td>
<td>42.8</td>
<td></td>
</tr>
<tr>
<td>Lecithin $\bar{X}$</td>
<td>53.7</td>
<td>36.5</td>
<td>24.9</td>
<td>44.6</td>
<td></td>
</tr>
<tr>
<td>$\bar{Y}$</td>
<td>49.1</td>
<td>28.9</td>
<td>19.1</td>
<td>37.4</td>
<td></td>
</tr>
</tbody>
</table>

*Bucco-lingual-masticatory
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