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BUPROPION AND THIOTHIXENE COMPARED WITH PLACEBO AND THIOTHIXENE IN THE TREATMENT OF DEPRESSED SCHIZOPHRENIC INPATIENTS

BY

ROBERT LOUIS DUFRESNE

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OF

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APPROVED:

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ABSTRACT

A combination of bupropion hydrochloride and thiothixene was compared with a combination of placebo and thiothixene in a double blind investigation in thirty-eight patients meeting the DSM-III criteria for schizophrenia and also for atypical depression. These patients had to demonstrate a Hamilton Depression Scale score of at least eighteen prior to study entry. Assessments for efficacy and safety were performed at baseline and at regular intervals throughout the study. Patients were given physical exams with complete clinical laboratory workups prior to and after the study active treatment phase to document the safety of the respective treatments.

Of the nineteen subjects originally included in each treatment group, eighteen completed four full weeks of study treatment. Patients in both treatment groups were not significantly different at baseline on all measures. A significantly greater number of subjects (9) dropped out from the bupropion and thiothixene group than from the placebo and thiothixene group (2) prior to reaching the full ten week period. The patients who dropped out were significantly more psychiatrically ill than those who remained as measured by the Brief Psychiatric Rating Scale.

Both groups became less depressed as measured on the Hamilton Depression Scale over four and ten weeks, though only when the dropouts were included in the analysis did the placebo and thiothixene group demonstrate a greater degree of improvement than the bupropion and thiothixene group. The overall psychiatric pathology as measured by the Brief Psychiatric Rating Scale was decreased to a significantly greater

degree by the placebo and thiothixene control group than by the bupropion and thiothixene group at four weeks but not at ten weeks. Global ratings of patients overall psychiatric status also showed improvement over time.

Treatment group effects on separate psychiatric syndromes as measured by the Brief Psychiatric Rating Scale factor scores were divergent. Significant decreases on the thought disorder and the anergia factor scores from baseline were observed for both treatment groups to a similar degree. However, patients in the thiothixene and placebo group demonstrated greater improvement over time than the bupropion and thiothixene group on the anxiety and depression factor score. Neither group showed improvement from baseline on the activation factor scores nor the hostilty and depression factor scores.

Neurological side effects were not significantly different between groups. No differences between group were observed on the physical and clinical chemistry examinations of patient health nor on electrocardiogram or electroencephalogram. The Treatment Emergent Symptom Scale showed statistically significant between group differences. The bupropion and thiothixene group reported twice the incidence of dry mouth and constipation than the placebo and thiothixene group, while the latter group reported increase in appetite, more menstrual disturbances, and a decrease in sex drive over four and ten weeks.

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TABLE OF CONTENTS

LIST OF TABLES

TABLE PAGE

INTRODUCTION

The treatment of depressive syndromes in schizophrenic patients has been problematic. The tricyclic antidepressants (TCA's) and monoamine oxidase inhibitors (MAOI's) have not been shown to be effective in treating depression as a secondary symptom of schizophrenia (Becker, 1985; Siris et al., 1978), and in fact have been implicated in inducing psychosis in previously stabilized schizophrenic patients (Siris et al., 1978). While some antipsychotic medications have been shown to be effective in treating both psychosis and depression (Becker, 1983), there is no established treatment for depression coexisting with schizophrenia if depression does not resolve as a result of treatment with the antipsychotic phenothiazines or butyrophenones. Furthermore, clinically significant symptoms of depression often occur in patients who have had their psychosis succesfully treated with antipsychotics (Mandel et al., 1982). Depression often is a secondary symptom in schizophrenia (Weisman et al., 1977; Siris et al., 1981; Carr, 1983; Becker,1985), and depressed schizophrenics are more likely to relapse following successful treatment than nondepressed schizophrenics (Mandel et al., 1982; Glazer et al., 1981).

The primary focus of the present study is to attempt to successfully treat this resistant patient population with the novel antidepressant bupropion. The pharmacological profile of this chemically distinct antidepressant makes it unlikely that it will potentiate the sedative and anticholinergic properties of the antipsychotic drugs, thus making the use of this medication in combination with antipsychotics feasible. As the population we are dealing with must be maintained on their antipsychotic in order to

prevent the relapse of their psychotic symptomotology, this would make bupropion an ideal pharmacotherapeutic agent for treating their depressive symptomotology without increasing the chance that adverse reactions will occur.

Bupropion hydrochloride is both chemically and pharmacologically a novel antidepressant compound. It is structurally unrelated to the tricyclic antidepressants (TCA's) or monoamine oxidase inhibitors (MAOI's) and is neither sedating, anticholinergic, nor cardiotoxic (Dufresne et al., 1984; Van Wyck Fleet et al., 1983). More importantly, bupropion appears to be effective in treating Major Depression in many patients who have in the past not responded to the TCA's and MAOI's (Stern et al., 1983).

While effective in treating major depression (Dufresne, et al 1984, Preskorn and Othmer, 1984), it has not been established whether bupropion can be useful in treating depression secondary to other psychiatric syndromes. Bupropion was chosen for this study because it is chemically and pharmacologically distinct from the TCA's and the MAOI's that have been used for this purpose in the past. Unlike the TCA's it does not block the reuptake of norepinephrine (NE) or of 5-hydroxytryptamine (5-HT) from synapses. Also, it does not have any effect on either type A or type B monoamine oxidase (Ferris et al., 1981 and 1983). It has been demonstrated in a drug discrimination paradigm in the rat that bupropion's internal cue is not blocked by neuroleptics while that of the tricyclic antidepressants was so affected (Blitzer and Becker, 1985). This led us to hypothesize that bupropion might be effective in treating depression in these patients when given concomitantly with an antipsychotic since its mechanism of action might

not be interfered with in the same manner as the TCA's. Previous studies in which the tricyclic antidepressant or monoamine oxidase inhibitors did not decrease depressive symptoms when given concomitantly with antipsychotic could be the result of the blockade of the more typical antidepressants' mechanism of action by the antipsychotic. The possibility that bupropion may work by a mechanism distinct from these agents makes for the chance of it being effective where these medications have previously failed. Clinical studies in depressive syndromes have demonstrated that bupropion is effective in patients found refractory to TCA's (Stern, 1983). Furthermore, the fact that bupropion is apparently a much safer medication than the MAOI's or TCA's which are still often used in attempts to treat depressive symptoms secondary to schizophrenia makes this study less of a risk to the subjects than their usual treatment. Bupropion, unlike TCA's, is not likely to potentiate the anticholinergic or sedative effects of antipsychotics as it does not possess these properties. (Van Wyck Fleet et al., 1983). Unlike MAOI's, there is no concern about a possible hypertensive crisis due to unmetabolized pressor substances such as tyramine (Fowle et al., 1983).

A secondary aspect of this study concerns whether the so called "negative symptoms" of schizophrenia can be influenced by bupropion treatment. These negative symptoms of schizophrenia can be more readily understood as deficit symptoms; that is, they describe the absence of certain perceptual skills or emotive behavior that are found in psychiatrically healthy individuals. Examples of these symptoms include anhedonia, apathy, emotional blunting, social isolation, poor hygiene, and poverty of speech. These symptoms are often prominent in chronic

schizophrenics and notoriously resistant to treatment (Andreasan, 1982). In a study of bupropion in major depressive syndrome Dr. Robert Becker and myself found that patients became more active and interested in their environment while receiving bupropion (Becker and Dufresne, 1982). Since withdrawal and emotional blunting are both prominent negative symptoms of schizophrenia, interest as to whether bupropion could effect these symptoms in schizophrenics was generated.

Other aspects of this study include assessment of adverse reactions to the treatment and particularly the interactive effects of bupropion and the antipsychotic thiothixene. Thiothixene (Navane) was chosen as the antipsychotic for this study due to previous evidence that it has some mood elevating properties when used in this patient population (Becker, 1983). It appears to be an adequate choice for treating this population; therefore, by the design of this study we are not withholding a proven treatment. The major objective of this study was to assess whether the bupropion-thiothixene combination is a better treatment than thiothixene alone. As bupropion will undoubtedly be used in combination with antipsychotics in the treatment of these patients upon its marketing in much the same manner as TCA's and MAOI's have been used, it is as valuable to learn if bupropion is not useful for the treatment of depression secondary to schizophrenia as it is to find that it is useful in this application.

Methodology and Procedures

This was a 70 day study in which thirty-eight hospitalized, depressed schizophrenic patients who received thiothixene in treatment of their psychotic symptoms additionally received either bupropion

(n=19) or placebo (n=19) in a double blind trial of efficacy and safety. During an initial stabilization period of at least one week the dose of thiothixene was adjusted to optimize antipsychotic response. Patients remained on the same dose of thiothixene for at least on week prior to being started on bupropion or identical placebo; this dose of thiothixene was fixed for the duration of the study. After two weeks of thiothixene treatment patients were required to meet a minimum score of eighteen on the Hamilton Depression Scale. Patients were then randomly assigned to receive a flexible dosing regimen of either bupropion 150-750 mg/day or placebo for up to ten weeks in a double blind fashion. The blind could not be broken according to Food and Drug Administration regulations until study completion; the only exception was in the case of a medical emergency.

Inclusion and Exclusion Criteria:

Patients were required to meet several strict inclusion and exclusion criteria in order to be included in the study. Each patient at baseline was required to meet DSM-III Diagnostic Criteria for either schizophrenia with superimposed atypical affective disorder or schizoaffective illness (A.P.A., 1980). The symptoms of the affective componet of their illness had to be persistent for at least two weeks prior to initial screening. These depressive symptoms had to remain prevalent during the the initial period in which they where stabilized on thiothixene. A minimum score of eighteen on the Hamilton Depression Scale had to be assessed at initial screening, weekly through thiothixene stabilization, and at baseline. Treatment with TCA's or MAOI's was not allowed for a minimum of two weeks prior to baseline.

Patients were excluded from the study if they suffered from an organic mental disorder, were incapable of conversation, had history or evidence of a seizure disorder, had a history of alcoholism in past two years, had a myocaridal infarction within the last two months, were pregnant or lactating, or had a history of intolerance to phenothiazine or thioxanthine antipsychotics.

Measures

Patients were assessed for therapeutic efficacy using the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Scale, and Clinical Global Impression Scale (Overall and Gorham, 1962; Hamilton, 1960, Guy, 1976). Extrapyramidal symptoms were assessed using the Dimascio Extrapyramidal Symptom rating scale and symptoms indicative of tardive dyskinesia were assessed using the Abnormal Involuntary Movement Scale (Guy, 1976). The negative symptoms of schizophrenia were assessed using the Brief Negative Symptom Scale (Dufresne et al., in preparation) and selected BPRS items. A variation of the Treatment Emergent Symptom Scale (Guy, 1976) was also included in the test battery to monitor for any adverse reactions to study medications. Each clinician assessed the same patient from study entry through termination.

Clinical laboratory tests were obtained on study subjects prior to baseline and at study termination. These included hematology, clinical chemistry, and urinalysis. Patients also received a thorough physical exam, electrocardiogram, and electroencephalogram prior to and at the termination of the study. Vital signs were taken on each rating day to assess for side effects such as orthostatic hypotension, hypertension, or tachycardia. These vital signs assessment included blood pressure

supine and standing, heart rate supine and standing, weight, temperature, and respiratory rate. Additional tests were ordered as necessary for proper clinical care of the study patients. Neurological side effects were assessed using the Abnormal Involuntary Movement Scale and the Dimascio Extrapyramidal Symptom rating scale at baseline, day 7, 14, 21, 28, 42,and 70 (Guy, 1976).

Analysis

Safety assessments were made at day 0, 7, 14, 21, 28, 42, 56, and 70 of study treatment. Safety assessments included an evaluation of vital signs, electrocardiogram, electroencephalogram, SMA-12, CBC with differential, and urinalysis as well as a complete physical exam. These tests were performed previous to and following the bupropion versus placebo phase. The assessments of therapeutic efficacy were analyzed using analysis of variance with repeated measures over time (Winer, 1971). Followup tests of simple effects or simple main effects were performed in cases of significant overall ANOVA's with the Tukey A procedure being employed to test for individual cell differences. Statistical evaluation of side effect assessments was made using the appropriate nonparametric techniques such as Wilcoxon sign test and Chi-square test of independence (Marascuilo and McSweeney, 1977, Downie and Starry, 1977).

This protocol has been approved by the Rhode Island Medical Center Institutional Review Board and the University of Rhode Island Institutional Review Board. Written informed consent was obtained from all subjects in accordance with federal regulations. A pregancy avoidance form was completed for every female who entered the study.

RESULTS

Efficacy

The bupropion and thiothixene combination was no more efficacious than the placebo and thiothixene combination. On many measures the control group was actually less symptomatic than the bupropion and thiothixene treatment group.

Analysis of variance with repeated measures was performed on all assessments for study periods ending at treatment day 28 and at day 70. All but one patient in each treatment group finished 28 days of study drug treatment; this was the minimal period of time a patient could remain in treatment and still be considered a completed study patient. Of the twenty-five patients who completed all ten weeks of the study, nine were being treated with bupropion and thiothixene while sixteen were those patients treated with placebo and thiothixene.

One of the difficulties in statistically analyzing results of clinical trials is that a patient is as likely to drop out of a study due to adverse reactions or lack of improvement while on a medication as they are if they respond so dramatically to treatment that they are discharged from the hospital. Although each group had only one dropout each at day 28, the patient dropout rate at day 70 was significantly higher in the bupropion and thiothixene group than in the placebo and thiothixene group (Chi-square = 5.729, df = 1, $p < .02$). Nine of the original nineteen patients completed ten weeks in the bupropion and thiothixene group while sixteen of the nineteen thiothixene and placebo treated patients completed ten weeks. Of the bupropion group, the ten subjects who did not complete 70 days of treatment were significantly more symptomatic on the BPRS at termination (Student's t = 2.29, p <

.05, df = 34) than the nine subjects who did complete the full 70 days. Patients who did not complete the full 70 days of bupropion therapy had a mean score of 52.4 (S.D. = 17.15) on the BPRS at termination and those who did complete treatment had a mean score of 33.3 (S.D. = 18.89). This would indicate that the patients who dropped prematurely from the bupropion group were more symptomatic than those who remained in treatment for the full 70 days, and that the significantly higher dropout rate was the result of deterioration rather than improvement. Analysis of change from baseline to termination of the bupropion and thiothixene group shows a mean improvement in those completing ten weeks of 6.44 (S.D. = 15.39), while those failing to complete ten weeks demonstrated a mean worsening of 3.30 points (S.D. = 16.19) on the BPRS. Statistical comparison of change from baseline on BPRS of the bupropion group patients fails to show a significant difference on Student's t-test (t = 1.34, N.S.). Thus, those patients who dropped out were more severely ill than those who did not, but deterioration during the study may not have been the main reason for this difference in psychiatric state.

Dose-Response Relationships

Neither dose of thiothioxene (r^2 = .03) or dose of bupropion (r^2 = .02) was significantly correlated with syptomatic change as measured by the Brief Psychiatric Rating Scale. The marked difference in dose of neuroleptic or antidepressant required to achieve therapeutic response in individual patients is well known, and neither dose of antipsychotic nor serum levels have ever shown a predictable dose response curve (Tang , 1985). Overall mean bupropion dose was 445.83

mg. per day (S.D. = 413.16) while that of the thiothixene was 21.58 mg. (S.D. = 16.23) per day.

Brief Psychiatric Rating Scale

In terms of psychotic features as measured on the Brief Psychiatric Rating Scale, bupropion and thiothixene treated patients (N= 18) and placebo and thiothixene treated patients (N=18) both demonstrated improvement over time ($F = 5.68$, $df = 4, 136$, $p < .0005$) with the control group again showing greater improvement ($F= 2.57$, $df = 4,136$, $p < .05$) over 28 days. Analysis of variance for patients completing ten weeks of treatment showed an overall improvement from baseline for both groups ($F = 9.34$, $df = 6, 138$, $p < .0001$) at each week post baseline (Tukey A followup test, $p<.01$). However, the thiothixene and placebo group (N=18) became significantly less symptomatic than the thiothixene and bupropion group (N=18) on study days 14, 21, and 28 for those patients completing four weeks on study drug (See tables I and II).

Five principal factors have been identified by principal factor analysis for the Brief Psychiatric Rating Scale (Guy, 1975). The content of these separate factors have been identified as representing the symptom complexes of anergia, anxiety and depression, thought disorder, hostility and suspiciousness, and activation. There were no significant changes between groups or over time on the hostility and suspiciousness or activation factors. Both groups showed significant ($F = 2.73$, $p < .05$, $df = 4,136$) improvement over time in terms of a decrease in thought disorder. While both groups demonstrated a decreased score on the anxiety-depression factor over time ($F = 12.16$, $p < .0001$, $df = 4,136$), the placebo and thiothixene control group

demonstrated significant improvement from baseline at all treatment ratings (Tukey A test, $p < .01$), whereas the bupropion group showed only a transient improvement from baseline at week three (Tukey A test, $p < .05$). On the anergia factor, the thiothixene and placebo group demonstrated a significant decrease from baseline at weeks one ($p < .05$) through four ($p < .01$) as tested using the Tukey A procedure (Winer, 1971). (See tables III through VI)

For the thought disorder factor on the Brief Psychiatric Rating Scale, there was a significant trend for improvement over time ($F = 2.73$, $df = 4,136$, $p < .05$) without a significant groups over time effect being present (See table VII). Significant improvement from baseline occurred at weeks one and two ($p < .01$) as well as week four ($p < .05$). Both groups revealed a lack of significant changes on the hostility-suspiciousness and the activation factors of the Brief Psychiatric Rating Scale upon analysis of variance.

Clinical Global Impressions

Overall psychiatric state as measured by the Clinical Global Impressions Scale improved significantly over time for patients completing four weeks ($F = 12.93$, $df = 4,136$, $p < .0001$) and for those completing all ten weeks ($F = 14.27$, $df = 6,138$, $p < .0001$). All mean weekly ratings showed significant improvement from baseline (Tukey A followup test, $p < .001$). There were no between group differences as measured with this assessment instrument (See tables VIII and IX).

Negative Symptoms and Depression

There were no differences in response to medication in terms of negative symptoms (tables X and XI). Both groups improved over time on these symptoms at four weeks ($F=4.88$, $p< .001$, $df = 4,136$) and at ten weeks ($F=5.53$, $p< .0001$, $df = 6,138$). The greatest improvement occurred at three weeks from baseline ($F = 17.89$, $p<.001$, $df = 1,136$), though both groups maintained improvement from baseline ($P<.05$) for the course of the study.

Depressive symptomotology as measured on the Hamilton Depression Scale was similarly effected by both treatments over four weeks. Both treatment and control groups got better over time ($F = 15.87$, $p < .0001$, $df = 4,136$) as compared to baseline (table XII) though there was no difference in efficacy between groups. All post baseline ratings were statistically significant from the baseline ratings though not different from each other. Patients remaining in the study for ten weeks (See table XIII) also improved significantly over time ($F = 17.46$, $df = 6, 138$, $p < .0001$), though there were no between group differences. Analysis of variance for all ten weeks using the last score forward method of handling of dropouts found that while both groups improved over time ($F = 13.29$, $df = 6, 216$, $p < .0001$), the placebo and thiothixene control group improved to a greater degree than the bupropion and thiothixene treatment group ($F= 4.51$, $df = 6,216$, $p < .0001$).

Safety

Experience with bupropion when used concomitantly with antipsychotic medication is rare; therefore this study is key to

investigating any possible interactive effects of using bupropion in combination with thiothixene. Previous clinical trials have prohibited the use of concomitant psychotropic medications with bupropion.

Analysis of clinical chemistry, hematology, and urinalysis data demonstrated no statistically or clinically significant differences between the control or treatment groups using repeated measures t-test (See table XIV). Analysis of the data using the Wilcoxon sign test found no differences between groups on physical exam, electroencephalogram, and electrocardiogram. Two patients with abnormal electrocardiograms who still qualified to enter the study both suffered from left anterior hemi-block conductance disorders; these patients had no difficulty tolerating treatment and showed no evidence of any new abnormalities. Three patients with mild diabetes mellitus and one with mild hypertension were managed without incident on the study and demonstrated no signs of worsening of their condition. One young male patient developed a petechia during the course of treatment with bupropion and thiothixene that subsided quickly after the withdrawal of bupropion. One middle aged female patient exhibited a mild transient case of hypertension and tachycardia after one month on bupropion and thiothixene that was likely linked to worsening in her psychiatric condition. There were no clinically significant alterations observed on electroencephalogram at the termination of study medication for any patient.

Data obtained on the Treatment Emergent Symptom Scale (Guy, 1976) was analyzed using the chi-square test of independence to determine if a difference in incidence of adverse effects was observed between groups. The data was analyzed with consideration of the frequency of reported

symptom per patient interview and examination for 28 days and for 70 days of study treatment (See table XV).

The bupropion and thiothixene treated patients reported more than twice the incidence of dry mouth (Chi-square of 5.81 and 4.69, df = 1, $p < .05$) and constipation (Chi-square of 4.67 and 9.6, df = 1, $p < .05$) than the placebo and thiothixene group at four and ten weeks. However a greater percentage of placebo and thiothixene treated patients reported an increase in appetite (Chi-squares of 3.10 and 6.95, $p < .10$ and $p < .01$ respectively), menstrual disturbance (Chi-square of 4.40, df =1, $p < .05$), and decreased sex drive (Chi-square of 2.85, $p < .10$) over both four and ten weeks.

Examination for neurological adverse reactions using the Abnormal Involuntary Movement Scale and Dimascio procedures (tables XVI, XVII, XVIII, XIX) yielded expected results. Little change occured in the symptoms of tardive dyskinesia over four weeks in both the treatment (n=18) and the control (n=18) groups and in those completing ten weeks of study treatment on bupropion and thiothixene (N=9) and placebo and thiothixene (N=16).

Acute extrapyramidal system disorders as measured on the DiMascio extrapyramidal symptom scale revealed that both groups demonstrated less extrapyramidal system movements over time for four weeks ($F = 6.33$, df = 4, 136, $p< .0001$) and for ten weeks ($F = 3.71$, df = 6, 138, $p < .01$). This is to be expected after an extended period of neuroleptic treatment. Tolerance to pseudoparkinson like extrapyramidal system disorders is known to occur with extended periods of neuroleptic treatment.

DISCUSSION

The lack of response to bupropion and thiothixene in comparison to placebo and thiothixene is consistent with the results of similar studies employing a tricyclic antidepressant and neuroleptic versus a placebo and neuroleptic. That is, the addition of an antidepressant to the therapeutic regimen offered no clear advantage (Becker, 1970 and 1976; Siris, 1978). In a trial comparing chlorpromazine and imipramine to the mood elevating antipsychotic thiothixene and placebo, Becker demonstrated that the treatment regimens gave similar good response on Hamilton Depression Scale, Brief Psychiatric Rating Scale, and the Katz Adjustment scale while the chlorpromazine and imipramine group experienced more sedative and cardiovascular side effects (Becker, 1976). In a study of 64 depressed schizophrenics this same investigator found a combination of amitriptyline and perphenazine to be no more efficacious than perphenazine and placebo with the suggestion that the amitriptyline may have interfered with the antipsychotic effect of the perphanazine (Becker, 1970). Brockington and collaborators demonsrated no positive effects of adding amitriptyline to a regimen of chlorprmazine in schizoaffective patients (Brockington et al.,1978), while Prusoff found a group of depressed schizophrenics showed improvement in depressive symptomotology with perphenazine and amitriptyline when compared to amitriptyline alone (Prussoff et al., 1978). However, three-quarters of those receiving combined therapy in Prussoff's study experienced an increase in blood pressure and in weight. In a review of the literature concerning the treatment of depressed schizophrenics Siris found that there were conflicting reports; some investigators reported an increase in positive

schizophrenic symptoms and some alleviation of depression with addition of tricyclic antidepressants or monoamine oxidase inhibitors while others reported no significant differences in efficacy (Siris, 1978). This study with the novel antidepressant bupropion shows a lack of benefit of the combination of bupropion and thiothixene to the mood elevating antipsychotic thiothixene alone.

In examining the result of a clinical pharmacology study, there are at least two key underlying issues to consider. First, in what way does all the knowledge that has been obtained in terms of a drugs pharmacological effects express itself in the data? What is consistent with previous studies with the agent and what is not? Secondly, in what way does what we know about the underlying mechanism and etiology of the disease interact with what we know about the drugs pharmacologic effects? In understanding these relationships we can better understand the implications of the findings and where they fit it in terms of clincal treatment for the disease and future research.

In terms of both the disease state of depression in schizophrenia and that of the mechanism of action of bupropion - or for that matter of any antidepressant - there are as many questions as answers. Past research into the clinical treatment of depression has been largely empirical, with deductions as to how an antidepressant is effecting the disease being inferred by what the treatment had in common with other effective treatments. Curious but also not suprising is the manner in which medicinal chemists have synthesized compounds structurally similar to prior compounds, with pharmacologists selecting the compounds for potential clincial trials based on their pharmacological similarity to agents previously found effective. This circular phenomenon has resulted

in many pharmacologically similar compounds that offer few new benefits to the treatment of psychosis or depression. The cycle is broken when a compound that does not possess a property previously thought integral to it being efficacious is nevertheless found to be clinically effective. For example, since effective antidepressants all had in common the abilty to increase synaptic NE or DA as did the MAOI's, the end effect of increasing the synaptic catecholamine levels was considered crucial to their mechanism of action for many years. This theory is still commonly cited as the mechanism of action in many pharmacology text books despite the fact that this effect is immediate while clincial response to antidepressants does not occur for at least two to three weeks.

Fortunately, the use of behavioral models of depression in animals has led to the development of novel antidepressant compounds that do not inhibit the reuptake or breakdown of serotonin or of norepinephrine (Shopsin et al., 1981). One such compound is bupropion. The question once more has become not if a compound works in depression but why does it work?

A review of the literature examining the results of clincal trials with bupropion in the treatment of major depressive syndrome reveal that the compound is significantly more effective than placebo (Zung, 1983) and is as effective as the positive control antidepressant amitriptyline (Chouinard, 1983). The medication has been found useful in all but a few clinical trials and has a side effect profile that rivals that of placebo with the exception of its ability to cause seizures in susceptible patients to the same degree as imipramine (Dufresne et al., 1984).

The existence of useful antidepressants such as bupropion that do not significantly block catecholamine reuptake has led to the formation of more inclusive theories as to the mechanism of action of antidepressants. The most recent theory that takes into account both the temporal relationship of neurochemical event and remission of depressive syptoms as well as the remarkable effectiveness of the so called "second generation" antidepressants is that of post synaptic beta receptor down regulation. Clinically effective compounds such as bupropion all seem to cause beta receptor subsensitivity at the same time that remission from depressive symptoms is found to occur (Gandolf et al, 1983; Sellinger-Barnette 1980) though this effect is disputed for bupropion (Ferris and Beaman, 1983). The two to three week period in which increased synaptic levels of norepinephrine are found with the TCA's or MAOI's readily explains their abilty to cause post synaptic beta receptor down regulation. In what manner could a drug such as bupropion, a drug pharmacologically disimilar to established antidepressants, create its therapeutic effect?

Bupropion does not inhibit type A or Type B monoamine oxidase, nor is it a potent blocker of NE or 5-HT reuptake (Ferris, R.M. et al., 1983; Dufresne et al., 1984). However, bupropion given before intracisternal injection of 6-hydroxydopamine prevented destruction of dopamine containing neurons via a dose related selective antagonism (Cooper et al., 1980). While studies conflict as to whether bupropion effects serum prolactin levels (Stern et al., 1979; Laakman, G., 1982), the electroencephalogram arousal effect of bupropion in rats is selectively blocked by the effective DA antagonist pimozide (Miller and Wheatley, 1978). Bupropion has a 100 fold less potent effect in

blocking dopamine reuptake into nerve endings of rat striatum than nomefensine. The speculation as to bupropions mechanism of action has therefore been focused on its small in vitro but apparently significant in vivo effect on dopaminergic transmission.

Recent findings indicate that bupropions mechanism of action is indeed dopaminergic in some manner. One clinical trial demonstrated an increase in serum homovanillic acid in depressed patients responding to bupropion (Golden et al., 1984), while another investigator has shown that bupropion may exert a DA facilitating effect by causing an increase in receptor affinty for DA, perhaps in the manner that benzodiazepines facilitate the binding of GABA to its receptor (Blitzer, 1985, personal communication). A previous clinical trial reported an alteration in perception with bupropion in some depressed patients in a manner similar to that seen with dopaminergic agonistic drugs such as L-DOPA or amantidine (Becker & Dufresne, 1982). The fact that many of these patients had been treated prior to the two week washout period at some time with dopamine antagonistic neuroleptic leads to an interesting speculation; could bupropion's small DA agonistic effect be amplified in these patients due to supersensitive DA receptors? Only two of those patients showing the altered perceptions showed any evidence of a coexiting psychotic component to their illness. Furthermore, a significant number of patients treated in this study showed signs of DA stimulation such as hand tremor and agitation (Dufresne et al., 1985). Nomefensine, an antidepressant that increases DA release as well as inhibiting NE reuptake in synapses resembles bupropion in that it is self-administered in rats and primates (Dufresne et al., 1984), has few anticholinergic and cardiovascular side effects, and has an energizing

stimulant effect in some patients (Shopsin et al., 1981). When compared with amitryptyline in a large double-blind trial bupropion treated patients reported more agitation and excitement, nauseau and vomiting, and decreased appetite than the positive control (Chouinard, 1983). All these effects could be related to a dopamine agonistic mechanism. An increase in dopaminergic transmission could account for post synaptic beta receptor down regulation.

Stepwise multiple regression was performed using the individual items of the Negative Symptom Scale as predictors with change from baseline on the Brief Psychiatric Rating Scale for both groups at day 28 (N = 18 for both groups) being the dependent variable. The single best predictor of nonresponse to treatment was the presence of emotional blunting. The presence of emotional blunting has been linked to enlargement of cerebral ventricles in schizophrenic patients (Andreasen, 1982). In this study, the presence of emotional blunting was an indicator of poor response to thiothixene treatment. Emotional blunting was negatively correlated ($r = -.51$) with improvement from baseline at four weeks and was the best predictor of thiothixene treatment nonresponse with a multiple R^2 of .2608 being observed ($F=5.65$, df = 1,18 , $p < .05$). No significant relationship between treatment nonresponse and emotional blunting was found in the bupropion and thiothixene treatment group patients. This finding is one more atypical difference in treatment response patterns between these groups that leads to speculation that bupropion interfered with thiothixene's mechanism of action in aleviating the anxiety and depression symptoms in these patients. Bupropions possible dopamine agonism worsened these symptoms in our sample of depressed schizophrenics whereas the drug

typically causes improvement in patients with major depressive syndrome.

The higher dropout rate of the placebo and thiothixene group at days 42 and 70 could lead one to suspect that improvement may have occured to a greater degree in this group partly due to their being able to tolerate a longer period of treatment with thiothixene than the bupropion and thiothixene group. This finding also suggests a dopamine agonistic effect of bupropion which interfered with the therapeutic effect of dopaminergic receptor blockade of the thiothixene in a subgroup of schizophrenics with a secondary depression. Primarily depressed patients should not, theoretically, be so effected. In fact, bupropion would reduce and not increase anxiety and depression in a patient suffering from a primarily depressive disorder.

The results of the current study supports the possibility that bupropion antagonized the therapeutic effect of thiothixene on some parameters. This would suggest that the effect of the mood elevating antipychotics in treating depressed shizophrenia is related to the unique effects that these drugs have in treating this syndrome. That is, bupropion causes an increase in dopaminergic transmission and subsequent beta receptor down regulation that may cause improvement in previously treatment resistant major depressive syndrome patients. Increasing the release of DA into the synapse or the binding affinity of DA to the receptor, as the case might be, would antagonize the therapeutic effect that the thiothixene is having on the symptoms of a syndrome that combines the symptomotology of major depressive syndrome and the schizophrenias but is characteristically neither in its neuropathology or in its response to pharmacologic intervention. Treating the depressive component of the disease as a separate entity

from the positive symptomotology of schizophrenia does not appear rational, as antidepressants do not impove the depressive symptoms and can exacerbate psychosis in many cases. Rather, viewing the syndrome as a disease which is distinct from major depressive syndrome and the schizophrenias, but which exhibits symptomatic components of each, offers a better structure in which to explore underlying pathology and possible treatments for this syndrome. Lack of any differences due to bupropion on the Abnormal Involuntary Movement Scale may suggest that bupropion's dopaminergic facilitating activity may be limited to mesolimbic but not striatonigral dopaminergic systems.

Since the addition of antidepressants to antipsychotics in these patients usually is ineffective, we may assume that this syndrome is more similar to the schizophrenias in etiology and pathology than the depressive spectrum disorders. A possible explanation for the effect that TCA's are found to have in a few studies may be related to the relief of antipsychotic induced akinetic symptoms due to the powerful anticholinergic effects of amitriptyline and pharmacologically similar antidepressants than relief of true depressive symptoms. Previous studies have shown the relief of akinetic syptoms in schizophrenics with pseudo-parkinsonism using anticholinergic medication that in some cases resembles the relief of many depressive symptoms (Van Putten and May, 1978). The results of a factor analytic study also suggests that the depressive symptoms of this syndrome is characteristically distinct from that of major depressive syndrome or schizophrenia (Becker, 1985). Avenues for future research should focus on controlled double-blind trials of single agents rather than combination therapies and further work to characterize this syndrome as a separate psychiatric disease

with a unique neuropathology requiring a unique pharmacotherapeutic strategy.

SUMMARY

Two groups of depressed schizophrenic patients were treated with either bupropion and thiothixene or placebo and thiothixene and assessed for efficacy and safety. On the Brief Psychiatric Rating Scale total scores, both groups improved over time at four and at ten weeks. However, the placebo and thiothixene group did better than the bupropion and thiothixene group over four weeks ($F=2.57$, $p < .05$), though not significantly so over ten weeks. On the Brief Psychiatric Rating Scale component scores for anxiety and depression, the placebo and thiothixene group improved over time to a greater degree than bupropion and thiothixene group. For the anergia component score, the placebo and thiothixene group improved significantly over time while the bupropion and thiothixene group did not. In regard to thought disorder, both groups improved over time to a similar degree. Neither group improved over time on the activation or the hostility and suspiciousness component scores.

On the Clinical Global Impression of severity of illness, both groups improved over time at four and ten weeks, but neither group did significantly better than the other. In regard to depressive symptomotology as measured on the Hamilton Depression Scale, both groups improved significantly over time with no between group differences for those patients completing both four and ten weeks. On the Negative Symptom Scale, both groups improved over time to a similar degree at both four and ten weeks.

A significantly greater number of patients (N=9) dropped out after four weeks of treatment in the bupropion and thiothixene group, while only two patients in the bupropion and thiothixene dropped out between

four and ten weeks of treatment with study medications. This unequal rate of premature study termination appeared to be the result of a worsening in psychiatric condition.

The use of bupropion in addition to thiothixene in the treatment of depressed schizophrenics appears to be unjustified and possibly contraindicated. The results and conclusions of this study is similar to most well controlled clinical trials in which an antidepressant medication is given in combination with an antipsychotic. This pharmacotherapeutic strategy is not recommended.

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Brief Psychiatric Rating Scale
Four Weeks

Treatment Period	Bupropion & Thiothixene N=18		Placebo & Thiothixene N=18	
	Mean	S.D.	Mean	S.D.
Baseline	44.4	11.6	45.3	9.0
Day 7	38.1	16.3	36.4	11.8
Day 14	40.8	14.9	35.8	10.5
Day 21	41.0	19.7	35.3	11.4
Day 28	42.5	17.7	31.9	10.9

Table 1. Average scores for patients remaining for four weeks on drug for the Brief Psychiatric Rating Scale. Totals above thirty on this scale represents a moderate level of psychotic symptoms, above forty-five represents pronounced psychotic symptomotology, and a total greater than sixty represents very severe psychopathology. Placebo and thiothixene group improved significantly over time while the bupropion only group did not. The placebo and thiothixene group demonstrated less symptomotology ($p < .05$) than the bupropion and thiothixene group at day 14, 21, and 28.

Brief Psychiatric Rating Scale
Ten Weeks

Treatment Period	Bupropion & Thiothixene N = 9		Placebo & Thiothixene N = 16	
	MEAN	S.D.	MEAN	S.D.
BASELINE	39.7	8.9	46.6	8.8
DAY 7	34.4	13.7	37.4	11.9
DAY 14	34.7	12.4	36.0	11.1
DAY 21	29.7	10.5	35.4	12.1
DAY 28	32.6	11.6	32.1	11.4
DAY 42	30.9	11.3	33.4	11.8
DAY 70	33.2	16.4	29.5	8.8

TABLE II. Brief Psychiatric Rating Scale total scores for those patients completing ten weeks of study treatment. Both groups improved from baseline ($p < .001$) while there was a trend for the placebo and thiothixene group to have improved to a greater degree ($p < .10$) over time . Significantly more patients dropped out of the bupropion and thiothixene group than the placebo and thiothixene group.

Anergia Factor Score

Treatment Period	Bupropion & Thiothixene N = 18 MEAN	S.D.	Placebo & Thiothixene N = 18 MEAN	S.D.
BASELINE	12.5	4.1	12.9	3.8
DAY 7	10.3	5.3	10.1	4.6
DAY 14	10.8	4.6	9.2	4.7
DAY 21	10.4	5.9	8.6	4.9
DAY 28	11.4	5.4	7.9	4.3

TABLE III. Anergia factor score for the Brief Psychiatric scale. The patients in the thiothixene and placebo group improved significantly ($p < .05$) from baseline while the bupropion group did not.

Anxiety and Depression Factor

Treatment Period	Bupropion & Thiothixene N = 18		Placebo & Thiothixene N = 18	
	MEAN	S.D.	MEAN	S.D.
BASELINE	12.4	3.2	13.6	2.9
DAY 7	10.6	5.0	9.9	3.9
DAY 14	11.3	5.5	9.7	3.4
DAY 21	9.8	5.1	9.1	3.5
DAY 28	10.8	5.0	8.0	3.7

TABLE IV. Bupropion and thiothixene group improved from baseline at week 3 only ($p < .05$) while placebo and thiothixene group showed significant improvement on anxiety and depression Brief Psychiatric Rating Scale factor score from baseline at week one and thereafter ($p < .01$).

BPRS Hostility and
Suspiciousness Factor Score

Treatment Period	Bupropion & Thiothixene N = 18		Placebo & Thiothixene N = 18	
	Mean	S.D.	Mean	S.D.
BASELINE	5.2	2.5	5.2	2.3
DAY 7	4.9	2.8	5.1	2.6
DAY 14	5.4	3.2	4.7	2.0
DAY 21	6.3	4.8	4.8	2.9
DAY 28	6.8	4.3	4.7	2.4

TABLE V. Hostility and suspiciousness factor score for the Brief Psychiatric Rating Scale for patients completing four weeks. There were no significant differences between groups or over time.

Activation Factor Score

Treatment Period	Bupropion & Thiothixene N = 18		Placebo & Thiothixene N= 18	
	MEAN	S.D.	MEAN	S.D.
BASELINE	5.8	3.3	5.9	2.7
DAY 7	5.3	2.8	5.2	2.4
DAY 14	5.7	2.9	5.6	2.5
DAY 21	5.9	3.4	6.1	3.0
DAY 28	5.4	3.3	5.3	2.2

TABLE VI. Brief Psychiatric Rating Scale activation factor score. There were no significant differences between groups or over time.

Thought Disorder Factor Score

Treatment Period	Bupropion & Thiothixene N = 18		Placebo & Thiothixene N = 18	
	Mean	S.D.	Mean	S.D.
BASELINE	8.3	3.8	8.0	3.3
DAY 7	7.2	3.4	6.4	2.6
DAY 14	7.3	3.3	6.3	2.5
DAY 21	7.5	3.7	7.2	2.9
DAY 28	7.9	3.8	6.2	2.3

TABLE VII. The thought disorder factor score of the Brief Psychiatric Rating Scale for patients completing four weeks. There were no between group differences. Both groups demontrated a decrease in thought disorder as compared from baseline that was statistically significant ($p < .05$) at days seven, fourteen, and twenty-eight.

Clinical Global Impressions

Treatment Period	Bupropion & Thiothixene N = 18		Placebo & Thiothixene N = 18	
	Mean	S.D.	Mean	S.D.
BASELINE	4.7	1.0	4.7	.67
DAY 7	4.1	1.6	4.1	.96
DAY 14	4.2	1.3	4.0	1.0
DAY 21	3.9	1.5	3.6	1.1
DAY 28	3.9	1.5	3.6	1.1

TABLE VIII. Clinical Global Impressions Severity of illness rating for patients completing four weeks of treatment. A rating of one represents absence of psychopathology. Ratings of three represents mild psychiatric illness, of four moderate illness, and of six severe psychiatric dysfunction. A rating of seven is reserved for the most extremely ill patient. Both groups show improvement ($F=12.93$, $df = 4,136$, $P < .0001$) over time. There were no between group differences.

Clinical Global Impressions

Treatment Period	Bupropion & Thiothixene N = 9		Placebo & Thiothixene N = 16	
	Mean	S.D.	Mean	S.D.
BASELINE	4.5	1.2	4.8	.66
DAY 7	3.8	1.6	4.3	.86
DAY 14	3.9	1.4	4.0	1.1
DAY 21	3.4	1.3	3.6	1.2
DAY 28	3.3	1.3	3.7	1.1
DAY 42	3.4	1.3	3.6	1.2
DAY 70	3.6	1.4	3.2	1.0

TABLE IX. Clinical Global Impressions severity of illness rating for patients completing ten weeks of treatment. Both groups show improvement over time. There are no between group differences.

Negative Symptom Scale
Four Weeks

Treatment Period	Bupropion & Thiothixene N=18		Placebo & Thiothixene N=18	
	Mean	S.D.	Mean	S.D.
Baseline	7.0	3.5	6.75	4.67
Day 7	3.93	3.82	5.62	4.86
Day 14	5.6	4.48	4.62	4.04
Day 21	3.66	4.15	4.06	4.42
Day 28	5.06	5.09	4.38	4.66

Table X. Lack of significant changes on the Negative Symptom Scale for patients completing four weeks of study treatment. Total scores of between five and ten can be interpreted as moderate levels of the negative symptoms of schizophrenia, while above ten represents pronounced negative symptomotology.

Negative Symptom Scale
Ten Weeks

Treatment Period	Bupropion & Thiothixene N = 9		Placebo & Thiothixene N = 16	
	MEAN	S.D.	MEAN	S.D.
BASELINE	5.6	3.0	7.4	4.7
DAY 7	3.6	3.3	6.1	5.0
DAY 14	4.4	4.2	4.4	3.8
DAY 21	2.7	2.1	4.3	4.7
DAY 28	3.7	2.8	4.6	4.8
DAY 42	3.2	2.8	4.2	4.4
DAY 70	2.4	2.2	3.7	4.0

TABLE XI. Both groups improved significantly over time ($p < .001$) while there were no between group differences.

Hamilton Depression Scale
Four Weeks

Treatment Period	Bupropion & Thiothixene N=18		Placebo & Thiothixene N=18	
	Mean	S.D.	Mean	S.D.
BASELINE	28.9	10.3	32.0	8.16
DAY 7	20.1	15.4	19.4	11.1
DAY 14	22.2	14.7	19.2	11.9
DAY 21	18.9	15.4	17.9	12.6
DAY 28	22.7	16.3	16.0	13.9

TABLE XII. Hamilton depression scale means for patients finishing four weeks. Total ratings above eighteen are considered to represent moderate depressive symptomotology, while total scores greater than thirty represent severe depressive psychopathology. There were no significant differences between bupropion and thiothixene versus the placebo and thiothixene groups over time. Both groups improved significantly over time ($F=15.87$, $p< .0001$) for all post baseline ratings.

Hamilton Depression Scale
Ten Weeks

Treatment Period	Bupropion & Thiothixene N=9		Placebo & Thiothixene N=16	
	MEAN	S.D.	MEAN	S.D.
BASELINE	23.9	6.6	31.8	8.6
DAY 7	15.7	11.7	19.4	11.6
DAY 14	15.4	12.0	17.8	11.9
DAY 21	12.0	12.6	16.2	12.0
DAY 28	14.7	12.4	14.8	13.8
DAY 42	12.0	11.1	14.4	12.5
DAY 70	13.1	16.5	10.7	11.3

TABLE XIII. For study patients completing ten weeks, both groups demonstrated improvement ($P < .01$) on the Hamilton Depression Scale.

TABLE XIV.
Clinical Laboratory Data

	Bupropion & Thiothixene N=18				Placebo & Thiothixene N=18			
	Baseline		Termination		Baseline		Termination	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
HEMATOLOGY								
Hemaglobin	15.1	1.3	14.57	1.5	15.3	1.2	14.8	1.2
Hematocrit	44.8	3.9	44.5	3.4	45.1	3.4	43.9	3.7
RBC x 10^{6}	5.0	.38	5.0	.49	5.0	.41	4.89	.44
Platlet Estimate	All WNL		All WNL		All WNL		All WNL	
Total WBC x 10^{3}	8.3	2.8	7.6	2.0	7.9	2.5	7.4	2.6
Differential								
Neutrophils (41-77% WNL)	65.9	7.4	63.0	9.6	64.3	10.5	61.56	7.0
Lymphocytes (22-44% WNL)	26.8	8.4	30.5	8.4	27.6	8.3	29.5	8.7
Monocytes (3-6% WNL)	3.8	3.2	4.7	2.4	5.11	3.4	5.12	3.1
Eosinophils (0-2.7% WNL)	2.8	2.3	1.5	1.5	2.11	2.1	3.00	2.7

TABLE XIV. (CONTINUED)
URINALYSIS

	Bupropion & Thiothixene N=18				Placebo & Thiothixene N=18			
	Baseline		Termination		Baseline		Termination	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Specific Gravity (1.009-1.026 WNL)	1.018	.007	1.021	.009	1.016	.005	1.017	.005
Acetone	0		0		0		0	
Protein (no. of positives)	0		0		0		1	
Glucose	0		0		0		0	
WBC	0		0		0		0	
RBC	0		1		0		0	

Table XIV. There were no significant differences between groups for clinical laboratory tests of hematology, blood chemistry, or urinalysis.

TABLE XV.
TREATMENT EMERGENT SYMPTOM SCALE
BUPROPION & THIOTHIXENE

ADVERSE REACTIONS (Percent Reporting)	BASELINE	FOUR WEEKS	TEN WEEKS
Hallucinations	15.79	6.67	8.74
Euphoria	5.26	2.67	1.94
Agitation	10.53	16.00	16.50
Irresponsible Behavior	5.26	6.67	5.83
Aggression	0.00	4.00	3.88
Insomnia	36.84	18.67	15.53
Tiredness	36.84	18.67	15.59
Drowsiness	10.53	4.00	5.83
Decreased Appetite	5.26	8.00	9.71
Increased Appetite	5.26	0.00	0.00
Headache	0.00	4.00	3.88
Myoclonus	0.00	0.00	0.00
Cramps	0.00	2.67	2.91
Rigidity	26.32	9.33	6.80
Tremor	31.58	18.67	17.48
Dystonia	0.00	0.00	1.94
Akathesia	15.79	9.33	7.77
Parasthesia	0.00	0.00	0.00
Tinnitus	5.26	0.00	0.00
Vertigo	5.26	2.67	1.94
Joint Pain	0.00	0.00	0.00
Muscle Pain	5.26	5.33	3.88
Menstrual Disturbance	0.00	0.00	0.00
Blurred Vision	21.05	13.33	12.62
Dry Mouth	21.05	28.00	27.18
Increased Salivation	0.00	0.00	0.00
Constipation	15.79	9.33	9.71
Diarrhea	5.26	0.00	0.00
Urinary Retention	0.00	0.00	0.00
Nocturia	0.00	1.33	0.97
Sweating	0.00	0.00	0.00
Nauseau/Vomiting	0.00	6.67	6.80
Impotence	5.26	1.33	0.97
Fainting/Dizziness	0.00	2.67	2.91
Palpitations	0.00	0.00	0.00
Peripheral Edema	0.00	0.00	0.00
Cold Extremities	0.00	0.00	0.00
Skin Lesion/Rash	0.00	1.33	0.97
Membrane Lesions	0.00	0.00	0.00
Alopecia	0.00	0.00	0.00
Hirsutism	0.00	0.00	0.00

TABLE XV. (Continued)
TREATMENT EMERGENT SYMPTOM SCALE
BUPROPION & PLACEBO

ADVERSE REACTIONS (Percent Reporting)	BASELINE	FOUR WEEKS	TEN WEEKS
Hallucinations	15.79	10.81	9.76
Euphoria	5.26	1.35	1.63
Agitation	10.53	9.46	6.50
Irresponsible Behavior	5.26	5.41	3.25
Aggression	0.00	1.35	.81
Insomnia	36.84	24.32	23.58
Tiredness	36.84	16.22	17.07
Drowsiness	10.53	1.35	3.25
Decreased Appetite	10.53	4.05	4.88
Increased Appetite	10.53	4.05	6.50
Headache	10.53	6.76	4.88
Myoclonus	0.00	0.00	0.00
Cramps	5.26	1.35	0.81
Rigidity	21.05	12.16	12.20
Tremor	5.26	21.62	20.33
Dystonia	5.26	2.70	1.63
Akathesia	21.05	12.16	9.76
Parasthesia	0.00	1.35	0.81
Tinnitus	0.00	0.00	0.00
Vertigo	0.00	0.00	0.81
Joint Pain	5.25	12.16	10.57
Muscle Pain	5.26	16.22	13.01
Menstrual Disturbance	0.00	6.76	4.88
Blurred Vision	15.79	8.11	8.94
Dry Mouth	10.53	12.16	15.45
Increased Salivation	0.00	1.35	0.81
Constipation	5.26	1.35	0.81
Diarrhea	0.00	0.00	0.00
Urinary Retention	0.00	0.00	0.81
Nocturia	0.00	1.35	1.63
Sweating	0.00	0.00	0.00
Nauseau/Vomiting	5.26	5.41	4.07
Impotence	5.26	6.76	4.88
Fainting/Dizziness	0.00	4.05	4.88
Palpitations	0.00	0.00	0.00
Peripheral Edema	0.00	0.00	0.00
Cold Extremities	0.00	0.00	0.00
Skin Lesion/Rash	10.53	2.70	6.50
Membrane Lesions	0.00	0.00	0.00
Alopecia	0.00	0.00	0.00
Hirsutism	0.00	1.35	0.81

Abnormal Involuntary Movement Scale

Treatment Period	Bupropion & Thiothixene N=18		Bupropion & Placebo N=18	
	Mean	S.D.	Mean	S.D.
Baseline	3.0	5.8	1.33	2.42
Day 7	2.1	4.1	1.61	2.35
Day 14	2.5	5.8	1.94	3.28
Day 21	2.8	5.7	2.61	3.34
Day 28	2.9	5.6	1.61	2.54

Table XVI. No significant differences over four weeks on symptoms of tardive dyskinesia.

Abnormal Involuntary Movement Scale
Ten Weeks

Treatment Period	Bupropion & Thiothixene N=9		Placebo & Thiothixene N=16	
	MEAN	S.D.	MEAN	S.D.
BASELINE	3.5	6.2	1.5	2.5
DAY 7	2.6	5.4	1.8	2.4
DAY 14	4.1	7.5	2.2	3.4
DAY 21	3.8	7.5	2.9	3.4
DAY 28	3.3	7.0	1.8	2.6
DAY 42	3.5	7.0	2.8	3.7
DAY 70	3.3	7.5	2.4	3.4

TABLE XVII. No effects were demonstrated on tardive dyskinesia symptoms for those patients completing ten weeks of study treatment.

DiMascio Extrapyramidal Symptom Scale

Treatment Period	Bupropion & Thiothixene		Placebo & Thiothixene	
	Mean	S.D.	Mean	S.D.
Baseline	3.72	2.9	3.44	3.3
Day 7	2.39	2.8	2.22	1.6
Day 14	2.33	3.1	1.61	1.2
Day 21	2.22	3.1	2.22	2.2
Day 28	1.83	2.9	2.17	2.9

Table XVIII. Improvement on EPS for both groups over treatment period ($F=6.33$, $p<.0001$). There was no significant difference in EPS symptoms between groups for those patients completing four weeks.

Dimascio Extrapyramidal System
Disorder Scale
Ten Weeks

Treatment Period	Bupropion & Thiothixene N=9		Placebo & Thiothixene N=16	
	MEAN	S.D.	MEAN	S.D.
BASELINE	2.4	2.1	3.4	3.3
DAY 7	1.3	0.9	2.3	1.7
DAY 14	1.4	1.2	1.6	1.3
DAY 21	1.3	1.8	2.2	2.1
DAY 28	0.9	0.7	2.4	3.0
DAY 42	0.9	0.7	2.5	2.5
DAY 70	0.9	1.6	1.4	1.7

TABLE XIX. Both groups demonstrated a decrease in extrapyramidal system symptoms over time for those patients completing ten weeks.