# SAFETY AND EFFICACY OF BUSPIRONE IN THE TREATMENT OF ALCOHOL DEPENDENCE

by

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*A thesis submitted to the Faculty of Graduate Studies and Research*

*in partial fulfillment of the requirements*

*for the degree of*

*Master of Science*

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"We shall be better and braver and less helpless if we think we ought to inquire, than we should have been if we indulged in the idle fancy that there was no knowledge and no use in seeking to know what we do not know."

Plato 427-347 B.C.

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## FOREWORD

Research on alcohol, a substance that has been historically both, a joy and a curse of humanity, is perceived as an urgent task from sociological and medical points of view. While an addicted smoker acts basically on his own health, an alcoholic affects not only himself, but also his family as well as his environment. Steps are being taken to diminish alcohol abuse by various preventive measures including public education and regulatory controls. However it is generally realized that to affect a major change in drinking habits, we have to better understand biological mechanisms underlying alcoholism and its treatment.

When I began my work in psychiatry, I was fortunate to become a member of Dr. Dongier's team at the Research Center of the Douglas Hospital. What attracted me was Professor Dongier's polyvalent approach to alcoholism: in other words a constant search for causation and treatment of different aspects of alcoholism. My research project consisted of a study of the effects of a new group of pharmacological agents in primary alcoholics.

Evaluation of drug effects appears to acquire an ever increasing significance in treatment modalities. A large number of new compounds has been isolated by pharmaceutical industry; also, our understanding of the mode of action of these drugs has improved due to progress made in molecular biology. Perhaps because of this new knowledge the word " research " acquired a true meaning: to " re-search " and challenge the old concepts. In the current study I have aimed to achieve three objectives: to review the pertinent literature; to analyze the data obtained in the course of this study and to explore the avenues for further research. The fact that I have practiced previously as an Internist, dealing with chronically ill patients, proved to be very helpful in my work.

During these studies I was constantly supervised and advised by Dr. Dongier. In course of many discussions he conveyed to me his approach to research on alcoholism as well as the principles of medical research in general; from the view point of learning experience, I consider the past three years to be the most fruitful of my life. I have also acquired further knowledge in biostatistics and epidemiology by attending courses and seminars at McGill University. As a student representative on the Council of the Faculty of Graduate Studies and Research, I become acquainted with the breadth and scope of research carried at McGill.

Other members of the Department of Psychiatry, including Dr. John Pecknold, Dr. Ante Padjen and Dr. Ng Ying-Kin were very helpful with advice in the course of my studies. Dr. Trevor Dennis, Director of the Graduate Program in Psychiatry was very helpful in various tasks related to registration in courses and plan of studies. My husband, Dr. T. S. Malec helped me greatly in statistical problems, which were beyond the ordinary analysis of the data obtained. During my tenure at the Douglas Hospital Research Centre I had opportunity to work with other members of Dr. Dongier's team: Mrs. Lucie Legault, Mrs. Diane Brisson and Ms. Marketa Fuchs, who were very helpful. Several McGill professors, because of their experience in alcohol research have gladly shared their knowledge; this includes Dr. S. C. Skoryna, Director of Gastro-Intestinal Research Laboratory and Dr. D. Waldron-Edward of the Department of Biochemistry; Mrs. Jean Cornellier, Executive Assistant, was kind enough to carry out the difficult task of editing and typing the thesis.

Perhaps I should conclude this forward with the quotation from the book of Motteaux on the " Life of Rabelais " - *" He (she) that has patience may compass anything ".*

ELIZABETH ANNA MALEC, M.D.

Montreal, March 14, 1994.

## ABSTRACT

The evaluation of drug effects acquires an increasing significance in psychiatric research due to the number of new compounds as well as the need for safety screening for side effects. The present study reports the results of the investigation of effects of buspirone in 57 primary chronic alcoholics, using a double blind method with a placebo control group. Buspirone was administered in doses of 20 mg/day after a two-week wash-out period during which patients in both groups received placebo capsules. After a further two weeks of the study, the buspirone dose was increased to 40 mg/day until completion of the investigation after twelve weeks. Five out of 36 subjects, who completed the study, became abstinent. Detailed characteristics of the study group were obtained, including socio-demographic data, alcohol consumption, Michigan Alcoholism Screening Test (MAST), Alcohol-Use-Inventory (AUI), Drinking Behavior Interview (DBI), and psychometric assessment: Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAM-A) and Hopkins Symptoms Checklist 90 - Revised (SCL-90-R). Statistical analysis of the results was carried out using multivariate analysis of covariance on repeated measures. The HAM-A scale results were improved significantly in patients receiving buspirone. Marked improvement was also observed in Interpersonal Sensitivity Scale (a subscale of SCL-90-R). MENTALIM subscale of AUI demonstrated a statistically significant improvement in the buspirone group, when compared to patients receiving placebo. The validity of self reports on alcohol consumption by patient was confirmed by a change in liver enzyme levels: Gamma-Glutamyl Transpeptidase (GGT), Alanine Aminotransferase (ALAT) and the results of the Edwards Hardship Scale. The scores on HAM-A and MADRS scales were higher among the drop-outs than in those who completed the study. The side effects of buspirone were minimal and a good tolerance of the drug was observed.

## List of Abbreviations:

ALAT - Alanine Aminotranferase

AUI - Alcohol Use Inventory

DBI - Drinking Behavior Interview

GGT - Gamma-Glutamyl Transpeptidase

HAM-A - Hamilton Anxiety Scale

MADRS - Montgomery-Asberg Depression Rating Scale

MAST - Michigan Alcoholism Screening Test

SCL-90-R - Hopkins Symptoms Checklist 90 - Revised

## RÉSUMÉ

L'évaluation des effets des produits pharmaceutiques prend une importance accrue en recherche psychiatrique. Cela est dû au nombre de nouveaux composés chimiques ainsi qu'au besoin d'une sélection sécuritaire pour tenir compte des effets secondaires. La présente étude fait état des résultats d'une recherche sur les effets résultant de l'utilisation du buspirone chez un groupe de 57 patients alcooliques chroniques primaires, étude parallèle à double insu, contrôlée par placebo. Le buspirone à été administré à la dose de 20 mg/jour après une "période de lavage" d'une durée de deux semaines durant lesquelles les patients des deux groupes ont reçu des capsules placebo. Après deux semaines additionnelles, la dose de buspirone fut portée à 40 mg/jour jusqu'à la fin de l'étude au terme de douze (12) semaines. Cinq des 36 patients qui participèrent entièrement à l'étude sont devenus abstinents Les caractéristiques du groupe ayant fait l'objet de l'étude sont détaillées et comprennent des données socio-démographiques, la consommation d'alcool, Le test de dépistge de l'alcoolisme du Michigan (MAST), le bilan d'usage de l'alcool (AUI), l'inventaire du comportement vis-à-vis de l'alcool (DBI) ainsi que des évaluations psychometriques l'échelle de depression de Montgomery-Asberg (MADRS), l'échelle d'anxiete de Hamilton (HAM-A) et le "Symptoms Checklist-90-R" (SCL-90-R). L'analyse statistique des résultats a été effectuée en utilisant l'analyse de covariance à plusieurs variables basée sur des mesures répétées. Les résultats selon l'échelle HAM-A ont dénoté une amélioration significative chez les patients ayant été traités avec le buspirone. Une amélioration importante a également été observée selon l'échelle de sensibilité interpersonnelle (une sous-échelle de SCL-90-R). Les sous-échelle MENTALIM de l'AUI dénote une amélioration statistiquement significative au sein du groupe traité par buspirone. La valeur des rapports par les patients eux-mêmes quant à leur consommation d'alcool à été confirmée par une diminution du niveau des enzymes hépatiques la gamma glutamyl transpeptidase (GGT), l'alanine aminotransferase

(ALAT) et par les résultats de l'échelle d'Edwards (Edwards Hardship Scale). Les résultats sur les échelles de HAM-A et MADRS sont plus élevés parmi les patients ayant abandonnés plutôt que chez ceux qui ont participé à l'étude au complet. Les effets secondaires du buspirone ont été minimes et l'on a observé une bonne tolérance au produit.

# I. INTRODUCTION

Alcohol abuse or dependence has been recorded as the most frequent psychiatric disorder in adult males in the United States (Myers et al 1984): 8.2 to 10.4% of the population is affected. Death cases related to alcohol abuse rank third as a cause of death, after cancer and heart disease. The rate of successful suicide is considerably higher when compared to non-alcoholics (Kessel and Grossman 1961). Fifty percent of admissions to psychiatric hospitals are due to alcoholism or to problems in which alcohol abuse is a participating disorder.

In spite of the high frequency of alcohol-related disabilities in the world, the rehabilitation of alcoholic patients has received little attention. These problems are frequently ignored as something that cannot be helped. For example, in 1988, the U.S. Supreme Court ruled that alcoholism is a "willful misconduct". Only a small percentage of patients, approximately 15%, receive assistance from general practitioners and other health professionals to overcome the drinking problem (Saxe et al 1985). Results of outcome studies vary; the relapse rates into alcoholism are estimated between 50% within a year and 75% within four years. Of the remaining 25% of alcoholics who are considered "abstinent" or improved, only about 5% are above the level of "natural history" of alcoholism; the remaining 20% would stop drinking without any formal assistance such as professional help or Alcoholic Anonymous (Miller and Hester 1986).

These facts justify a constant search for new pharmacological agents to affect craving, protracted withdrawal symptoms, and other psycho-pathological components of alcoholism. A combination of pharmacological and psycho-social approaches in the treatment of alcoholics presents a challenging task for clinical research in the next decade.

## II. TOWARD PHARMACOTHERAPY OF ALCOHOL DEPENDENCE

Alcoholism appears to be a multifactorial disorder, including the effects of environmental factors which interact with biological mechanisms of behavior such as genetically transmitted susceptibility (Dongier 1993).

According to DSM-III-R classification, two types of drinking problems can be recognized: alcohol abuse and alcohol dependence. According to the Institute of Medicine, alcohol abuse is defined as a heterogeneous set of behavioral characteristics affecting psychological and social function as well as health (Institute of Medicine, 1987). The dependence on alcohol is related to three parameters: loss of control of consumption, withdrawal symptoms and tolerance as a state of adaptation .

In reference to neurochemical processes in the central nervous system, the existence of hypothetical ethanol receptor site has been suggested, as a part of the GABA-BDZ receptor complex. Nonetheless, researchers have been unable to identify a specific receptor on which alcohol exerts its effects. According to Tabakoff and Hoffman (1991), complex interactions between neurotransmitters, neuropeptides and hormones take place resulting in dysregulation of alcohol intake.

The treatment of alcohol dependence constitutes a formidable scientific and medical challenge. With reference to treatment options, four neurotransmitter systems are currently being studied: GABA-ergic, opiatergic, serotonergic and dopaminergic.

The results of treatment using drugs which affect the GABA-ergic system are contradictory (Yu and Ho 1990). However, Lhuintre et al (1990) have shown that acamprosate (a structural analog of GABA) prolongs the duration of abstinence in weaned alcoholics and reduces the number of dropouts.

Opiatergic system mediates the effects of alcohol intake on opiate-receptor activity. Levels of endorphins in acute and chronic alcohol abuse increase significantly (Borg 1982). In non-alcoholics with a positive family history and low levels of plasma endorphins, these increase after administration of alcohol (Gianoulakis 1982). An opiate antagonist, naltrexone, has been recently shown to decrease the rate of relapse in rehabilitated subjects to the extent of 50% reduction ( Volpicelli et al 1990) .

The serotonergic system, which is the subject of our study is probably involved in the regulation of drinking patterns. According to Tollefson (1989), acute alcohol consumption produces a rise in serotonin levels in the central nervous system; in chronic alcoholics, the serotonin level is decreased. The serotonin re-uptake inhibitors (SSRI) affect transiently alcohol intake by decreasing the number of drinks on drinking days (Naranjo et al 1987). Buspirone, a partial 5-HT1A agonist, has been shown in an initial study to reduce craving, anxiety and depression in primary alcoholics (Bruno 1989). Positive findings have been reported in the treatment of anxious alcoholics (Tollefson 1992, Kranzler et al 1994). On the other hand, some antagonists of 5-HT3 receptors such as ondansetron have been found to reduce intake of alcohol, more pronounced in heavy drinkers (Sellers et al 1991). Recent preliminary study with 5-HT2 antagonist, ritanserin, by Monti and Altervin (1991) has shown that in alcoholics this drug decreases the compulsion to drink.

The ability of ethanol to alter the brain dopaminergic activity has been extensively studied. According to Wise and Rompre (1989), the mesocephalic dopaminergic reward system plays a role in reinforcing ability of many drugs of abuse including ethanol. With respect to dopaminergic activity, alcohol exhibits a diphasic action: low, acute doses enhance dopaminergic action, while chronic administration decreases it and causes desensitization of dopaminergic

receptors (Hunt and Majchrowicz 1983). Controlled studies using bromocriptine an agonists of postsynaptic receptors, showed significant improvement in alcohol consumption (Borg 1983) and various psychopathological parameters of alcoholic patients (Dongier et al 1991).

## III. REVIEW OF LITERATURE

### 1. Historical notes on development of Azaspirones.

Until recently, benzodiazepines were the most widely used drugs in the treatment of anxiety. It has been estimated that approximately 20 such pharmacological agents are available to patients suffering from Generalized Anxiety Disorder (GAD). Nevertheless, several investigators have shown that benzodiazepines produce frequently undesirable side effects such as drowsiness, a decrease in concentration and a psychomotor impairment (Gershon 1982, Lader 1982, Newton et al 1982). It was also observed that benzodiazepines have a potential to create dependency and abuse, as well as withdrawal symptoms upon discontinuation of the treatment (Fontaine et al 1984, Murphy et al 1989). A lethal overdose when combined with alcohol or barbiturates was also reported (Baldessarini 1990).

According to Robins (1984) in the United States, approximately 3.8% of the general population suffers from Generalized Anxiety Disorder. It would therefore be desirable to develop drugs with lesser side effects but at least equal anxiolytic action.

Eison (1990) reviewed the early history of a new class of drugs, the azaspirones, which appear to suit, almost ideally, this purpose. Four compounds of this group were synthesized in 1968, 1979, 1980 and 1983 respectively: buspirone, gepirone, ipsapirone and tandospirone (Eison 1990) The chemical structures of these drugs are shown in Figure 1.

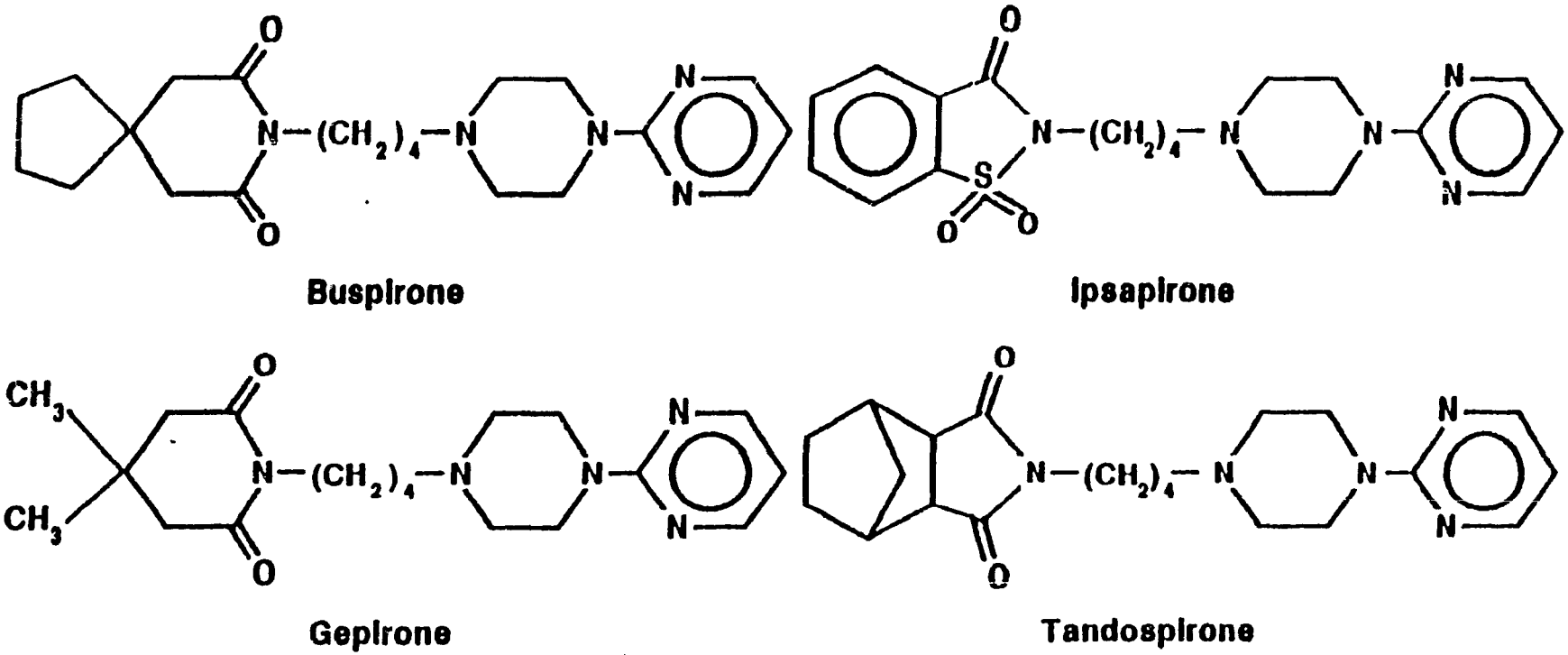



**Figure 1:** Chemical structure of buspirone, gepirone, ipsapirone and tandospirone [after Eison A.S., J. Clin. Psychopharmacol.10, p.35, 1990].

## 2. Aspects of behavioral action of buspirone.

Preclinical behavioral studies in laboratory animals played a significant role in predicting the efficacy and safety of buspirone. Research on the behavioral effects of the buspirone as a potential anxiolytic has focused on its effects on punished or conflict behavior. The indication of anxiolytic activity of buspirone was derived from the study in which taming of aggressive rhesus monkeys was observed following buspirone administration (Tompkins et al 1980). Riblet in 1982 demonstrated that buspirone inhibited the foot-shock induced fighting in mice. Buspirone attenuated the shock-induced suppression of drinking in Vogel's test. This effect was comparable to that of benzodiazepines (Riblet 1982, Eison 1986). An anticonflict effect of buspirone was also observed in monkeys and pigeons (Geller and Hartmann 1982, Barrett 1986). Buspirone inhibited conditioned avoidance response in rats trained to jump a barrier to avoid electric shock; this confirmed the tranquilizing activity of the compound (Riblet 1984, Eison 1990).

Buspirone inhibits apomorphine induced stereotypy in rats (Riblet 1982) and blocks apomorphine's emetic effect in the dog (Allen 1974) but does not antagonize the contralateral rotation induced by apomorphine in rats with lesion in substantia nigra (McMillen et al 1983). It has been suggested that apomorphine induced behavior are complexly mediated and are subject to polysynaptic multitransmitter (dopamine, serotonin) regulation (Riblet 1984).

Clinical studies have subsequently confirmed the antianxiety activity of buspirone (Goldberg and Finnerty 1982, Rickels et al 1982, Wheatley 1982, Pecknold et al 1989).

## 3. Neuropharmacology of buspirone

The mechanism of action of buspirone differs from the benzodiazepines. According to Taylor (1985) buspirone does not possess an affinity for benzodiazepine receptor and has no effect on gamma-aminobutyric acid (GABA) neurotransmitter system. Cross-tolerance to the benzodiazepines has not been demonstrated (Lader and Olajide 1987). However, it may otherwise affect components of this system (Skolnick et al 1984).

Comparative studies on the effects of benzodiazepines and azaspirones on the noradrenergic system of the locus coeruleus have been carried out by Sanghera et al (1983); buspirone in a variety of doses has no effect or slightly increases the firing rate of the locus coeruleus whereas diazepam depresses it. A higher dose of buspirone (more than 10 mg/kg) raises the levels of MOPEG-SO4 (3-methoxy-4 hydroxyphenylglycol sulfate). MOPEG-SO4 is the major noradrenaline metabolite in the brain. There are also data to indicate that buspirone lowers NA levels in striatum and hippocampus (Mennini 1986).

Cimino et al (1983) reported the effects of benzodiazepines and buspirone on the cholinergic system of the brain. According to these findings, benzodiazepines increase the levels of acetylcholine in the brain while buspirone produces a dose-related decrease of acetylcholine content in the striatum.

Initial studies with this drug indicated that buspirone has actions on the dopaminergic system. Following an acute administration of buspirone the elevation of dopamine metabolites (homovanillic acid, dihydroxyphenylacetic acid) in the striatum and the nucleus accumbens in rats was observed. Furthermore it was also observed that buspirone reduced the degree of catalepsy caused by potent dopamine receptor blockers such as haloperidol (Riblet 1982, McMillen and McDonald 1983). It was concluded that buspirone

have both antagonist and agonist dopaminergic activity (Taylor 1982), displaying, however, greater potency as a selective presynaptic dopamine antagonist (McMillan et al 1983).

Buspirone possesses high affinity to the serotonergic receptor of type 1A (5-HT1A); it exerts a diphasic action on 5-HT1A receptors. Acute administration with this compound decreases 5-HT neuronal firing activity by activating the somatodendritic 5-HT receptors. During the course of administration of buspirone, a 5-HT1A agonist, 5-HT autoreceptors become desensitized with subsequent changes in tonic activation of postsynaptic 5-HT1A receptors in the dorsal hippocampus. The long-term administration of buspirone causes anxiolysis which is attributable to an enhancement of 5-HT neurotransmission (Blier and de Montigny 1990 ), Figure 2 .

## 4. Pharmacokinetics

Buspirone is absorbed rapidly from the gastro-intestinal tract and metabolized extensively. The usual therapeutic dose is 20 to 30 mg daily. "First-pass" metabolism reduces the bioavailability of an oral dose of buspirone to about 4% (Gammans 1985). Peak plasma concentrations of buspirone of 1.0-3.9 ng/ml are attained in less than 1 hour after a single 20 mg dose (Goldberg 1984). Administering the drug with food may reduce its rate of absorption, but may also decrease the extent of "first-pass" effect. In man, approximately 95% of buspirone is plasma protein bound. The extensive metabolism of buspirone results in less than 1% being excreted unchanged. Urinary and fecal excretion account for 65% and 35% respectively of dose. The elimination half-life of

## *5-HT$_{1A}$ AGONISTS AND 5-HT NEUROTRANSMISSION*

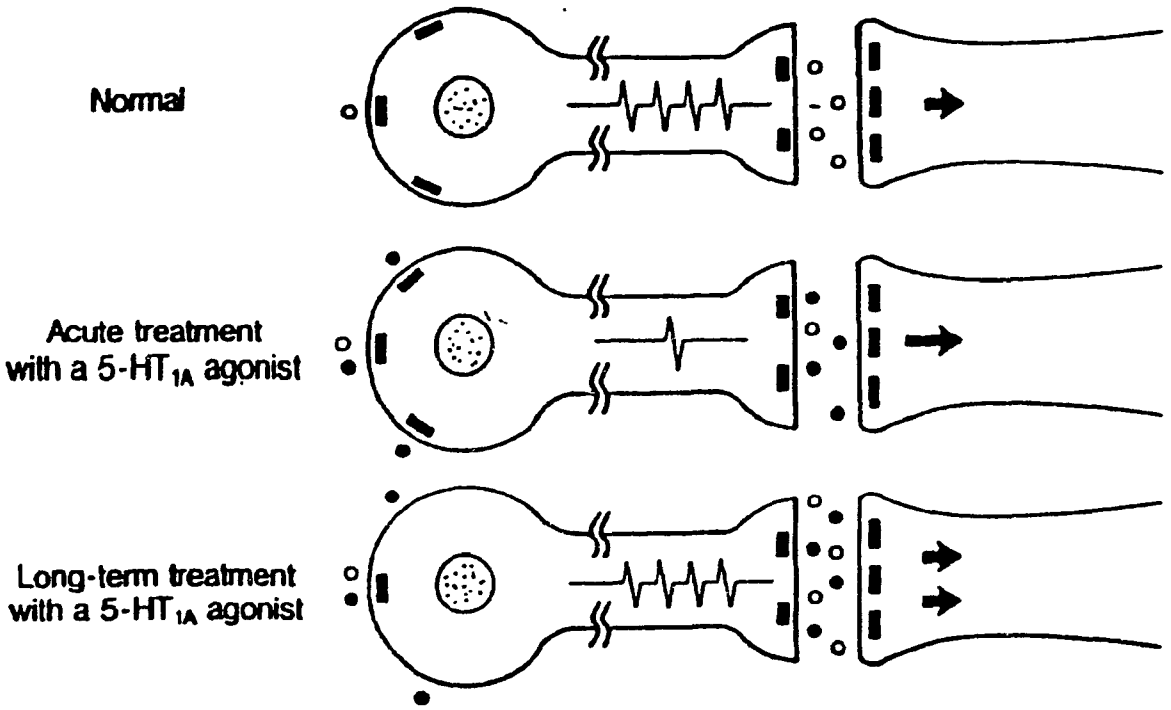



**Figure 2:** A diagram showing the adoption of the firing activity of dorsal raphae 5-HT neurons following somatodendritic 5-HT autoreceptor desensitization during administration of 5-HT1A agonist (acute and long-term treatment). Open dots = 5-HT molecules; Closed dots= 5-HT1A agonist. [after Blier P. and De Montigny C., J. Cardiovasc. Pharmacol.15, (Suppl. 7), pp. 425-485, 1990].

buspirone ranges from 2-8 hours in healthy subjects and is significantly lengthened in renal (Caccia et al 1988) and hepatic insufficiency (Gammans 1985). It is unclear whether the active metabolite 1-(2-pyrimidinyl)piperazine (1-PP) contributes significantly to the anxiolytic effects of buspirone (Caccia et al 1986).

## 5. Clinical studies

Clinical comparative studies on the anti-anxiety action of buspirone and diazepam have been conducted by several groups of investigators. For the purpose of this report, many articles have been reviewed, reflecting the consensus of medical opinion (Goldberg and Finnerty 1982, Rickels et al 1982, Wheatley 1982, Pecknold et al 1989). The advantage of the Canadian data presented by Pecknold is that buspirone was already used clinically for at least 7 years and the findings could be viewed in perspective. Noteworthy fact is that buspirone was given twice daily, whereas before, a three times daily schedule was used. Using Hamilton Anxiety Scale (HAM-A), Pecknold et al (1989) considered separately the psychic and somatic factors. When the effects on the psychic factor of the HAM-A Scale is considered separately, the effect of buspirone and diazepam are not significantly different. However, buspirone, but not diazepam, has markedly improved the HAM-A somatic factor scale, when compared to the placebo group. This study also demonstrates the significance of placebo effect in the assessment of pharmacotherapy. As many as 43% of patients receiving placebo were diagnosed as "ill" at the baseline and attained a "not ill" status at the end-point.

The first double-blind studies, comparing buspirone and diazepam in two separate series, were carried out by Goldberg and Finnerty in 1979 and in 1982

respectively. The results, judging from the Hamilton Scales for Depression and Anxiety, as well as the Lipman-Rickels Symptoms Checklist (SCL-56), showed that buspirone relieves both anxiety and associated depression.

A multicenter-efficacy study was conducted by Wheatley in 1982. He included results obtained by 300 general practitioners in different parts of Great Britain, comparing groups of patients receiving diazepam (Valium), buspirone and placebo, in doses ranging from 5 to 10 mg, three times daily. A significant improvement was observed in all groups after 2 weeks. However, after 3 weeks, only patients receiving buspirone and diazepam reported that they felt significantly better, but not those receiving placebo; this seems to demonstrate again the importance of the initial "placebo" effect. Drowsiness was reported much more frequently by patients receiving Valium than those receiving buspirone.

Rickels et al (1982) compared efficacy of buspirone with that of diazepam and placebo over a four-week treatment period in anxious patients. Buspirone produced significantly more improvement than diazepam in the anger-hostility factor of Profile of Mood States (POMS). In addition, trends favoring buspirone, but not diazepam, over placebo were found in the depression and interpersonal sensitivity factor of Hopkins Symptom Checklist (HSCL).

Feighner et al (1982) claimed that both anxiety and depression are more positively affected by buspirone than by diazepam. Feighner et al (1982) conducted a double-blind trial, using 15 mg/day of diazepam or respectively 16.5 mg/day of buspirone for a four-week period, preceded by a seven-day placebo washout period; the results were evaluated using HAM-A Scale, the Covi Anxiety Scale and the Raskin Depression Scale. Buspirone was more effective than diazepam in scores on the impaired cognition factor of the SCL-56 and confusion factor of Profile of Mood States (POMS). Feighner et al (1982) concluded that

buspirone is a better choice for the treatment of general anxiety and for the patients with anxiety and coexisting depression.

Fabre (1990) suggested recently that high doses of buspirone (up to 90 mg/day) are helpful in the management of patients suffering from major depression. Jacobsen (1991) used somewhat lower doses (30 mg/day) in patients treated previously for six weeks with fluoxetine; these patients were classified after four weeks of fluoxetine treatment as "antidepressant non-responders". The results were evaluated using the 21-item HAM-D Scale and the Clinical Global Impression (CGI) Scale, administered prior and after buspirone treatment. Patients who reported "good" or "fair" response after 3 weeks of buspirone treatment were continued on this medication combined with antidepressant therapy for another four months. According to Jacobsen (1991), a large majority of these patients, who did not respond to fluoxetine, improved significantly after the addition of buspirone to the therapeutic regime. It is of interest that patients, suffering from a winter-period relapse of depression, also improved when buspirone was administered concomitantly with non-MAO inhibitors. Jacobsen's group of patients is too small to draw definite conclusions but the subject of the anti-depressant effects of buspirone seems worthwhile to pursue.

Seidel et al (1985) evaluated the effects of buspirone in volunteer subjects suffering from chronic insomnia; two parameters were considered: sleep pattern and daytime function. The sleep-inducing effects of buspirone alone or administered together with flurazepam, triazolam and placebo were evaluated. The results were evaluated using Multiple Sleep Latency Test (MSLT) and psychomotor performance. Buspirone did not produce a reduction in day-time wakefulness; only slight interaction with flurazepam and not with triazolam was

observed. Seidel et al (1985) concluded that anxiety / tranquillity and alertness / sleepiness are neuropharmacologically distinct dimensions.

Cole et al (1982) evaluated the possibility of buspirone abuse in recreational users of sedative drugs; this seems to be an important issue because many occasional users become habituated to anxiolytic drugs. This study demonstrated that high doses of buspirone (40 mg) produced increased physical sedation and increased physical and mental dysphoria and lower abuse-liability scores; small doses (10 mg) had no significant effect. Cole et al (1982) concluded that buspirone is unlikely to reinforce the occasional use of illicit drugs.

Caccia et al (1988) studied the effects of buspirone in patients with renal insufficiency. Although no definite recommendation was made by Caccia's group, the results obtained indicate that buspirone in doses of 20 mg/day does not produce any significant side effects in patients with mild or moderate renal impairment. However, in six anuric patients, the levels of 1-PP, the active buspirone metabolite [1-(2 pyrimidinyl)piperazine)] were significantly increased; it was recommended that in anuric patients, the dosage of buspirone be reduced by 25-50%.

According to Bohm et al (1990), buspirone can be prescribed without any reservation, to elderly patients suffering from anxiety or neurotic depression. A double-blind, placebo-controlled, study of 40 patients (20 patients suffering from anxiety and 20 patients with neurotic depression) demonstrated that doses of buspirone ranging from 5 to 30 mg/day, given over a four-week period, significantly improved ($p<0.05$) the HAM-A and HAM-D rating scores as well as the Clinical Global Impression (CGI) Scale. In this study of a randomly assigned treatment, only insignificant adverse effects such as dryness of mouth, headaches and diarrhea, were observed in a small percentage of patients.

## 6. Rationale for use of buspirone in research on alcoholism

Tollefson (1989) reviewed the data on the relationship between alcohol and serotonin (5-hydroxytryptamine or 5-HT). These data show that decreased levels of 5-HT in the brain may modulate alcohol intake. Alcoholics display a variety of abnormalities of 5-HT neurotransmission. A major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) is decreased in the cerebrospinal fluid, as discussed in a review on alcohol and serotonin (Tollefson 1989). Reduced levels of 5-HIAA in CSF of alcoholics indicate a decreased 5-HT neurotransmission (Ballenger et al 1979). More recently, Roy et al (1990) confirmed these findings. Banki (1981) proposed an inverse relationship between 5-HIAA levels in CSF and the time passed since the last consumption of alcohol; a shorter interval corresponds to a higher level of the metabolite. An interesting finding was made by Boismare (1987) that the affinity of platelets to serotonin is increased in subjects that consume alcohol.

Pharmacological studies have demonstrated the similarity of response of brain tissue to alcohol between humans and animals; therefore, a brief reference will be made to these studies. Murphy et al (1982) demonstrated the link between preference for alcohol and cerebral 5-HT levels in rats. Naranjo et al (1986) described a variety of 5-HT agonists (precursors and reuptake inhibitors) which reduce alcohol consumption. Direct 5-HT1A agonists, such as buspirone (a partial agonist), reduce alcohol consumption in rodents (Privette et al 1988, Kostowski and Dyr 1992), and in monkeys (Collins and Myers 1987). Selective 5-HT1A receptor agonists [8-hydroxy-2-(di-N-propylamine) tetralin] and ipsapirone, acting on the same type of receptor, were shown to decrease alcohol intake as well as preference for ethanol in a "free-choice" situation in rats (Swensson et al 1993).

Given the evidence that voluntary use of alcohol is modulated by brain serotonin level, a possible strategy for treatment of alcoholism may be to attempt a direct stimulation of serotonergic receptors. Perhaps administration of buspirone would increase serotonergic neurotransmission and reduce alcohol intake. Furthermore, buspirone does not interact with the acute effects of alcohol (Riblet et al 1982, Mattila et al 1982). It has a low abuse liability in alcoholics (Griffith et al 1986), and does not cause withdrawal symptoms upon discontinuation (Murphy et al 1989). It should also be noted that buspirone has a favorable side-effect profile (Newton 1986).

These data provided the basis for clinical trials with buspirone in alcoholic patients. Bruno (1989) conducted a double-blind study in primary alcoholics, using doses of 20 mg/day; he found a significant decrease in craving, anxiety and depression; buspirone-treated subjects had a significantly lower discontinuation rate, than the placebo treated group.

Several studies were conducted on the effects of buspirone in abstinent alcoholics, with comorbid anxiety disorder. Tollefson et al (1992) reported a significant reduction of anxiety scores and an overall clinical improvement in buspirone-treated subjects; unfortunately, alcohol consumption was not directly measured. In contrast to these findings, Malcolm et al (1992), in an investigation of severely anxious alcoholics, found no difference in measures of either anxiety or alcohol consumption between the two treatment groups. Recently, Kranzler et al (1994) conducted a double-blind study of 61 anxious alcoholics to evaluate the effects of buspirone as an adjunct to relapse prevention psychotherapy. They concluded that buspirone treatment retained patients for a longer period of time in the study and observed a slower return to heavy drinking and fewer drinking days.

Several uncontrolled studies, using buspirone in chronic alcoholics, were conducted. Kranzler and Meyer (1989) reported a decrease in anxiety and the desire to drink. Olivera et al (1990) treated patients with anxiety and substance dependence, including alcohol, during a twelve-month period; a significant reduction in anxiety was observed. Dougherty and Gates (1990) attempted to treat alcohol withdrawal syndrome using buspirone to replace benzodiazepines and other traditional agents; they concluded that buspirone may play a significant role in the detoxification of alcoholics.

## IV. OBJECTIVES

In the current study, the three objectives of the investigation of the effects of buspirone in alcoholic subjects can be summarized as follows:

1. Assessment of the efficacy of buspirone on the regulation of craving and alcohol consumption in patients who demonstrated a motivation to decrease alcohol intake or to abstain from it.

2. Evaluation of the effects of buspirone in improving coexisting psychopathological conditions related to alcohol abuse, especially with reference to anxiety and depression.

3. Determination of the safety level of buspirone administration was the third objective. Moskowitz and Smiley (1982) reported that buspirone does not impair driving skills of alcoholics and Mattila et al (1982) showed that buspirone does not potentiate the effects of alcohol on psychomotor skills, which are a significant factor to be considered when medication is given to alcoholic patients.

## V. METHODOLOGY

### 1.General Comment

In designing the methodology for this investigation, the protocol has been established to assess the efficacy and safety of buspirone in alcohol dependence. Our interest was centered on a group of primary alcoholics who were not supported by any psychotherapy by our research group.

### 2. Study Design

Following a preliminary screening for inclusion criteria, all patients were placed for a two-week period on placebo ("wash-out"): one capsule twice a day. The external appearance of the placebo capsules manufactured by Bristol-Myers Squibb, was identical to that of buspirone. After this period, patients were assigned in a randomized fashion either to the buspirone group, the dosage being 10 mg capsules twice daily, or to placebo capsules for a period of two weeks. On the third week of the study the dosage of buspirone was increased to 20 mg twice a day, while patients in the control group received an increased dose of the placebo "medication" twice daily. The investigator who administered the medication was not aware whether the patient was assigned to the buspirone or placebo group. The randomization codes were kept by Bristol-Myers Squibb central office.

## 3. Study Group

A group of 57 adult chronic alcoholics of both sexes, 25 to 60 years of age, was completely examined and periodically followed at bi-weekly intervals for a twelve-week period, after the initial two weeks of placebo administration.

## 4. Recruitment of Subjects

Male and female patients, meeting the criteria for alcohol dependency according to DSM-III-R, were recruited after a 20-30 minute telephone interview. Advertisements were placed in the media. All of the recruited subjects expressed a desire to reduce alcohol consumption of or to abstain from it. They also agreed to the double-blind design of the study and signed a consent form. Subjects were not compensated for their participation in the study. A detailed monitoring of the patients status was kept. The protocol provided that the patients may undergo concomitant psychological or psychosocial treatment (e.g. Alcoholics Anonymous membership, individual or group psychotherapy), but no biological treatment.

## 5. Inclusion Criteria

(a) DSM-III-R criteria for alcohol dependence.

(b) Duration of alcohol abuse (longer than 6 months).

(c) Patients from all ethnic groups, of both sexes, ranging in age from 25 to 60.

(d) All patients signed the consent form and agreed to the double-blind type of study.

(e) Social Stability Index, SSI $\geq 8$ (Wilcox 1981).

In order to reduce the number of patients dropping out from the study, the Social Stability Index was used. The Index comprises 6 items which are essential to social stability: 1) residence/accommodation 2) family contact 3) expected family contact 4) past employment 5) present job status 6) legal status.

(f) For additional source of information on drinking behavior of the subject, an informant was used (spouse, friends living with the subject, etc.)

## 6. Exclusion criteria

According to the protocol, the following patients were excluded:

(a) Major organic brain syndrome, which includes conditions such as Korsakoff syndrome, multi-infarct dementia, cerebrovascular accidents, head trauma or significant cognitive deficit.

(b) Patients who abstained for more than fifteen days prior to initial contact.

(c) Patients with secondary alcoholism. Secondary alcoholism was considered to be present when major psychiatric disorder pre-existed prior to the onset of alcohol abuse; these include conditions such as schizophrenia, panic attacks, major depression or anti-social personality.

(d) Patients using sedatives, antidepressants, anxiolytic agents or neuroleptics as medication, or illicit drugs within two weeks prior to the commencement of the study.

(e) Patients with hepatic and renal disorders, and those with gastrointestinal disorders when an interference with absorption of test medication was in question. All patients were tested for hepatic insufficiency, using as criterion an elevation in liver enzymes three times the upper normal limit (ASAT, ALAT,

GGT). All patients were tested for blood creatinine level; those with levels higher than 2 mg/deciliter were excluded.

(f) Patients with clinically relevant laboratory-tested abnormalities, either treated or untreated, unless they were linked to alcohol abuse.

(g) Patients with major cardiovascular, hematological or endocrinological disorders.

(h) Patients with a history of buspirone hypersensitivity.

(i) Patients with a history of substance abuse (other than alcohol), according to the DSM-III-R criteria; this includes drugs such as amphetamines, cocaine, cannabis, benzodiazepines or opiates. To maintain this important exclusion criterion, urine of all patients was tested for the presence of these substances at the onset and at the end of the study.

(j) Nursing mothers.

(k) Pregnant women or those who, according to history, did not practice adequate contraception or did not have negative pregnancy test prior to enrollment and randomization.

(l) Patients with epilepsy.

(m) Patients who were treated or investigated within the past four weeks with other clinical trial drugs.

## 7. Initial assessment

At the time of the initial screening visit, a comprehensive medical and psychiatric history was taken. The socio-economic parameters were also recorded. The data collected included the following:

(a) Physical examination including neurological assessment, carried out personally by the author.

(b) Laboratory evaluation:

Hematology: hemoglobin concentration, hematocrit, WBC with differential, erythrocyte and platelet counts.

Serum Chemistry: Total protein, albumin, Total cholesterol, Triglycerides, Urea nitrogen, Uric acid, Total bilirubin, Alkaline Phosphatase, ASAT, ALAT, GGT, Glucose, Creatinine, Ca, P, Na, K, Cl.

(c) Routine Urine Analysis: pH, sugar, protein, sediment, etc.

(d) Socio-demographic data: Gender, age, ethnic group, marital status, employment status, type of occupation, income level legal status were recorded.

**8. Drinking Behavior Assessment**

(a) Michigan Alcoholism Screening Test (MAST)

The MAST (Selzer 1971) was administered to all patients at the initial visit, prior to the "wash-out" period. MAST, in its original form, consists of 25 items. The test has been validated by numerous investigators and is currently used routinely as a screening test for alcoholism as well as a reliable measurement of the degree of severity of the problem (Skinner 1979).

(b) Alcohol Use Inventory (AUI)

The Alcohol Use Inventory, a self-administered questionnaire including 228 items, represents the best currently used method for objective assessment of alcohol related conditions. Horn, Wanberg and Foster (1990) published a Guide to the Alcohol Use Inventory after extensive factor analytical studies of

alcohol-related problems. The AUI is employed to assess the nature of an individual's pattern of alcohol use and problems related to this pattern. It is also helpful in planning of the therapy. The AUI is a set of 24 scales. It contains 17 primary scales which measure benefits, styles, consequences, and concerns associated with use and abuse of alcohol. These 17 primary scales form the base for 6 higher-order scales. One of these, DISRUPT 1, is a direct measure of the dependence syndrome; DISRUPT 2 appears to indicate an excessive disruptive use of alcohol, although it is less face-evident. The DISRUPT scales are closely associated with alcohol-dependence syndrome described by Edwards et al (1976); The syndrome is characterized by compulsion to drink, recurrent alcohol withdrawal symptoms and loss of control associated with consumption. The DISRUPT factor is very similar to the Alcohol Dependence Scale used in alcoholism research (Skinner and Horn 1984).

The 3rd-order scale ALCINVOL is a general factor scale measuring broad involvement with alcohol. It includes a set of items extracted from all primary and second level scales.

(c) Drinking Behavior Interview (DBI)

This test is based on a questionnaire which indicates in a quantitative and linear manner the severity of impairment caused by alcohol. The following three components of alcohol abuse are considered: 1) pattern of drinking; 2) social impairment; 3) occupational impairment. The scoring is based on "arbitrarily selected weights for the items chosen", on the basis of clinical experience (Shelton et al 1969). Although it is not a well validated instrument it was included in our protocol for purpose of comparison with Bruno's study (1989).

Socioeconomic status of the patient affects the results of the scores of DBI. The DBI test was administered to all patients at the initial visit and every 2 weeks for the duration of the treatment.

(d) Alcohol Consumption Diary

Patients were asked to list the amount and type of alcohol they had consumed at every visit, including the initial period. Each patient was provided with a "Diary of Alcohol Consumption" form on which they reported the quantity of alcohol ingested. The alcohol equivalents of standard drinks were then calculated. Alcohol consumption was then calculated in relation to body weight and the Ethanol Consumption Index was established.

(e) Craving for alcohol

Craving for alcohol was assessed using a visual analog scale. A 10 cm line, representing the range of craving from 0 (on the left) to 10 (on the right), was marked by the patient, according to his experience. Each patient was requested to mark the degree of craving for alcohol he had experienced during the day of interview, at each bi-weekly visit. In addition, a five-point-rating-scale was obtained for the week preceding the bi-weekly interview during the entire period of the study.

(f) Data obtained from the informant

On four occasions, during the course of treatment, the person living with the subject was asked to provide information about the patient's behavior and alcohol consumption. If the patient was living alone, an employer, a neighbor, or

the landlord, became the "informant". At that time, the Edwards Hardship Scale (Edwards et al 1977) was administered to the informant by telephone. This scale consists of the following 10 items: restlessness at night, failure of personal hygiene, lack of participation in family activities, quarreling, threats towards wife or other family members, violence towards wife, attempts to injure wife, continuous raving (for hours), attempts to break furniture, jealousy.

(g) Liver enzymes

B The self-report of the subject was cross-checked with a collateral report and by determination of liver enzyme levels (GGT, ASAT and ALAT).

## 9. Psychiatric Assessment

(a) Montgomery-Asberg Depression Rating Scale (MADRS)

This test was devised in 1979 by Montgomery and Asberg, and has been gaining popularity as a comprehensive assessment of depression. Originally, it was designed to measure the effect of treatment with antidepressants in the course of the clinical trials. It consists of 10 items which are chosen from the depression component of the Comprehensive Psychological Rating Scale (CPRS). (Montgomery and Asberg 1979 ). The scale assesses the severity of depression and is not intended as a diagnostic tool.

MADRS was administered to all patients at the initial visit and at bi-weekly intervals for the duration of the study.

(b) Hamilton Anxiety Scale (HAM-A)

The HAM-A test is the oldest and probably the most frequently used test for assessment of anxiety. The test consists of 14 items, divided into two subgroups of 7 items evaluating respectively psychic and somatic anxiety. The HAM-A scale was shown to be effective in the assessment of anxiolytic drugs (Hamilton 1959, Hamilton 1969).

The HAM-A scale was administered to all patients at the initial screening visit and at bi-weekly intervals for the following 14 weeks.

(c) Hopkins Symptoms Checklist 90 - Revised (SCL-90-R)

The SCL-90-R comprises 9 factors which assess the specific areas of distress: 1) somatization 2) obsessive-compulsive symptoms 3) interpersonal sensitivity 4) depression 5) anxiety 6) hostility 7) phobic anxiety 8) paranoid inclination 9) psychoticism. In addition, 3 general scores are derived from the nine primary scales: General Symptoms Index (GSI), Positive Symptoms Distress Index (PSDI), and Positive Symptoms Total (PST).

The SCL-90-R was shown to be useful not only in discerning patients with respect to the severity of the illness but also in the assessment of therapy over a period of time, as well as in non-pharmacological aspects of the study (Derogatis et al 1976). Its reliability and validity are well established.

The SCL-90-R checklist was used at the initial screening visit and at bi-weekly intervals for the duration of the study.

## 10. Compliance

Following the wash-out period, the number of capsules returned by the patient was counted and compared with the number given to the patient for the past weeks; the procedure was followed during the entire treatment period. When the adherence was below the 80% level, the treatment was discontinued.

## 11. Assessment of Adverse Effects

The side-effects of the medication were assessed at each visit using the uniform symptoms' checklist provided in the Case Report Form. Patients were asked whether they are having any physical or mental problems, which they attributed to the medication. Any symptoms which aggravated a pre-existing condition or arose in the course of the treatment were analyzed. The patient was asked to list the severity and time of observed side effects and how they were treated. If significant side-effects were reported, the dose of medication was adjusted downwards, according to the protocol and clinical judgment of the investigator.

In addition, the investigator assessed the physical status of the patient at the initial visit and every two weeks for the duration of the treatment; resting blood pressure in a horizontal position, heart rate, temperature and weight were recorded.

## 12. Concomitant Medication

A few subjects experienced alcohol withdrawal symptoms requiring concomitant medication. In such cases, chlordiazepoxide in doses not exceeding

300 mg within 24-48 hours was given; therefore this was considered of little clinical significance.

Patients were not allowed to take any other investigational drugs, nor any psychotropic medication during the period of this study.

## 13. Determination of Sample Size

The sample size was calculated in order to provide 95% power to detect a treatment difference of 30 units in endpoint mean scores on the DBI scale, using a two-tailed test at p=0.05. The method used is described by Fleiss (1986). Thirty units or the DBI was considered to be the minimum clinically important difference that the study should be capable of detecting. The calculations were based on standard deviation for the DBI obtained in the study comparing buspirone and placebo in the treatment alcoholism by Bruno (1989), in which the observed standard deviation of DBI was approximately 25 units. In order to allow for the possibility of greater variability in the DBI scores in the proposed study, the standard deviation was estimated to be 32.5 units, i.e., 30% greater than in the study of Bruno. Using these values, the required sample size per treatment group was estimated to be 30 patients in order to allow for an attrition rate of up to 50%.

## 14. Statistical analysis

The data were obtained on a bi-weekly basis recording seven data points after the two week period of wash-out. The multivariate analysis of covariance on repeated measures was employed. The Mauchly's Sphericity Test and the Levene's Test of Homogeneity of Variance were carried out to confirm

appropriateness of the multivariate option. Use of the covariates allowed the mathematical adjustment of the baseline differences between the treatment groups. The covariates represented the baseline value of each of the measures. Homogeneity of variance, correlation matrices and parallelism of slopes were examined before allowing the baseline measure as a covariate. A priori analysis of contrasts was used to examine the pattern of changes during the time. Details of the method are listed in The Advanced Statistics Guide SPSS (Norusis 1985). The statistical testing included factor TIME representing the overall changes in both treatment groups combined over a time. The postulated null hypotheses were, that there is no significant change in the tested variable during the course of the study. The second aspect of the analysis was to test the interaction of TIME x TYPE OF TREATMENT that related to the null hypothesis, that there is no significant difference in the magnitude of response between the active and the placebo group over the time of the study. The level of significance was accepted at p value $\leq 0.05$. The analysis of side effects, demographic characteristics, and calculation of the number of abstinents, was done at the end of the study using Chi-square or Fisher's Exact Test when appropriate.

The independent samples t-test, Chi-Square or Fisher's Exact Test were used to assess the process of randomization and the One Way Analysis of Variance was used to compare the drop-outs.

## VI. RESULTS

### 1. Patient Population

One hundred and nine subjects have satisfied the strict inclusion criteria for acceptance to the protocol of study. Twenty-one patients failed to keep the appointment and twenty-three subjects were excluded after the initial assessment for the following reasons: a) elevated liver enzymes (ten subjects); b) failure to appear for subsequent visit (eight subjects); c) non-compliance with conditions of wash-out period (two subjects); d) positive test for urine drug screening (one subject); e) concomitant use of medication (one subject). All subjects met the DSM-III-R criteria for alcchol dependence. The ratings of anxiety and depression were also evaluated at this time.

Fifty-seven patients (47 men and 10 women) met all inclusion criteria. The socio-demographic analysis of the study group is shown in Table I, and the test of randomization of the baseline characteristics in Table II.

In spite of the randomization procedure, carried out according to the computer generated list of random numbers, a more extensive psychopathology was present in the active treatment group, including anxiety (HAM-A Scale and anxiety subscale of SCL-90-R), depression (MADRS and SCL-90-R depression subscale), ALCINVOL subscale of AUI and general scores of SCL-90-R (PST, GSI and PSDL), Table II. To exclude possible circumstantial effects, an appropriate statistical procedure (analysis of covariance) was used. The buspirone group of patients (Table II) exhibited also a more severe involvement in alcoholism without statistical significance; this included alcohol consumption, craving, length of abuse, MAST, AUI subscales (DISRUPT 1 and DISRUPT 2)

and DBI. The Edwards Hardship Scale showed no difference between baseline characteristics of the buspirone and the placebo group.

**Table I. Socio-demographic characteristics of the study group.**

| Characteristic | Subdivision | frequency | percent |
|---|---|---|---|
| gender | female | 10 | 17.5 |
| | male | 47 | 82.5 |
| marital status | single | 13 | 22.8 |
| | common law | 7 | 12.3 |
| | married | 20 | 35.1 |
| | separated/divorced | 15 | 26.3 |
| | widowed | 2 | 3.5 |
| type of employment | laborer | 14 | 24.6 |
| | clerical worker | 3 | 5.3 |
| | skilled craftsman | 6 | 10.5 |
| | manager | 5 | 8.8 |
| | professional | 15 | 26.3 |
| | other | 14 | 24.6 |
| employment status | not employed | 13 | 22.8 |
| | full time | 28 | 49.1 |
| | part time | 6 | 10.5 |
| | student | 3 | 5.3 |
| | retired | 4 | 7 |
| | housewife | 1 | 1.8 |
| | other | 2 | 3.5 |
| income | none | 1 | 1.8 |
| | 0 - 5,000 $ | 0 | 0 |
| | 5,001 - 15,000 $ | 19 | 33.3 |
| | 15,001 - 30,000 $ | 15 | 26.3 |
| | above 30,000 $ | 22 | 38.6 |
| legal problems | no problem | 54 | 94.7 |
| | minor | 3 | 5.3 |

**Table II. Population characteristics at the baseline**

| Characteristic | Active n=28 | | Placebo n=29 | | P value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| age | 41 79 | 7.61 | 41 48 | 8.00 | 0.88 |
| social stability index | 9.71 | 1.61 | 10.79 | 1.35 | 0.008 |
| alcohol consumption | 7 24 | 12.87 | 4.87 | 4.44 | 0.36 |
| years of alcohol abuse | 17.65 | 8.74 | 15.83 | 8.62 | 0.44 |
| craving rating scale | 2.61 | 0.99 | 2.24 | 1.19 | 0.21 |
| MAST | 29.79 | 11.04 | 27 66 | 6.88 | 0.39 |
| DBI | 30.48 | 19.55 | 23.42 | 18.72 | 0.21 |
| AUI: | | | | | |
| -alcinvol | 29.54 | 12.84 | 23.45 | 10.57 | 0.055 |
| -disrupt1 | 14 39 | 7.55 | 11 69 | 5.95 | 0.14 |
| -disrupt2 | 7 25 | 2.98 | 6.35 | 2 70 | 0.23 |
| Edwards Hardship Scale | 3.54 | 3 07 | 2.90 | 2.44 | 0.23 |
| GGT | 71.79 | 62 15 | 56.58 | 44 08 | 0.29 |
| ASAT | 36.04 | 18.14 | 35 62 | 22.91 | 0.94 |
| ALAT | 41 11 | 27 05 | 38 66 | 27.17 | 0.73 |
| Hamilton Anxiety | 15.08 | 9 62 | 8 81 | 5.40 | 0.008 |
| Depression (MADRS) | 14 58 | 8.45 | 10.27 | 7 88 | 0.07 |
| SCL-90-R : | | | | | |
| -anxiety | 1.1 | 0.73 | 0.58 | 0.45 | 0.004 |
| -depression | 1.22 | 0.85 | 0.79 | 0.79 | 0.08 |
| -PST | 45.54 | 19.47 | 32.12 | 18.86 | 0.017 |
| -GSI | 0.99 | 0.67 | 0.54 | 0.44 | 0.009 |
| -PSDL | 1.79 | 0.60 | 1.38 | 0.37 | 0.007 |

## 2. Social Stability Index (SSI)

SSI was used to assess the social stability of the subjects entering the study; the assessment of SSI is used to predict the outcome of treatment of alcoholics on an outpatient basis (Wilcox 1981). The testing was carried out at the time of initial screening visit. One-way ANOVA method was used to determine the differences in SSI between completers in the active and placebo groups, active group drop-outs and placebo group drop-outs.

It was found that those patients who dropped out from the placebo group had a significantly lower score of SSI than the placebo completers ($p = 0.025$). In the active treatment group, the drop-out subjects tended to have higher SSI scores ($p = 0.051$); as a result the placebo completers had a higher SSI score than the active group completers.

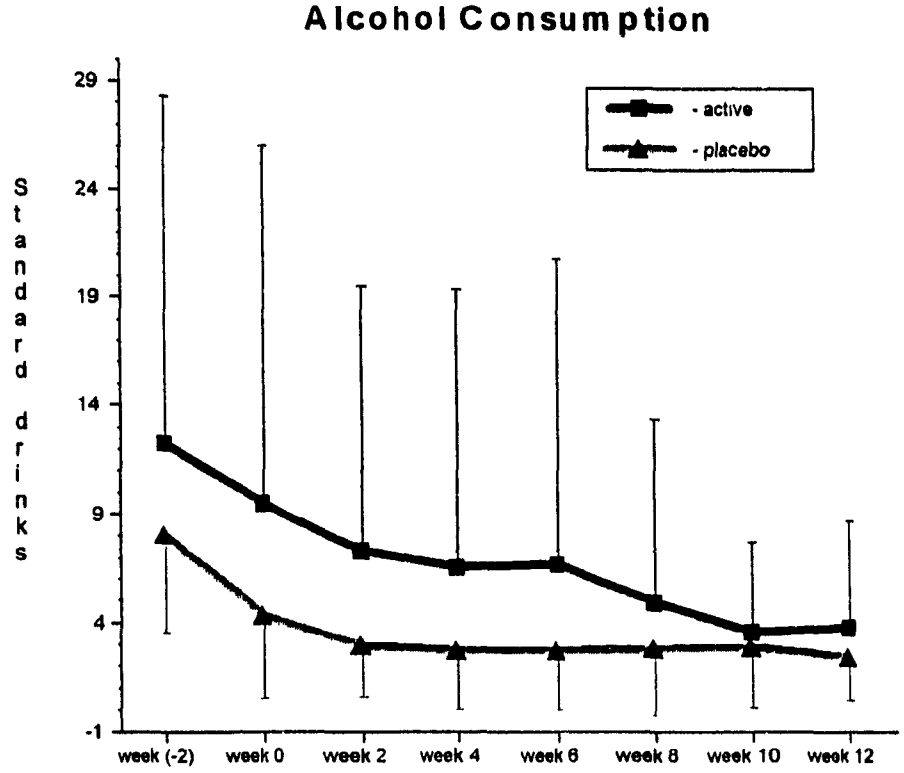
## 3. Alcohol consumption.

Data on alcohol consumption were obtained in the two-week of wash-out period and for the following twelve weeks of treatment at bi-weekly intervals. The results are presented in fig. 3.

Between week 6 and 10 of the treatment period, there was a notable drop in the level of alcohol consumption in the active, but not in the placebo group, suggesting an effect of buspirone. In the active group, the level of alcohol consumption was higher, but it diminished gradually and at the end of the study, the alcohol intake was very similar to that of the placebo group.

Multivariate analysis of covariance did not reveal significant differences between the treatment groups. The factor **Time** and the interaction **Time x Type of Treatment** were analyzed. The results are shown in the Table III.

Figure 3.




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| - active | 12 19 | 9 47 | 7 28 | 6 56 | 6 69 | 4 88 | 3 53 | 3 77 |
| - placebo | 8.01 | 4.31 | 2 96 | 2 73 | 2 74 | 2 8 | 2 87 | 2 38 |

**Table III.**

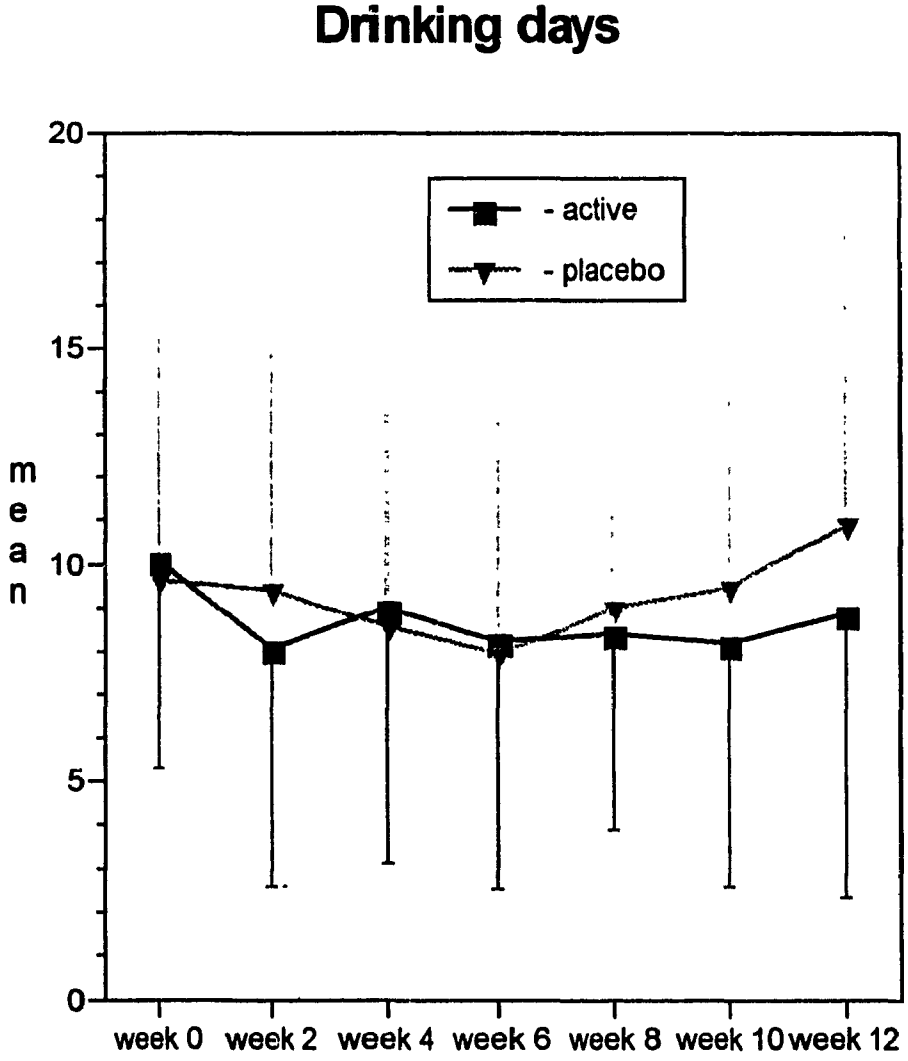
| FACTOR | TEST | Value | F | Hypothesis DF | Error DF | P value |
|---|---|---|---|---|---|---|
| Time | Pillais | 0.50 | 4.66 | 6 | 28 | 0.002 |
| Time x Type of Treatment | Pillais | 0.14 | 0.76 | 6 | 28 | 0.61 |

The conclusion is that independently of the kind of intervention (buspirone vs. placebo) there is a significant reduction in the alcohol consumption level over the 12 weeks of trial. There is however no statistically significant difference between the active and the placebo groups in that aspect.

**4. Frequency of alcohol use.**

The number of days on which alcohol was consumed was recorded in the wash-out period and at bi-weekly intervals during the twelve weeks of the treatment. The statistical analysis included seven data points. The results are shown in figure 4.

**Figure 4.**




| | week 0 | week 2 | week 4 | week 6 | week 8 | week 10 | week 12 |
|---|---|---|---|---|---|---|---|
| - active | 10.06 | 8.06 | 9 | 8.19 | 8.37 | 8.13 | 8.88 |
| - placebo | 9.6 | 9.4 | 8.55 | 7.95 | 9 | 9.45 | 10.9 |

The factor **Time** and the interaction **Time x Type of Treatment** were analyzed using the multivariate analysis of covariance. No statistically significant changes in the frequency of alcohol use over the time of the trial (Pillais, p=0.45), nor any difference between the treatment groups (Pillais, p=0.70) were observed.

**5. Abstinence.**

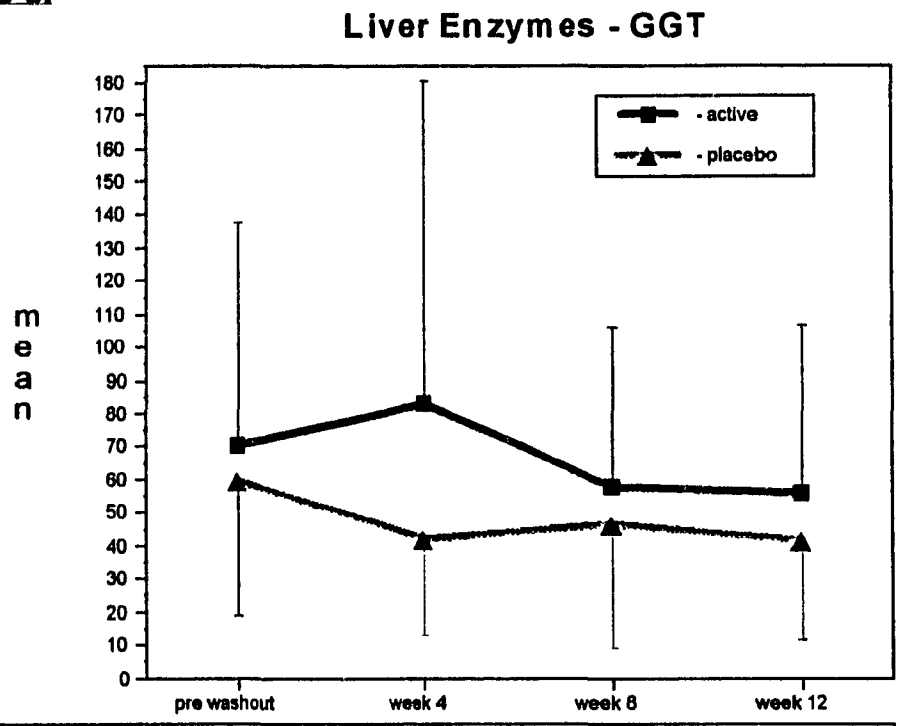
The analysis of the proportion of patients who attained abstinence at the last two weeks of the study showed that only 2 of the 16 in the active and 3 of the 20 in the placebo treated patients reported a complete abstinence during the last two weeks of the study ($Chi^2$=0.04, p=0.83).

**6. Analyses of Liver Enzymes Changes.**

Reduction of alcohol consumption may be indirectly demonstrated by monitoring change in the liver enzymes levels. Measure of GGT, ASAT and ALAT was performed at the pre-wash-out period and subsequently at weeks 4, 8, 12 of the study as shown in figures 5, 6, 7.

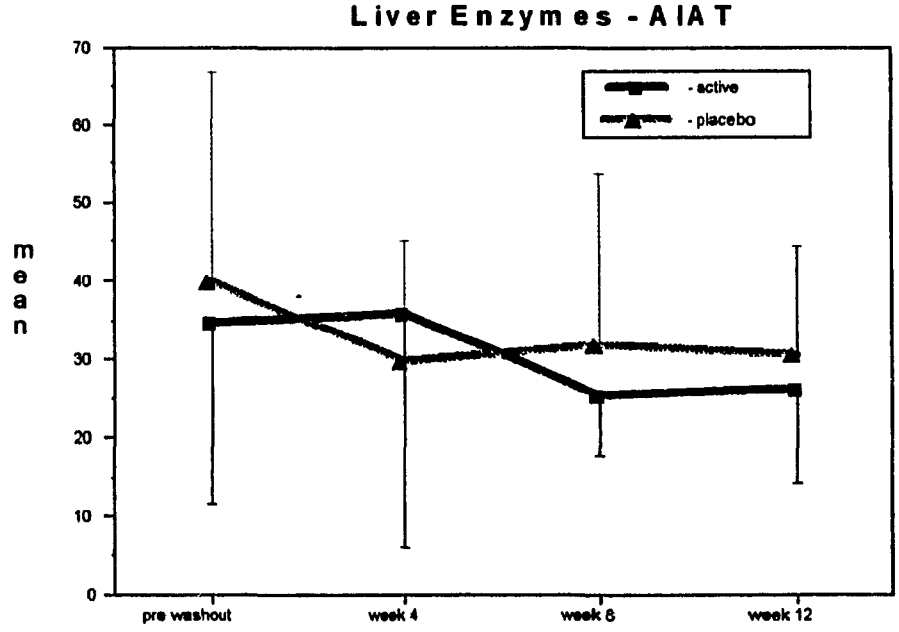
Multivariate analysis of covariance included four data points. The factor **Time** and the interaction **Time x Type of Treatment** were analyzed. There was an overall tendency in both treatment groups towards a decrease in blood levels of the liver enzymes. For GGT and AlAT these changes reached the level of statistical significance, meaning that both groups significantly improved during the period of the study. The results of the statistical analysis are shown in tab IV.

**Figure 5.**



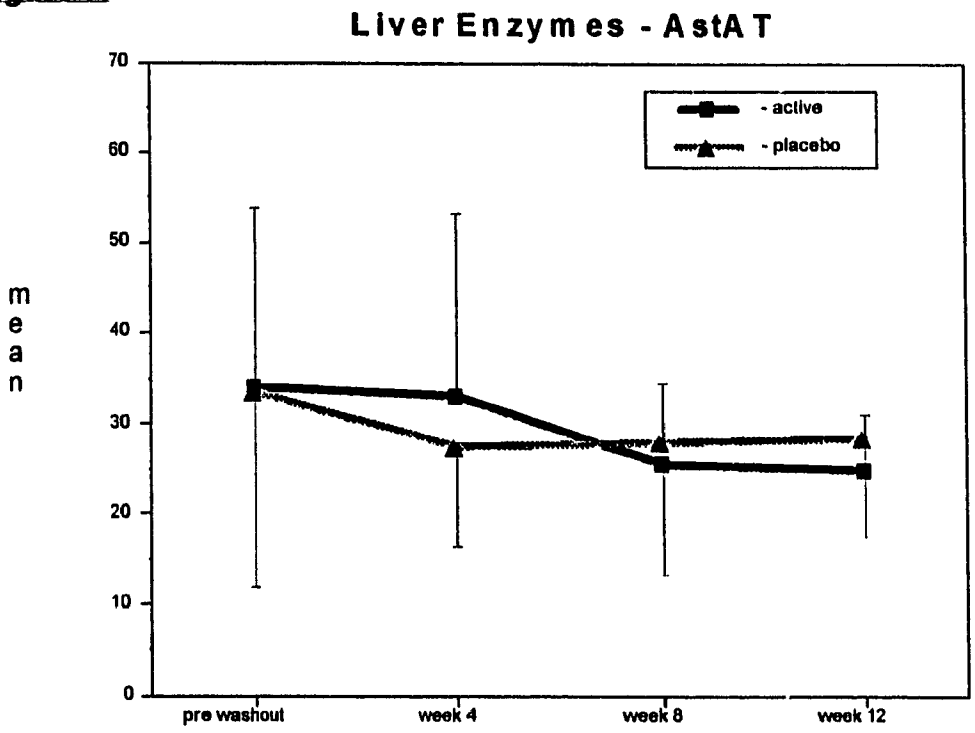

| | | | | |
|---|---|---|---|---|
| - active | 70 00 | 82 81 | 57 38 | 55.37 |
| - placebo | 59.30 | 41 84 | 46.32 | 41.47 |

**Figure 6.**




| | | | | |
|---|---|---|---|---|
| - active | 34 5 | 35 81 | 25 25 | 26 19 |
| - placebo | 39 9 | 29 74 | 31 68 | 30 58 |

**Figure 7.**




| | | | | |
|---|---|---|---|---|
| - active | 33.94 | 32 81 | 25 37 | 24 75 |
| - placebo | 33.45 | 27 37 | 27 84 | 28.37 |

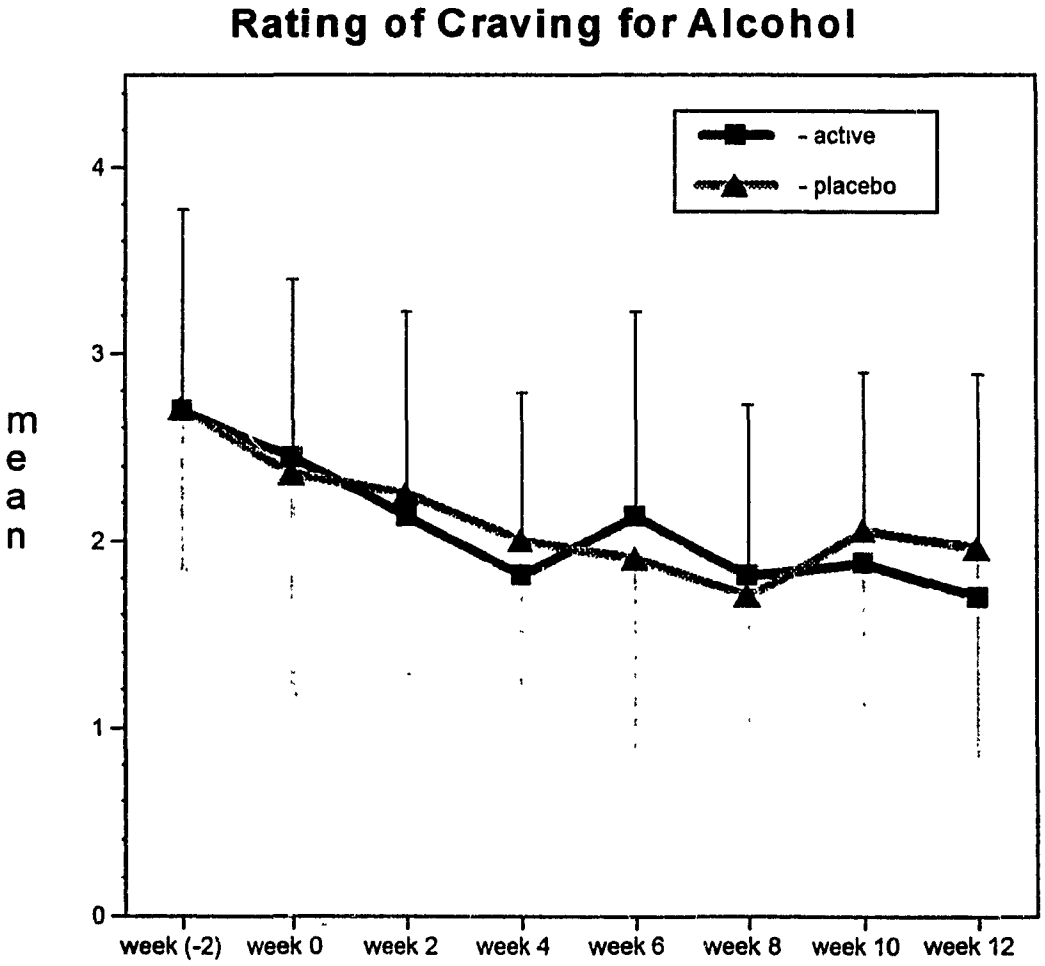
**Table IV.**

| Blood level of liver enzymes | TIME | TIME x TYPE OF TREATMENT |
|---|---|---|
| GGT | P= 0.012 | P= 0.224 |
| AlAT | P= 0.043 | P= 0.402 |
| AstAT | P= 0.135 | P= 0.312 |

## 7. Craving for alcohol

The rating of craving for alcohol was obtained at bi-weekly intervals for the twelve-week duration of the study. The results are shown in figure 8.

**Figure 8.**




| | week (-2) | week 0 | week 2 | week 4 | week 6 | week 8 | week 10 | week 12 |
|---|---|---|---|---|---|---|---|---|
| - active | 2 69 | 2.44 | 2.13 | 1.81 | 2.13 | 1.81 | 1 88 | 1.69 |
| - placebo | 2 70 | 2.35 | 2 25 | 2.00 | 1.90 | 1 70 | 2.05 | 1.95 |

The multivariate analysis of covariance did not reveal significant differences between the treatment groups. Factor **Time** and the interaction **Time x Type of Treatment** were analyzed. The results are shown below in table V.

| FACTOR | TEST | Value | F | Hypothesis DF | Error DF | P value |
|---|---|---|---|---|---|---|
| Time | Pillais | 0.33 | 2.31 | 6 | 28 | 0.062 |
| Time x Type of Treatment | Pillais | 0.14 | 0.74 | 6 | 28 | 0.62 |

A reduction in the craving for alcohol, approaching the level of statistical significance, during the twelve weeks of the trial was observed in both groups. There is no statistically significant difference between the active and the placebo groups in this aspect.

Measure of craving for alcohol on a visual analog scale did not reveal statistically significant changes over time (Pillais = 0.274, p=0.144) and between the two groups (Pillais = 0.101, p=0.078) .

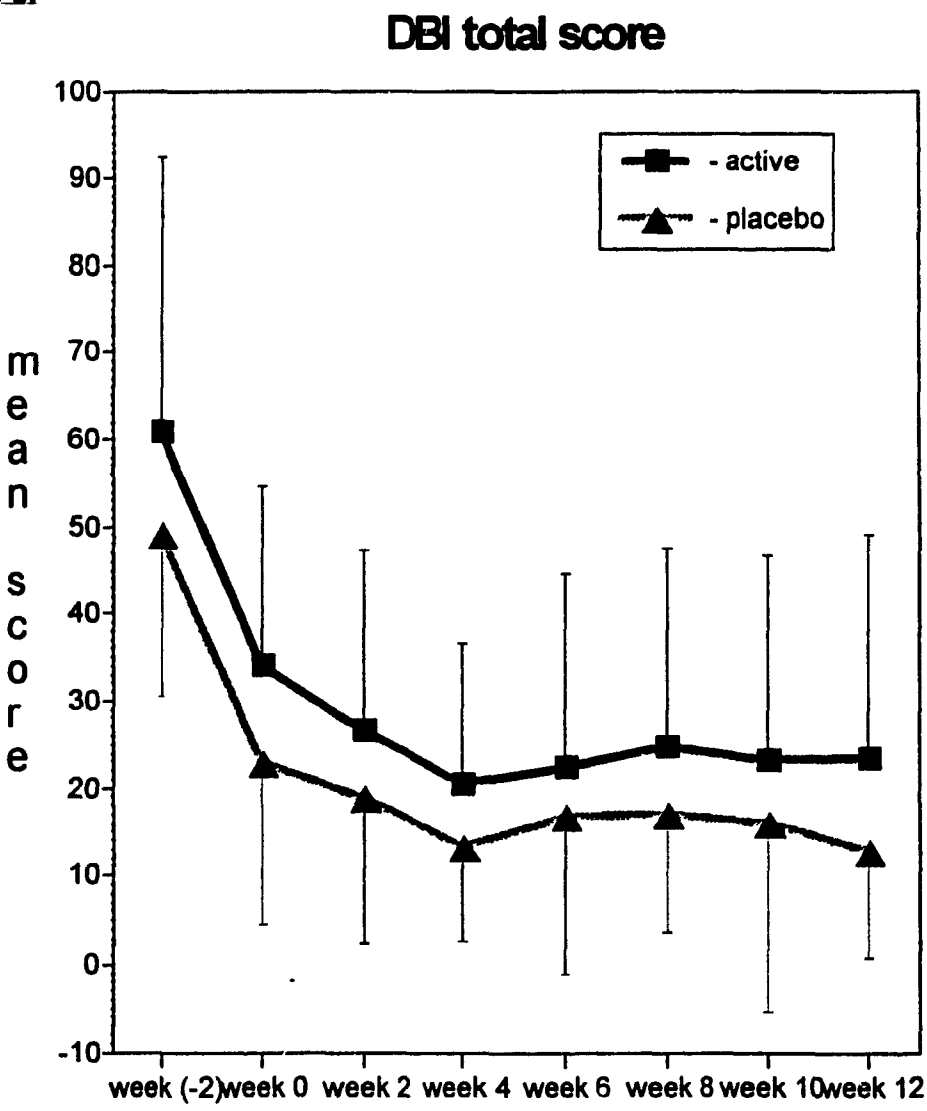
**8. Drinking Behavior Inventory (DBI).**

Measurements were carried out bi-weekly during the wash-out and during the twelve-week trial period. The results are shown in figure 9.

The analysis included baseline ( week 0 ) and seven data points, at bi-weekly intervals, to the end of the study at week 12. A continuous drop of the scores up to week 4 can be observed, with an ensuing plateau following this period. Multivariate analysis of covariance did not reveal significant differences between the treatment groups. Factor **Time** and the interaction **Time x Type of Treatment** were analyzed. The results of the statistical analysis of the total DBI score and its constituent factors are shown in Table VI.

**Treatment** were analyzed. The results of the statistical analysis of the total DBI score and its constituent factors are shown in Table VI.

**Figure 9.**




| | week (-2) | week 0 | week 2 | week 4 | week 6 | week 8 | week 10 | week 12 |
|---|---|---|---|---|---|---|---|---|
| - active | 60.88 | 34.00 | 26.50 | 20.50 | 22.19 | 24.56 | 23.19 | 23.44 |
| - placebo | 49.20 | 22.75 | 18.90 | 13.15 | 16.65 | 16.90 | 15.79 | 12.80 |

**Table VI.**

| DBI score | TIME | TIME x TYPE OF TREATMENT |
|---|---|---|
| Total | P=0.001 | P=0.785 |
| Type of drinking | P=0.002 | P=0.753 |
| Effect on family and social life | P=0.045 | P=0.814 |
| Effect on job | P=0.643 | P=0.315 |

There is a highly significant reduction in the total DBI score reflecting an improvement of the alcohol-related impairments (effects of alcohol on family and social life, and improvement of the drinking behavior). No changes in the work-related impairment were observed. The groups did not differ significantly in their response.

## 9. Alcohol Use Inventory (AUI).

The inventory was used at the initial assessment and at the end of the trial. Analysis of variance was performed on all the subscales of AUI. The factor **Time** was tested for the overall change of the score in both groups combined and the interaction of factors **Time x Type of Treatment** was tested for differences in the magnitude of response between the treatment groups. The results of the testing are demonstrated in Table VII.

The improvement in MENTALIM score in the buspirone group was significantly greater when compared to the placebo group (p=0.023). In all, but two scales (MARICOPE, HELPBEFR), there was a statistically significant

reduction of scores in both treatment groups, indicating an improvement over the study period.

**Table VII. Alcohol Use Inventory**

| AUI | TIME | TIME x TYPE OF TREATMENT |
|---|---|---|
| ***Primary Scales*** | | |
| SOCIALIM | P<0.001 | P=0.508 |
| MENTALIM | P<0.001 | P=0.023 |
| MANGMOOD | P<0.001 | P=0.854 |
| MARICOPE | P=0.056 | P=0.238 |
| GREGARUS | P=0.020 | P=0.214 |
| COMPULSIV | P<0.001 | P=0.483 |
| SUSTAIND | P<0.001 | P=0.508 |
| LCONTROL | P<0.001 | P=0.439 |
| ROLEMALA | P<0.001 | P=0.167 |
| DELIRIUM | P<0.001 | P=0.739 |
| HANGOVER | P<0.001 | P=0.193 |
| MARIPROB | P<0.001 | P=0.763 |
| QUANTITY | P<0.001 | P=0.399 |
| GUILTWOR | P<0.001 | P=0.868 |
| HELPBEFR | P<0.114 | P=0.201 |
| RECEPTIV | P<0.001 | P=0.391 |
| AWARENES | P<0.001 | P=0.461 |
| ***Second Level Scales*** | | |
| ENHANCED | P<0.001 | P=0.177 |
| OBSESSED | P<0.001 | P=0.456 |
| DISRUPT1 | P<0.001 | P=0.524 |
| DISRUPT2 | P<0.001 | P=0.701 |
| ANXCONCN | P<0.001 | P=0.746 |
| RECEPAWAR | P<0.001 | P=0.390 |
| ***Broad (Third Level) Scales*** | | |
| ALCINVOL | P<0.001 | P=0.425 |

## 10. Edwards Hardship Scale (EHS).

The Edwards Hardship Scale represents a check list of alcohol-related symptoms as obtained from next-of-kin evaluation. EHS was administered at the base-line and at the week 4, week 8 and week 12 of the study. The analysis was conducted with MANCOVA method, applying the baseline value as a covariance. Both groups improved significantly during the time of the trial (Pillais, p=0.038), without statistically significant difference between the treatment groups (Pillais, p=0.484).

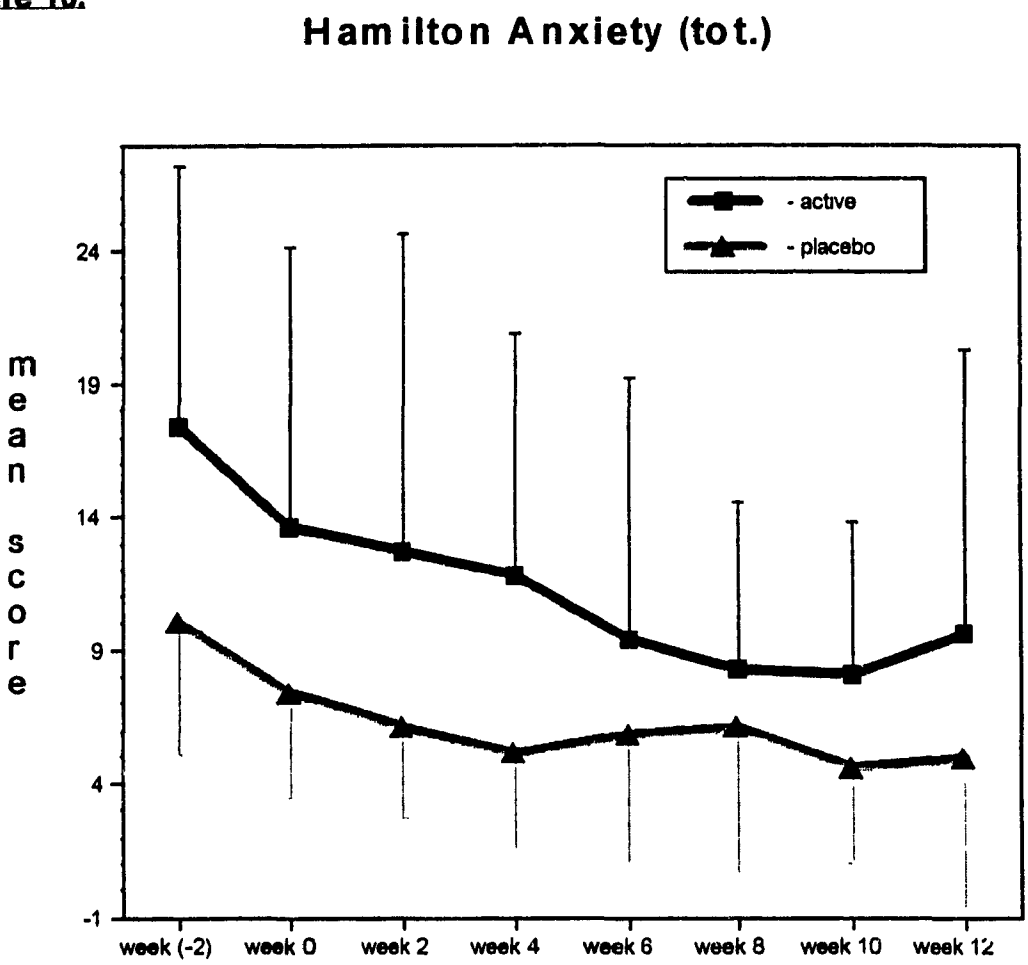
## 11. Hamilton Anxiety Scale (HAMA)

The assessment was conducted bi-weekly throughout the twelve weeks of the trial with seven data points. The results are shown in figure 10.

A significantly higher level of anxiety was initially observed in the active treatment group. At week 4 to week 8 of the buspirone treatment, a notable drop in the level of anxiety was observed in the active, but not in the placebo group. Multivariate analysis of covariance revealed a statistically significant difference between the buspirone and the placebo groups. Factor **Time** and the interaction **Time x Type of Treatment** were analyzed. The results are shown in Table VIII.

There was a significant reduction in the level of anxiety measured by the Hamilton Anxiety Scale. Statistically significant difference was revealed between the active and the placebo groups. A greater improvement in the active treatment group caused the final score of anxiety to approach the level of placebo group, who were initially less affected.

**Figure 10.**




| | week (-2) | week 0 | week 2 | week 4 | week 6 | week 8 | week 10 | week 12 |
|---|---|---|---|---|---|---|---|---|
| - active | 17 38 | 13 64 | 12 69 | 11 75 | 9.38 | 8 25 | 8.06 | 9 63 |
| - placebo | 10 05 | 7 35 | 6 10 | 5.15 | 5 80 | 6 10 | 4 58 | 4 95 |

**Table VIII.**

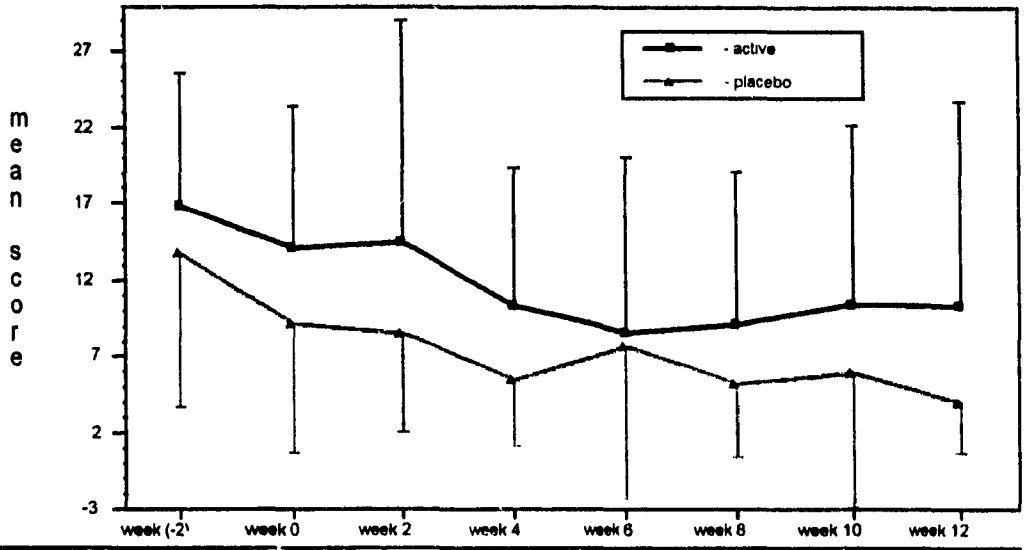
| FACTOR | TEST | Value | F | Hypothesis DF | Error DF | P value |
|---|---|---|---|---|---|---|
| Time | Pillais | 0.50 | 3.79 | 6 | 23 | 0.009 |
| Time x Type of Treatment | Pillais | 0.40 | 2.51 | 6 | 23 | 0.05 |

## 12. Montgomery-Asberg Depression Rating Scale (MADRS)

Depression was assessed at bi-weekly intervals for the twelve weeks duration of the study. The results are shown in figure 11.

**Figure 11.**

Montgomery-Asberg Depression Rating Scale




| | week (-2) | week 0 | week 2 | week 4 | week 6 | week 8 | week 10 | week 12 |
|---|---|---|---|---|---|---|---|---|
| - active | 16 88 | 14 07 | 14 44 | 10 38 | 8 56 | 9 12 | 10 44 | 10 31 |
| - placebo | 13 70 | 9 18 | 8 50 | 5 45 | 7 65 | 5 20 | 5 95 | 4 05 |

Statistical analysis included seven data points, the baseline through week twelve of the trial. Multivariate analysis of covariance did not reveal significant differences between the study groups. The results are shown in Table IX.

**Table IX.**

| FACTOR | TEST | Value | F | Hypothesis DF | Error DF | P value |
|---|---|---|---|---|---|---|
| Time | Pillais | 0.37 | 2.21 | 6 | 23 | 0.079 |
| Time x Type of Treatment | Pillais | 0.08 | 0.31 | 6 | 23 | 0.93 |

## 13. Hopkins Symptoms Checklist 90 - Revised (SCL-90-R)

The SCL-90-R was administered bi-weekly during the twelve-week period of the study. The statistical analysis included seven data points; week 0 (baseline) through week twelve (end of the study). Multivariate analysis of covariance was conducted. The baseline values were employed as covariates after confirming parallelism of slopes, homogeneity of variances and presence of a significant correlation with ensuing measures. The factor **Time** and the interaction **Time x Type of Treatment** were tested. The results are presented in Table X.

**Table X.**

| SCL-90-R score | TIME | TIME x TYPE OF TREATMENT |
|---|---|---|
| **Global Severity Index** | P= 0.002 | P= 0.852 |
| **Positive Symptoms Total** | P= 0.003 | P= 0.222 |
| **Positive Symptoms Distress Level** | P= 0.012 | P= 0.712 |
| **Somatization** | P= 0.062 | P= 0.835 |
| **Obsessive/Compulsive** | P< 0.001 | P= 0.619 |
| **Interpersonal Sensitivity ***** | P= 0.001 | P= 0.067 |
| **Depression** | P= 0.007 | P= 0.884 |
| **Anxiety** | P= 0.014 | P= 0.913 |
| **Anger/Hostility** | P= 0.071 | P= 0.232 |
| **Phobic Anxiety** | P= 0.055 | P= 0.384 |
| **Paranoid Ideation** | P= 0.088 | P= 0.285 |
| **Psychoticism** | P= 0.019 | P= 0.782 |

Most of the measures demonstrated an improvement of the psychopathology over time, irrespective of the treatment group. A reduction in all measures of SCL-90-R was observed, reaching or approaching the level of statistical significance. The Interpersonal Sensitivity Subscale was affected to a higher degree in the buspirone group, with a trend towards statistical significance when compared to the placebo group (Pillais=0.377, p=0.067).

## 14. Analysis of Side Effects.

The table presents the profile of side-effects encountered in both treatment groups.

**Table XI.**

| SIDE EFFECT | ACTIVE COMPLETERS (n=28) | PLACEBO COMPLETERS (n=29) | P * value |
|---|---|---|---|
| dizziness | 16 | 5 | 0.004 |
| lightheadedness | 7 | 0 | 0.005 |
| drowsiness | 4 | 0 | 0.051 |
| nausea | 8 | 1 | 0.012 |
| paresthesia | 3 | 0 | 0.112 |
| headache | 3 | 3 | 1.00 |
| nervousness | 0 | 1 | 1.00 |
| diarrhea | 1 | 2 | 1.00 |

** $Chi^2$ test with continuity correction or the Fisher's Exact test (two -tailed),*

Buspirone was well tolerated and only two patients required modification of the dosage (a decrease from 40 mg/day to 30 mg/day). Symptoms as dizziness, lightheadedness, drowsiness and nausea were significantly more

frequent in the active than in the placebo treated subjects. No subject in the buspirone group discontinued the treatment because of side effects. In fact, there was only one drop-out case in the placebo group, because the patient thought that the "medication was too strong"; this was elucidated only after the trial was terminated.

**15. Analysis of drop-outs.**

An analysis of patients who discontinued the study was carried out to obtain an insight into the characteristics of these subjects. Rates of drop-out from the study are is plotted in figure 12. The study end-point for each patient was defined as the date when the medication was discontinued or the date when the patient was lost to follow-up. All 57 patients were included in the analysis.

There were no significant differences detected between the treatment groups in the rate of drop-out ($Chi^2$, p=0.27). As shown in Table XII, there were no significant differences between the groups in reasons for study discontinuation ($Chi^2$, p=0.405).

**Figure 12.**

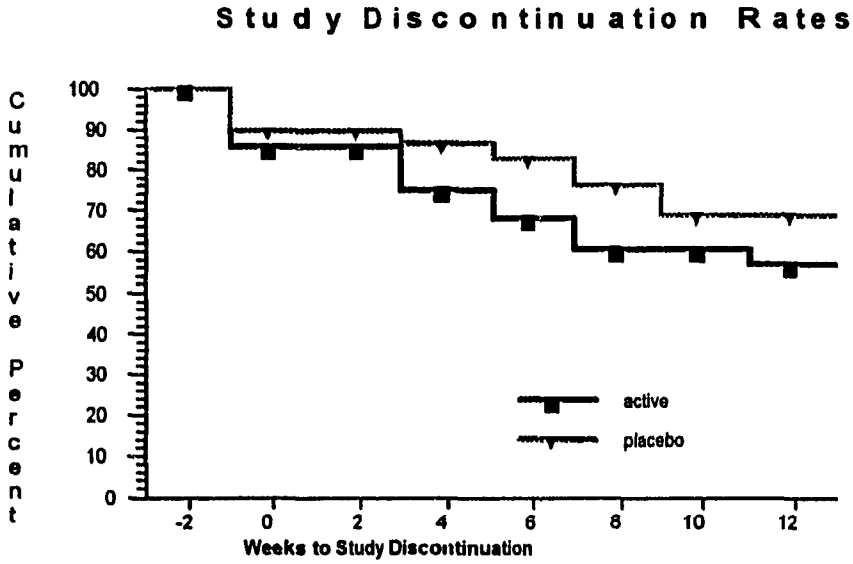
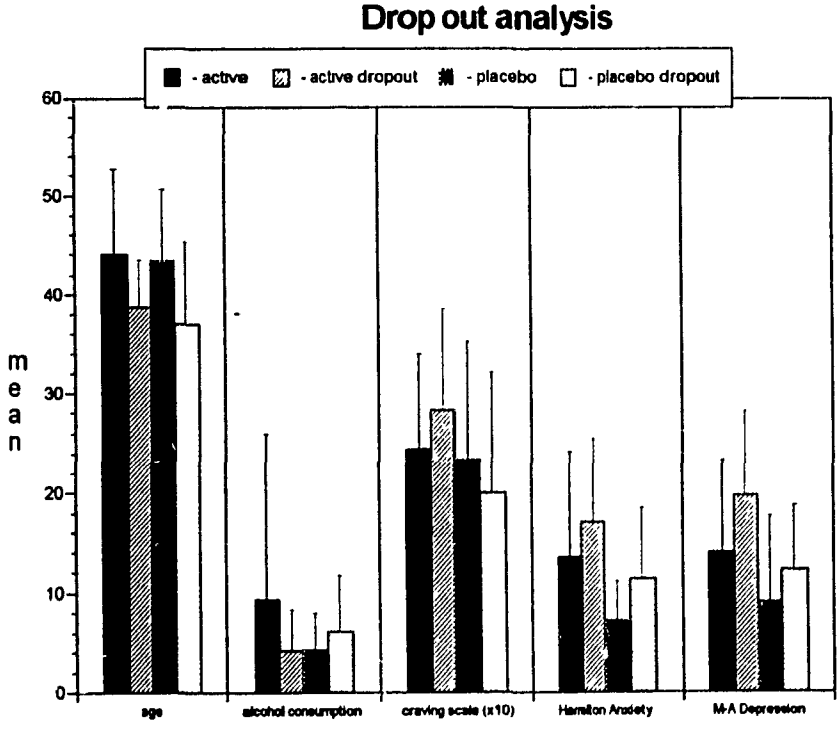


**Table XII.**

| REASON FOR STUDY DISCONTINUATION | Buspirone | Placebo | Total |
|---|---|---|---|
| lack of compliance | 5 | 3 | 8 |
| lost to follow-up | 5 | 4 | 9 |
| inadequate efficacy | 2 | 0 | 2 |
| adverse events | 0 | 1 | 1 |
| development of exclusion criteria | 0 | 1 | 1 |

Analysis of drop-outs was conducted to examine a possibility of patients "selection" due to effects of buspirone. Our hypothesis was that in the placebo, but not in the buspirone group, the sicker subjects would have a tendency to discontinue the treatment. The results are shown in figure 13.

**Figure 13.**



The drop-out cases consisted of younger subjects of the study population. This difference reached the level of statistical significance as shown by analysis using the One Way ANOVA (p=0.046).

In the placebo group, a tendency toward higher alcohol consumption was observed in patients who discontinued the study, when compared to the completers. Conversely, in the buspirone group, those patients who completed the study had a higher alcohol consumption than those who dropped out.

The scores of anxiety (HAM-A) and depression (Montgomery-Asberg) were higher among the drop-outs independently of treatment group.

**16. Final Global Evaluation.**

Both groups have taken the medication regularly, which provides an adequate basis for our study hypothesis. An average compliance was 93.2% in the buspirone and 95.1% in the placebo group. The non-compliers were excluded from the study. Statistical testing of compliance did not reveal any significant difference between the study groups (Pillais, p=0.251).

There was no difference between the treatment groups in their evaluation of the efficacy of the treatment (Chi-square, p=0.97).

13 out of 23 (57%) buspirone treated subjects and 13 of 21 (62%) placebo subjects guessed that they received the active medication. Chi-square did not reveal significant difference between the groups (p=0.60), meaning that the "blinding procedure" was effective.

## VII. DISCUSSION

### 1. Patient Population

Following personal interviews of 80 subjects, a group of 57 patients was selected and randomized to receive either buspirone or placebo treatment. 47 patients were men and only 10 female subjects were included. This is in accordance with the prevalence of alcoholism in males versus females. Maddox et al (1986) reported, that only one of four chronic alcoholics seeking the treatment was a woman. Thirty six patients completed the treatment; the number of patients in the placebo group who did not complete the study (9 subjects) was not statistically different from that in the buspirone group (12 subjects). These findings are similar to those of Malcolm et al (1992), but are not in agreement with reports of Bruno (1989), Tollefson et al (1992) and Kranzler et al (1994), who observed that buspirone-treated subjects remained longer in the study. On the other hand, the overall low drop-out rate in our study may be due to the relatively good social adjustment of the patients as confirmed by the Social Stability Index score (Table II). The subjects were equally divided between professionals and managers (35.4%), and laborers and craftsmen (35.1%); 22.8% were unemployed and 7% were retired. Considering that our study lasted 12 weeks, the total attrition rate compares favorably with the drop-out rate observed in the conventional therapy of alcoholism. According to Rees (1986), the drop-out rate within the first month of the therapy varies between 28% and 80%.

## 2. Psychopathology.

Patients with a history of anxiety, occurring prior to the onset of alcohol dependence, were excluded from our study at the time of the initial assessment. Therefore, if anxiety existed, it was secondary to alcohol dependence. According to Weissman (1980), anxiety secondary to alcoholism is frequent, ranging from 30% to 44%. The mean value of anxiety scores in both of our treatment groups was significantly reduced at the end of the twelve-week study period ($p<0.01$). The Hamilton Anxiety Rating Scale (HAM-A) revealed a superiority of buspirone, when compared to the placebo group, with reference to alleviation of anxiety symptoms ($p=0.05$), as shown in Table VIII. This confirms the results of Bruno (1989), Tollefson et al (1992) and Kranzler et al (1994) who also demonstrated an anxiolytic effect of buspirone.

A considerable drop in the level of anxiety occurred in the buspirone group after four weeks of the treatment. It corresponds with the fact, that the anxiolytic action of buspirone requires a period of at least 3-4 weeks (Cohn et al., 1986; Feighner, 1987).

Analysis of Interpersonal Sensitivity Scale (one of the SCL-90-R subscales) showed a greater improvement of patients treated with buspirone (Table X); a trend towards statistical significance ($p = 0.067$) was demonstrated. The others SCL-90-R subscales, analyzed with respect to the type of intervention, demonstrated reduction of symptoms reaching or approaching the level of statistical significance in both treatment groups. These results do not appear to be in conflict with the findings of Tollefson et al (1992) insofar as the direction of changes in SCL-90-R is considered.

Another concomitant state associated with alcohol abuse is depression. The severity of depression in our group of patients was recorded on the

Montgomery-Asberg Depression Rating Scale (MADRS); a statistical trend towards reduction of the ratings was observed in both treatment groups (p = 0.08), but no difference was observed between them. The Depression Subscale of SCL-90-R confirmed these findings. Using Hamilton Depression Rating Scale (HAM-D), Tollefson et al (1991) reported a statistical trend in mood improvement in buspirone-treated patients (p=0.09). On the other hand a statistically significant improvement of HAM-D scores was reported by Bruno (1989), however, depressive symptoms were less prominent in his patients' population.

**3. Drinking behavior.**

It is worthwhile to note that in our study of 36 chronic alcoholics, the consumption of alcohol decreased in the buspirone treated group between Week 6 and Week 10 of the treatment; no such effect was observed in the placebo group. This drop occurred four weeks after the dose of buspirone was increased from 20 to 40 mg daily. It is possible that the effect of buspirone on craving and consumption requires a higher dose and occurs later than the anxiolytic effect. Bruno (1989) observed in a group of chronic alcoholics a significant decline in drinking after three months of study, independently of whether buspirone or placebo was given. This finding was confirmed in our study since after week 12, a marked decrease in alcohol consumption (p = 0.002) was observed in both groups of patients (Table III).

Only five patients in our study became totally abstinent at the time of completion of the treatment; this indicates that patients are more frequently interested (or capable) to decrease alcohol consumption, rather than become totally abstinent. The number of drinking days did not change significantly during the study period. Kranzler at al (1992) reported a favorable effect of buspirone

on frequency of drinking, but his study population consisted of alcoholics who were abstinent at the baseline, and had tendency to relapse over the course of the study.

The reduction of alcohol consumption was confirmed by the fact that a concurrent decrease of the liver enzymes occurred in both groups: GGT, $p = 0.012$; ALAT, $p = 0.043$. Similar results were obtained when the Edwards Hardship Scale was used, assessing the effects of drinking behavior by an independent report of a collateral person. These findings confirm the validity of alcoholic self-reporting in our study. A similar conclusion was reached by Kranzler et al (1994).

Bruno (1989) observed a significant effect of buspirone on craving in chronic alcoholics ($p = 0.001$); this finding could not be confirmed in our study, nor by Malcolm et al (1992).

The Drinking Behavior Interview (DBI) showed a significant improvement in both treatment groups, reflecting an amelioration in alcohol-related impairments. There was a significant reduction on the subscales dealing with the type of drinking ($p = 0.002$) and the family/social life scale ($p = 0.045$). The work-related subscale did not change; however, it should be noted that 22.8% of patients in our group were unemployed and 7% were retired.

Analysis of Alcohol Use Inventory demonstrated a significantly higher improvement of MENTALIM subscale in the buspirone-treated patients ($p = 0.023$, Table VII). This finding may be related to the anxiolytic properties of buspirone as the higher scores in MENTALIM subscale characterize people who use alcohol to overcome a feeling of inadequacy, shyness, mistrust, and lack of self-confidence. Similar conclusions were reached by Rohsenow (1982), who observed, during a three-month follow-up study of heavy social drinkers, that scores of MENTALIM and SOCIALIM subscales of AUI were significantly

correlated with measures of anxiety and depression, but were not related to the amount of drinking (Rohsenow 1982).

**4. Side effects profile.**

Buspirone in the dose of 40 mg, used in our study, appears to be a safe medication in alcohol abusers. It was associated with mild and transient side effects. This is consistent with findings of other authors (Bruno, 1989; Tollefson, 1992). Not a single patient from the buspirone group discontinued the study due to medication intolerance (Table XII), although in two cases, the dosage of buspirone had to be lowered from 40 to 30 mg per day.

**5. Analysis of drop-outs.**

Analysis of subjects who discontinued the treatment provides an insight into their characteristics. In both treatment groups, the subjects who dropped out were significantly younger than those who completed the study ($p = 0.046$). Baseline anxiety and depression scores were higher in the drop-outs than in the completers; the difference in anxiety level was statistically significant ($p = 0.016$). In contrast to drop-outs from the active treatment group, the drop-out subjects in the placebo group had a significantly lower Social Stability Index ($p=0.025$). This may indicate that buspirone facilitates the treatment completion of those with lower Social Stability Index.

**5. Study effect.**

The therapeutic effect of participation in our study was observed in some of the efficacy parameters (e.g. alcohol consumption, DBI, AUI). This resulted in improvement irrespective of whether buspirone or placebo was used. Importance of the initial wash-out period should also be emphasized in minimizing this phenomenon.

## VIII. CONCLUDING COMMENTS

In view of a very moderate success of existing psycho-social treatments of alcoholism, effective pharmacological adjutants would be most welcome. Our study confirms several important aspects of the few existing papers on buspirone use in the treatment of alcoholics. Buspirone was shown to affect the secondary anxiety component in chronic alcoholism; it is reasonable to postulate that a combination of psychotherapy with buspirone could have a synergistic effect. The question centers around the point which of the characteristics of the patients are amenable to a specific treatment modality. As we observed, there were noticeable inter-individual variation in the pattern of response to buspirone. It may be noted that subjects in our group with high baseline anxiety scores responded better to buspirone therapy. This is in agreement with Kranzler et al (1994) and Tollefson et al (1992). Our group of patients is not sufficiently large to draw definitive conclusions in this respect; however, all five patients with HAM-A scores higher than 15, responded well to the treatment.

One other aspect of this study warrants a comment. The analysis of characteristics of drop-out subjects suggests the role of buspirone in retaining in the treatment of subjects with lower social stability and a higher alcohol consumption. Further research is indicated to assess the action of buspirone in patients who present a higher risks for droping-out from the treatment.

## IX. COMMENTS ON ALCOHOL RESEARCH: QUO VADIS?

In the course of writing this essay, I have reviewed the literature on alcoholism in order to obtain a better understanding of this complex subject. I read numerous articles which are not quoted, because they were not relevant to the matter discussed. However, certain comments which occurred to me, while reading about the "joy and curse" of humanity, could be recorded, if for no other reason, because of the spontaneity of my impressions.

Undoubtedly, considerable progress has been made in understanding the causative factors of chronic alcohol abuse. Alcoholism, like cancer, hypertension or renal insufficiency, is not one disease, but rather a group of disorders leading to the "final cause" of Keynes (1952) in his treatise on probability. The variety of individual response to the same level of alcohol intake is constantly emphasized by Dongier (1989). It seems to be related to preexisting psychological states and mood disorders creating a puzzling situation of causation of primary alcoholism.

With respect to treatment, it seems correct to state that biological specialists treat alcoholism by medication while behavioral specialists use cognitive and behavioral therapy. It is unlikely that in the near future, we will be able to devise an ideal method of treatment. Again, the individual approach appears to be the most logical. Buspirone may be useful in the treatment of chronic alcoholics because of its specific effects on anxiety states; certainly, behavioral therapy will always remain a significant component of treatment of chronic alcoholics to reinforce abstinence.

A promising line of research in alcoholism is the analysis of genetic traits. Considerable progress has been made in animal research by breeding strain with high or low affinity to alcohol. In the so-called Long-Sleep (LS) and Short-Sleep (SS) mice (Kakihana et al 1966), the difference is related to the hypnotic

Sleep (SS) mice (Kakihana et al 1966), the difference is related to the hypnotic effects of alcohol. Dudek and Abbott (1984) have distinguished several genotypes of crossbreeds between the LS and SS mice by biomedical genetic analysis of response to ethanol. Neurochemical correlates of alcohol tolerance in different strains of mice have also been reported (Kiianmaa and Tabakoff 1983). Several clinical studies provided consistent evidence for genetic component of alcoholism (Cotton 1979, Cadoret et al 1980, Littrel 1988). Interesting and important research is carried out to identify trait markers associated with a vulnerability toward alcoholism. Their identification may help clinicians develop more specific and effective prevention and treatment programs. Some genetically defined subtypes of alcoholics may be suitable for buspirone therapy.

Another subject of current interest is the possibility that 5-HT3 antagonists may counteract craving for alcohol. It has been suggested that ethanol produces a transient increase in serotonergic function, which activates the mesolimbic dopaminergic reward system (Costall et al 1990). Toneatto et al (1991) postulated that 5-HT3 antagonists inhibit the firing of mesolimbic dopaminergic neurons, induced by alcohol abuse. Sellers (1991), on the basis of the use of ondansetron in the treatment of alcoholics, stated that 5-HT3 receptor antagonists may become a part of the armamentarium in the treatment of alcoholism.

These examples demonstrate the ever-expanding scope of research on alcoholism, the most frequent self-induced disease in human subjects. "There is no end in our researches; our end is in the other world" (Michel de Montaigne 1556).

## REFERENCES


Allen L. E., Ferguson H. C., Cox R. H. (1974). Pharmacologic effects of MJ 9022-1, a potential tranquilizing agent. Arzneim. Forsh. 24, 917-922.

American Psychiatric Association (1987). Diagnostic and Statistical Manual of Mental Disorders. Third Edition, Revised. American Psychiatric Press, Washington D.C.

Baldessarini R. J. (1990): Drugs and the treatment of psychiatric disorders. In Gilman A.G., Rall T.W., Nies A.S., Taylor P. Eds. The pharmacological basis of therapeutics. Pergamon Press, New York, pp 383-435.

Ballenger J. C., Goodwin F. K., Major L. F., Brown G. L., (1979). Alcohol and central serotonin metabolism in man. Arch. Gen. Psychiatry 36, 224-227.

Banki C. J. (1981). Factors influencing monoamine metabolites and tryptophan in patients with alcohol dependence. Neural Trans. 50, 98-101.

Barett J. E., Witkin J. M., Mansbach R. S. et al (1986). Behavioral studies with anxiolytic drugs. III. Antipunishment actions of buspirone in the pigeon do not involve benzodiazepine receptor mechanism. J. Pharmacol. Exp. Ther. 238, 1009-1013.

Blier P. and De Montigny C. (1990). Electrophysiological investigation of the adaptive response of the 5-HT system to the administration of 5-HT-1A receptor agonist. J. Cardiovasc. Pharmacol. 15 (Suppl 7), 425-485.

Bohm O., Robinson D. A., Gammans R. E. et al (1990). Buspirone therapy in anxious elderly patients: a controlled clinical trial. J. Clin. Psychopharmacol. 10 (Suppl 3), 475-515.

Boismare F., Lhuintre J. P., Daoust M., et al (1987). Platelet affinity for serotonin is increased in alcoholics and former alcoholics: A biological marker for dependence ? Alcohol and Alcoholism 22, 155-159.

Borg S., Kvande H., Rydberg U. et al (1982). Endorphin levels in human cerebrospinal fluid during alcohol intoxication and withdrawal. Psychopharmacology 78, 101-103.

Borg V. (1983). Bromocriptine in the prevention of alcohol abuse. Acta Psychiatr. Scand. 68, 100-110.

Bruno F. (1989). Buspirone in the Treatment of Alcoholic Patients. Psychopathology 22 (Suppl 1), 49-59.

Caccia S., Conti I., Vigano G. et al (1986). 1-(2-Pyrimidinyl)-Piperazine as active metabolite of buspirone in man and rat. Pharmacology 33, 46-51.

Caccia S., Vigano G. L., Mingardi G. et al (1988). Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. Clin. Pharmacokinetics 14, 171-177.

Cadoret R. J., Cain C. A., Grove W. M. (1980). Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. Arch. Gen. Psychiatry 37, 561-563.

Cimino M., Ponzio F., Achilli G. et al (1983). Dopaminergic effects of buspirone, a novel anxiolytic agent. Biochem. Pharmacol. 32, 1069-1074.

Cohn J. B., Bowden C. L., Fisher J. G., Rodos J. J. (1986). Double blind comparison of buspirone and clorazepate in anxious outpatients. Am. J. Med. 80 (Suppl 3B), 10-16.

Cole J. O., Orzack M. H., Beake B. et al. (1982). Assessment of the abuse liability of buspirone in recreational sedative users. J. Clin. Psychiatry 43, 69-74.

Collins D. M. and Myers R. D. (1987). Buspirone attenuates volitional alcohol intake in the chronically drinking monkey. Alcohol 4, 49-56.

Costall B., Naylor R. J. and Tyers M. B. (1990). The psychopharmacology of 5-HT-3 receptors. Pharmacol Ther. 181-202.

Cotton N. S. (1979). The familial incidence of alcoholism: A review. J. Stud. Alcohol 40, 89-116.

De Montaigne O. (1568). Of experience: Essays book III, Chapter 13, p.497. In: Strauss M.B., Ed. Familiar Medical Quotations, Little Brown, Boston, 1968.

Derogatis L. R., Rickels K., Rock A. (1976). The SCL-90 and the MMPI: A step in the validation of a new self-report scale. Br. J. Psychiatry 128, 280-289.

Dongier M. (1989). Progrès récents dans l'étude de l'alcoolisme. Revue Can. de Psychiatrie 34, 49-54.

Dongier M. (1993). Brain, alcohol and alcoholism treatment. Ann. Roy. Coll. Phys. Surg. Can. 26, 26-28.

Dongier M., Vachon L., Schwartz G. (1991). Bromocriptine in the Treatment of Alcohol Dependence. Alcohol. Clin. Exp. Res. 15, 970-977.

Dougherty R. J. and Gates R. R. (1990). The role of buspirone in the management of alcohol withdrawal: a preliminary investigation. J. Subst. Abuse Treat. 7, 189-192.

Dudek B. C. and Abbott M. E. (1984). A biometrical genetic analysis of ethanol response in selectively bred long-sleep and short-sleep mice. Behav. Genet. 14, 1-19.

Edwards G., Gross M. M., Keller M., Moser J. (1976). Alcohol-related problems in disability perspective: A summary of the consensus of WHO group of investigators on criteria for identifying and classifying disabilities related to alcohol consumption. J. Stud. Alcohol. 37, 1360-1382.

Edwards G., Orford J., Egert S. et al. (1977). Alcoholism: a controlled trial of treatment and advice. J. Stud. Alcohol 38, 1004-1031.

Eison A. S. (1990). Azapirones: History of Development. J. Clin. Psychopharmacol 10, 2S-5S.

Eison A. S., Eison M. S., Stanley M. et al (1985). Serotonergic mechanisms in the behavioural effects of buspirone and gepirone. Pharmacol. Biochm. Behav. 24, 701-707.

Fabre L. F. (1990). Buspirone in the management of major depression: a placebo-controlled comparison. J. Clin. Psychiatry 51 (Suppl 9), 55-61.

Feighner J. P., (1987). Buspirone in the long-term treatment of generalized anxiety disorder. J. Clin. Psychiatry 48 (Suppl 12), 3-6.

Feighner J. P., Meredeth C. H. and Hendricson G. A. (1982). A double-blind comparison of buspirone and diazepam in outpatients with generalized anxiety disorder. J. Clin. Psychiatry 43, 103-107.

Fleiss J. L. (1986). The design and analysis of clinical experiments. Wiley, New York.

Fontaine R., Chouinard G., Annable L. (1984). Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. Am. J. Psychiatry 141, 845-852.

Gammans R. (1985). The metabolism and pharmacokinetics of buspirone. In: Rec. Adv. Drug Treatm. Psychiatry. Academic and Professional Services, New York, pp 12-18.

Geller I. and Hartmann R. J. (1982). Effects of buspirone on operant behavior of laboratory rats and Cynomologus monkeys. J. Clin. Psychiatry 43, 25-32.

Gershon S. (1982). Drug interaction in controlled clinical trials. J. Clin. Psychiatry 43, 95-98.

Gianoulakis C., Angelogianni P., Meaney M. et al (1990). Endorphins in individuals with high and low risk for development of alcoholism. In: Proceedings of the symposium "Opioids, bulimia and alcohol abuse and alcoholism." New York. Quoted after Dongier M. (1993). Brain, alcohol and alcoholism treatment. Annales CRMCC 26, 26-28.

Goldberg H. L. (1984). Buspirone Hydrochloride: A unique new anxiolytic agent. Pharmacokinetics, clinical pharmacology, abuse potential and clinical efficacy. Pharmacotherapy 4, 315-324.

Goldberg H. L. and Finnerty F. J. (1979). The comparative efficacy of buspirone and diazepam in the treatment of anxiety. Am. J. Psychiatry 136, 1184-1187.

Goldberg H. L. and Finnerty R. (1982). Comparison of buspirone in two separate studies. J. Clin. Psychiatry 43, (Sec. 2), 87-91.

Grant K. A., Valverius P., Hudspith M. et al (1990). Ethanol withdrawal seizures and the NMDA receptor complex. Eur. J. Pharmacol. 176, 289-296.

Griffith J. D., Jasinski D. R., Casten G. P., McKinney G. R. (1986). Investigation of the abuse liability of buspirone in alcohol-dependent patients. Am. J. Med. 80 (Suppl 3B), 30-35.

Gulya K., Grant A., Valverius P. et al (1991). Brain regional specificity and time-course of changes in the NMDA receptor-ionophor complex during ethanol withdrawal. Brain Res. 547, 129-134.

Hamilton M. (1959). The assessment of anxiety states by rating. Brit. J. Med. Psychol. 32, 50-55.

Hamilton M. (1969). Diagnosis and rating of anxiety. In: Studies of anxiety, Lader M. H., Brit. J. Psychiatry. Spec. Pub. 3, 76-79.

Horn J. L., Wanberg K. W., Foster F. M. (1990). Guide to the Alcohol Use Inventory (AUI). National Computer Systems Inc., Minneapolis.

Hunt W. A. and Majchrowicz E. (1983). Studies of neurotransmitters interactions after acute and chronic ethanol administration. Pharmacol. Biochem. Behav. 18, 371-374.

Institute of Medicine (1987). Causes and consequences of alcohol problems: An agenda for research. National Academy Press, Washington.

Iorio K. R., Reinlib L., Tabakoff B. et al (1991). NMDA-induced $\Delta(Ca^{2+})i$ enhanced by chronic ethanol treatment in cultured cerebellar granule cells. Alcoholism Clin. Exp. Res. 15, p.333 (Abstract 132).

Jacobsen F. M. (1991). Possible augumentation of antidepressant response by buspirone. J. Clin. Psychiatry 52, 217-220.

Kakihana R., Brown D. R., McClearn G. E. et al (1966). Brain sensitivity to ethanol in inbred mouse strains. Science 154, 1574-1575.

Kessel N. and Grossman G. (1961). Suicide in alcoholics. Br. Med. J. 2, 1671-1672.

Keynes J. M. (1952). A treatise on probability. Mc Millan, London, pp 466.

Kiianma K. and Tabakoff B. (1983). Neurochemical collectors of tolerance and strain differences in the neurochemical effects of ethanol. Pharmacol. Biochem. Behav. 18 (Suppl 1), 383-388.

Kostowski W. and Dyr W. (1992). Effects of 5-HT-1A receptor agonists on ethanol preference in the rat. Alcohol 9, 283-286.

Kranzler H. R., Burleson J. A., Del Boca F. K. et al. (1994). Placebo-controlled trial of buspirone as an adjunct to relapse prevention in anxious alcoholics. Personal communication of H.R. Kranzler, January 5-th.

Kranzler H. R., Meyer R. E., (1989). Open trial of buspirone in alcoholics. J. Clin. Psychopharmacol. 9, 379-380.

Lader M. (1982). Psychological effects of buspirone. J. Clin. Psychiatry 43, 62-67.

Lader M. and Olajide D. (1987). A comparison of buspirone and placebo in relieving benzodiazepine withdrawal symptoms. J. Clin. Psychopharmacol. 7, 11-15.

Lhuintre J. P. et al (1990). Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol and Alcoholism 25, 613-22.

Littrell J. (1988). The Swedish studies of adopted children of alcoholics. J. Stud. Alcohol 49, 491-499.

Maddox G., Robins L. N. , Rosenberg N., Eds. (1986). Nature and extent of alcohol problems among the elderly. Springer, New York.

Malcolm R., Anton R. F., Randall C. L. et al (1992). A placebo-controlled trial of buspirone in anxious inpatient alcoholics. Alcohol. Clin. Exp. Res. 16, 1007-1013.

Mattila M. J., Aranko K. and Seppala T. (1982). Acute effects of buspirone and alcohol on psychomotor skills. J. Clin. Psychiatry 43 (Sec. 2), 56-60.

Mc Millen B. A. and Mc Donald C. C. (1983). Selective effects of buspirone and molindone on dopamine metabolizm and function in the striatum and frontal cortex of the rat. Neuropharmacology 22, 273-278.

Mc Millen B. A., Matthews R. T., Sanghera M. K. et al. (1983). Dopamine receptor antagonism by the novel antianxiety drug, buspirone. J. Neurosci. 3, 733-738.

Mennini T., Gobbi M., Ponzio F., et al (1986). Neurochemical effects of buspirone in rat hippocampus: Evidence for selective activation of 5-HT neurons. Arch. Int. Pharmacodyn.Ther. 279, 40-49.

Miller W. R. and Hester R. K. (1986). In-patient alcoholism treatment. Who benefits? Am. Psychol. 41, 794-805.

Montgomery S. A. and Asberg M. (1979). A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382-389.

Monti J. M. and Alterwain P. (1991). Ritanserin decreases alcohol intake in chronic alcoholics. Lancet 337: 60.

Moskowitz H. and Smiley A. (1982). Effects of chronically administered buspirone and diazepam on driving-related skills performance. J. Clin. Psychiatry 43, 45-55.

Murphy J. M., Mc Bride W. J., Lumeng L., Li T.K. (1982). Regional brain levels of monoamines in alcohol-preffering and nonpreffering lines of rats. Pharmacol. Biochem. Behav. 16, 145-149.

Murphy S. M., Owen R., Tyrer P. (1989). Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Br. J. Psychiatry 154, 529-534.

Murphy S. M., Owen R., Tyrer P. (1989). Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Br. J. Psychiatry 154, 529-534.

Myers R. D., Weissman M. W., Tischler G. L. et al (1984). Six-month prevalence of psychiatric disorders in three communities. Arch. Gen. Psychiatry 41, 959-967.

Naranjo C. A., Sellers E. M., Lawrin M. O. (1986). Modulation of ethanol intake by sertonin uptake inhibitors. J. Clin. Psychiatry 47 (Suppl 4), 16-22.

Naranjo C. A., Sellers E. M., Sullivan J. T. et al (1987). The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin. Pharmacol. Ther. 41, 266-74.

Newton R. E., Carter G. P. , Alma R. D. et al (1982). The side-effect profile of buspirone in comparison to active controls and placebo. J. Clin. Psychiatry 43, 100-102.

Newton R. E., Marunych J. P., Alderdice M. et al (1986). Review of the side effect-profile of buspirone. Am. J. Med. 80 (Suppl. 3B), 17-21.

Norusis M. J. (1985). SPSS-X, Advanced statistics guide.McGraw-Hill Book Company, New York, pp 195-293.

Olivera A. A., Sarvis S., Heard C. (1990). Anxiety disorders coexisting with substance dependence: Treatment with buspirone. Cur. Ther. Res. Clin. Exp. 47, 52-61.

Pecknold J. C., Matas M., Howarth B. G. et al (1989). Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo. Can. J. Psychiatry 34, 766-771.

Privette T. H., Hornsby R. L., Myers R. D. (1988). Buspirone alters alcohol drinking induced in rats by tetrahydropapaveroline injected into brain monoaminergic pathways. Alcohol 5, 147-152.

Rees D. W., (1986). Changing patients' health beliefs to improve compliance with alcoholism treatment: a controlled trial. J. Stud. Alcohol 47, 436-439.

Riblet L. A., Eison A. S., Eison M. S. et al (1984). Neuropharmacology of buspirone 17 (Suppl.3), 68-78.

Riblet L. A., Taylor D. P., Eison M. S. et al (1982). Pharmacology and neurochemistry of buspirone. J.Clin. Psychiatry 43, 11-16.

Rickels K., Schweizer E., Csanalosi I. et al (1988). Long-term treatment of anxiety and risk of withdrawal: prospective comparison of clorazepate and buspirone. Arch. Gen. Psychiatry 45, 444-450.

Rickels K., Weisman K., Norstad N. et al (1982). Buspirone and diazeparn in anxiety: a controlled study. J. Clin. Psychiatry 43, (Sec.2), 81-86.

Robins L. N., Helzer J. E., Weissman M. M. et al (1984). Lifetime prevalence of specific psychiatric disorders in three sites. Arch. Gen. Psychiatry 41, 949 - 58.

Robins L. N., Locke B. Z., Regier D. A. (1984). An overview of psychiatric disorders in America. In Robins L.N. and Regier D.A. Eds.Psychiatric disorders in America. Macmillan, New York, pp 328-366.

Rohsenow D. J. (1982). The alcohol use inventory as a predictor of drinking by male heavy social drinkers. Addictive Behaviours 7, 387-395.

Roy A., Virkkunen M., Linnoila M., (1990). Serotonin in suicide, violence, and alcoholism. In Coccaro E. F. and Murphy D.L.,Eds. Serotonin in Major Psychiatric Disorders. American Psychiatric Press, Washington D.C., pp 187-208.

Sanghera M. K., McMillen B. S. and German D. C. (1983). Buspirone, a non benzodiazepine anxiolytic increases locus coeruleus noradrenergic neuronal activity. Eur. J. Pharmacol. 86, 106-110.

Saxe L. Dougherty D. Esty K. (1985). The effectiveness and cost of alcoholism treatment: A public policy perspective. In: Mendelson J. H., Mello N. K. (Eds). The diagnoses and treatment of alcoholism. McGraw-Hill, New York, pp. 485-539.

Sellers E.M., Higgins G. A., Tomkins D. M. (1991). Serotonergic receptor subtypes and alcohol consumption. In: Proceedings of 20th Congress of American College of Neuropsychopharmacology, p.84 (Abstract).

Selzer M. L. (1971). The Michigan Alcoholism Screening Test: the quest for a new diagnostic instrument. Am. J. Psychiatry 127, 1653-1658.

Shelton J., Hollister L. E., Gocka E. T. (1969). The Drinking Behaviour Interview (an attempt to quantify alcoholic impairment ). Dis. Nerv. Sys. 30, 464-467.

Skinner H. A. (1979). A multivariate evaluation of the MAST. J. Stud. Alcohol 40, 831-844.

Skinner H. A. and Horn J. L. (1984). Alcohol Dependence Scale Users' Guide. Addiction Research Foundation, Toronto.

Skolnick P., Steven M. P. and Weissman B. A. (1984). Preclinical Pharmacology of Buspirone Hydrochloride. Pharmacotherapy 4, 308-314.

Smiley A. and Moskowitz H. (1988). Effects of long-term administration of buspirone and diazepam on driver steering control. Am. J. Med. 80 (Suppl 3B), 22-29.

Svensson L., Engel J., Hard E. (1989). Effects of the 5-HT receptor agonist, 8-OH-DPAT, on ethanol preference in the rat. Alcohol 6, 17-21.

Tabakoff B. and Hoffman P. L. (1991). Neurochemical effects of alcohol. In Frances R. J. and Miller S. I., Eds. Clinical Textbook of Addictive Disorders. Guilford Press, New York, pp 501-525.

Taylor D. P. (1985). Mechanism of action of buspirone. In: Rec. Adv. Drug Treat. Psychiatry. Academic and Professional Services, New York, pp 13-18.

Taylor D. P., Riblet L. A., Stanton H. C., et al (1982). Dopamine and antianxiety activity. Pharmacol. Biochem. Behav. 17 (Suppl.1), 25-35.

Tollefson G. D. (1989). Serotonin and alcohol: Interrelationships. Psychopathology 22 (Suppl 1), 37-48.

Tollefson G. D., Lancaster S. P., Montague-Clouse J. (1991). The association of buspirone and its metabolite 1-pyrimidinylpiperazine in the remission of comorbid anxiety with depressive features and alcohol dependency. Psychopharmacology Bull. 27, 163-170.

Tollefson G. D., Montague-Clouse J., Tollefson S. L., (1992). Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (Buspirone). J.Clin. Psychopharmacol. 12, 19-26.

Tompkins E. C., Clemento A. J. and Taylor D. P. (1980). Inhibition of aggressive behavior in rhesus monkeys by buspirone. Res. Commun. Psychol. Psychiatr. Behav. 5, 337-352.

Toneatto T., Romach M. K., Sobell L. C., Sobell M. B. et al (1991). Ondansetron, a 5-HT-3 antagonist, reduces alcohol consumption in alcohol abusers. Alcohol. Clin. Exp. Res. 16, 368 (Abstract).

Volpicelli J. R., O'Brien C. P., Alterman A. I. et al (1990). Naltrexone and the treatment of alcohol dependence. In: Reid L.D., Ed. Opioids, bulimia and alcohol abuse. Springer, New York, pp 195-214.

Weissman M. M., Myers J. K., Harding P. S. (1980). Prevalence and psychiatric heterogeneity of alcoholism in United States urban community. J. Stud. Alcohol 41, 672-81.

Wheatley D. (1982). Buspirone: Multicenter efficacy study. J. Clin. Psychiatry 43 (Sec. 2), 92-94.

Wilcox B. L. (1981). Social support, life stress, and psychological adjustment. Am. J. Community Psychol. 9, 371-386.

Wise R. A. and Rompre P.-P. ( 1989). Brain dopamine and reward. Annu. Rev. Psychol. 40, 191-225.

Yu S. and Ho I. K. (1990). Effects of acute barbiturate administration, tolerance and dependence on brain GABA system: comparison to alcoho! and benzodiazepines. Alcohol 7, 261-269.