THE EFFECTS OF CLOBAZAM AND LORAZEPAM ON PATIENTS' PSYCHOMOTOR PERFORMANCE AND ANXIETY

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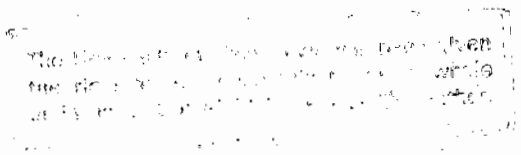

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ABSTRACT

Psychomotor performance, drowsiness and anxiety were measured in 70 anxious outpatients in a randomized double-blind, placebo-controlled trial comparing the 1,5 benzodiazepine clobazam (10 mg two times a day) to lorazepam (1 mg two times a day). Carefully selected tests were administered pre-treatment and at 2 and 9 days after treatment. Compliance was checked by blood assays.

There was a significant improvement in anxiety in the clobazam, lorazepam and placebo groups at 2 days and a further improvement at 9 days but only in the clobazam and lorazepam groups. The lorazepam patients had a significantly higher overall drowsiness rating than the clobazam and placebo groups. Both the clobazam and placebo groups showed an improvement over time in choice reaction time, the Digit Symbol Substitution Test, Purdue Pegboard tests and the Inglis paired-associate learning test. There was no change in critical flicker fusion threshold. The lorazepam-treated patients demonstrated exactly the same pattern on psychomotor performance tests except that there was an impairment in two of the Purdue pegboard tests on day 2. On the basis of previous volunteer studies with lorazepam, a far more general and consistent impairment of psychomotor performance was expected with that drug. This indicates that the finding derived from normal volunteers cannot necessarily be extrapolated to anxious patients. The possible reasons for the

different responses in volunteers and patients are discussed. The practical implications of the various findings and the recommendations for future research are also considered.

1. THE BENZODIAZEPINES

1.1 EXTENT OF PRESCRIPTION OF THE BENZODIAZEPINES

The benzodiazepines are among the most widely prescribed classes of drugs. From 1964 - 1972, the number of prescriptions for anxiolytic drugs doubled in the United States. Virtually all of this increase was attributable to an increase in the use of benzodiazepines, specifically diazepam (Blackwell, 1973). Hollister (1981) writes that one might have concluded, were one to extrapolate from the curve, that by 1984 everyone in the United States would be on diazepam. However, 1972 was the peak of use and in the subsequent 7 years, prescriptions for these drugs have declined by about 22 percent.

Information about the use of benzodiazepines comes from prescription audits, national and local household surveys, and surveys conducted in family practice. In the United States during 1973 the total number of prescriptions filled in drug stores for all drugs was 1 500 million. Of these, 223,2 million were for psychotherapeutics and 80 million of them were benzodiazepines (Rickels, 1981). Survey data taken during 1972 indicate() that 15 percent of respondents had used a benzodiazepine over the previous year in the United States. In Western European countries use ranges from a low of 10 percent in Spain to a high of 17 percent

in Belgium, with the United Kingdom reporting an incidence of 14 percent. In the United States one third of the benzodiazepine users were high users, they had taken their medication regularly for two months or more, one third were intermediate users and the remaining third were low users (Rickels, 1981). There is a prevalence of use in females over males, the approximate proportion is two female users for every male user (Bellantuono et al., 1980).

1.2 TYPES OF BENZODIAZEPINES

The phenothiazine tranquilisers were developed in the early 1950s. They made a tremendous contribution to the drug treatment of severe psychological problems, specifically schizophrenia. In addition, antidepressant drugs had been developed to treat depression. However, by 1960 the drug treatment of anxiety symptoms was not promising. The barbiturates had a general nonspecific sedative effect and meprobromate, although initially thought to be an improvement, was later shown to add little if any therapeutic benefit to that available from the barbiturates (Greenblatt and Shader, 1974). Thus the development of the benzodiazepines which began in the early 1960s has made a major contribution in the drug treatment of anxiety.

The first benzodiazepine to be developed was chlordiazepoxide (trade name - librium). This was followed by the development of diazepam (most commonly used trade name - valium). Other

important well known benzodiazepines include nitrazepam (trade name - mogodon) and lorazepam (trade name - ativan). All these benzodiazepines have the nitrogen atoms situated at positons 1 and 4 in the heterocyclic ring and are called 1,4 benzodiazepines. A diagram of the chemical structure of diazepam, the most commonly used 1,4 benzodiazepine, can be seen in Appendix 1. In the early 1970s a benzodiazepine with the nitrogen atoms in positions 1 and 5 in the heterocyclic ring was developed. This 1,5 benzodiazepine is called clobazam (trade name - urbanol) and a diagram of its chemical structure can be seen in Appendix 1.

1.3 THE CLINICAL INDICATIONS OF THE BENZODIAZEPINES

The benzodiazepines have a well established set of clinical indications that follow closely their pharmocological effects. These indications are: anxiolytic, hypnotic, muscle relaxant, anticonvulsant, and anaesthetic (Hollister, 1981).

The efficacy of the benzodiazepines in alleviating anxiety has been established in double-blind, placebo controlled studies. Bellantuono et al. (1980) in their review of these studies, report that out of a total of 85 studies comparing a benzodiazepine with a placebo, 44 results showed the drug to be much better, 26 showed the drug to be slightly better, 14 showed no difference and one study showed the drug to be worse than the placebo.

The benzodiazepines are mainly prescribed as antianxiety agents and to alleviate sleep disturbances. The muscle relaxant properties of benzodiazepines (mainly diazepam) are an indication for their use in some neurological disturbances for symptomatic relief of muscle spasms and spasticity. The muscle relaxant effect when combined with the sedative effect make the benzodiazepines useful for anaesthetic and pre-anaesthetic procedures (Bellantuono et al., 1980). Some benzodiazepines also have a role in anticonvulsive treatment.

1.4 THE EFFECTS OF THE BENZODIAZEPINES

The benzodiazepines have a number of effects: anti-anxiety, anticonvulsant, muscle relaxant and sedation. Sedation is viewed as having two components: (a) the patient's subjective reports of drowsiness, sluggishness and apathy, and (b) objective indications of impaired performance on various tasks. Aspects of this latter component will be considered in detail in later parts of the introduction.

The sedative effect can be useful if the drug is prescribed as a night-time hypnotic and here drowsiness and sleep are the desired effects. However, if the benzodiazepines are given during the daytime as antianxiety agents they are meant to reduce anxiety without producing generalised sedation (Greenblatt and Shader, 1974). Any behavioural impairment is undesirable and particularly so for those persons who are involved in working with heavy machinery

or who drive a motor vehicle (Clayton, 1976 and Kibrick and Smart, 1970).

Silverstone (1974) considers whether accidents are more common among patients taking psychotropic drugs than among similar patients not taking psychotropic drugs. In considering this question he writes (p.452):

> "The epidemiological information to date is inconclusive. On the one hand are studies which suggest that centrally acting drugs other than alcohol are a relatively unimportant factor in road traffic accidents. On the other hand there are studies which implicate centrally acting drugs much more. An example of the first is that reported by Walker (1971) in which blood samples were taken from those dying within 15 min of a single vehicle road traffic accident. The proportion of those who were found to have barbiturates (7 percent) or tranquillizers (1 percent) in their blood was not greater than that expected in the general population of California where the study took place. In sharp contrast to that finding is the earlier report by Murray (1960) describing a ten-fold increase in the expected road traffic accident rate among 68 drivers taking chloradiazepoxide over a 90 day period. Similarly a Japanese survey of taxi drivers who were taking tranquillizers revealed an increased accident rate among them as compared to non drug takers (Milner, 1972)."

1.5 ANXIETY

Since the benzodiazepines are mainly prescribed to alleviate anxiety, the following will be briefly considered; a definition of anxiety; methods of alleviation of anxiety and the advantages and disadvantages of the anxiolytics for alleviating anxiety.

1.5.1 A Definition of Anxiety

Anxiety is not an easy concept to define and there are various approaches to viewing the concept depending on one's theoretical orientation. A very useful approach is to list the major characteristics of anxiety. This is done very adequately by Lewis (p.14, 1980):

"1. It is an emotional state, with the subjectively experienced quality of fear or a closely related emotion.

2. The emotion is unpleasant.

3. It is directed towards the future.

4. There is either no recognisable threat, or the threat is, by reasonable standards, quite out of proportion to the emotion it seemingly evokes.

5. There are subjective bodily discomforts during the period of the anxiety. These include the sense of constriction in the chest, tightness in the throat, difficulty in breathing and weakness in the legs.

6. There are manifest bodily disturbances. These include dryness of mouth, sweating, palpitations, abdominal pain and giddiness."

Lewis (p.15) also lists those attributes which at some time have been included in the criteria of anxiety, but which he feels should be dispensed with as criteria of recognition of anxiety. Anxiety may be:

"1. normal (student taking an examination) or pathological.

2. mild or severe.

3. mainly detrimental to thought and action, or in some respects advantageous.

4. episodic or persistent (chronic)

5. due to physical disease (e.g. delirium tremens) or psychogenic.

6. accompanying other features of mental disorder or alone.

7. may for the duration of the attack affect perception and memory or may leave them intact."

1.5.2 Methods of Alleviation of Anxiety

Any approach that hopes to deal successfully with psychological problems will need to take account of the fact that those problems, e.g. anxiety, do not occur in isolation from the persons environment. Thus an adequate assessment of the person-environment system is essential. Different approaches tend to concentrate on different aspects of this system. Thus a broader approach such as family therapy would focus on the person's family environment whereas more individual approaches would concentrate more directly on the person. Psychotherapeutic approaches to anxiety problems include psychotherapies within the psychoanalytic, behavioural and humanistic-existential orientations. Drug treatment of anxiety problems can be viewed as a biologically based approach focusing on the individual.

1.5.3 Disadvantages and Advantages of Anxiolytics

The drug treatment of anxiety has various advantages. It has been shown in carefully controlled studies to be effective

in reducing anxiety. Anxiolytics are not time-consuming to administer and they do not require the use of techniques outside the experience of most doctors (Lader and Marks, 1971). Therefore in situations when the supply of trained psychotherapists and social workers is inadequate to meet the needs of the population drug treatment offers a useful alternative. However, unlike psychotherapy which generally increases the person's ability to deal with anxiety (e.g. relaxation training), drug treatment only alleviates the person's discomfort. Thus ideally psychotherapeutic approaches are preferred relative to drug treatment. Unfortunately psychotherapeutic approaches are frequently not available, are often financially unfeasible, or may in some instances represent in the patient's opinion an unacceptable alternative (Rickels, 1981). Therefore, as previously discussed, the benzodiazepines are widely prescribed and constitute the most commonly used approach to alleviate anxiety.

1.6 EVALUATION OF DRUGS - CLINICAL TRIALS

All prescribed drugs are evaluated according to their efficacy and safety (Taber, 1969). This is a complex process beginning with animal studies and then assessing the effects of these drugs in humans. The final phase and the crucial test of effectiveness of a drug is the controlled clinical trial. Uncontrolled trials are also carried out in the early stages of research. These involve administering

the pharmacologic agent to subjects and observing the target effects. The most important limitation of this approach is the failure to assess the contribution of placebo effects in psychotropic drug research. It is well known that target symptoms may appear or disappear either spontaneously in response to the aura of investigation, in response to the expectation of change, or because of investigator bias. For these reasons, the relevant pharmacologic agent should always be evaluated relative to a placebo which is an inert chemical substance administered in a way to make it indistinguishable from the pharmacologic agent. Uncontrolled trials can suggest whether further controlled study is indicated (Greenblatt and Shader, 1974).

The controlled clinical trial includes the use of a placebo. Neither the subjects nor the investigator is aware whether the substance taken is active or the placebo. This is known as a double-blind trial and is designed to deal with the placebo effect and investigator bias. However, the controlled clinical trial has not solved all the methodological problems of psychotropic drug research and numerous valid criticisms have been raised (Greenblatt and Shader, 1974).

Five of these points will be considered. A summary of the points of debate is presented by Greenblatt and Shader in the form of claims and counter-claims.

The first involves the claim that administering a placebo to a symptomatic patient is unethical. This is met by the following counter-claims:

> "(a) The treatment of millions of patients with a drug whose efficacy is not established is hardly ethical.
>
> (b) Depriving a neurotic patient of active medicaiton during a drug study is not akin to withholding penicillin from a patient with pneumoccal penumonia.
>
> (c) An active medication may be used instead of placebo as a reference substance" (Greenblatt and Shader, p.55, 1974).

The second is the claim that controlled trials are performed in a rigid, sterile, investigative setting and results therefore are not applicable to the setting of the usual doctor-patient relationship. This is countered by the assertion that valid psychopharmacological research may be performed within ongoing private practices and clinics, with no disruption of the therapeutic relationship.

The third claim is that the onset of action of the drug may not occur within the duration of the trial. The counter-claim to this is that the effects of anti-anxiety agents, when they occur, are almost always seen within seven days of therapy. Most drug trials last at least this long.

Fourthly, it is claimed that overall results of studies on large numbers of patients do not predict whether the drug will be of benefit to an individual patient. However,

nothing can unequivocally predict an individual's response to a drug. Physicians deal with probabilities, most reliably provided from experience with large numbers of patients.

The fifth important claim is that "double-blind" is seldom realistically valid. Both patient and investigator can distinguish between active and inactive medications on the basis of pharmacologic effects and side effects. There is no definitive counterclaim to this potential of non-blindness in the double design. This is a weakness which must be recognized and with which investigations must live. It should be noted that between 30% to 60% of anxious patients respond to placebo improving in anxiety and showing some side-effects similar to those found when they are given benzodiazepines. Thus the potential for non-blindness is less in clinical trials involving benzodiazepines than in clinical trials in general.

Another set of problems which plagues psychotropic drug research involves the "nonspecific" factors in drug therapy: characteristics of patient, physician, treatment setting, and disease which influence the response to drug and placebo, and hence the potential drug-placebo difference. The studies assessing non-specific factors in anti-anxiety drug therapy are summarized by Greenblatt and Shader. For example, Rickels et al. (1971) found that males improved more on drug than females, but the same on placebo. The influence of the various factors differs from study to study

and in some cases different investigators have found the same nonspecific factor to influence results in different directions. These nonspecific factors have to be considered when interpreting results of studies. A positive result could be due either to strong drug effects which overwhelm the nonspecific factors or to a fortuitous combination of non-drug factors which exaggerate the drug-placebo differences. A negative result could be due to an ineffective drug or to the influence of non-specific factors. Far more research has to be done on the influence of nonspecific factors in the drug treatment of anxiety. One possible result of further research is that generalizations about drug efficacy will be made with increasing reservation and limitation (that is with more specificity and sophistication).

2. PSYCHOMOTOR FUNCTION

2.1 DEFINITION

Hindmarch (p.190, 1980) has defined psychomotor performance as "the coordination of sensory and motor systems involved in the execution of skilled tasks resulting in regulated performance to meet the demands of the task and the needs of the individual". This coordination of the motor system with sensory inputs to achieve synchronised, integrated behaviour and performance of skilled tasks is one of the most important functions of the cerebral cortex and associated sub-cortical centres. The range of behaviour is extensive in that the level of skill required for its performance ranges from simple coordination as in picking up a small object to the complex sensori-motor integration involved in car driving.

Hindmarch (p.190, 1980) represents the various aspects involved in psychomotor performance schematically: this is reproduced overleaf as Figure 1.

Hindmarch then goes on to the various tests of psychomotor function which have been shown to be sensitive to a wide range of psychoactive drugs. These are summarized in Figure 2 which is reproduced from Hindmarch (p.201, 1980). This figure also clearly indicates the various components of performance, i.e. sensory, central nervous system, motor and overall coordination activity. This is discussed

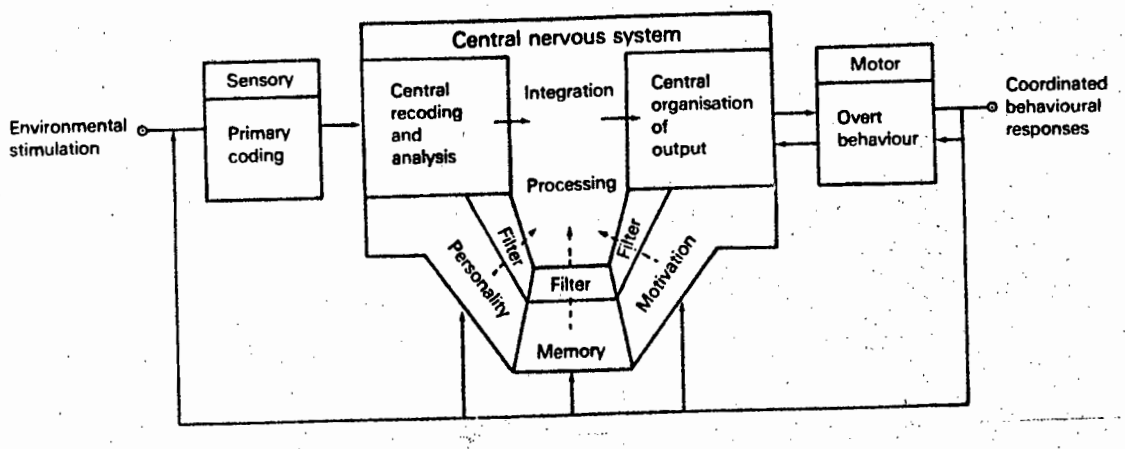


FIGURE 1: Psychomotor performance results from the co-ordination of sensory and motor systems through the integrative and organisational processes of the brain and central nervous system. The processing of sensory information is influenced by personality, memory and individual motivation, while the overall function of the integrative mechanism is governed by the state of arousal of the central nervous system. Complex feedback and adaptive systems complete the process by which environmental stimuli produce appropriate, co-ordinated behavioural responses.

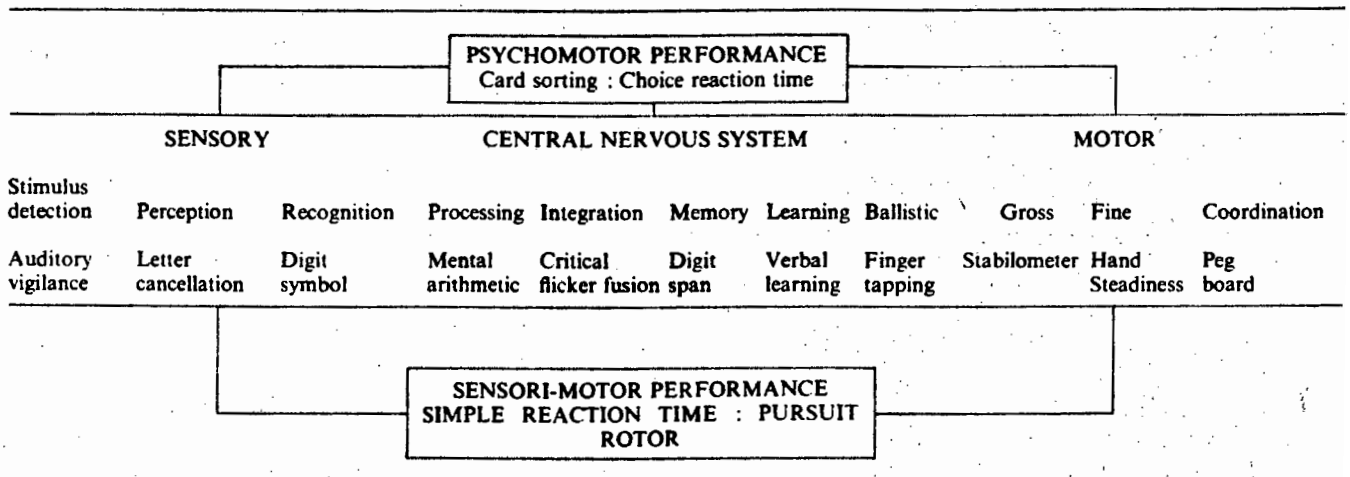


FIGURE 2: A summary of tests of psychomotor function which have been shown to be sensitive to a wide range of psychoactive drugs.

further on page 21 of this introduction.

The relationship between arousal and performance and the relationship between anxiety and performance which are both important in understanding drug effects on psychomotor performance will now be considered.

2.2 AROUSAL AND PERFORMANCE

Our level of conscious awareness fluctuates over time. These fluctuations in conscious awareness are not discrete steps but represent a continuously variable state from sleep at one end to extreme panic at the other end. The major stimulant and sedative drugs can be thought of as an artificial means of altering the level of arousal of an individual. Stimulant drugs shift the individual towards a state of higher arousal while sedatives will shift him in the opposite direction (Clayton, 1970).

There is an inverted U relationship between degree of arousal and psychomotor performance. Up to a certain critical point increased arousal leads to improved performance, however, beyond this critical point further arousal leads to a deterioration of performance. This relationship is relevant when one wishes to interpret the effects of drugs, that alter the level of arousal, on performance.

Besides this general effect, on the level of arousal and the consequent effect on psychomotor performance, sedative and

stimulant drugs also have two more specific influences on alertness which alter performance. Performance or repetitive tasks, such as observing a radar screen does not proceed uniformly. Instead, it is punctuated by a series of brief involuntary rest pauses lasting a second or two, when the subject takes time off from the task in order to recuperate. These rest pauses are noticed subjectively as lapses of attention and are often followed by a brief period of feeling more than usually wide awake. Objectively they appear in performance as blocks or gaps when no response is made. Clayton (1970) writes that the exact physiological basis of these pauses is unknown, but their onset is probably due to the gradual accumulation, in the nervous system, of an inhibitory process which the pause allows to be dissipated. These involuntary rest pauses are more likely to occur in states of low arousal and one way in which sedative drugs impair performance on vigilance tasks is by increasing the likelihood of rest pauses occurring (Clayton, 1970). Stimulant drugs, on the other hand, delay the onset of rest pauses and increase the chances that the subject is paying attention when a signal occurs during a vigilance task. This changing of the frequency with which the brain takes a rest is one way in which it reacts to shifts in its arousal level whether this is induced by drugs or the external environment. Normally then rest pauses only become a nuisance under rather special conditions of extreme monotony and even then only after sufficient time has elapsed for a rest pause to become necessary.

There is, however, another more immediate way in which our attention to the environment is altered in different states of physiological arousal. As arousal level rises the number and range of stimuli to which we pay attention diminishes. We become less distracted by stimuli that are not our immediate concern.

These several ways in which an individual's responsiveness to the environment can be altered by drugs normally occur together. Thus, the individual whose arousal level is shifted upward by a stimulant drug will become generally more alert, will show narrowing of attention, and will be less affected by monotony. The person's psychomotor performance will therefore be improved. Alternatively, a person taking a sedative drug will become generally less alert, will be more distracted by irrelevant stimuli and will be more affected by monotony and consequently their psychomotor performance will deteriorate.

2.3 ANXIETY AND PERFORMANCE

Yerkes and Dodson (1908) described the relationship between drive strength and performance. There is an inverted U-shaped curve relating drive to performance. The relationship implies that for each task there is an optimum drive level, both above and below which performance falls off. The optimum drive level varies with different tasks. For easy tasks this optimum drive level is high, whereas for difficult tasks it is low. These relationships are

perform taks which are very easy.

The inverted U-relationship between drive (e.g. anxiety) and performance can be used to explain why an anxious person's performance can improve if they are taking anxiolytic medication. If their initial anxiety level is high thus situating them on the downward part of the inverted U-curve a decrease in anxiety brought about by medication would result in them being situated more towards the top of the U-curve, that is to say, their performance will improve. Depending on the person's initial anxiety level anxiolytic medication may also result in diminished performance or no alteration in performance level. The same possibilities of performance either not changing or improving or deteriorating depending on the person's initial state also apply to arousal level which as previously indicated also has a U-shaped relationship with performance.

2.4 THE SELECTION OF ASSESSMENTS AND POPULATION GROUPS IN PSYCHOMOTOR PERFORMANCE STUDIES

Wittenborn (1980) discusses the need to develop a standard battery of tests to assess the behavioural consequences of psychotropic substances. He writes (p.171); "No standard battery would be sufficient to show all of the therapeutic potential or all of the untoward reactions consequent to many psychotropic substances. Nevertheless, knowledge of psychotropic substances in terms of a limited spectrum of responses could serve as standard benchmarks and would make all drugs subject to at least minimal comparison."

This knowledge would be useful in identifying at an early stage those drugs that caused considerable psychomotor impairment. In addition the knowledge could also help to facilitate the identification of psychotropic substances of therapeutic promise. The probable nature of the therapeutic consequences of a new drug might be suggested by considering the therapeutic effect of those familiar drugs which involve a pattern of behavioural responses similar to the new substance. Besides these two practical advantages the knowledge gained from such research will be of value in its own right, and even in the absence of immediate practical application it can be the basis for the generation of further knowledge which may indeed be practical.

The establishment of a standard assessement battery to assess the effects of psychotropic drugs on psychomotor performance involves the consideration of two questions. First, what assessments would best serve the purposes of such a program? Second, what population should be chosen to provide the standard referent responses?

2.4.1 The Selection of Assessments

A broad spectrum of psychomotor tests has been used in studying the behavioural effects of the benzodiazepines. Wittenborn asserts that researches have not been systematic in their selection of psychomotor tests. One reason for this is that there is no theory to guide the researcher in the selection of the behaviours and tests most appropriate

for showing psychotropic drug effects. Wittenborn therefore proposes that the best alternative is to use a pragmatic approach and to choose measures that are generally sensitive to detecting behavioural effects. A sensitive measure is one which has been shown to be able to detect significant differences in the behavioural effects of a 1,4 benzodiazepine relative to a placebo in a large proportion of the studies using that measure. Thus ciritical flicker fusion threshhold is a very sensitive measure; in five studies there were five discriminations between drug and placebo. Other measures which Witenborn in his review found to be very sensitive in studies during the first day of medication given to non-patient volunteers are measures of learning and memory, time estimation, the digit symbol substitution test, cancellation and card sorting. All significant effects showed the 1,4-benzodiazepine to have a detracting or disruptive behavioural consequence. These effects are discussed in more detail in a later section of the introduction.

Another important criterion which is not discussed by Wittenborn but emphasized by Kleinknecht and Donaldson (1975) and Hindmarch (1980) is to select tests so that the total battery would assess the whole range of the important components of psychomotor performance. The components and the various tests are clearly shown in the figure reproduced from Hindmarch (p.201, 1980). This is figure 2 on page 14 of this introduction. The major components are:

(a) Sensory function and sensory processing ability. The majority of sensory activity is made up of three levels

of information processing, i.e. detection, perception and recognition of a stimulus. A sensitive test of stimulus detection is the auditory vigilance test. A sensitive test of the perception stage is the letter cancellation assessment. A sensitive test of the recognition stage is the digit symbol substitution test.

(b) Central nervous system function and central processing ability. The two major subcomponents in the area of central nervous system function are integration and processing. A sensitive measure of central nervous system integration (level of arousal) is the critical flicker fusion threshhold. Sensitive measures of central processing ability are mental arithmetic and tests of memory (digit span test) and learning (verbal learning) tasks.

(c) Motor function and behavioural coordination. This component can be further classified into four components, ballistic activity, gross body balance, fine motor control and motor manipulative activity (coordination). The four corresponding sensitive psychomotor tests for each of these subcomponents are finger tapping (ballistic activity), Stabilometer performance (gross body balance) the Hand Steadiness Test (fine motor control) and the PegBoard Test (coordination).

It is also important to include at least one test of overall psychomotor (sensori-motor) performance which involves the

coordination of the sensory and motor system by the central nervous system. Sensitive tests in this area are Simple and Choice reaction time, The Pursuit Rotor test and card sorting.

2.4.2 The Selection of Population Group

Wittenborn is interested in ascertaining the behavioural effects of the benzodiazepines as distinct from their therapeutic effects. Studies on the behavioural effects of benzodiazepines in a patient population are not suitable for ascertaining the behavioural effects per se because the patient's therapeutic response will affect their performance. Since people adapt during the continued administration of psychotropic substances the person's initial response to the drug is the best indication of the behavioural effect per se. For these reasons Wittenborn states that the best way of determining behavioural effects per se is to study the initial effects (during the first day of medication) on non-patient subjects.

So if one is interested in obtaining a clear picture of the behavioural effects of benzodiazepine the approach advocated by Wittenborn is certainly appropriate. However, benzodiazepines are prescribed to anxious persons and one is primarily interested in the behavioural effects of continued benzodiazepine therapy on these anxious persons.

If it can be shown that equivalent results are found in

volunteer and anxious patient groups then volunteer studies could serve as clear basis for predicting with a large degree of confidence what will happen in anxious patients. However, until this has been unequivocally shown, and this is certainly not the case at the moment, volunteer studies can at best only suggest what will happen in anxious patients. There is therefore a definite need for studies that assess the psychomotor performance changes in patients during benzodiazepine therapy.

Most research assessing the psychomotor effects of the benzodiazepines has been carried out on non-anxious volunteers, primarily males. (Kleinknecht and Donaldson, 1975, in their review report that 79% of the subjects in the studies they reviewed were male whereas only 21 percent were female. They write that this proportion is not likely to be representative of the clinical uses of diazepam). In fact most benzodiazepines are prescribed to anxious persons mainly females (the appropriate proportion is two female users for every male user (Bellantuono et al, 1980)). (See page 1). Thus this research can be criticized for failing to carry out relevant studies on the actual group of persons (anxious mainly females not non-anxious volunteers mainly males) who receive benzodiazepine therapy.

There are a number of factors that have contributed to this situation. Research on volunteers is far easier to carry out from both a practical and ethical point of view than research on patients. Another factor seems to be the

unthought out acceptance of the idea that results found in volunteers can be used to predict with confidence what will happen in patients. The evidence confirming or disproving this idea is in fact only now being gathered.

Another criticism of research assessing the psychomotor effects of the benzodiazepines is the almost total lack of research reports that actually state their rationale of test selection. The criteria of test selection discussed previously in this introduction were ascertained by reading various reviews of psychomotor performance studies. This had been done prior to reading Hindmarch's 1980 review which carefully discussed similar criteria to the ones I had decided on. Most research papers simply state which psychomotor performance measures are being used without discussing why these measures are being used.

Before this section of the introduction is concluded it will be worthwhile to consider another issue relating to volunteer studies. Research in general investigates the effect of independent variables on dependent variables on a sample. The results found in this sample are then viewed as being representative of the population from which the sample came. There is some evidence that volunteers have different characteristics from those who do not volunteer for behavioural research (Rosenthal and Rosnow, 1969, and Ayd, 1972).

Rosenthal and Rosnow write:

> "On the basis of studied conducted both in the laboratory and in the field, it seemed reasonable to postulate with some confidence that the following characteristics would be found more often among people who volunteer than among those who do not volunteer for behavioural research:
>
> 1. Higher educational level,
> 2. Higher occupational status,
> 3. Higher need for approval,
> 4. Higher intelligence,
> 5. Lower authoritarianism.
>
> Two additional and somewhat more complicated relationships may also be postulated:
> (a) In survey-type research volunteers tend to be better adjusted than nonvolunteers, but in medical research volunteers tend to be more maladjusted than nonvolunteers.
> (b) For standard tasks women tend to volunteer more than men, but for unusual tasks women tend to volunteer less than men." (p.111)

They write further:

> "To the extent that true volunteers differ from nonvolunteers, the employment of volunteer samples can led to seriously biased estimates of various population parameters." (p.112).

These characteristics of volunteers subjects should certainly be taken into account when research with volunteers is carried out. One specific factor which is highly relevant to studies attempting to assess the effects of benzodiazepines is the extent of anxiety of the volunteer subjects. Ayd (1972) found that the psychopathology detected in medical research volunteers is usually mild. He asserts that the proper appraisal of the extent of psychopathology can be of value in defining the limits and specific effects of a drug. Another approach is to screen out those volunteers that

deviate from the norm on a relevant characteristic, for example, anxiety level.

2.5 APPROACHES TO ASSESSING PSYCHOMOTOR PERFORMANCE

There are a number of approaches to assessing psychomotor impairment (Biehl, 1979). The most important approaches are: (a) Laboratory tests which assess important aspects of performance e.g. reaction time, co-ordination, concentration, etc. (b) Laboratory studies where psychological tests are used as indicators of car driving performance. (c) Laboratory studies with simulation where a car driving situation is reproduced as realistically as possible. (d) Field studies of car driving performance in test areas or in real traffic conditions.

All these approaches are important to gain a clear picture of the psychomotor changes brought about by psychoactive drugs (for example the benzodiazepines). This study falls into the first category. The first approach is easier to employ from a practical standpoint. It yields general knowledge of how psychomotor performance is affected. The other approaches yield more specific practical information about car driving performance.

An important issue relating to the validity of the first approach is the extent that findings in the laboratory relate to car driving performance. Hakkinen (1976)

has conducted interesting research into this issue.

He looked at bus and tram driver accidents and ascertained the number of accidents that occurred over a specified time period. He found that there was a significant correlation between the accident coefficient (the number of accidents per year of exposure) of the first 8-year period of time and the second period of time which was an average of 9 years. This showed that the accident behaviour (accident proneness) of professional city bus and tram drivers was very constant. In addition, Hakkinen found that results on certain laboratory tests of psychomotor performance correlated significantly with the accident coefficient. These tests involved eye-hand coordination tasks and the more accident prone drivers did worse than the safe drivers on these tests.

Hakkinen found that the correlations of the psychomotor test variables with the accident criterion in different exposure periods were of the same order of magnitude. Correlations in the second period were approximately equal to those in the first period of time. Multiple regression analysis showed that the psychomotor tests could explain 50 to 65% of the total variance in accident proneness. In fact, if the results on the psychomotor tests were used to exclude those drivers who did badly on the tests when assessed after the first period of time then the number of accidents in the second period would have been greatly reduced.

Hakkinen's study reveals that the use of generalised assessments of psychomotor performance in the laboratory does have more specific relevance to the practical situation of car driving.

3. THE EFFECTS OF THE BENZODIAZEPINES ON PSYCHOMOTOR PERFORMANCE

3.1 THE EFFECTS OF THE 1,4 BENZODIAZEPINES ON THE PSYCHOMOTOR PERFORMANCE OF VOLUNTEERS

A number of important review articles will be considered to ascertain the general trends of how the 1,4 benzodiazepines affect psychomotor performance in volunteers as assessed on laboratory tests.

McNair (1973) reviewed research studies which were concerned with the behavioural effects of two benzodiazepines (chlordiazepoxide and diazepam) as well as another antianxiety drug - meprobromate. He found that only 12 percent of the studies were carried out on patients. He writes that "this paucity of studies directly relevant to clinical practice should be a matter of clinical concern." (p.612).

Significant effects on performance had been reported in about one third of the specific measure employed in the studies with the benzodiazepines. When the benzodiazepines were administered significant impairment occurred five times as often as facilitation (27 percent compared to 5 percent). He classified the measures administered in the various studies into categories. Then for each measure he tallied the instances of significant impairment

or facilitation of performance and the instances of nonsignificant effects on performance. The percentage of significant findings were considered to constitute an index of sensitivity of each measure of drug effect. The most sensitive tests in the benzodiazepines studies were: the pegboard test, learning paired associates, the digit symbol substitution test, critical flicker fusion threshhold, choice reaction-time and tapping speed. For example, out of the seven occasions when the digit symbol substitution test was administered significant impairment was found on five occasions.

In general McNair criticizes the studies of the effect of antianxiety drugs on human performance; "Almost two decades of laissez-faire research in the area have yielded no adequate, systematic data base for meaningful inferences" (p.615). He stresses that as a minimum scientists should select the best and most appropriate performance measures available. One important criterion the sensitivity of the measures.

Kleinknecht and Donaldson (1975) reviewed the literature describing psychomotor effects of diazepam. Of the 22 studies cited, only two were based on psychiatric population. The authors classified the various tasks used to assess drug effects into six major groups based on apparent similarity of functions tapped. These groupings were: reflex speed; critical flicker fusion threshhold; concentration and vigilance; decision making; learning and memory; perceptual

motor performance. Reflex speed as measured by simple reaction time tasks and tapping speed were not considered to be adversely affected by therapeutic levels (up to 15 mg/day) of diazepam. Critical Flicker Fusion Threshhold was sensitive to diazepam and even small doses lowered the threshhold. Concentration and vigilance as measured by letter cancellation and the digit symbol substitution test showed some impairment. There was generally a slowing down of performance (number completed in a given unit time). Various performances involving decision making (that is card sorting and choice reaction time) showed indications of a dose-related response: two studies using diazepam 10 mg showed no effect, whereas two studies based on 20 mg reported an effect. Three studies of learning and memory were reviewed. Because of the dissimilarity of the tasks involved, concluding statements were not offered with confidence. There is indication of impairment. It was suggested that the deficit may be in the consolidation process rather than in short term memory per se. The tasks grouped under perceptual motor performance are tracing (where time to complete a task is increased) and motor skill tasks involving driving simulators (where impairment is noted in one out of three studies), and pegboard performance (where impairment was found).

Kleinknecht and Donaldson also report that studies indicate that subjects taking diazepam tend to underestimate

the passage of time. In addition, they are unable to assess accurately their level of impairment and they may, therefore, not compensate adequately for any induced performance deficits.

Wittenborn (1979 and 1980) critically reviews the effects of benzodiazepines on psychomotor performance. He concluded that there is no general contrast in the qualitative effect of the various benzodiazepines. The effects of diazepam, lorazepam, chlordiazepoxide and nitrazepam are basically similar. In order to summarize the effects of the benzodiazepines, he classified the various tests according to what he judged to be the essential nature of the operation measured. In the studies he reviewed there were no instances where the benzodiazepines improved performance. The detracting effect was dose related. Less impairment was found at low doses than at higher doses. This conclusion is also discussed by Greenblatt and Shader (1974) in their review of the psychomotor effects of the benzodiazepines. They write:

> "reduction of anxiety often occurs after single doses of 5 to 20 mg of chlordiazepoxide or 2 to 4 mg of diazepam-doses which do not consistently produce intellectual and motor impairment in the laboratory. In some individuals, however, daily doses of 60 to 100 mg of chlordiazepoxide or 30 to 40 mg of diazepam are

> necessary to reduce anxiety or agitation. Clearly, such patients should be cautioned regarding the possible hazards of high dosage." (p.179).

Wittenborn grouped the various tests into 16 categories of psychomotor function. He then ranked them in order of the relative incidence of impairment. This is the ratio between the number of studies showing impairment in a given function and the number of studies that tested the respective function and this ratio is also known as the sensitivity of a function.

The most sensitive functions (showing impairment in most instances of assessment) were critical flicker fusion threshhold, memory, the digit symbol substitution test, cancellation and card sorting.

Hindmarch (1980) discusses psychomotor function and how it is affected by psychoactive drugs. His paper also includes a consideration of studies that assess the initial effects of the 1,4 benzodiazepines on performance in volunteers. In the Section on psychomotor performance, I have already discussed his approach to considering psychomotor function in terms of various components and he lists the tests which assess the various components which have been sensitive to a wide range of psychoactive drugs in general. This is shown

in summary form in Figure 2 on Page 14 of this introduction. In doing this he includes those studies that assess the initial effects of the 1,4 benzodiazepines on performance in volunteers. His findings are similar to Wittenborn's conclusions.

In general one can conclude that the 1,4 benzodiazepines have a dose-related detracting effect on performance in volunteers during their initial one to three days of medication. Assessments that have been shown to be relatively sensitive in detecting this impairment are the digit symbol substitution test, letter cancellation tests, critical flicker fusion threshhold, verbal learning and memory tests, pegboard test, card sorting and choice reaction time. It should be noted that impairment is generally but not always found on these tests. For example, Wittenborn (1979) states that in the ten instances he reviewed which used the digit symbol substitution test impairment was found in six out of ten applications.

3.2 PATIENT STUDIES WITH THE 1,4-BENZODIAZEPINES

A number of reviewers have commented on the lack of studies that assess the effect of the 1,4 benzodiazepines on patients.

McNair (1973) reviewed studies which investigated the effect of anti-anxiety drugs on human performance and noted that only 11% of these involved patients. He writes that it is startling that, considering the widespread use of anti-anxiety agents, we have so little directly relevant clinical information about the effects on performance of the drugs in patients. Kleinknecht and Donaldson (1975) in their review paper on the effects of diazepam on performance write:

> "Although diazepam is typically given only to medical, psychiatric, or dental patients, 17 of the 23 studies reviewed used young, "normal", healthy, volunteer subjects, primarily male" (p.403).

The studies that researched the effects of the 1,4 benzodiazepines on psychomotor performance in patients will now be considered. This will be done to ascertain if the effects found differ from those found in volunteers. Thus the studies will be considered briefly: that is the specific 1,4 benzodiazepines used, the specific psychomotor tests utilized and whether impairment was reported on those tests will be indicated.

Silverstone (1973) found that pursuit rotor performance was not impaired by either diazepam or lorazepam. Bond, James and Lader (1974) assessed patient's performance on the digit symbol substitution test, card sorting, auditory reaction time, key tapping, symbol copying, Gibson Spiral

maze, a cancellation task, arithmetic tasks and tachistoscopic recognition of numbers. The 1,4 benzodiazepines used were diazepam, chlordiazepoxide and medazepam. The only impairments found were on the Gibson spiral maze for paitents taking diazepam or chlordiazepoxide but not in those taking medazepam.

Tansella, Zimmermann-Tansella, and Lader (1974) found that N-desmethyldiazepam impaired performance on the digit symbol substitution test but not on card sorting. Malpas, Legg and Scott (1974) found that nitrazepam did not impair performance on either the digit symbol substitution test or on card sorting. Salkind and Silverstone (1975) found that flurazepam did impair performance on auditory reaction time but did not impair performance on key tapping and the pursuit rotor task except at higher doses.

Saario, Linnoila and Mattila (1976) found impaired performance in patients given diazepam on choice reaction time, critical flicker fusion, a tracking task, proprioception and auditory reaction time. Uhlenhuth et al. (1977) found that diazepam impaired choice reaction time. Dureman, Malmgren and Norman (1978) assessed the effect of clorazepate on critical flicker fusion, car driving in a simulator and on a bead and needle task. No impairment was reported.

Zimmermann-Tansella, Tansella and Lader (1979) found that diazepam impaired performance on card sorting, the Gibson spiral maze, cancellation tasks and key tapping. Simple

and choice reaction, the digit symbol substitution test, symbol copying and arithmetic performance were not impaired. Church and Johnson (1979) reported impairment on the digit symbol substitution test and choice reaction time but no impairment on digit span performance in patients given flurazepam. Saxena, Singh and Porter (1980) found that both lorazepam and diazepam impaired choice reaction time and key tapping. Linnoila, Erwin and Logue (1980) found no impairment in patients who were given flurazepam and who were assessed on simple reaction time, continuous performance, visual vigilance and digit span performance.

Salkind, Hanks, and Silverstone (1979) found that patients taking diazepam had impaired performance on the digit symbol substitution test but not on the pursuit rotor test. Paitents taking clobazam showed no impairment on either of the tests. This study will be considered again when the effects of clobazam on paitent's performance are discussed.

An overall consideration of these studies shows certain trends. The volunteer studies showed that impairment of performance is dose related. Higher doses are more likely to produce impairment. A similar trend is found in patient studies. For example Salkind and Silverstone (1973) showed that 30 mg flurazepam, and not 15 mg, significantly impaired performance on both the pursuit rotor test and the tapping speed test.

The tests that are sensitive to detecting impairment in

volunteer studies are also the most sensitive tests in detecting impairment in patients. However, the number of significant impairments in performance that are reported is less than in volunteers. This important conclusion can be clearly highlighted by considering the results of studies that included the digit symbol substitution test. It has already been noted that Wittenborn (1980) in his review of volunteer studies reported that in ten applications of the digit symbol substitution test significant impairment was found on six occassions. In the patient studies which I reviewed I found eight applications of the digit symbol substitution test and impairment was found in only two of these applications.

One possible explanation for the lesser frequency of significant impairment found in patients is the effect brought about by their lowered anxiety level as a result of benzodiazepine treatment. A previous section of the introduction discussed how too high a level of anxiety can impair performance and a decrease in anxiety level can result in improved psychomotor performance in patients thus offsetting the impairment of performance brought about by the sedative effect of the benzodiazepines.

3.3 THE EFFECTS OF CLOBAZAM ON PSYCHOMOTOR PERFORMANCE

The studies that have assessed the effect of clobazam on psychomotor performance in volunteers will now be considered.

Since the research investigating the psychomotor effects of clobazam on volunteers in relatively recent no comprehensive reviews exist as yet (unlike the 1,4 benzodiazepines were a number of reviews exist). This section will therefore consider the various specific studies in more detail than was done for the 1,4 benzodiazepines.

The first study reported was conducted by Berry et al. (1974). They conducted two studies. The first was after a single dose where the alternatives were clobazam 10 mg alone, clobazam 10 mg plus alcohol, alcohol alone, placebo, and diazepam 10 mg. This single-dose regimen was given at weekly intervals using a latin square design such that each subject received each treatment once. At hourly intervals after treatment for up to six hours the subjects were tested for braking reacting time on a driving simulator, pursuit rotor performance and arithmatic performance. Clobozam did not increase braking reaction time when compared with placebo, but diazepam 10 mg did produce a siginificant increase at 1-3 hours after ingestion. Pursuit rotor performance was significantly impaired one and two hours after dosage with diazepam and after two hours with clobazam. Whether these changes on pursuit rotor were relative to placebo was not indicated. Arithmetic performance was not significantly affected by diazepam or clobazam. In the second part of the study, four subjects received clobazam 10 mg three times daily for two weeks and two subjects received diazepam 5 mg three times daily for two weeks. Assessments were made before and after the

final dosage on day 14. After this period of continuing treatment there was an improvement in psychomotor performance, particularly after treatment with clobazam.

Since no placebo control was used in the repeated dose study the results cannot be interpreted with confidence. The enhanced psychomotor performance could be due to an unidentified practice effect. This whole study can also be criticized for being very briefly reported and for using a very small sample size. In addition the dosage of 10 mg diazepam used in the first part of the study is not equivalent in potency to 10 mg clobazam; 5 mg diazepam is the equivalent dosage to 10 mg clobazam. All these factors indicate that this study should be interpreted with caution.

Borland and Nicholson (1974) investigated the immediate effects on human performance of clobazam (20 mg), chlordiazepoxide hydrochloride (20 mg) and diazepam (20 mg). Choice reaction time and adaptive tracking performance (similar to the pursuit rotor test) were assessed. Five healthy male subjects were used each receiving all three medications on different occasions. Each drug was ingested at 09.00h and performance has measured at 09h 30min (0.5h), 11h 30min (2.5h), 14h 30min (5.5h) and 18h 30min (9.5h after ingestion).

With diazepam decrements in performance on adaptive tracking were observed at o,5h and 2,5h. With clobazam

performance at individual times did not differ significantly from control, but there was evidence of an improvement in performance during the day. There was no evidence of impaired performance on adaptive tracking after chlordiazepoxide hydrochloride. Reaction time was slowed at 0,5h, and 2,5h and 9,5h after diazepam and at 0,5h and 2,5h after chlordiazepoxide hydrochloride. No changes in reaction time were observed after clobazam.

This study showed that clobazam unlike diazepam and chlordiazepoxide hydrochloride did not have any detracting effect on adaptive tracking or on reaction time.

Hindmarch and his co-workers have carried out numerous studies on the psychyomotor effects of clobazam.

Parrot and Hindmarch (1975a, 1975b, 1977, 1978) investigated the effect of clobazam and other drugs on critical flicker fusion threshhold and choice reaction time. They reported that unlike the 1,4 benzodiazepines clobazam did not cause a lowering of critical flicker fushion threshhold. There were no significant changes in CFF threshhold produced by either 10 mg or 20 mg clobazam. In the choice reaction time tasks the subjects were presented with a stimulus light paired with a buzzer and had to respond by pressing the appropriate colour coded key which then terminated both stimulus light and buzzer. Responses were measured under two buzzer conditions; (a) where the buzzer was soft toned and mainly informative in fuction and (b) where the buzzer was loud and raucous.

A decrement in performance was found in the first condition but not in the second. The authors explain these differential changes in response speed as depending on the anxiolytic properties of clobazam. They hypothesize that by reducing state anxiety the overall drive or motivation to respond quickly is lowered. In the low reinforcement condition (soft toned buzzer) speeds were therefore reduced but in the high reinforcement condition (loud buzzer), where incentives to respond quickly are intrinsic to the task, response speeds were as fast as they would be normally. A similar differential effect was found for flurazepam. Nitrazepam, however, reduced reaction time at both high and low reinforcement conditions. This the authors write is probably due to the sedative as opposed to anxiolytic activity of the drug.

These studies indicated that clobazam has far less of a detrimental effect on CFF threshhold and choice reaction time.

Hindmarch, Hanks and Hewatt (1977) assessed the effects of clobazam (20 mg) on car-driving ability, choice reaction time, and the digit symbol substitution test. No significant detrimental effect on any of the performance measures was found. However, an examination of the raw data from two of the ten subjects showed a marked decrement in both car-driving ability and psychomotor performance. The authors note that this noticeable interference with car

driving performance in individual cases was not associated with length of car driving experience, or personality or any other easily identifiable factor, and can only be attributed to a specific "sensitivity" of certain individuals to the drug administered, since the impairment of car driving ability and of psychomotor performance was not generally found.

Hindmarch and Parrott (1978) and Hindmarch (1979) again showed that clobazam did not impair choice reaction time or lower critical flicker fusion (CFF) threshholds. Furthermore, these two studies produced evidence that clobazam in fact elevates CFF threshholds. In the 1979 study ten anxiety rated volunteers received 10 mg clobazam three times a day for a period of five days. Measures were taken the morning of the first, fourth and fifth days. The CFF threshholds were significantly elevated on the fourth and fifth day of the study; +0,8 Hz, p less than 0,01 and +1,6 Hz, p less than 0,01 respectively. These results led Hindmarch to hypothesize that the anxiolytic activity of clobazam could be due, in part at least to its ability to increase critical flicker fusion threshholds, that is central nervous system arousal and intergrating ability. This elevation that Hindmarch found is in sharp contrast to the reduction of CFF threshholds produced by the 1,4 benzodiazepines. In addition in the 1978, Hindmarch and Parrott also found that clobazam did not impair performance on a concept identification test.

Hindmarch (1979) once again showed that clobazam did not impair CFF threshhold, choice reaction time and stabilometer performance. In this study CFF threshholds were significantly elevated. Hindmarch and Parrott (1980) again confirmed that 10 mg and 20 mg doses of clobazam did not impair choice reaction time. The 10 mg dosage had no effect on CFF threshhold. However, the 20 mg dosage resulted in a significant reduction in CFF threshhold. This is the only occassion that clobazam resulted in significant reduction in CFF threshhold all other research findings have shown clobazam to either not effect CFF threshholds or to result in significant elevation of CFF threshholds.

HIndmarch and Parrott (1979) measured the effects of clobazam (30 mg) and dipotassium chlorazepate (15 mg) a 1,4 benzodiazepine on choice reaction time, critical flicker fusion (CFF) threshhold, a concept identification task and mental arithmetic. Clobazam did not impair performance on any of these tasks. Once again it was found that clobazam was associated with a significant increase in CFF threshhold. Dipotassium chlorazepate produced a slight depression of CFF threshhold when compared to placebo but the results were not significant. In the concept identification task dipotassium chlorazepate significantly increased the response latency for the correct solution of the easy concepts, however, there was no impairment at the more difficult level. The choice reaction time and mental arithmetic taks were not impaired by dipotassium chlorazepate.

Hindmarch and Gudgeon (1980) investigated the effect of lorazepam (1 mg three times daily) and clobazam (10 mg three times daily) as compared to placebo on twelve female volunteers. The medication was taken for three days and testing was carried out on the morning of the fourth day after taking a further single dose of medication. The subjects were assessed on concept identification task, motor manipulation measured on a pegboard, mental arithmetic tasks, letter cancellation tasks and five car handling tasks. In addition subjective ratings of alertness were obtained on visual analogue rating scales and side effects were recorded.

The concept identification and pegboard tasks were not affected by either clobazam or lorazepam. The mental arithmetic tests involving the serial subtraction of numbers showed a significant difference between the three treatment means for the time taken to sequentially subtract either twenty 3s or 7s from a five digit number. Lorazepam impaired performance for the serial subtraction of 3s or 7s whereas clobazam impaired performance only in the one task the subtraction of 3s.

In the letter cancellation task the time taken to cancel either 1, 2, 3, or 4 letters from pages of random letters was impaired by lorazepam for 2 and 4 letter cancellations and by clobazam only for 4 letter cancellations.

Lorazepam impaired performance on four of the five driving tests whereas clobazam did not result in any impairment on

the car driving tests. Lorazepam was perceived as resulting in subjective feelings of drowsiness as measured by the visual analogue scale and was also associated with significantly more sedative side effects than clobazam. Thus although clobazam did cause some impairement (serial subtraction of 7s and cancellation of 4 letters) it produced far fewer incidences of impairment and far less subjective evidence of sedation.

Wittenborn, McGrough and Nash (1979) compared the effects of diazepam (5 mg three times daily) and clobazam (10 mg three times daily) against placebo effects over the course of the initial day of medication. Tests were administered at hourly intervals and the data were analyzed from the standpoint of contrasts at each session and from the standpoint of trends that occurred during the course of the day. Seven measures were taken. Four of these measures, the digit symbol sybstitution test, a test of numerical ability, a time estimation test and a simple vigilance test, provided no significant distinction among the three medication groups. The spontaneous perceptual reversals reported by the subject, while gazing at the Necker cube for one minute were counted for each of the ten hourly sessions comprising the daily sequence. The pattern of acquisition over the day was impaired in the diazepam group. In the complex vigilance task there was significant impairment in the diazepam group. The clobazam group did not show any impairment in fact there were indications of enhancement of performance as shown by a significant general trend

toward fewer incorrect responses. The other test of performance involved the assessment of equilibrium by a balance beam procedure. In this test there was also an indication of enhancement of performance in the clobazam group which was associated with relatively fewer missteps. Commenting on these results the authors wrote,

> "it is suggested that 5 mg three times daily may be near the threshhold for psychomotor detraction during the initial day of diazepam medication and that clobazam 10 mg three times daily has no appreciable detracting, and may have some enhancing effects" (p.75).

The various studies on volunteers indicate that clobazam is virtually free of detrimental effects on psychomotor performance. Those tests adversely effected by 1,4 benzodiazepines are generally not adversely effected by clobazam. Specifically critical flicker fusion threshhold (CFFT) is consistently significantly lowered by the 1,4 benzodiazepines, for clobazam Hindmarch and his associates have shown five instances when CFFT was not changed, one instance where CFFT was significantly lowered (after 20 mg of clobazam a fairly high dose and five instances of significant elevation. Another exception to these general findings (of clobazam not having a detrimental effect on performance) was in the Hindmarch, Hanks and Hewett (1977) study where two of the ten subjects showed impaired performance. This finding could only be explained by attributing the impairment to a specific "sensitivity" of these two individuals. This "sensitivity" has not been reported in any other studies.

Although research indicates that clobazam does not have the objective indication of sedation (impairment in performance) there is evidence that drowsiness (considered as a subjective indication of sedation) occurs in patients receiving clobazam. In clinical trials assessing clobazam's anxiolytic effects drowsiness is the most commonly reported side-effect (Koeppen, 1979). Three times as many patients report drowsiness when treated with clobazam (about 17%) relative to those receiving placebo (about 6%) (Brogden et al., 1980). In double-blind studies comparing clobazam with diazepam the overall incidence of reported drowsiness is very slightly less for clobazam. In discussion on Ban's (1979) paper Stonier comments that drowsiness reported by patients receiving clobazam may reflect something other than sedation. Most clinical trials simply note the incidence of drowsiness and in order to investigate this phenomenon it is important to gain a more precise assessment by ascertaining the degree of drowsiness experienced by the particualr patient.

Only two studies have investigated psychomotor performance in patients receiving clobazam. Doongaji et al. (1979) conducted a double-blind clinical trial on out-patients diagnosed as "anxious neurotics" by two independent psychiatrists. The patients responded equally well in terms of anxiety reduction to clobazam (30 - 40 mg daily) and to diazepam (15 - 20 mg daily). Clobazam was superior to diazepam on the 15th day of the trial on the hand steadiness test (a measure of motor co-ordination), although this

difference was not detected at any other evaluation period (measures were taken on days 8, 15, 22 and 29). It was especially patients with high initial error scores who showed improved performance on clobazam the difference was significant on day 15 of the trial.

Salkind, Hanks, and Silverstone (1979) conducted a double-blind clinical trial comparing clobazam, diazepam and placebo in anxious patients attending a general practitioner. Both clobazam and diazepam significantly reduced anxiety whereas placebo did not. Two measures, the digit symbol substitution test (DSST) and the pursuit rotor test, were assessed prior to treatment and after two weeks of treatment. They compared the variation in performance in the three groups. The placebo group showed a significant improvement in performance on both tests due to learning effects. The clobazam group showed an improvement in both tasks but significantly so only for the DSST. The diazepam group performance did not change. This indicates that diazepam produced an impairment in performance (objective sedation) in both the DSST and the pursuit rotor test that negated the learning effect seen in the placebo group. The authors do not comment on the lack of significant improvement in the clobazam group on the pursuit rotor test. Since the placebo group showed significant improvement on this test and therefore one can conclude that clobazam also enduced impaired performance on the pursuit rotor test. Clobazam of course did not produce impaired performance on the DSST.

4. AIMS AND OBJECTIVES OF THE PRESENT STUDY

Both the studies investigating the effect of clobazam on patient's performance measured only limited aspects of psychomotor performance and were mainly concerned with anxiety changes. Both compared clobazam to diazepam and there is a clear need to make a comparison with lorazepam, another widely prescribed 1,4 benzodiazepine (Hedges et al., 1971; Siassi et al., 1975 and McCurdy, 1979). Neither the Doongaji nor the Salkind study referred to previously included a short-term (after 24-48 hours of treatment) assessment. This is the period when impairment of performance due to sedation is very likely to be shown (Wittenborn, 1979a).

The present study then aims to systematically investigate the effects of clobazam and lorazepam relative to placebo on patients' performance. A shorter-term assessment (after two days) and a longer-term assessment (after nine days of treatment) will be included to ascertain if there are any changes in drug effects on performance over time. This will allow drug accumulation and/or adaptation effects to be ascertained. A number of carefully selected performance measures will be used, one important selection criterion being that these measures should have a relatively high sensitivity in detecting impairment in persons (non-anxious volunteers) receiving a 1,4 benzodiazepine relative to those receiving a placebo. Another important criterion being that the

total battery of measures should assess the whole range of the important components of psychomotor performance.

The primary emphasis will be on performance effects, but anxiety changes and the incidence and degree of drowsiness will also be investigated. The results of the study will have implications as to the generalization of previous research findings on drug induced performance changes in volunteers to patients.

5.1 SUBJECTS

The patients were selected from those patients who had been prescribed a 1,4 benzodiazepine by a doctor at Retreat Day Hospital. A day hospital was chosen due to the availability of patients and the greater likelihood that the patients would return for subsequent assessments as most would live relatively near to the hospital. All patients assessed as needing 1,4 benzodiazepine treatment were referred to the investigator either by a doctor or by the pharmacist.

Patients who were excluded from the study were: (a) those that were on concomitant psychotropic medication or any other medications likely to affect psychomotor performance, (b) patients with alcoholic problems, (c) patients who have taken tranquillizers over the last three weeks, (d) patients under the age of 18 or over the age of 65.

In total, 120 patients were started on the trial medication. It was hoped that 70 to 80 patients would complete the trial (this allows for a 33,3 to 42% drop-out rate), so that on completion of the trial there will be approximately 23-27 patients per treatment group. The sample size of 70 to 80 was ascertained by considering various statistical and practical criteria (Gilbert, 1977).

5.2 APPARATUS

The main criteria on which the laboratory measures which would assess aspects of psychomotor performance were selected, was that previous studies have shown that the measures have a relatively high sensitivity to detecting drug (1,4 benzodiazepine) - placebo differences, i.e., significant impairment relative to placebo. Another important criterion was that the tests take a fairly short time to complete, so as not to take up too much of the patient's time. The tests were also selected so that the total battery would assess a variety of important aspects of performance. In terms of the tests discussed in the introduction (p. 14 and p. 21); one test was selected that assessed sensory function and sensory processing ability - that is the Digit Symbol Substitution Test (DSST) which involves the recognition phase of information processing: One test was selected that assessed central Nervous System Integration (Alertness) - that is the assessment of Critical Flicker Fusion Threshhold (CFFT); One test was selected that assessed central processing ability - that is the Inglis Paired Associate Learning Test (INGLIS) which involves verbal learning and memory; one test was selected that assessed motor function and behavioural coordination - that is the Purdue Pegboard Test (PPT) which primarily involves the coordination component of motor function and one test was selected which assesses overall psychomotor performance - that is the Choice Reaction Time (CRT) test.

5.2.1 The Digit Symbol Substitution Test

This is a performance sub-test of the Weschler Adult Intelligence Scale. The test assesses the ability to sustain concentration as well as a number of other aspects including motor coordination, visual acuity and speed of performance (Matarazzo, 1972; Mirsky and Kornetsky, 1964). The reliability of the test has been established in studies assessing the reliability of the W.A.I.S. (Matarazzo, 1972).

5.2.2 Critical Flicker Fusion Theshold (CFFT)

This is the frequency at which the patient perceives a flickering light as a stable non-flickering light source. The subject was required to discriminate flicker in one of a set of four light-emitting diodes as the frequency changes from a lower to a higher frequency. This measure is viewed as giving an indication of cortical arousal and integration (Hindmarch, 1978). Since pupil size effects CFFT an artificial pupil was used to control for pupil size (Smith and Misiak, 1975). This consists of spectacles which are movable perspex transluscent discs with two millimeter holes drilled in each lens. The CRT and CFFT measures were carried out in darkened conditions which were kept uniform for all assessments. The CRT was carried out prior to the CFFT and thus patients were given time (about 15 minutes) to adapt to the semi-darkness. This period of dark adaptation is important (Smith and Misiak, 1975). The patients were given two practice trials

and three actual trials. The mean of the three trials was taken as the measure of CFFT.

5.2.3 Memory Performance

Memory performance on short-term tasks has been shown to be impaired in persons receiving 1,4 benzodiazepines and memory performance has not been investigated with clobazam. The memory test would be one that took a brief time to administer. McNair (1973) in his review on the effects of antianxiety drugs on human performance noted that learning paired-associates was a measure which had high sensitivity in detecting drug effects. On considering these criteria it was decided to use the Inglis Paired-Associate Learning Test (Inglis, 1959). This test has been shown to be sensitive to memory impairments and to be relatively independent of general intelligence level (Inglis, 1959; Caird and Sanderson, 1962). The test was designed to assess memory impairment in elderly patients. It is viewed as a test of the acquisition phase of learning. The patients were read three pairs of words.

They were then given the first word of a pair as a stimulus and were expected to respond with the correct second word as a response. The first words of the pairs are presented one by one in a random order. The material was presented in this way until the patient got three consecutive correct responses for each pair. Inglis,

constructed two equivalent sets of pairs of words.

Since there are three assessments in this study a third equivalent set of three pairs of words was constructed on the basis of similarities in abstractness-concreteness, imagery values, word association values, and Thorndike-Lorge frequency of the nouns (Paivio, 1968). The three forms of the test are in Appendix 2.

5.2.4 Purdue Pegboard Test

This test is primarily a measure of coordination and dexterity. It involves placing small pins into a set of holes. Patients did three separate tasks. The first involved placing as many pins as possible into a row of holes in 30 seconds with the preferred hand. The second involved placing pins in two rows of holes with both hands for 30 seconds. This third involved constructing assemblies of pins, collars and washers with both hands for 90 seconds. Adequate reliability has been ascertained for this test (Tiffin, 1968).

5.2.5 Choice Reaction Time (CRT)

This will be measured on the Leeds Psychomotor Tester which is a portable apparatus capable of measuring critical flicker fusion threshold and choice reaction time. The patient responds as quickly as possible moving

their index finger of the preferred hand to extintuish one of six stimulus lights which illuminate on a random basis. The test involves a decision making component and speed. (Kleinknecht and Donaldson, 1976). There were 10 practice trials, and then 20 test trials, the mean of which was taken as the performance measure. The positioning of the response panel with respect to the subject's finger and hand was kept constant so that repeated measures would be reliable (Hindmarch, 1975a). The stimulus light in the choice reaction time task are fairly widely separated so that a high level of sustained attention was needed to maintain an optimum performance level (Hindmarch, 1978).

5.2.6 Assessment of Anxiety

The Hamilton Anxiety Rating Scale was used to assess anxiety (Hamilton, 1958). This is a rating scale of high reliability which is used in much of the research on antianxiety drugs. It consists of ascertaining by interview the occurrence and degree of severity of psychological and physiological manifestations of anxiety states (Appendix 4). In addition, a visual analogue scale of anxiety which the patient filled in by placing a cross on a 10 centimetre line according to their degree of anxiety-calmness, was used (Appendix 5). Visual analogue scales are viewed by some investigators as useful measures of mood states (Aitken, 1969; Zealley and Aitken, 1969). A visual analogue scale of the patient's

motivation in their daily activities was also given (Appendix 6). This is in order to explore possible motivational changes during drug treatment. Wittenborn (1979a & b) noted that clobazam may induce motivational enhancements. Luria (1975) has reported adequate reliability and validity of visual analogue scales.

5.3 PROCEDURE

Once a patient had been referred to the investigator by a pharmacist or a doctor the investigator assessed if the patient was interested and suitable for inclusion in the study. The nature of the study was explained to the patients in an appropriate way. They were told that they would receive medication that would help them to relax and that should help to alleviate their particular complaints; for example insomnia and headaches. They were told that a possible detrimental effect of the treatment is that some patients experience mild transient drowsiness and that they should avoid alcohol over the nine days that they are taking the capsules. In addition, they were informed that their ability to perform quickly would be assessed. If the patient agreed to participate in the study, they were told that they would be compensated for travelling expenses. Informed consent in writing was obtained from all patients (Appendix 3). The informed consent form was drawn up on the basis of the recommendations in the Declaration of Helsinki (The World Medical Association, 1975).

If a particular patient had not improved after the nine days of treatment they were if necessary given their original prescribed medication. Previous research has shown that many patients (about 40%) with anxiety problems do respond to a placebo favourably (Greenblatt and Shader, 1974). This research has been passed by the Ethical Review Committee at the University of Cape Town Medical School.

The procedure of the study was the standard procedure for conducting a clinical trial (Taber, 1969). The patients were allocated randomly and on a double-blind basis to either of the following treatments: (a) 10 mg. clobazam capsule twice a day, (b) a 1 mg. lorazepam capsule twice a day, and (c) 1 placebo capsule twice a day. (10 mg. of clobazam is equivalent to 1 mg lorazepam (Koeppen, 1979)). All capsules looked identical and were enclosed in coded containers. The containers were coded in groups of three. The first group is A1, A2 and A3; the second is B1, B2 and B3 - and so on. The type of drug contained in each group of three containers had been randomized. The first patient received A1, the second A2 and so on. The investigator and patient were thus blind to the type of medication dispensed. The containers were made up and coded by the firm funding the study, Roussel Laboratories South Africa. A copy of the code was kept by the head pharmacist at the hospital in case it is necessary to know what treatment a particular patient is receiving for urgent medical reasons (Taber, 1969).

The patients were assessed before starting treatment, at two days after starting treatment, and again at nine days, when treatment stopped. A particular patient was assessed at the same time of day for each visit, for example early in the morning for all three assessments so as to control for time of day effects on performance. The patients were asked not to drink alcohol or smoke cigarettes or to drink more than one cup of coffee on the days on which they are assessed as this would effect their psychomotor performance (Lewis at al, 1969; Barlow and Baer, 1967). If a particular patient had been smoking or drinking alcohol or excessive coffee on the initial day of attending the hospital they were not assessed on that day but on the next day.

Once the initial biographical information (age, marital status, occupation and educational level) was obtained from the patient the assessments were administered by the investigator in a standardized manner in the following order: (a) Hamilton Anxiety Rating Scale, (b) Visual Analogue Scale for anxiety, (c) Visual Analogue Scale for motivation, (d) Digit Symbol Substitution Test, (e) Purdue Pegboard Tests, (f) Choice Reaction Time, (g) Critical Flicker Fusion Threshold, (h) Inglis Paired-Associate Learning Test. A similar order of assessments was used at the two and nine day appointments. The occurence and degree of drowsiness (Absent = 0, Mild = 1. Moderate = 2, Severe = 3 and Very Severe = 4) was also noted at the day two and day nine assessments. The time

taken to complete the assessments was about 45 to 60 minutes.

The patients were encouraged to do their best on the psychomotor performance tests. This was done in a standard manner so as to maintain constant conditions of motivational instructions throughout the study. The subjects' level of motivation is known to effect psychomotor performance (Hindmarch, 1980).

After the assessment at nine days, five millilitres of blood was drawn by a nursing sister. Blood assays for clobazam or lorazepam were carried out by the Department of Pharmacology, Stellenbosch University at Tygerberg Hospital. The method of assay involved electron capture detection and gas chromatography and was partly adapted from Peat and Kopjak (1979).

A number of other measures were used to ensure compliance. The patients were encouraged to take their capsules. At the end of the first visit only the necessary dosage of four capsules which would be taken between the initial and the day two appointments was dispensed, to encourage the patients to return for their day two visit for further medication. This made a check on compliance after two days relatively easy. The capsules for the next seven days of treatment were dispensed after completion of the day two assessments. Since there would be an additional ten capsules beyond the

14 required for one week of treatment between the second and third visits, the patients were asked to return their remaining capsules on their third visit and then these were counted as a further check on compliance. In addition, the patients were asked about their degree of adherence to the twice-a-day dosage schedule to ascertain compliance (Blackwell, 1976).

After the completion of the final assessments and blood sampling the patient was given a booklet "Coping with Tension" (Ackerman, 1979) which contains some useful information including a short description of relaxation exercises which the investigator briefly discussed with the patient.

5.4 STATISTICAL ANALYSIS

A two-way analysis of variance was used to analyse the results on each measure. Factor A is type of drug. There are three levels, placebo, clobazam, and lorazepam. Factor B (repeated measures)is time of assessment. Here there are three levels, before treatment, at two days (short-term), and at nine days (longer-term). Thus the major aims of the research, differences between treatments, changes over time and the interaction between these two independent variables, can be explored.

Intercorrelations between the various dependent variables

was also explored. Since a number of two way anovas will be conducted on data from the same subjects a more stringent level of significance (less than 5%) was used to minimise the chance of Type I errors. Homogeneity of error variance (an important assumption of the anova) was checked. Since the number of drop-outs was different in each treatment group unequal sample sizes arose. Appropriate statistical solutions have been employed to deal with this, that is "unweighted means analyses" (Gilbert, 1977b).

6. RESULTS

TABLE 1: Details of number of patients, age and sex distribution and education level.

Type of Treatment	Placebo	Clobazam	Lorazepam
Initial number of patients	40	40	40
Number of patients who completed treatment and whose blood assays indicated that they were complying with treatment	20	27	23
Age range	18-63	18-51	20-57
Median age	35	38	32
Number of males who completed and complied with treatment	1	4	2
Median school standard passed	5	5	5

A total of 70 patients out of 120 successfully completed treatment. The blood assays of these 70 patients indicated that they had complied with treatment. Seventy-three patients completed their treatments but three patients had to be excluded from the study because their blood assays indicated that they had been taking some other form of benzodiazepine in addition to the trial medication. Two

of these patients were in the clobazam group and one in the placebo group.

As can be seen from Table 1 the three treatment groups are broadly comparable and the slight differences between them are not significant. Specifically the difference in drop-out rates in the three treatment groups was shown to be no different from what one would expect by chance when a Chi-square analysis (Section 6.3) was carried out. The groups were made up predominately of female patients. The median school standard passed (Std. 5) was similar for each group. The age ranges and median ages of the three groups differ very slightly.

6.1 TWO WAY ANALYSIS OF VARIANCE (WITH REPEATED MEASURES ON FACTOR B)

For clarity of presentation each of the variables will be considered separately.

6.1.1 Hamilton Anxiety Scale

TABLE 2: Mean (± s.d.) Hamilton Anxiety Scale (HAS) Scores.

	Pre-treatment (B1)	After 2 days (B2)	After 9 days (B3)
Placebo (A1)	20,65 (± 3,9)	14,30 (± 3,8)	13,15 (± 4,4)
Clobazam (A2)	22,74 (± 4,7)	15,07 (± 4,8)	12,07 (± 5,0)
Lorazepam (A3)	23,91 (± 4,3)	14,78 (± 3,5)	11,39 (± 3,0)

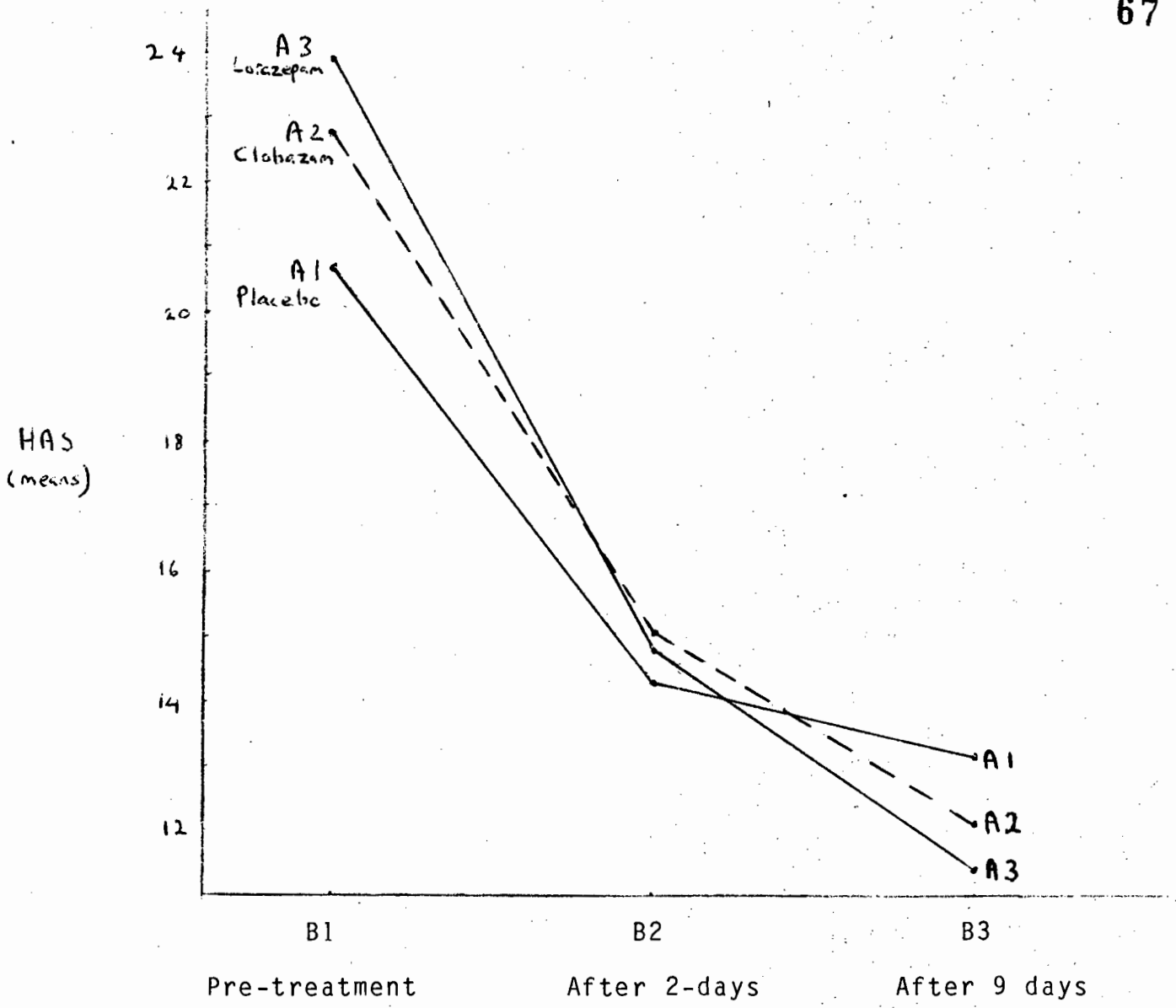


FIGURE 4: HAS Cell mean profile.

The means of the three treatment groups at the three times of assessment for the Hamilton Anxiety Scale are shown in Table 2 and illustrated in Figure 4. The cell mean profile indicates that there are different trends in anxiety changes in the three treatment groups during the course of treatment.

The two-way analysis of variance will indicate if these trends are significant.

TABLE 3: Anova summary table for HAS scores.

Source	df	MS	F ratio
Between subjects			
A (type of treatment)	2	9,18	0,225
Subjects	67	40,79	
Within subjects			
B (time of assessment)	2	1959,46	282,14**
AB (interaction)	4	37,6	5,41**
Residual	134	6,95	

** $p < 0,01$

Table 3 shows that the interaction (AB) effect is significant ($p < 0,01$) and therefore the main effects cannot be interpreted and simple main effects have to be investigated. A significant interaction effect implies that there are different trends at each level of a particular factor. The simple main effect analysis will indicate specifically which of these trends are significant.

TABLE 4: Simple main effects summary table for HAS

Source	df	MS	F ratio
A at B1	2	57,94	3,18*
A at B2	2	3,45	0,19
A at B3	2	16,70	0,91
Within	201	18,23	
B at A1	2	326,32	46,98**
B at A2	2	817,00	117,64**
B at A3	2	964,70	138,90**
Residual	134	6,95	

* $p < 0,05$

** $p < 0,01$

The significant ($p < 0,05$) F ratio for A at B1 (Table 4) means that the treatment groups (A) differed significantly from each other in HAS scores at pre-treatment (B1). The specific significant differences will be ascertained by a Tukey HSD (honestly significant difference) analysis.

The significant ($p < 0,01$) F ratios for B (time of assessment) at A1 (placebo), B at A2 (clobazam) and B at A3 (lorazepam) mean that there were different changes in HAS scores in each of the three treatment groups over the course of the three assessments. The specific significant differences will be elucidated by Tukey HSD analysis. These different

trends can be seen in Figure 4. For example, the placebo group has an initial HAS score below the other treatment groups but after 9 days of treatment it has a higher HAS score.

TABLE 5: Tukey HSD results for A at B1, i.e. three treatment groups at pre-treatment assessment (B1).

	Placebo (A1)	Clobazam (A2)	Lorazepam (A3)
A1 (20,65)+	-	3,80*	5,72**
A2 (22,74)		-	2,21
A3 (23,91)			-

* $p < 0,05$

** $p < 0,01$

\+ Note the actual means being compared are shown on the left hand column of the table - this convention will be adopted for clarity in all the other Tukey HSD tables.

Table 5 shows that the mean HAS score ofthe placebo group (A1) is significantly ($p < 0,05$) lower than the mean HAS score of the clobazam group (A2), and that the mean HAS score of the placebo group (A1) is significantly ($p < 0,01$) lower than the mean HAS score of the lorazepam group (A3). The mean HAS of the clobazam group (A2) do not differ significantly from those of the lorazepam group (A3).

TABLE 6: Tukey HSD results for B at A1, i.e. three assessment times for placebo group (A1).

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (20,65)	-	10,78**	12,73**
B2 (14,30)		-	1,95
B3 (13,15)			-

** $p < 0,01$

Table 6 shows that the mean HAS score in the placebo group at pre-treatment (B1) differs significantly ($p < 0,01$) from the mean HAS score at 9-days (B3) and that the mean HAS scores at pre-treatment (B1) also differ significantly ($p < 0,01$) from the mean HAS score at 2-days (B2). The mean HAS scores at 2-days (B2) do not differ significantly from those at 9-days.

TABLE 8: Tukey HSD results for B at A3, i.e. three assessment times for lorazepam group (A3).

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (23,91)	-	16,62**	22,79**
B2 (14,78)		-	6,17**
B3 (11,39)			-

** $p < 0,01$

Table 8 shows that the mean HAS scores drop significantly ($p < 0,01$) in the lorazepam group (A3) from pre-treatment (B1) to the 2-day assessment (B2) and continue to drop significantly ($p < 0,01$) to the 9-day assessment (B3). The change from B1 to B3 is also thus significant ($p < 0,01$).

6.1.2 Visual Analogue Scale for Anxiety

TABLE 9: Mean (± s.d.) Visual Analogue Scale for Anxiety (VAS-A) Scores.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	76,40 (± 21,7)	42,65 (± 28,5)	27,05 (± 27,9)
Clobazam (A2)	81,89 (± 21,1)	54,00 (± 33,7)	27,04 (± 27,4)
Lorazepam (A3)	86,90 (± 11,2)	41,13 (± 27,8)	23,04 (± 19,6)

The means of the three treatment groups at the three times of assessments for the Visual Analogue Scale for Anxiety are shown in Table 9 and illustrated in Figure 5. The cell mean profile indicates slightly different trends in anxiety scores in the three treatment groups during the course of treatment. The 2 way analysis of variance will indicate if these trends are significant.

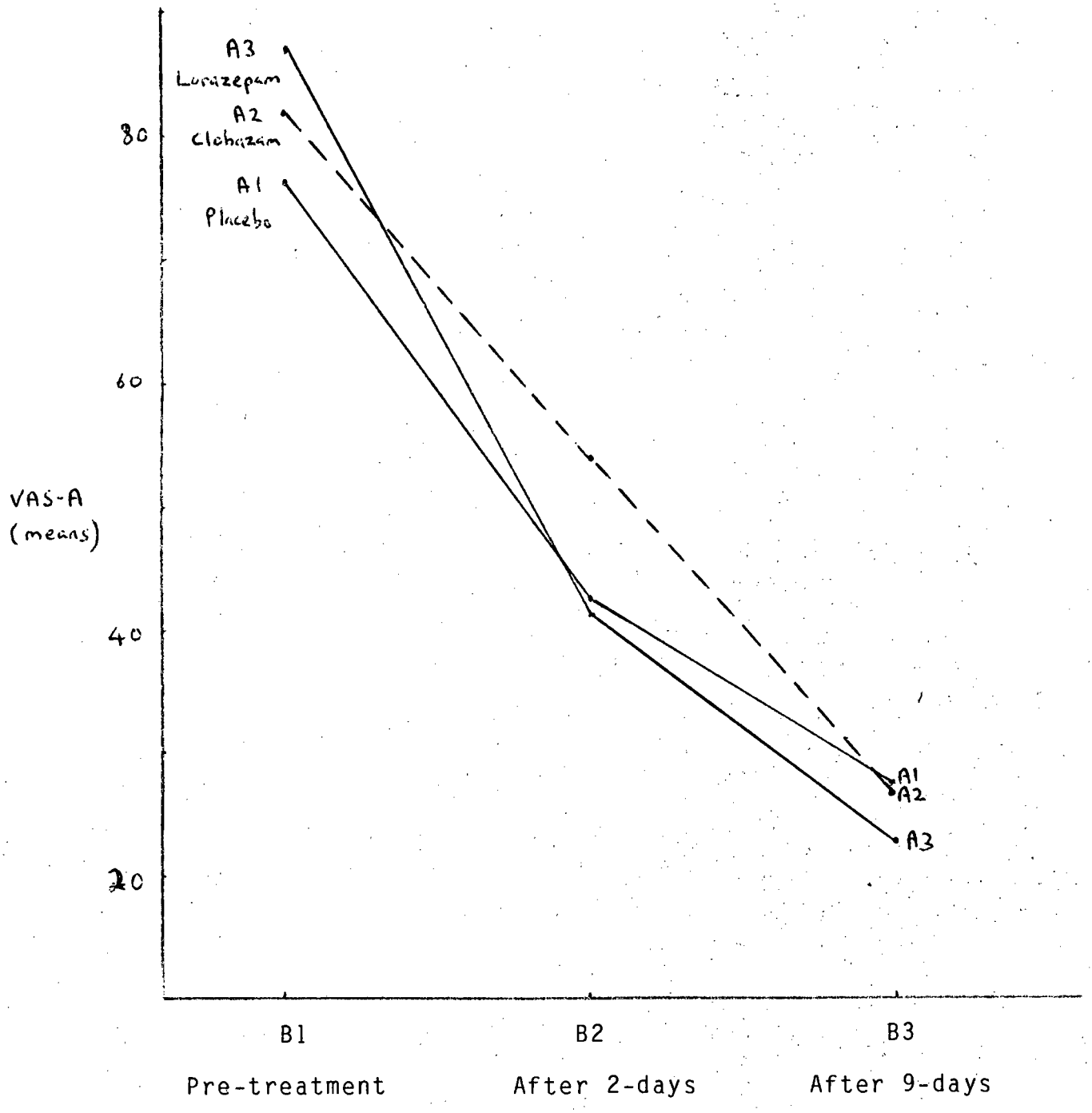


FIGURE 5: VAS-A Cell Mean Profile.

TABLE 10: Anova summary table for VAS-A.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	572,28	0,49
Subjects	67	1147,89	
Within subjects			
B (Time of assessment)	2	55505,37	147,57**
AB (Interaction)	4	661,36	1,76
Residual	134	376,13	

** $p < 0,01$

Table 10 shows that the interaction (AB) effect is insignificant and therefore the main effects can be interpreted. The significant ($p < 0,01$) B main effect indicates that there was a general drop in VAS-A scores during treatment. The lack of a significant interaction effect indicates that the drop in VAS-A was similar for all three treatment groups. A Tukey HSD analysis will reveal specifically how the overall B means differ.

TABLE 11: Tukey HSD results for overall B means, i.e. the overall average VAS-A mean scores of all three treatment groups combined are compared at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (81,73)	-	15,40**	24,17**
B2 (45,93)		-	8,72**
B3 (25,71)			-

** $p < 0,01$

Table 11 shows that the overall VAS-A means drop significantly ($p < 0,01$) from pre-treatment to the 2-day assessment and continue to drop significantly ($p < 0,01$) from the 2-day assessment to the 9-day assessment. The drop in VAS-A overall average mean is also significant ($p < 0,01$) from pre-treatment to the 9-day assessment.

6.1.3 Visual Analogue Scale for Motivation

TABLE 12: Mean (± s.d.) Visual Analogue Scale for Motivation (VAS-M) Scores.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	61,0 (± 33,5)	70,6 (± 28,4)	72,9 (± 27,2)
Clobazam (A2)	54,4 (± 34,0)	71,2 (± 28,4)	72,1 (± 32,4)
Lorazepam (A3)	43,3 (± 34,7)	50,3 (± 29,9)	63,2 (± 26,7)

The means of the three treatment groups at the three times of assessment for the Visual Analogue Scale for Motivation are shown in Table 12 and illustrated in Figure 6. The cell mean profile indicates essentially similar trends for the various treatment groups during the course of treatment. The 2 way analysis of variance will indicate what specific changes are significant.

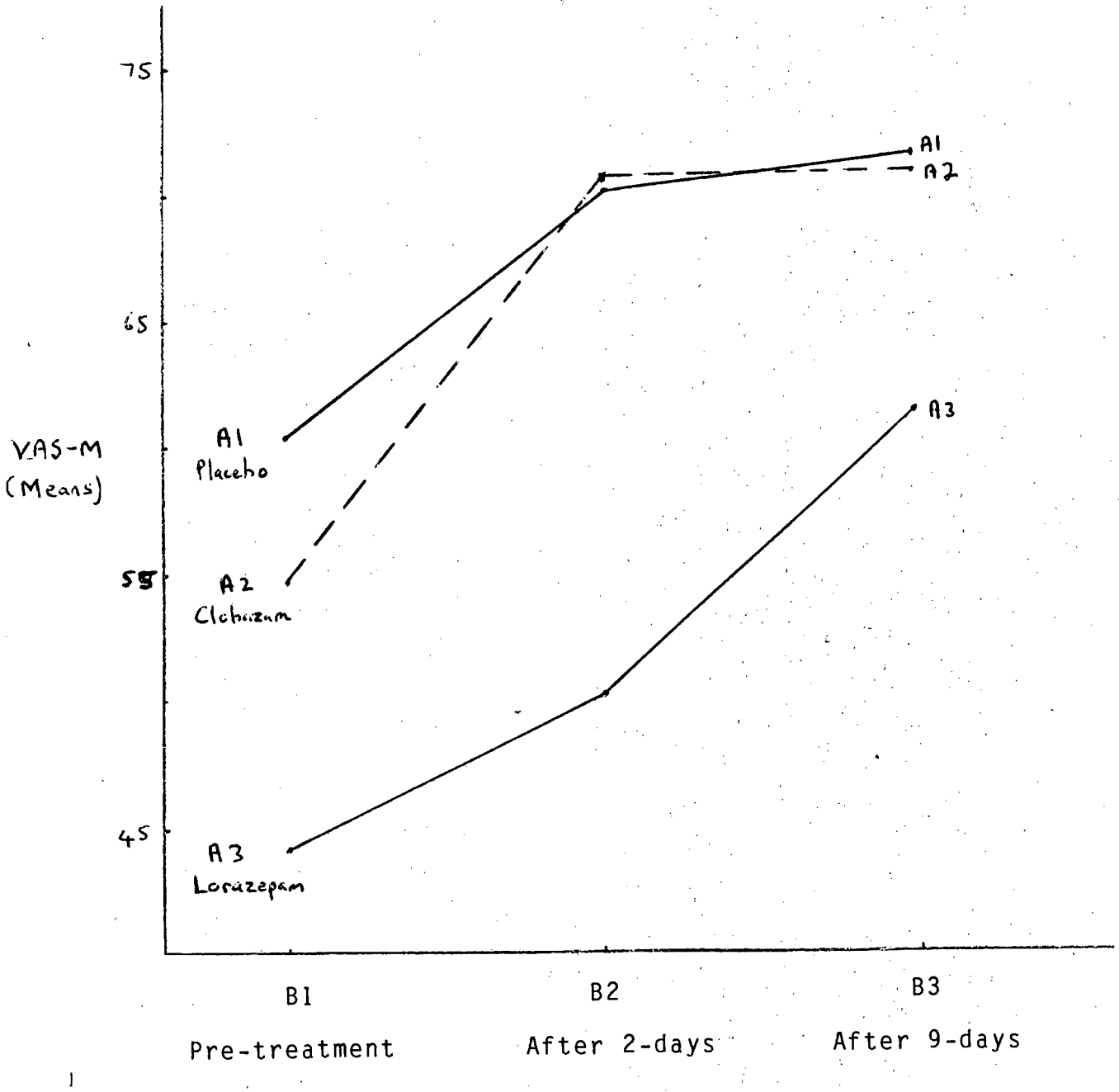


FIGURE 6: VAS-M Cell Mean Profile.

TABLE 13: Anova summary table for VAS-M

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	5126,91	2,89
Subjects	67	1775,05	
Within subjects			
B (Time of assessment)	2	4890,83	9,10**
AB (Interaction)	4	330,94	0,62
Residual	134	537,22	

** $p < 0,01$

Table 13 shows that he interaction (AB) effect is insignificant and therefore the main effects can be interpreted. The significant ($p < 0,01$) B main effect indicates that there was a general increase in VAS-M scores during treatment. The insignificant interaction shows that this increase in VAS-M was similar for all three treatment groups. A Tukey HSD analysis will reveal specifically how the overall B means differ.

TABLE 14: Tukey HSD results for overall B means, i.e. the average VAS-M mean scores of all three treatment groups are compared at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (52,88)	-	4,04*	5,97**
B2 (64,08)		-	1,92
B3 (69,41)			-

* $p < 0,05$

** $p < 0,01$

Table 14 indicates that the overall VAS-M mean increases significantly ($p < 0,05$) from pre-treatment to the 9-day assessment. The increase from day-2 assessment to the day-9 assessment is not significant. The increase from the pre-treatment assessment to the assessment after 9-days is significant ($p < 0,01$).

6.1.4 Drowsiness Ratings

TABLE 15: Mean (± s.d.) Drowsiness Rating Scores.

	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	0,40 (± 0,7)	0,10 (± 0,4)
Clobazam (A2)	0,82 (± 0,8)	0,55 (± 0,7)
Lorazepam (A3)	1,26 (± 0,7)	1,04 (± 0,8)

Table 15 shows the mean drowsiness scores for the three treatment groups at the 2-day and 9-day assessments. There was no assessment of drowsiness level at pre-treatment. The means are illustrated in Figure 7. This cell mean profile indicates a general trend for the mean drowsiness to drop. The 2 way analysis of variance will indicate which changes are significant.

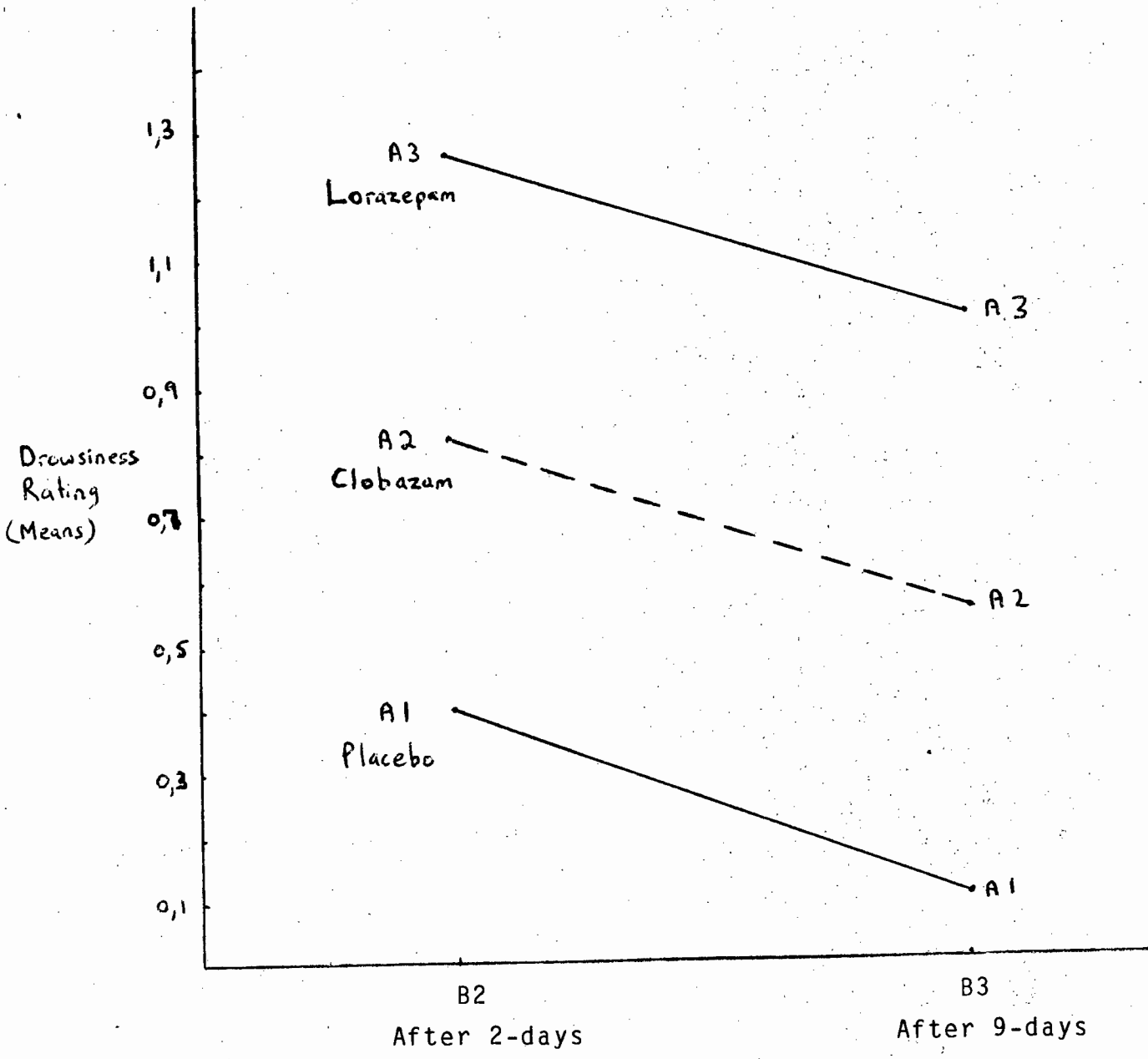


FIGURE 7: Drowsiness Rating Cell Mean Profile.

TABLE 16: Anova summary table for Drowsiness Rating Scores.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	9,36	12,27**
Subjects	67	0,76	
Within subjects			
B (Time of assessment)	1	2,31	7,88**
AB (Interaction)	2	0,02	0,07
Residual	67	0,29	

** $p < 0,01$

Table 16 shows that the interaction (AB) effect is insignificant, therefore the significant ($p < 0,01$) A and B main effects can be interpreted. The significant A main effect indicates that the overall mean drowsiness ratings for the three treatment groups differ. A Tukey HSD analysis will indicate which specific differences are significant. The significant B main effect shows that the overall mean drowsiness at the 2-day assessment (the mean of the three treatment groups is 0,82) is significantly higher than the overall mean drowsiness level at the 9-day assessment. The overall mean at 9-days is 0,56. There is an overall significant drop in drowsiness rating from the 2-day assessment to the 9-day assessment.

TABLE 17: Tukey HSD results for overall A means, i.e. the average drowsiness rating scores for both times of assessment for each of the three treatment groups.

	Placebo (A1)	Clobazam (A2)	Lorazepam (A3)
A1 (0,25)	-	3,38	6,76**
A2 (0,68)		-	3,77*
A3 (1,15)			-

* $p < 0,05$

** $p < 0,01$

Table 17 indicates that the overall mean clobazam drowsiness rating does not differ significantly from the placebo rating. The lorazepam rating is significantly higher ($p < 0,01$) than the placebo rating and also significantly higher ($p < 0,05$) than the clobazam rating.

6.1.5 Digit Symbol Substitution Test

TABLE 18: Mean (± s.d.) Digit Symbol Substitution Test (DSST) Scores.
Mean Number completed in 90 seconds.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	23,8 (± 9,9)	30,3 (± 12,6)	30,6 (± 15,1)
Clobazam (A2)	24,9 (± 9,3)	31,0 (± 11,3)	33,7 (± 12,7)
Lorazepam (A3)	21,7 (± 8,3)	25,1 (± 8,5)	29,0 (± 10,6)

Table 18 shows the means of the three treatment groups at the three times of assessment for the Digit Symbol Substitution Test, these means are illustrated in Figure 8. A 2 way analysis of variance will show what specific changes are significant.

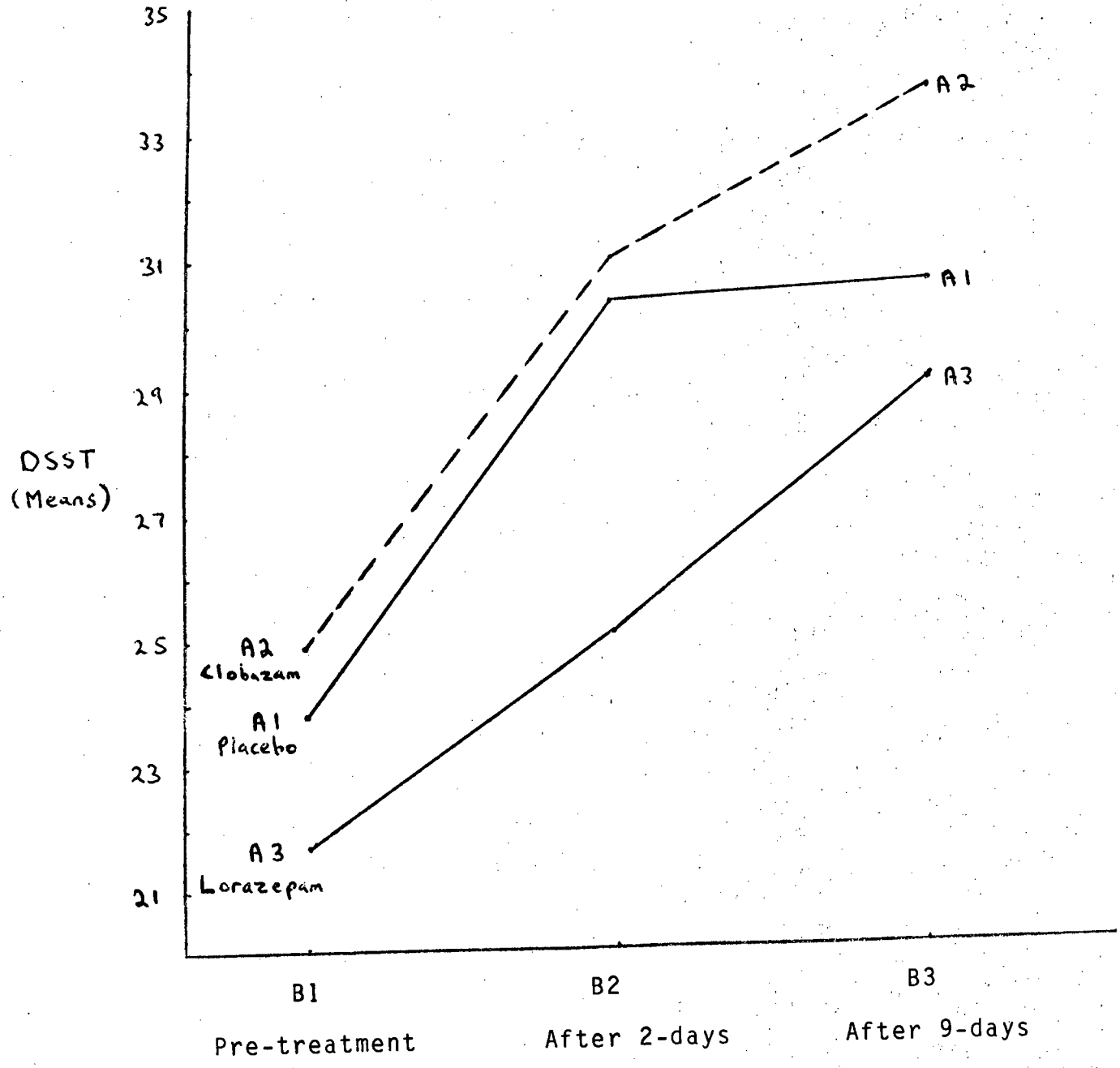


FIGURE 8: DSST Cell Mean Profile.

TABLE 19: Anova summary table for DSST.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	371,1	1,11
Subjects	67	3334	
Within subjects			
B (Time of assessment)	2	1052,9	67,89**
AB (Interaction)	4	27,5	1,77
Residual	134	15,5	

** $p < 0,01$

The results in Table 19 indicate that the interaction (AB) effect is insignificant. This implies that there is no difference in the trends between the three treatment groups and therefore overall means, i.e. the main effects can be interpreted. The B main effect is significant ($p < 0,01$). There is a general significant increase in DSST mean over the course of treatment. A Tukey HSD analysis will show which of the overall B means differ significantly.

TABLE 20: Tukey HSD results for overall B means, i.e. the average DSST means for all three treatment groups are compared at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (23,47)	-	11,32**	4,84**
B2 (28,80)		-	16,16**
B3 (31,08)			-

** $p < 0,01$

The Tukey HSD analysis in Table 20 shows all the changes to be significant. The DSST overall means increase significantly from the pre-treatment assessment to the assessment after 2-days and continue to increase significantly to the 9-day assessment. The increase from pre-treatment to the 9-day assessment is also therefore significant.

6.1.6 Critical Flicker Fusion Threshhold

TABLE 21: Mean (± s.d.) Critical Flicker Fusion Threshhold (CFFT).
Mean number of cycles per second.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	21,38 (± 2,6)	20,99 (± 2,5)	21,23 (± 2,2)
Clobazam (A2)	21,20 (± 2,4)	21,16 (± 1,9)	21,17 (± 0,2)
Lorazepam (A3)	21,42 (± 2,5)	21,22 (± 2,4)	20,75 (± 2,2)

The means of the three treatment groups at the three times of assessment for the Critical Flicker Fusion Threshhold are shown in Table 21. Since all the means are very similar a cell mean profile would not serve to illustrate any trends and hence no graph has been drawn. A 2 way analysis of variance will reveal if there are any significant changes.

TABLE 22: Anova summary table for CFFT scores.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	0,08	0,01
Subjects	67	13,65	
Within subjects			
B (Time of assessment)	2	1,32	1,18
AB (Interaction)	4	1,15	1,02
Residual	134	1,12	

Table 22 shows that there are no significant changes in CFFT scores.

6.1.7 Inglis Paired-Associate Learning Test

TABLE 23: Inglis Paired-Associate Learning Test (Inglis) Scores.
Number of trials needed to attain three consecutive correct responses for each pair of words.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	11,75 (± 7,3)	8,3 (± 3,5)	9,9 (± 4,9)
Clobazam (A2)	11,93 (± 7,6)	9,11 (± 6,0)	8,52 (± 4,5)
Lorazepam (A3)	13,43 (± 11,8)	10 (± 10,7)	8,26 (± 6,0)

The means of the three treatment groups at the three times of assessments for the Inglis Paired-Associate Learning Test are shown in Table 23 and illustrated in Figure 9. The scores show a tendency to decrease and the 2 way analysis will reveal what changes are significant.

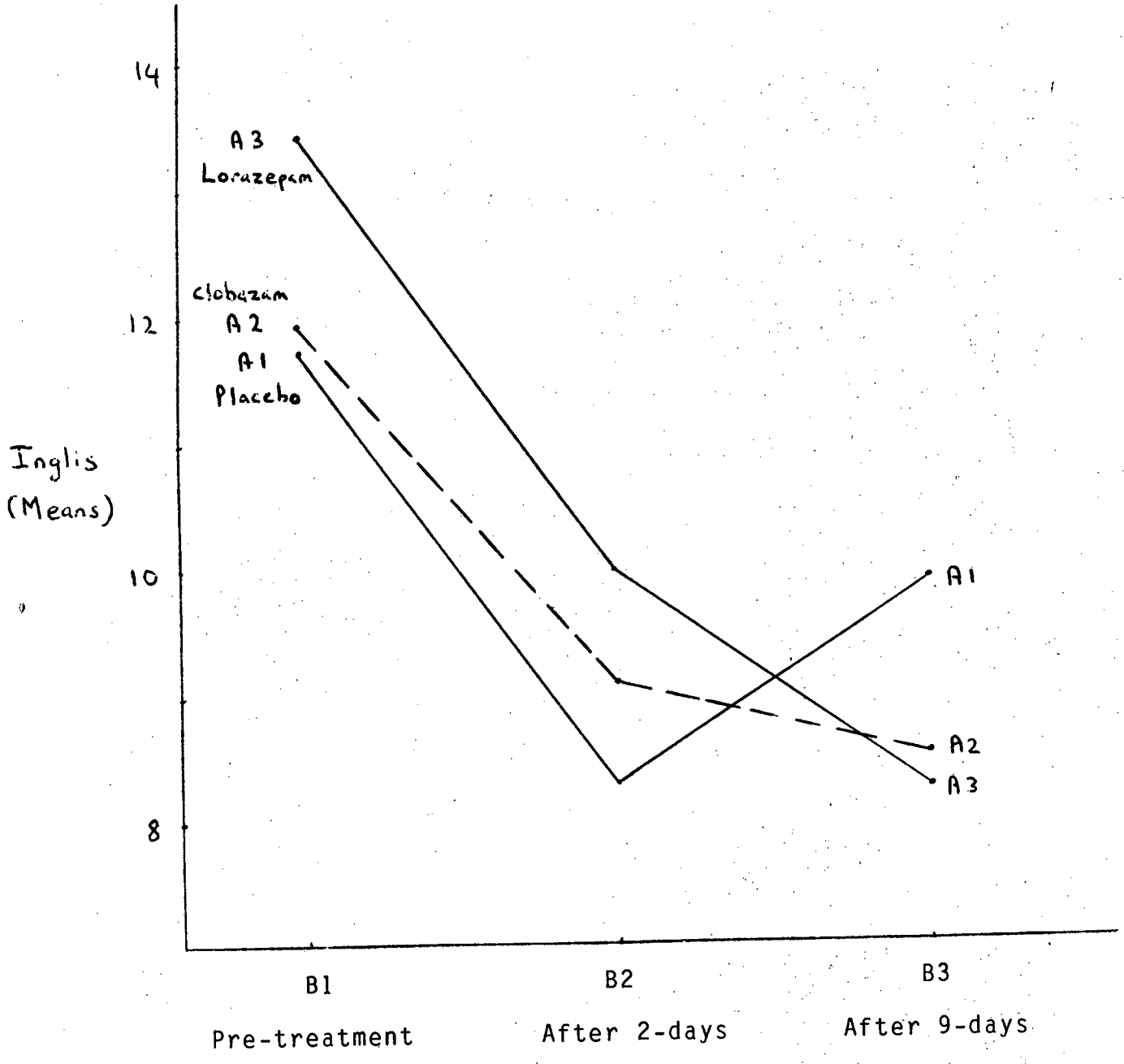


FIGURE 9: Inglis Cell Mean Profile.

TABLE 24: Anova summary table for Inglis scores.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	9,93	0,08
Subjects	67	124,51	
Within subjects			
B (Time of assessment)	2	259,78	12,89**
AB (Interaction)	4	22,13	1,10
Residual	134	20,16	

** $p < 0,01$

Table 24 shows that the interaction effects are insignificant. Therefore the main effects can be interpreted. The B main effect is significant ($p < 0,01$). This indicates that there is significant change in the overall B means (time of assessment). The overall mean at a particular time of assessment differs from other overall means at a particular time of assessment and a Tukey HSD analysis which shows which specific overall B means differ.

TABLE 25: Tukey HSD results for overall B means, i.e. the overall average Inglis mean scores of all three treatment groups are compared at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (12,37)	-	6,02**	6,41**
B2 (9,14)		-	0,38
B3 (8,93)			-

** $p < 0,01$

Table 25 indicates that the overall mean (B2) of Inglis scores at 2 days is significantly ($p < 0,01$) lower than the mean at pre-treatment (B1). The overall Inglis means at B2 and B3 do not differ significantly. The reduction in overall Inglis mean from pre-treatment (B1) to the assessment at 9-days (B3) is significant ($p < 0,01$).

6.1.8 Purdue Pegboard Test - Preferred Hand Task

TABLE 26: Mean (± s.d.) Purdue Pegboard Test (PPT)-Preferred Hand Scores.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	13,1 (± 1,8)	14,6 (± 1,7)	15,1 (± 1,9)
Clobazam (A2)	13,3 (± 1,9)	14,2 (± 1,8)	14,1 (± 1,8)
Lorazepam (A3)	13,5 (± 2,0)	13,6 (± 1,7)	14,6 (± 1,6)

The means of the three treatment groups at the three times of assessment for the Purdue Pegboard Test - Preferred Hand task are shown in Table 26 and illustrated in Figure 10. The cell mean profile shows that there is an improvement in performance. The 2 way analysis of variance will reveal if there are any significant improvements.

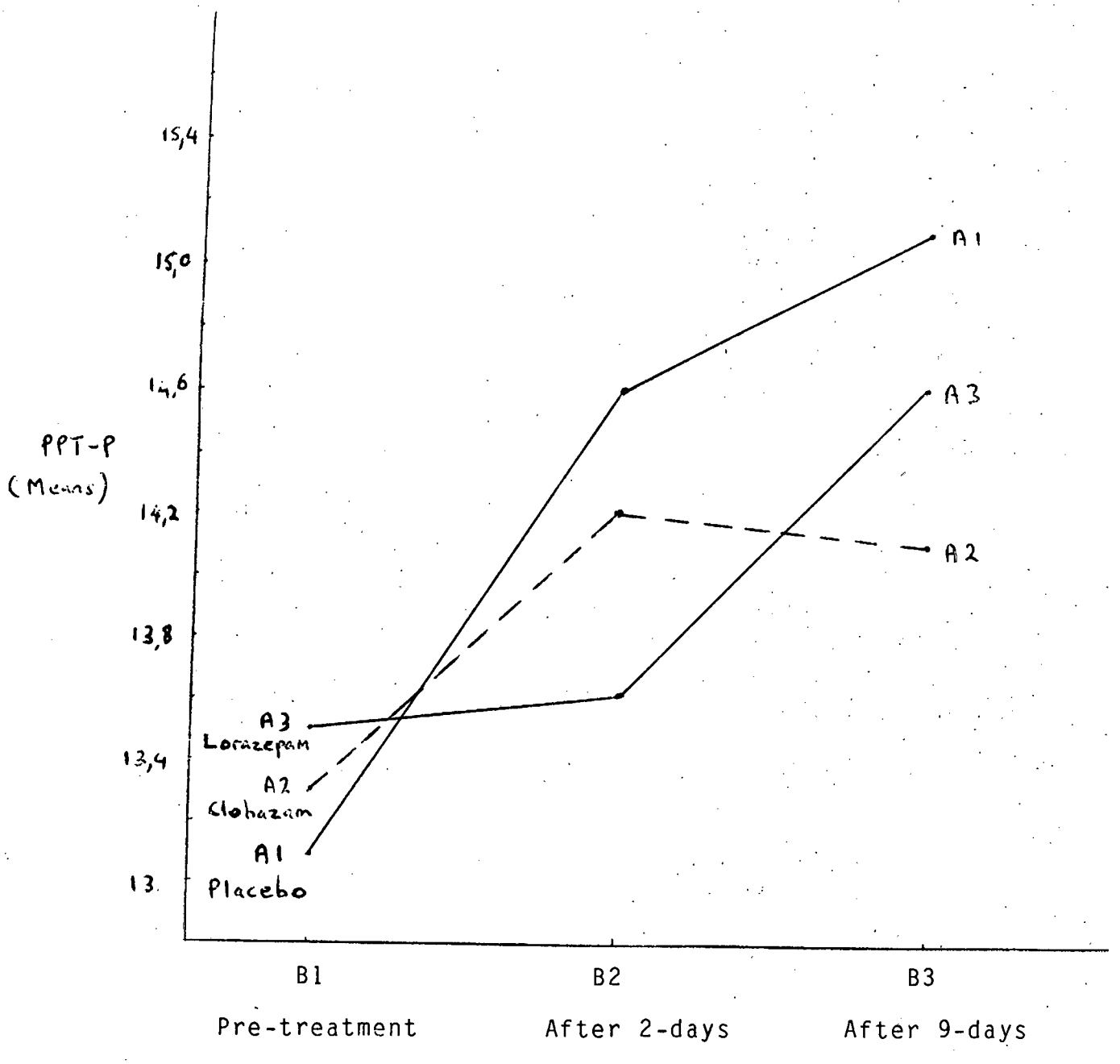


FIGURE 10: PPT-Preferred Hand Task Cell Mean Profile.

TABLE 27: Anova summary table for PPT - Preferred Hand scores.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	2,81	0,37
Subjects	67	7,62	
Within subjects			
B (Time of assessment)	2	29,95	26,33**
AB (Interaction)	4	4,72	4,15**
Residual	134	1,14	

** $p < 0,01$

The 2 way analysis of variance (Table 27) shows that the interaction (AB) effect is significant ($p < 0,01$). This means that the main effects cannot be interpreted and an analysis of the simple main effects is required to ascertain the specific significant changes.

TABLE 28: Simple main effects summary table for PPT - Preferred Hand scores.

Source	df	MS	F ratio
A at B1	2	0,98	0,29
A at B2	2	5,41	1,64
A at B3	2	5,58	1,69
Within	201	3,30	
B at A1	2	21,67	19,04**
B at A2	2	6,33	5,57**
B at A3	2	9,10	7,99**
Residual	134	1,13	

** $p < 0,01$

The simple main effects analysis (Table 28) reveals three significant ($p < 0,01$) results. The mean placebo (scores) differ from each other at one or more of the times of assessment (B at A1). This also applies to the clobazam group (B at A2) and to the lorazepam group (B at A3). A Tukey HSD analysis will reveal which specific cell means differ significantly.

TABLE 29: Tukey HSD results for B at A1, i.e. mean PPT-Preferred Hand scores for placebo group at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (13,05)	-	6,69**	8,38**
B2 (14,55)		-	2,10
B3 (15,05)			-

** $p < 0,01$

The analysis (Table 29) shows that the pre-treatment mean (B1) is significantly ($p < 0,01$) lower than the mean at the 2-day assessment (B2) and the mean at the 9-day assessment (B3). The means at the 2-day assessment and the 9-day assessment do not differ significantly.

TABLE 30: HSD results for B at A2, i.e. mean PPT-Preferred Hand scores for clobazam group at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (13,30)	-	4,33**	3,79*
B2 (14,19)		-	0,54
B3 (14,07)			-

* $p < 0,05$
** $p < 0,01$

The analysis (Table 30) indicates that there is a significant ($p < 0,01$) improvement in performance from pre-treatment (B1) to the 2-day assessment (B2). The mean at the 2-day assessment (B2) does not differ from the mean at the 9-day assessment (B3). The mean at the 9-day assessment is significantly ($p < 0,05$) greater than the pre-treatment (B1) mean.

TABLE 31: HSD results for B at A3, i.e. mean PPT-Preferred Hand scores for lorazepam group at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (13,48)	-	0,39	5,09**
B2 (13,57)		-	4,69**
B3 (14,61)			-

** $p < 0,01$

The analysis (Table 31) shows that the mean score at pre-treatment (B1) does not differ significantly from the mean score at 2-days (B2). The mean at 9-days is significantly higher ($p < 0,01$) than the mean at 2-days and the pre-treatment mean.

6.1.9 Purdue Pegboard Test - Both Hands Task

TABLE 32: Mean (± s.d.) Purdue Pegboard Test (PPT) - Both Hands Scores.
Mean number completed in 30 seconds.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	10,2 (± 1,3)	10,5 (± 1,2)	11,2 (± 1,5)
Clobazam (A2)	9,9 (± 1,4)	10,2 (± 1,8)	10,5 (± 1,6)
Lorazepam (A3)	9,7 (± 1,4)	10,0 (± 2,0)	10,2 (± 1,6)

Table 32 shows the means of the three treatment groups at the three times of assessment for the Purdue Pegboard Test (PPT) - Both Hands - Section. The means are illustrated in Figure 11. There is a tendency for performance to improve and the 2 way analysis of variance will show which changes are significant.

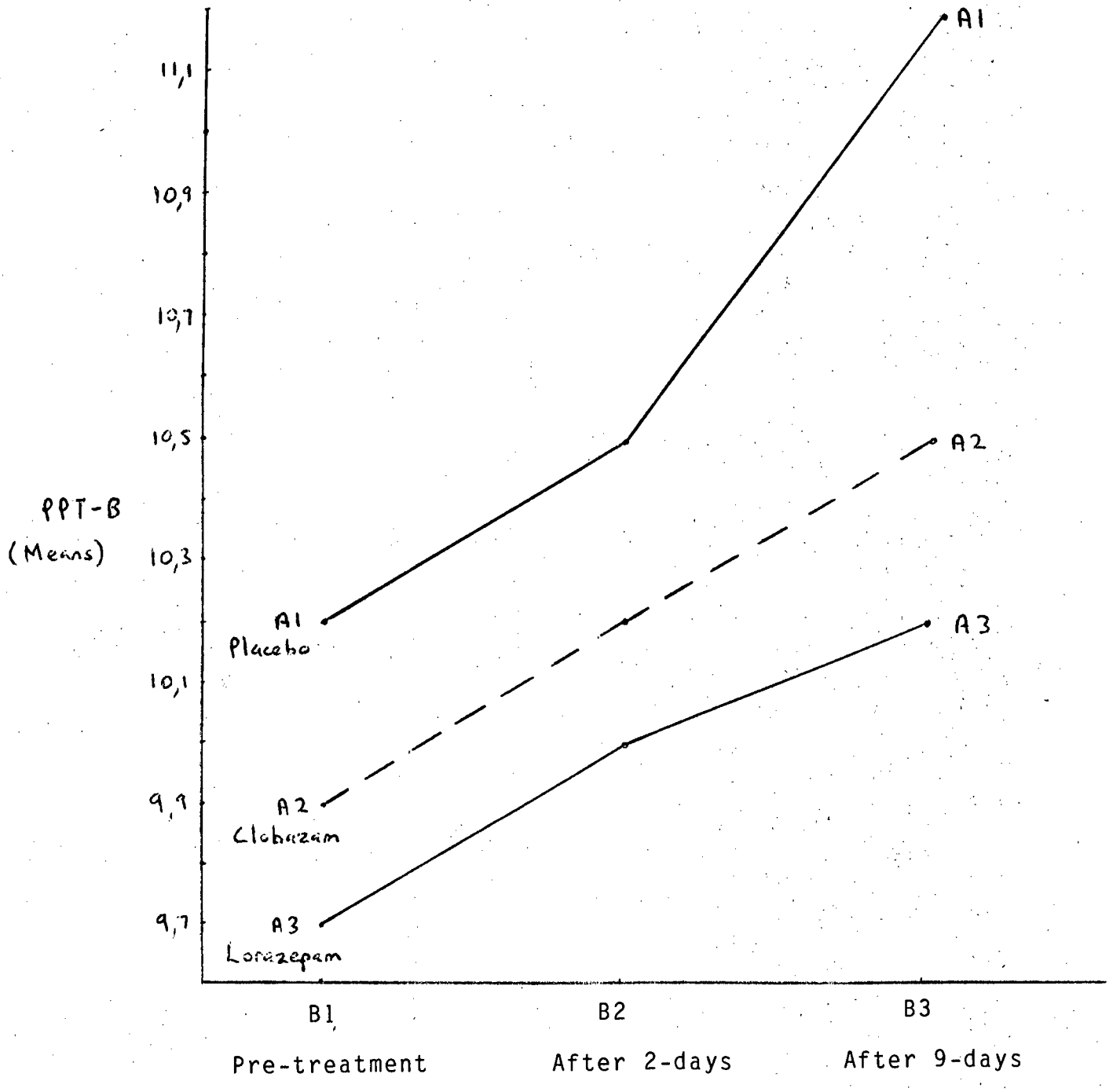


FIGURE 11: PPT - Both Hands Task Cell Mean Profile.

TABLE 33: Anova summary table for PPT - Both Hands scores.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	7,46	1,25
Subjects	67	5,97	
Within subjects			
B (Time of assessment)	2	8,80	12,91**
AB (Interaction)	4	0,37	0,55
Residual	134	0,68	

** $p < 0,01$

Table 33 shows that the interaction effect is not significant and therefore the significant ($p < 0,01$) B main effect can be interpreted. The significant B main effect indicates that the overall average PPT - Both Hands means at the various times of assessment differ from one another. A Tukey HSD analysis will show which differences are significant.

TABLE 34: Tukey HSD results for overall B means, i.e. the overall average PPT - Both Hands scores of all three treatment groups are compared at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (9,91)	-	3,17	7,22**
B2 (10,23)		-	4,05*
B3 (10,63)			-

* $p < 0,05$

** $p < 0,01$

Table 34 indicates that the overall PPT - Both Hands mean at pre-treatment (B1) does not differ significantly from the overall mean at 2-days (B2) but does differ significantly ($p < 0,01$) from the overall mean at 9-days which is significantly greater. The overall mean at B3 is also significantly greater ($p < 0,05$) than the overall mean at B2.

6.1.10 Purdue Pegboard Test - Assembly Task

TABLE 35: Mean (± s.d.) Purdue Pegboard Test (PPT) - Assembly Scores.
Mean number completed in 90 seconds.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	43,5 (± 8,0)	47,0 (± 8,9)	48,3 (± 6,8)
Clobazam (A2)	42,1 (± 7,9)	46,5 (± 6,2)	46,0 (± 7,8)
Lorazepam (A3)	40,7 (± 7,4)	41,3 (± 8,0)	46,0 (± 9,4)

The means of the three treatment groups at the three times of assessment for the PPT - Assembly task are shown in Table 35 and illustrated in Figure 12. The cell mean profile indicates a tendency for performance to improve with slightly different trends for the three treatment groups. A 2 way analysis of variance will reveal which changes are significant.

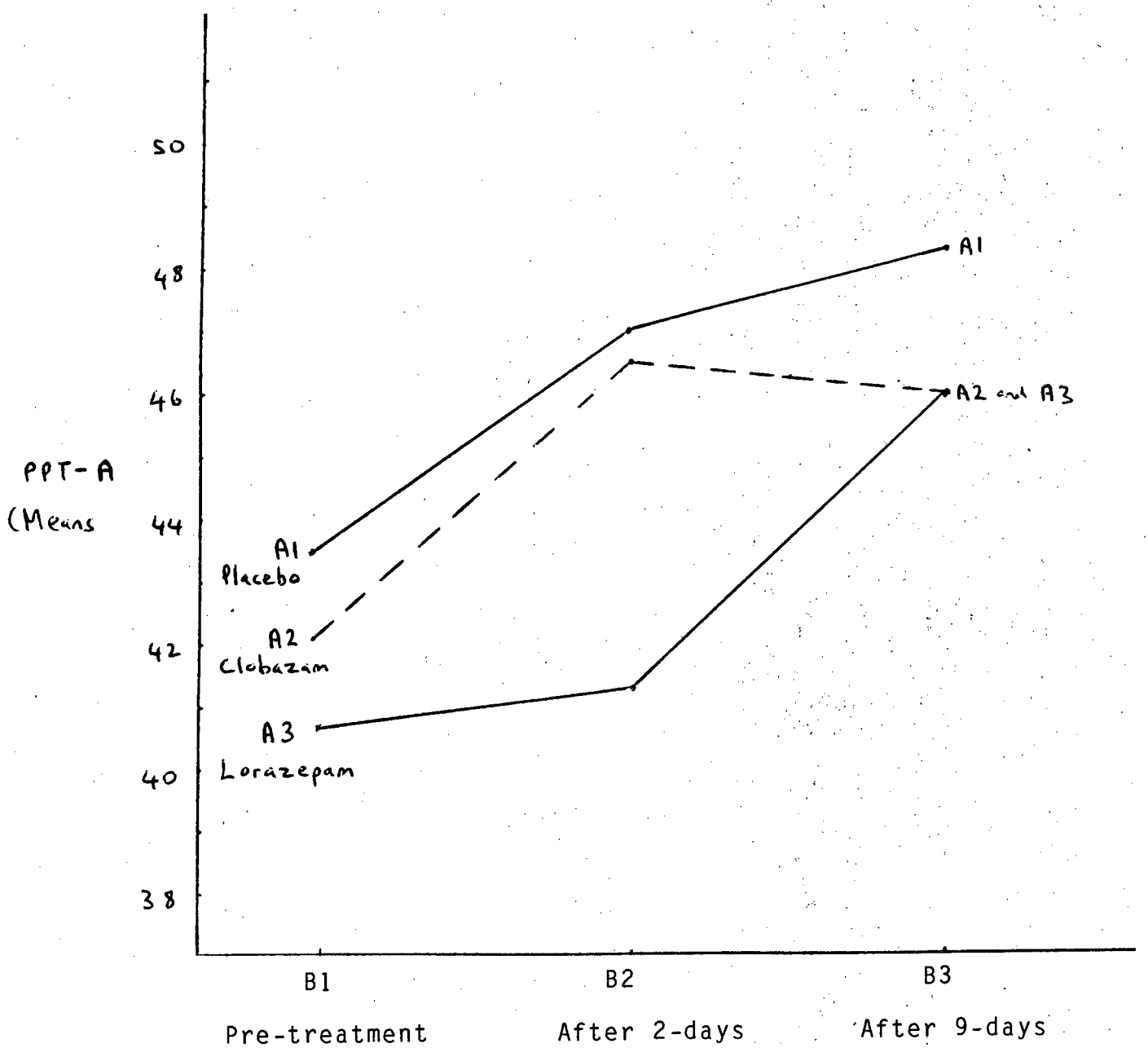


FIGURE 12: PPT - Assembly Task Cell Mean Profile.

TABLE 36: Anova summary table for PPT - Assembly scores

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	227,01	1,50
Subjects	67	150,90	
Within subjects			
B (Time of assessment)	2	376,75	22,78**
AB (Interaction)	4	43,49	2,63*
Residual	134	16,54	

* $p < 0,05$

** $p < 0,01$

The 2 way analysis variance (Table 36) shows that the interaction (AB) effect is significant ($p < 0,05$). This means that the main effects cannot be interpreted and an analysis of the simple main effects is required to ascertain the specific significant trends.

TABLE 37: Simple main effects summary table for PPT - Assembly scores.

Source	df	MS	F ratio
A at B1	2	81,02	1,32
A at B2	2	224,98	3,67*
A at B3	2	37,82	0,62
Within	201	61,32	
B at A1	2	121,25	7,33**
B at A2	2	140,53	8,51**
B at A3	2	195,78	11,84**
Residual	134	16,54	

* $p < 0,05$

** $p < 0,01$

The simple main effects analysis (Table 37) reveals three significant ($p < 0,01$) results and one significant ($p < 0,05$) result. The mean placebo scores differ from each other at one or more of the times of assessment (B at A1). This also applies to the clobazam group (B at A2) and to the lorazepam group (B at A3). In addition, the three treatment groups differ significantly ($p < 0,05$) at the 2-day assessment (A at B2). A Tukey HSD analysis will show which specific cell means differ significantly.

TABLE 38: Tukey HSD results for A at B2, i.e. mean PPT-Assembly scores for the three treatment groups at the assessment after 2-days.

	Placebo (A1)	Clobazam (A2)	Lorazepam (A3)
A1 (47,05)	-	0,67	6,49**
A2 (46,48)		-	6,29**
A3 (41,35)			-

** $p < 0,01$

The analysis (Table 38) shows that the clobazam and placebo means do not differ significantly. The lorazepam is significantly ($p < 0,01$) less than the clobazam mean and the placebo mean.

TABLE 39: Tukey HSD results for B at A1, i.e. mean PPT - Assembly scores for placebo group at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (43,55)	-	3,85*	5,22**
B2 (47,05)		-	1,37
B3 (48,3)			-

* $p < 0,05$

** $p < 0,01$

The analysis (Table 39) shows that the mean at the 2-day assessment is significantly ($p < 0,05$) greater than the mean at 9-days. The mean at 9-days is significantly ($p < 0,01$) greater than the pre-treatment mean. The means at 2-days and at the 9-day assessment do not differ significantly.

TABLE 40: Tukey HSD results for B at A2 i.e. mean PPT - Assembly scores for the clobazam group at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (42,15)	-	5,53**	4,87**
B2 (46,48)		-	0,67
B3 (45,96)			-

** $p < 0,01$

The analysis (Table 40) shows that the mean at the 2-day assessment is significantly ($p < 0,01$) greater than the mean at pre-treatment. The mean at 9-days is significantly ($p < 0,01$) greater than the mean at pre-treatment. The mean at 9-days does not differ from the mean at the 2-day assessment.

TABLE 41: Tukey HSD results for B at A3 i.e. mean PPT - Assembly scores for the lorazepam group at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (40,70)	-	0,77	6,31**
B2 (41,35)		-	5,54**
B3 (46,04)			-

** $p < 0,01$

The analysis (Table 41) indicates that the mean at the 2-day assessment does not differ from the mean at pre-treatment. The mean after 9-days is significantly ($p < 0,01$) greater than the mean after 2-days and the pre-treatment mean.

6.1.11 Choice Reaction Time

TABLE 42: Mean (± s.d.) Choice Reaction Time (CRT) Scores.
Mean number of seconds taken to react.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
Placebo (A1)	0,657 (± 0,07)	0,629 (± 0,07)	0,594 (± 0,06)
Clobazam (A2)	0,666 (± 0,08)	0,643 (± 0,06)	0,625 (± 0,08)
Lorazepam (A3)	0,674 (± 0,07)	0,663 (± 0,06)	0,621 (± 0,06)

The means of the three treatment groups at the three times of assessments for the choice reaction time test are shown in Table 42 and illustrated in Figure 13. The cell mean profile indicates that there is a tendency for the CRT times to improve. A 2 way analysis of variance will reveal any significant changes.

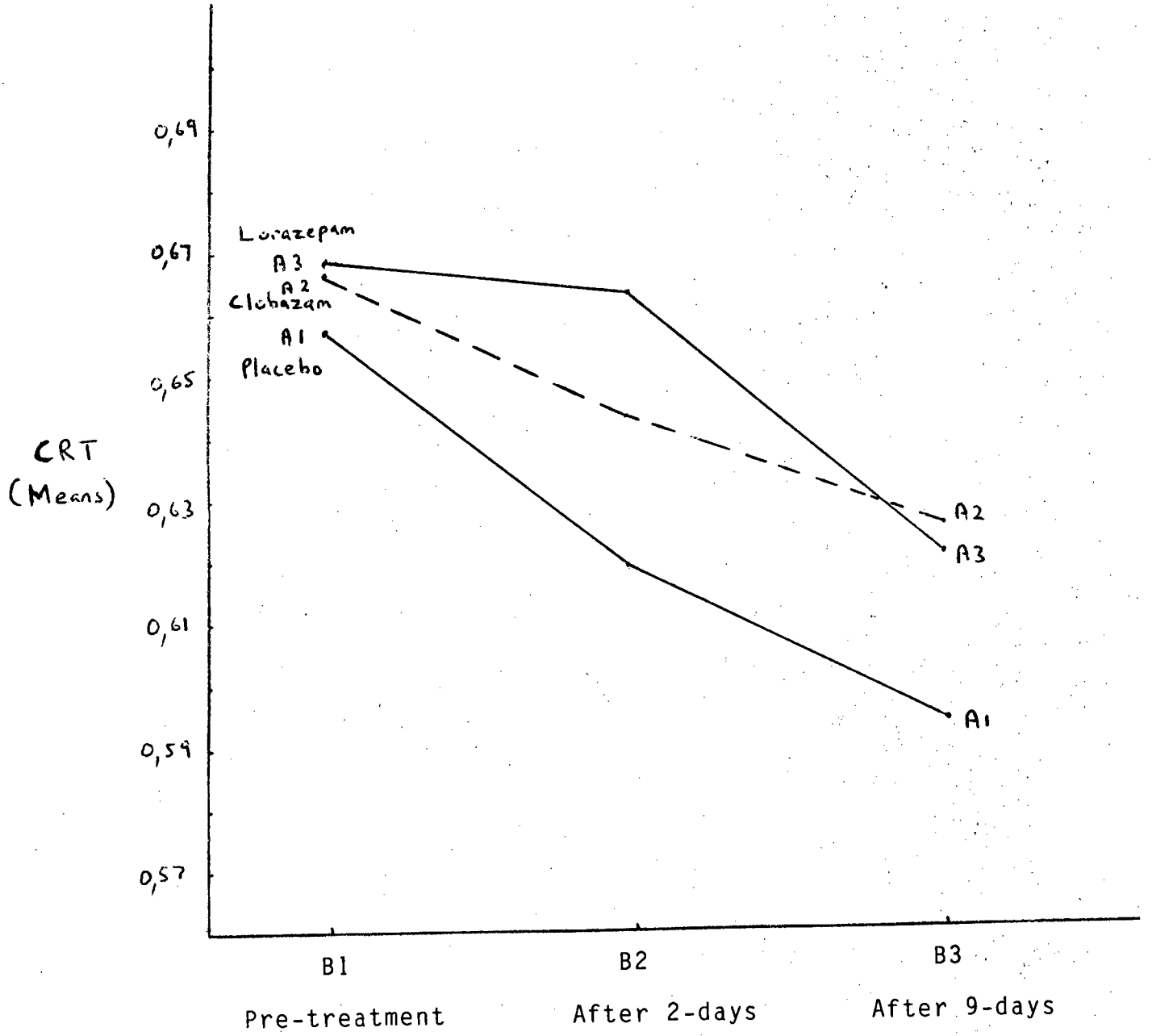


FIGURE 13: CRT Cell Mean Profile.

TABLE 43: Anova summary table for CRT scores.

Source	df	MS	F ratio
Between subjects			
A (Type of treatment)	2	0,012	1,02
Subjects	67	0,01	
Within subjects			
B (Time of assessment)	2	0,048	34,43**
AB (Interaction)	4	0,001	1,02
Residual	134	0,0014	

** $p < 0,01$

Table 43 indicates that the interaction effect is not significant and therefore the significant ($p < 0,01$) B main effect can be interpreted. This significant B main effect implies that the overall average CRT at the various times of assessments differ and a Tukey HSD will reveal the specific significant differences.

TABLE 44: Tukey HSD results for overall B means, i.e. the overall average CRT mean scores for all three treatment groups combined are compared at the three times of assessment.

	Pre-treatment (B1)	After 2-days (B2)	After 9-days (B3)
B1 (0,666)	-	4,70**	10,47**
B2 (0,645)		-	5,77**
B3 (0,619)			-

** $p < 0,01$

Table 44 reveals that all the means differ significantly ($p < 0,01$) from each other. There is an improvement from pre-treatment to the 2-day assessment and to the 9-day assessment in CRT.

6.2 HOMOGENEITY OF ERROR VARIANCE

All the F_{max} ratios were insignificant and therefore there is homogeneity of variance for all the two-way anovas.

6.3 CHI-SQUARE ANALYSIS OF PATIENTS WHO COMPLETED AND COMPLIED WITH TREATMENT.

The chi-square (X^2 = 1,057) is insignificant, thus the number of patients in each treatment group does not differ significantly (20 in placebo group, 27 in clobazam group and 23 in lorazepam group).

6.4 CORRELATIONS BETWEEN THE DEPENDENT VARIABLES

TABLE 45: Correlation Matrix for Placebo group at Pre-treatment-

	HAS	VAS-A	VAS-M	DSST	PPT-P[1]	PPT-B[2]	PPT-A[3]	CRT	CFFT	Inglis
Var. No.	1	2	3	4	5	6	7	8	9	10
1	-									
2	,302	-								
3	-,327	-,297	-							
4	-,254	,234	,268	-						
5	-,365	,120	,220	,867**	-					
6	-,058	,003	,105	,181	,348	-				
7	-,153	-,135	,042	,299	,397,	608**	-			
8	,114	-,029	,194	-,160	-,110	-,314	-,333	-		
9	-,202	,025	,050	-,108	-,195	-,222	-,116	,196	-	
10	,146	-,072	,031	-,043	-,078	-,132	-,415	,304	,195	-

** $p < 0,01$

1. PPT - P - Purdue Pegboard Test - Preferred Hand Task
2. PPT - B - Purdue Pegboard Test - Both Hands Task
3. PPT - A - Purdue Pegboard Test - Assembly Task

TABLE 46: Carrelation Matrix for Placebo group at 2-days.

Var. No.	HAS 1	VAS-A 2	VAS-M 3	DSST 4	PPT-P 5	PPT-B 6	PPT-A 7	CRT 8	CFFT 9	Inglis 10	Drowsiness 11
1	-										
2	,767**	-									
3	,015	,114	-								
4	-,153	-,020	,270	-							
5	-,304	-,226	,133	,563**							
6	-,390	-,096	,096	,282	,504*	-					
7	-,286	-,125	-,107	,246	,254	,746**	-				
8	,320	,206	,077	-,216	-,107	-,396	,417	-			
9	-,154	-,009	,188	-,247	-,192	,132	,045	-,069	-		
10	-,008	-,081	,199	,356	,165	-,113	-,320	,407	-,019	-	
11	,283	,322	-,324	,164	,202	,223	,143	-,145	,117	,339	

* $p < 0,05$

** $p < 0,01$

TABLE 47: Correlation Matrix for Placebo group at 9-days.

	HAS	VAS-A	VAS-M	DSST	PPT-P	PPT-B	PPT-A	CRT	CFFT	Inglis	Drowsiness
Var. No.	1	2	3	4	5	6	7	8	9	10	11
1	-										
2	,701**	-									
3	-,195	-,098	-								
4	-,276	-,255	-,085	-							
5	,091	,040	-,383	,652**	-						
6	-,441*	-,445*	,203	,519*	,264	-					
7	-,409	-,493*	-,024	,525*	,204	,688**	-				
8	,371	,393	-,087	-,528*	-,165	-,277	-,668**	-			
9	-,154	,057	-,377	,036	,029	,086	,019	,086	-		
10	,124	,085	,112	,122	-,196	-,137	-,632	,576**	,110	-	
11	-,061	-,051	-,483*	-,128	,134	-,080	-,198	,096	,242	,149	-

* $p < 0,05$

** $p < 0,01$

TABLE 48: Correlation Matrix for Clobazam group at Pre-treatment.

Var. No.	HAS 1	VAS-A 2	VAS-M 3	DSST 4	PPT-P 5	PPT-B 6	PPT-A 7	CRT 8	CFFT 9	Inglis 10
1	-									
2	,563**	-								
3	-,098	-,375	-							
4	-,124	-,291	-,069	-						
5	000	-,276	-,035	,709**	-					
6	-,318	-,416*	-,073	,662**	,597**	-				
7	-,429*	-,291	,025	,542*	,419*	,659**	-			
8	,095	,477*	-,098	-,259	-,245	-,331	-,123	-		
9	-,206	-,313	-,035	,260	-,069	,457*	,205	-,056	-	
10	,249	-,042	-,047	,004	,160	-,098	-,086	-,025	-,119	-

* $p < 0,05$

** $p < 0,01$

TABLE 49: Correlation Matrix for Clobazam group at 2-days.

	HAS	VAS-A	VAS-M	DSST	PPT-P	PPT-B	PPT-A	CRT	CFFT	Inglis	Drowsiness
Var. No.	1	2	3	4	5	6	7	8	9	10	11
1	-										
2	,613**	-									
3	-,168	-,360	-								
4	-,437*	-,412*	-,047	-							
5	-,254	-,267	-,152	,589**	-						
6	-,366	-,425*	,080	,574**	,644**						
7	-,317	-,216	,138	,457*	,378	,678**	-				
8	,246	,522**	-,105	-,246	-,231	-,521**	-,129	-			
9	-,149	-,259	,231	,084	,016	,359	,228	-,228	-		
10	0,13	-,045	-,218	-,127	,124	-,220	-,130	,032	-,090	-	
11	,292	,465*	,239	-,252	-,391*	-,393*	-,393*	,494**	-,063	-,272	-

* $p < 0.05$

** $p < 0,01$

TABLE 50: Correlation Matrix for Clobazam group at 9-days

	HAS	VAS-A	VAS-M	DSST	PPT-P	PPT-B	PPT-A	CRT	CFFT	Inglis	Drowsiness
Var. No.	1	2	3	4	5	6	7	8	9	10	11
1	-										
2	,704**	-									
3	-,211	-,495*	-								
4	-,294	-,205	-,056	-							
5	-,130	-,104	-,149	,609**	-						
6	-,410*	-,267	-,059	,622**	,573**	-					
7	-,299	-,279	,242	,565**	,332	,769**	-				
8	,530**	,677**	-,217	-,352	-,175	-,294	-,295	-			
9	,205	,101	,160	,401	,150	,119	,230	-,018	-		
10	,053	,159	-,219	-,292	,031	-,196	-,315	,143	-,201	-	
11	,373	,486*	-,078	-,170	-,090	-,300	-,203	,430*	,300	-,136	-

* $p < 0,05$

** $p < 0,01$

TABLE 51: Correlation Matrix for Lorazepam group at Pre-treatment.

	HAS	VAS-A	VAS-M	DSST	PPT-P	PPT-B	PPT-A	CRT	CFFT	Inglis
Var. No.	1	2	3	4	5	6	7	8	9	10
1	-									
2	,073	-								
3	-,196	-,311	-							
4	-,168	-,118	,243	-						
5	-,033	-,053	,213	,676**	-					
6	-,225	-,078	,222	,601**	,518**	-				
7	-,193	-,414*	,338	,239	,236	,638**	-			
8	-,329	,342	-,103	-,343	-,421*	-,443*	-,329	-		
9	,175	-,324	-,150	-,007	-,342	-,012	,116	-,034	-	
10	,196	-,080	,106	-,253	-,127	-,445*	-,287	,282	,183	-

* $p < 0,05$

** $p < 0,01$

TABLE 52: Correlation Matrix for Lorazepam group at 2 days.

	HAS	VAS-A	VAS-M	DSST	PPT-P	PPT-B	PPT-A	CRT	CFFT	Inglis	Drowsiness
Var. No.	1	2	3	4	5	6	7	8	9	10	11
1	-										
2	,435*	-									
3	-,576**	,081	-								
4	-,293	-,225	,139	-							
5	-,166	-,335	-,083	,805**	-						
6	-,306	-,143	,438*	,803**	,638*	-					
7	,016	-,089	,289	,371	,250	,580**	-				
8	,070	,229	-,170	-,470*	-,685**	-,404	,151	-			
9	,163	-,421*	-,132	-,145	-,182	-,082	,043	,202	-		
10	,021	-,064	-,228	-,205	-,170	-,380	-,145	,025	-,009	-	
11	,295	,084	-,055	,142	-,131	,066	-,263	,200	,350	-,370	-

* $p < 0,05$

** $p < 0,01$

TABLE 53: Correlation Matrix for Lorazepam group at 9 days.

	HAS	VAS-A	VAS-M	DSST	PPT-P	PPT-B	PPT-A	CRT	CFFT	Inglis	Drowsiness
Var. No.	1	2	3	4	5	6	7	8	9	10	11
1	-										
2	,607**	-									
3	-,599**	-,399	-								
4	-,478*	-,010	,226	-							
5	-,501*	-,070	,224	,867**	-						
6	-,620**	-,227	,131	,697**	,704**	-					
7	-,088	,138	-,173	,273	,238	,472**	-				
8	,160	,095	-,252	-,365	-,411	-,360	-,035	-			
9	,074	-,058	-,225	-,026	-,299	-,110	-,189	,355	-		
10	,257	,257	-,100	-,245	,261	-,048	-,058	-,081	-,123	-	
11	,290	,396	-,141	,014	-,107	,017	-,115	-,108	-,125	,218	-

* $p < 0,05$

** $p < 0,01$

The results of the correlation matrices (tables 45 to 53) will be considered in terms of trends that emerge in the relationship between certain variables. The relationship that will be considered are those that are of a practical and/or theoretical interest. The following relationships will be considered:-

(a) The relationship between HAS and VAS-A scores (i.e. the two measures of anxiety).

(b) The relation between HAS and VAS-M scores and between VAS-A and VAS-M scores (i.e. the measures of anxiety and the VAS measure of motivation).

(c) The relationship between the various performance measures - DSST, the three pegboard tests, CRT and Inglis tests (CFFT is considered later).

(d) The relationship between the measures of anxiety and the performance variables.

(e) The relationship between the drowsiness rating and the various performance measures, and the relationship between the drowsiness rating and the anxiety and VAS-M variables.

(f) The relation between CFFT and the other variables.

(a) <u>The relationship between HAS and VAS-A scores</u>

The correlation coefficient (Pearson product-moment) between these two measure is significant in seven out of a possible nine instances. The correlations

are positive and high. There is thus a strong trend for scores on the HAS to be equivalent in magnitude to scores on the VAS-A. For example a patient with a high anxiety score on the HAS is likely to have a high anxiety score on the VAS-A.

(b) The relationship between the measures of anxiety and the VAS-M scores

The correlation coefficient between HAS and VAS-M is significant and negative in two out of a possible nine instances. The correlation coefficient between VAS-A and VAS-M is significant and negative in only one instance out of a possible nine instances. There is thus a trend for scores on the anxiety measures to be related to score on the VAS-M. The correlation is negative and hence patients who have a high VAS-M score will have low anxiety scores. Since only three out of 18 correlations are significant this trend is not very strong.

(c) The relationship between the various performance variables

The correlations between the DSST, the three pegboard tests, CRT test and the Inglis test are significant in 46 out of a possible 144 occasions. In some cases the correlations are negative in others positive but in

all of these 46 instances the correlation indicate that a patient who performs well on one of these tests has good performance on the other tests (alternatively bad performance on one of these tests is likely to go with bad performance on the other tests). There is thus a fairly strong trend for performance on the various measures to be related.

(d) The relationship between the measures of anxiety and the performance measures

There are 18 significant correlations (out of a possible 108 instances) between either HAS or VAS-A and the various performance measures. The correlation are either positive or negative but in all 18 instances they show an inverse relationship between anxiety and performance. Specifically this means that higher anxiety is associated with poor performance or alternatively low anxiety is associated with good performance. Since 18 correlations out of 108 are significant the trend is not very strong.

(e) The relationship between the drowsiness rating and the other variable

There are four significant correlations between drowsiness and performance for the clobozam group at the 2-day

assessment and one significant correlation between drowsiness and a performance variable (CRT) for the clobozam group at the 9-day assessment. No other correlations between the drowsiness rating and performance are significant. There are thus five instances of significant correlations between drowsiness rating and the performance variables out of a possible 36 instances. The significant correlation show drowsiness rating to be inversely related to performance (higher drowsiness associated with poorer performance). This trend only occurs in the clobozam group and not in the placebo or lorazepam group. The trend in the clobazam group is fairly strong (five out of 12 instances).

In two instances the correlation between drowsiness rating and the VAS-A is significant. The occurs in the clobazam group at the two and nine day assessments. The correlations are positive indicating that higher drowsiness rating are associated with higher VAS-A scores. These are the only instances of significant correlation between drowsiness rating and the VAS-A or HAS or VAS-M score. There are thus only two significant correlations out of a possible 18 instances. The trend for drowsiness to be related to be anxiety measures or the VAS-M measure is therefore minimal.

(f) The relationship between the CFFT and the other variables

There are only three significant correlation between CFFT and the other variables. The correlation between VAS-A and CFFT is significant in the lorazepam group at the 2-day assessment. The correlations is negative indicating an inverse relationship between VAS-A score and CFFT. This implies that a higher anxiety score is associated with lower CFFT and vice versa. Since there is only one instance of a significant correlation between the anxiety measures and CFFT out of a possible 18 instances the trend is very minimal.

There are no instances of significant correlations between CFFT and the VAS-M or the drowsiness ratings. The other two significant correlations are between CFFT and two performance variables. There is a significant positive correlation between CFFT and PPT-B in the clobozam group at the pre-treatment assessment and between CFFT and DSST in the clobozam group at the 9-day assessment. This is also a minimal trend as there are only two significant correlations out of a possible 45 instances. The direction of the correlations indicate that higher CFFT is associated with good performance and alternatively low CFFT is associated with poor performance.

7. DISCUSSION

The non-adherence rate of 41,67 percent compares favourably to the rate found in out-patients. Blackwell (1976) writes that non-adherence is reported in between 25 and 50 percent of outpatients. The slight differences in the final total of patients who completed and complied with treatment in each treatment group are not significantly different from what would be expected by chance. This study is interested in the effects of the drugs on anxiety and performance on those patient who actually complete and comply with treatment and hence there is no reason in this case to consider the non-adherent patients.

Most of the patients who successfully completed the trial and complied with treatment were females (92,5 percent). The predominance of female patients is representative of the actual proportion of benzodiazepine users (approximate 70 percent females) (Bellantuono et al., 1980). As discussed in the introduction (Section 2.4.2) many studies assessing the psychomotor effects of the benzodiazepines have utilized male subjects. The median educational level of the patients (Standard Five) is relatively low and the implications of this will be discussed at a later stage when the generalisability of the findings are considered.

.1 THE ANXIETY, DROWSINESS AND PERFORMANCE CHANGES

The results of the Hamilton Anxiety Scale (HAS) show that there is an initial significant improvement in anxiety at 2 days in all three treatment groups. A further improvement at 9 days was evident only in the benzodiazepine groups. This indicated an initial placebo effect which was not enhanced with time. Thus from the standpoint of anxiolytic efficacy clobazam and lorazepam were superior to placebo. Bellantuono et al. (1980) who reviewed the studies that have assessed the anxiolytic efficacy of the benzodiazepines reported that out of a total of 85 studies, 44 results showed the drug to be much better than the placebo, 26 showed the drug to be slightly better than the placebo, 14 showed no difference and one study showed the drug to be worse than the placebo. The results of this study can be classed as showing that clobazam and lorazepam are slightly better than placebo. Substantial placebo effects are generally found with anxious patients (Greenblatt and Shader, 1974). In addition, even greater placebo effects have been found in previous studies that have involved patients of a relatively low educational level (Rickels et al., 1970; Hesbacher et al., 1970).

Another significant result that emerged for the HAS mean scores is the initial significant difference between the placebo group and the drug groups. The placebo group pre-treatment HAS score is significantly lower than both

the clobazam and the lorazepam group. The actual difference in mean scores is not very large. The initial mean placebo score (20,65) is only just over 2 digits lower than the initial clobazam score (22,74) and just over 3 digits lower than the initial lorazepam score (23,91). It is unlikely that such small initial differences will have any important influences on either the anxiety changes or the performance changes observed in the study. Since the patients are randomly assigned to the three treatment groups, this initial difference arose entirely by chance. If the initial placebo group mean score had been lower (say 15), then this far lower initial anxiety level could have had considerable influence on anxiety and performance changes over the course of treatment. Anxiety changes in the placebo group would probably be far less because of the initial lower anxiety and psychomotor performance would probably be initially at a higher level of the lower anxiety state of the placebo group. Since the placebo group is used as a comparison group in the interpretation of anxiety and performance changes in the drug groups, a large initial difference in placebo and drug group anxiety levels could have made interpretation of the results far more complicated than if no difference or relatively small differences are found. Luckily the initial differences found in this study, although significant, are relatively small.

This small difference in anxiety score does not seem to have had any important influence over the initial psychomotor performance level. If there had been a major

influence one would predict a higher initial performance level in the placebo group as of the lower initial anxiety level. This is not found. There are no significant differences in the initial psychomotor performance level in any of the psychomotor tests. The placebo group's initial performance ranks first on two of the performance tests, second on two of the performance tests and third on the remaining three performance tests. Hence the initial small difference in placebo anxiety level from the drug groups has not had any influence on initial performance level and can therefore be ignored when the performance changes are interpreted. Similarly the initial lower anxiety mean score has not greatly influenced the anxiety changes in the placebo group. If there had been a major influence one would have expected far less initial change in the placebo group than the large change observed in anxiety level from pre-treatment to the 2-day assessment. The initial lower placebo HAS mean score has also been ignored when the anxiety changes have been interpreted.

The results of the visual analogue scale-anxiety (VAS-A) scores showed a general tendency similar in all three treatment groups for anxiety level to decrease. The decrease from pre-treatment (overall average mean of 81,73) to the 2-day assessment (overall average mean of 45,93) was greater (a difference of 35,8) than the drop from the 2-day assessment to the 9 day assessment (overall average mean of 25,71). The latter difference is 20,22. Both

decreases were significant ($p < 0,01$). As previously discussed, for the HAS there were different trends for each of the treatment groups. The drug groups showed a continual significant decrease but the placebo group showed an initial significant decrease followed by a levelling off. Therefore, a fairly similar result is found for the VAS-A scale except that the placebo group does not show the levelling off of anxiety level to the same extent as shown by HAS measurements. In actual fact, the change in VAS-A mean score from day-2 to day-9 is lowest in the placebo group, but the change is not small enough to result in a significant interaction effect such as the one found for the HAS.. The correlation coefficients between VAS-A scores and HAS scores also show that there is a strong trend for scores on the VAS-A to be equivalent in magnitude to scores on the HAS.

The visual analogue scale-motivation (VAS-M) scores do not show different trends for the three treatment groups. There is an overall tendency for motivation level to increase from pre-treatment to the 2-day assessment. The increase from the 2-day assessment to the 9 day assessment is far less and insignificant. The overall change from pre-treatment to the 9-day assessment is also significant. The changes in motivational levels (assessed by the VAS-M) found are probably directly related to the general improvement felt by the patients brought about by a lowering of anxiety level. The correlation coefficients between VAS-M and

the anxiety measures do in fact show a slight trend (3 significant correlations out of a possible 18 instances) for improved motivation to be associated with decreased anxiety. The rudimentary assessment of motivational level was included to assess if clobazam treatment resulted in motivational enhancement. Since there was no difference in the extent of improvement of motivation in the three treatment groups this assessment does not indicate that clobazam is in any way resulting in motivational enhancement over and above that found in the placebo and lorazepam group.

The overall drowsiness rating of the lorazepam group is significantly greater than both the clobazam group and the placebo group. The clobazam and placebo groups do not differ in overall drowsiness rating. There is also a significant decrease in overall drowsiness rating from the day-2 assessment to the 9-day assessment. These results indicate a greater subjective sedative effect in the lorazepam group as compared to the clobazam and placebo group. The extent of drowsiness decreased as treatment progressed in all three treatment groups. In the introduction it was pointed out that the average incidence of drowsiness in clinical trials with clobazam is about 17 percent in those patients treated with clobazam relative to about 6 percent for those patients receiving a placebo. In double-blind studies comparing clobazam with diazepam the overall incidence of reported drowsiness is very slightly less for clobazam. A detailed examination of the incidence of

drowsiness in the three treatment groups reveals that for the placebo group at the 2-day assessment the incidence of reported drowsiness is 35 percent made up of 20 percent mild drowsiness (rating of 1) and 15 percent moderate drowsiness (rating of 2). In the clobazam group at the 2-day assessment the incidence of reported drowsiness is 55,5% made up of 29,6% mild drowsiness and 25,9% moderate drowsiness. In the lorazepam group the reported incidence at 2 days is 87% made up of 47,8% mild and 39,1% moderate drowsiness. At 9 days the incidence in the placebo group is 5% (1 patient reported moderate drowsiness), in the clobazam group 40,7% (25,9% mild and 14,8% moderate) and in lorazepam 69,6% (34,8% mild and 34,8% moderate).

The incidence of moderate drowsiness assessed at 9-days for the placebo group (5%) and the clobazam group (14,8%) are very similar to the average figures found in clinical trials for clobazam (17%) and placebo (6%). It is fairly likely that drowsiness is usually assessed after about one week of treatment and that often at least moderate drowsiness needs to be reported by a patient for it to be noted by an investigator as an incidence of drowsiness. This study shows the need to include a shorter term evaluation of drowsiness. In addition, it is necessary to gain a more detailed assessment of drowsiness by ascertaining the degree of drowsiness experienced by a particular patient instead of simply noting the incidence of drowsiness. The latter approach is generally applied in clinical trials.

The lack of pre-treatment assessment of drowsiness rating is similar to the standard adopted in clinical trials of assessing side-effects once treatment has commenced. This assumes an initial equivalent minimal drowsiness level in all three treatment groups. This is probably correct but not necessarily so. Thus a slight criticism of the approach used in this study and in other clinical trials is the lack of pre-treatment assessment of drowsiness. Using a pre-treatment assessment would have been more thorough although probably unnecessary. Further aspects of the findings on the degree of drowsiness will be dealt with in a later part of the discussion.

The digit symbol substitution test (DSST) mean scores show similar trends in all three treatment groups. Performance improves significantly from pre-treatment to the 2-day assessment and continues to improve significantly to the 9-day assessment. The overall change from pre-treatment to the 9-day assessment is thus also a significant improvement. The general overall improved performance can be accounted for by a learning effect and also probably by a reduction in anxiety level. Salkind and Silverstone (1979) also observed an improvement in DSST performance in their patient study and they attributed this to a learning effect. As discussed in the introduction, it is also very likely that a reduction in anxiety will result in improved performance. When the effects of the 1,4 benzodiazepines (including lorazepam) on psychomotor performance were

considered in the introduction (Section 3.1), it was noted that the DSST was sensitive in detecting impaired performance in non-anxious volunteer subjects. Thus on the basis of volunteer studies one would have expected impaired performance in the lorazepam group. This is not found, the lorazepam group shows a similar trend to that found in the placebo and clobazam group, of improved performance. This finding will be considered again later in the discussion, but at this point it should also be noted that as indicated in the introduction, research shows that patients have significant impairment on fewer occasions than volunteers on a specific test such as the DSST. The clobazam group also shows improved performance and this lack of any indication of impaired performance is similar to that found in volunteer studies with clobazam.

The critical flicker fusion threshhold (CFFT) results show that there are no significant changes in any of the drug groups. This lack of change is what one would expect in the placebo group. Volunteer and patient studies with clobazam have indicated that clobazam either does not affect CFFT or results in significantly elevated CFFTs. Therefore the lack of change found in the clobazam group confirms the previously findings with clobazam. Volunteer studies with lorazepam have shown that a consistent and significant reduction in CFFT. Hence on the basis of these studies one would have expected a reduction in CFFT in the lorazepam group. This reduction is not found in

this study. This finding will be considered again in a later part of this discussion.

The Inglis paired-associate learning test mean scores show similar trends in all three treatment groups. There is an initial significant improvement in performance from pre-treatment to the 2-day assessment followed by a lack of improvement in performance from the 2-day to the 9-day assessment. The overall improvement in performance from pre-treatment to 9-days is significant. The general improvement in performance in all three treatment groups can be explained by a learning effect and an improvement in performance due to a lowering of anxiety. The lack of general improvement from 2-day assessment to the 9-day assessment indicates that for the Inglis test performance had improved critically to a peak level and would not improve beyond this even though the patients' anxiety was generally reduced. This shows a different learning curve to what was found for the DSST.

On the basis of previous studies on volunteers one would have expected that the lorazepam group would show impairment on this memory test. Once again this study shows that the expected impairment is not found in patients. The clobazam group shows no impairment on this memory test and this is what one would predict on the basis of volunteer studies.

The Purdue pegboard test-preferred hand task (PPT-P) mean scores show different trends in performance improvement over time in the three treatment groups. This is the first psychomotor performance measure to show different trends in the three treatment groups. In the placebo group there is an initial significant improvement in performance from pre-treatment to the 2-day assessment. Performance continues to improve slightly but the change from the 2-day to the 9-day assessment is insignificant. The overall change from pre-treatment to the 9-day assessment is also significant. The improved performance in the placebo group can be attributed to a learning effect and to the reduction of anxiety resulting in improved performance.

In the clobazam group there is a similar initial significant improvement in PPT-P performance from the pre-treatment assessment to the 2-day assessment. Performance at the 9-day assessment is at a slightly lower level than performance at the 2-day assessment but this change is insignificant. The overall change from pre-treatment to the 9-day assessment is also significant. Thus the clobazam group shows a similar trend (of initial improved performance followed by a levelling off) as that found in the placebo group.

On the other hand, the lorazepam group shows a different trend to that found in the placebo and clobazam groups. There is no initial significant improvement from pre-treatment to the 2-day assessment. There is a significant improvement

from the 2-day assessment to the 9-day assessment. The overall change from the pre-treatment to the 9-day assessment also shows a significant improvement. The lack of initial significant improvement in the lorazepam can be explained as being due to the sedative effect of the drug. By the 9-day assessment the patients in the lorazepam group had adapted to the sedative effect (i.e. tolerance to the drug has occurred) and their PPT-P performance improves to a similar extent as that found in the other treatment groups. This is the first instance where the impairment in performance expected on the basis of volunteer studies on lorazepam is found. If the patients had only been assessed at pre-treatment and at 9-days the impaired performance due to the sedative effect of lorazepam would not have been detected. Once again the clobazam group shows no indication of impaired performance and this is what would be expected on the basis of results of previous research on clobazam.

The Purdue pegboard test-both hands task mean scores show similar trends in all three treatment groups. The initial improvement in performance is not significant but the improvement from the 2-day assessment to the 9-day assessment is significant. The overall improvement from pre-treatment to 9-days is significant. These improvements can be accounted for by a learning effect and anxiety reduction. The lack of impairment in the clobazam group is expected on the basis of findings on volunteers. On the other hand,

one would have expected impairment in the lorazepam group on the basis of volunteer studies.

The Purdue pegboard test-assembly task mean scores show very similar trends as that found for the preferred hand task. There are different trends in performance improvement over time in the three treatment groups. In the placebo group there is a significant initial improvement from pre-treatment to 2-days followed by a slight insignificant improvement. The overall change from pre-treatment to the 9-day assessment is significant. The clobazam group shows a similar trend of initial significant improvement followed by a lack of significant improvement. In the lorazepam group there is a different trend. There is no initial improvement from pre-treatment to the 2-day assessment. The change from 2-days to 9-days is significant reaching a similar level of improvement to that found in the other two treatment groups. The change from pre-treatment to 9-days is significant. The lack of initial improvement in the lorazepam group results in significant differences in the means of the lorazepam group from the placebo and clobazam means at the 2-day assessment.

The lack of initial improvement found in the lorazepam group can be attributed to the sedative effect of the drug which resulted in impaired performance. By the 9-day assessment the patients in the lorazepam group had adapted to the sedative effect and their PPT-A performance improves

to a similar extent as that found in the other treatment groups. On the basis of volunteer studies one would have expected impairment in the lorazepam group. If the patients had been assessed at pre-treatment and at 9-days the impairment in performance in the lorazepam group would not have been detected. The clobazam group shows no indication of impaired performance and this is what one would expect on the basis of findings on volunteers.

The three treatment groups show similar trends in mean scores for the choice reaction time task. There is an initial significant improvement from pre-treatment to 2-days followed by a further significant improvement from 2-days to 9-days. This improvement can be attributed to a learning effect and anxiety reduction. Impairment would have been expected in the lorazepam group on the basis of volunteer studies. Once again the clobazam group showed no impairment and this is what one would have predicted on the basis of volunteer studies.

In general the results show that there is far less impairment in the lorazepam group that what would be predicted on the basis of results from volunteer studies. The performance tests were selected on the basis that they are sensitive in detecting impaired performance in volunteers given 1,4 benzodiazepines (including lorazepam). Thus impaired performance would be expected in most, if not all, of the performance tasks. Impaired performance is only found on

two of the pegboard tests. This shows very clearly that there is much less impairment in this group of patients than what would be expected on the basis of volunteer studies. As discussed in the introduction (Section 3.2), previous studies have also found a lesser frequency of impaired performance in patients. On the basis of the findings of this study and previous findings on patient groups it can be asserted that volunteer performance changes cannot serve as a definative basis for predicting what will happen in patients given 1,4 benzodiazepine treatment.

On the occasions where performance impairment was found in the lorazepam group the patients showed initial impairment due to sedation followed by adaptation to the sedative effect and improvement in performance to the level found in the other treatment groups. These changes highlight the need for both a short-term and longer term assessment. Most volunteer studies include only a short-term assessment and many patient studies have only long-term (after one week) assessments.

The clobazam group shows clear indications of less sedation than that found in the lorazepam group. There is no impairment on any of the performance tasks for patients in the clobazam group whereas the lorazepam group does show initial impairment on two of the pegboard tests. The clobazam group does not show significantly greater drowsiness ratings than the placebo group, in contrast the lorazepam

group does show significantly greater drowsiness ratings. Since less impairment is found in the lorazepam group than that found in volunteer subjects, the degree of differentiation from the clobazam group is much less than found in volunteer studies with clobazam and lorazepam.

7.2 THE RELATIONSHIPS BETWEEN THE DEPENDENT VARIABLES

The intercorrelations between the anxiety measures and the visual analogue scale of motivation have already been discussed.

The fairly strong trend for performance on the various performance variables to be related is what one would expect. A patient doing well on one of these pegboard tasks is very likely to do well on the other pegboard tasks and on other performance tasks which involve a speed component particularly choice reaction time and to a lesser extent the digit symbol substitution test. There are, in fact, only three significant correlations between the Inglis paired-associate learning test and the other performance measures indicating that the Inglis test shares less of the skills than the other performance variables.

The trend for performance to be inversely related to anxiety level is what would be predicted by the general inverted-U relationship between anxiety and performance. The fairly strong trend for drowsiness rating to be inversely related

to performance in the clobazam group is very interesting. This implies that those patients with high drowsiness ratings have poor performance and those patients with low drowsiness ratings have good performance. One would expect the subjective indication of sedation (drowsiness) to be related to the objective indication of sedation (impaired psychomotor performance). This relationship is surprisingly not shown in the lorazepam group where there are no significant correlations between drowsiness rating and the performance variables. Some of the correlations are fairly substantial and approach significance. The relationship between subjectively experienced drowsiness and impaired psychomotor performance certainly needs to be investigated in future studies. Quite possibly the lack of correlation between drowsiness level and impaired performance may be specific to this study.

The few significant correlations between critical flicker fusion threshhold and the other variables are in the direction expected on the basis of previous experiments. Lower CFFT are associated with high anxiety levels (Goldstone, 1955). Lower CFFT (lower arousal levels) are generally associated with poorer performance (Claridge, 1967). The two instances of significant positive correlation between drowsiness rating and the visual analogue scale of anxiety measure are not expected. The finding of only two significant correlations out of a possible 18 indicates a very minor relationship and is thus probably of minimal importance.

Before the implications of the various findings are discussed, two important issues need to be considered. The first is the problem associated with doing a number of statistical tests on data from a single subject group. This is the problem of Type I errors. The second issue concerns the generalisability of the findings.

7.3 TYPE I ERRORS

A type I error is the faulty conclusion that there are significant differences between measures when in fact the differences are actually due to chance. The probability of a type I error for one particular statistical test is equal to alpha (α) the level of significance. The values of alpha generally chosen in research are either 0,05 or the stricter level of 0,01. If one computes b independent tests of significance on the b dependent variables measured, then the probability of at least one type I error on all b tests is $1 - (1 - \alpha)^b$ (Gilbert, 1977c). In this study there were 11 dependent variables (b = 11) and the probability of c type I error for α = 0,05 is p = 0,4013 and the probability of a type I error for α = 0,01 is p = 0,0956. If the level of significance chosen was 0,05 it can be seen that the probability of a type I error increases to a totally unacceptable level. However, if the significance level is 0,01 then the probability of a type I error is still at an acceptable level of approximately 0,1. All except one of the ten significant two way anovas were significant at

the 0,01 significance level and thus the degree of significance in nine instances was sufficient to decrease the chances of type I errors on any one statistical test to 0,1.

Another important factor specific to this study is the concern with trends in the changes in groups of dependent variables in both the two-way anovas and the correlations. There is relatively little emphasis laid on a finding of statistical significance in one particular dependent variable in the two-way anova analysis. This implies that since the probability of a type I error (when 11 tests are carried out and alpha set at 0,01) is approximately equal to 0,1 then possibly one out of the ten significant findings could be due to chance. Since this study is interested in changes in groups of dependent variables (all the psychomotor performance measures) a single type I error is not going to affect the conclusions drawn from the findings. Similar arguments apply to the conclusions drawn from the correlations where one is interested in the trends in the relationship between groups of dependent variables.

7.4 THE GENERALISABILITY OF THE FINDINGS

When a random sample is drawn from a certain population group then the research findings derived from the sample are generalisable to the population group (Plutchik, 1974). There are thus two aspects which need to be discussed.

Is the sample used in this study random? To what population group are the results generalisable?

The patients who participated in this research were those patients with anxiety problems who were prescribed a benzodiazepine tranquillizer by a doctor and who then agreed to take part in the study. Most patients who were referred to the investigator agreed to participate. Only about ten patients did not agree to take part in the study because it would be inconvenient for them to return for another two appointments over the next nine days.

The sample of patients can be considered to be a random sample of outpatients attending Retreat Day Hospital with anxiety problems who are viewed by a general practitioner as requiring benzodiazepine treatment. The sample is a selection of these patients over the particular time period when the study was conducted relative to a longer period of time over which similar patients receive similar treatment. This implies that the conclusions are certainly generalisable to patients with similar levels of anxiety who attend Retreat Day Hospital at other times.

With a lesser degree of confidence the results can be generalised to outpatients with similar levels of anxiety and similar educational levels who attend other hospitals. This generalisation would not be based on the strict criterion that the sample must be randomly drawn from a

population (that is not on formal procedures of inference). Other non-statistical inferences to patient groups of different educational level can be made with less confidence. Further empirical investigations assessing the relationship between educational level and psychomotor performance on laboratory tests would be needed to adequately answer this question. Interestingly enough, the findings on psychomotor performance changes found in this study show similar trends to the findings found in other patient studies. Possibly the objective indications of sedation (impaired performance) are similar in most patients of a particular anxiety level regardless of other characteristics of the patients.

The next parts of the discussion deal with some wider topics that relate to the findings of this study.

7.5 REASONS FOR THE DIFFERENT INDICATIONS OF IMPAIRED PERFORMANCE IN PATIENT AND VOLUNTEER GROUPS

The findings of this study indicate clearly that the frequency of significant impairment on laboratory tests of psychomotor performance is less in patients than in volunteers given a 1,4 benzodiazepine (lorazepam). An overall consideration of all psychomotor performance studies on patient groups leads one to conclude that the findings in this study are consistent with previous findings

of a lesser frequency of impairment in patients relative to volunteers.

A major reason for the lesser frequency of impairment in patients is the initial higher level of anxiety experienced by the patients. The U-shaped relationship between anxiety and performance was discussed in the introduction (Section 2.3). Patients with relatively high initial levels are likely to have initially impaired performance. This has been shown in various studies (Lader and Marks, 1971). When these patients are given a benzodiazepine their anxiety levels are reduced and their psychomotor performance thus improves. The benzodiazepines also have a sedative effect which will result in impaired performance in the patients, however, at the same time, because the patients are becoming less anxious, their performance is improving. The overall result is that there is a lesser frequency of impaired performance in patients than in volunteers where only the sedative effect would be operating as the volunteers are non-anxious.

This explanation assumes an essentially similar effect of the benzodiazepine in anxious patients and non-anxious volunteers. However, there is some evidence that this may not be the case. DiMascio and Barrett (1965) and Barett and DiMascio (1966) found different effects in volunteers who had been divided into high and low anxious groups. The high anxious group of volunteers responded

to the benzodiazepines in the expected manner, their level of anxiety was significantly reduced. The low anxious group in both studies responded unexpectedly, their levels of anxiety increased significantly. This indicates that the benzodiazepines are possibly having different physiological effects in the low and high anxious groups. This could also result in different degrees of psychomotor performance impairment. Possibly volunteers' performance is disrupted by taking a benzodiazepine (their anxiety increases) and this effect is not found in patients. Another possible occurrence is that the benzodiazepines have different sedative effects in volunteers relative to patients.

The discussion of Hollister (1981) about benzodiazepine receptors is also relevant to this issue. A remarkable discovery during the past two years has been the identification of specific receptors in the brains of animals and man that bind benzodiazepines. Hollister speculates that there is an endogenous ligand that binds to these receptors. In fact, several candidates for just such ligands have been proposed. The situation with the opiate drugs is analogous. Opiate receptors have been found and the endogenous opiate (endorphins) have been discovered. Hollister speculates further that those patients who have high levels of trait anxiety may in fact be deficient in the endogenous ligand for the benzodiazepine receptor. This could mean that treatment with benzodiazepines would be far

more specific than ordinarily believed.

I would speculate further that if what Hollister hypothesizes is correct then it does have relevance to the different frequency of psychomotor performance impairment found in anxious patients relative to non-anxious volunteers. Non-anxious volunteers would not lack this hypothesized endogenous ligand and when they were given a benzodiazepine there would be a resultant excess of benzodiazepine molecules which could lead to impaired performance either by sedation or some other means.

The two reasons proposed for the different frequency of impairment in volunteers and patients are not mutually exclusive and both may be relevant.

7.6 THE PRACTICAL IMPLICATIONS OF THE FINDINGS

A question that is important in ascertaining certain aspects of the practical implications of the findings is: How different is the sedative effect of clobazam to that of the 1,4 benzodiazepines (for this study lorazepam)? Certainly patients who receive a 1,4 benzodiazepine do experience both subjective sedation (drowsiness) and objective sedation (impaired performance). The frequency of impaired performance is less than in volunteers but it is still enough to be of practical significance. More research is needed but one can certainly even at this stage say

that patients who receive a 1,4 benzodiazepine should be cautioned about the possible detrimental effects of the treatment on performance.

Further research on the relationship of general findings of impaired psychomotor performance on laboratory tests to the specific practical situations such as car driving is needed. However, even at this stage it can be stressed that the cautioning about possible detrimental effects on psychomotor performance is particularly relevant to those patients who drive a car and to those patients whose occupations involve working with dangerous machinery.

This study indicated some initial impairment for at least two days. At nine days there was no longer impaired performance. Further research is needed to ascertain at what point the patients adapt to their medication so that their performance is no longer impaired.

To what extent should patients who receive clobazam be cautioned about possible impaired performance? This study did not find any indications of impaired performance in the clobazam group. Subjective drowsiness ratings did not differ significantly from the placebo group. This would certainly seem to imply that clobazam is relatively free of both objective and subjective indications of sedation and that patients who are given clobazam need not be cautioned about possible detrimental effects. However, a further

careful consideration of the findings in this and other studies reveals that the situation may not be as clear cut as this.

Lader (1979) discusses the physiological and biochemical studies on the benzodiazepines and concludes that

> "on theoretical grounds based on recent work, the anxiolytic and sedative properties of a benzodiazepine could be mediated through different pathways and perhaps different neuro transmitters. If so, then the ingenuity of medicinal chemists should make feasible the development of a drug which is anxiolytic without being sedative." (p.103 S).

Is clobazam this drug?

Although clobazam in this study is free of significant impairment or drowsiness, there are indications that it is not totally free of sedation. Some patients (eight) do report moderate drowsiness, especially at the day two assessment. When the individual psychomotor performance data for these patients are examined closely, it is clear that some of these patients do not show a similar extent of improved performance as found in the other clobazam patients. This is confirmed by the fairly strong trend for drowsiness ratings to be inversely related to performance (there are five out of twelve significant correlations in the clobazam group at two days). It seems that certain patients do experience both drowsiness and slightly impaired performance. As noted in the introduction (Section 3.3) one study on volunteers also found that

certain subjects (two of the ten subjects) were sensitive to clobazam showing impaired performance although no general statistically significant indications of impaired performance were found when the results of all the volunteers who received clobazam were analysed (Hindmarch, Hanks and Hewett, 1977). Previous research on both volunteers and clobazam has only rarely discerned statistically significant indications of impaired performance, on most occasions there is no impairment or significant improvement is found.

On the basis of this study and on previous research with clobazam on both volunteers and patients a number of conclusions concerning the sedative effect of clobazam can be stated. Clobazam is far less likely to result in impaired performance in patients than the 1,4 benzodiazepines. However, it seems that certain patients especially those who experience moderate drowsiness may also experience impaired performance. Further research in this area is needed and hence only tentative suggestions can be made as to the practical implications of these findings. A possible recommendation is that patients who take clobazam should still be cautioned about possible initial drowsiness with associated impaired performance although this is less likely to occur than in patients receiving a 1,4 benzodiazepine.

7.7 RECOMMENDATIONS FOR FUTURE RESEARCH

A number of specific areas still need further investigation. The relationship between drowsiness and impaired performance needs to be studied. Assessments at other time periods need to be carried out to ascertain at what point full adaptation to sedative effects takes place.

In addition to these specific ideas a general overall strategy can be recommended for research into psychomotor performance changes induced by drugs. An adequate number of studies should be carried out on volunteers to ascertain the behavioural effects per se of a particular drug. In the past investigators have tended to mainly use volunteer subjects and this study shows the necessity for doing at least as many studies as that done on volunteers on the actual patient group who will be receiving the drug. A standard battery of tests which have been shown to be sensitive to detecting impairment and which would assess all the important components of behaviour should be developed and used in these studies. In addition to these general assessments of psychomotor performance on laboratory tests specific studies on the performance of both volunteers and patients on practically relevant tasks such as car driving are also needed to be conducted for any particular drug which has properties that result in impaired performance.

REFERENCES

Ackerman, M. (Editor). Coping with tension. Cape Town: Lay Publications Department, Medical Association of S.A., 1979.

Aitken, R.C. Measurement of feelings using visual analogue scales. Proceedings of the Royal Society of Medicine, 1969, 62, 989-993.

Ameer, B. and Greenblatt, D.J. Lorazepam: a review of its clinical pharmacological properties and therapeutic uses. Drugs, 1981, 21, 161-200.

Ayd, F.J. Motivations and rewards for volunteering to be an experimental subject. Clinical Pharmacology and Therapeutics, 1972, 13, 771-781.

Ban, T.A. and Amin, M.M. Clobazam: uncontrolled and standard controlled clinical trials. British Journal of Clinical Pharmacology, 1979, 7, 135S-138S.

Barlow. D.H., and Baer, D.J. Effect of cigarette smoking on the critical Flicker Fusion Frequency of heavy and light smokers. Perceptual and Motor Skills, 1967, 24, 151-155.

Barrett, J.E. and DiMascio, A. Comparative effects on anxiety of the "minor tranquilizers" in "high" and "low" anxious student volunteers. Journal of Clinical Psychiatry 1966, 27, 483-486.

Bellantuono, G., Reggi, B., Tognoni, G. and Garattini, S. Benzodiazepines: clinical pharmacology and therapeutic use. Drugs, 1980, 19, 195-219.

Berry, C., Gelder, M.G. and Summerfield, A. Experimental analysis of drug effects on human performance using information theory concepts. British Journal of Psychology, 1965, 56, 255-265.

Berry, P.A., Burtles, R., Grubb, D.J., Hoare, M.V. An evaluation of the effects of clobazam on human motor coordination, mental acuity and mood. British Journal of Clinical Pharmacology, 1974, 1, 346P.

Biehl, B. Studies of clobazam and car-driving. British Journal of Clinical Pharmacology, 1979. 7, 85S-90S.

Blackwell, B. Psychotropic drugs in use today. The role of diazepam in medical practice. Journal of the American Medical Association, 1973, 225, 1637-1641.

Blackwell, B. Treatment Adherence. British Journal of Psychiatry, 1976, 129, 513-531.

Bond, A.J., James, D.C. and Lader, M. Physiological and psychological measures in anxious patients. Psychological Medicine, 1974a, 4, 364-372.

Bond, A.J., James, D.C. and Lader, M.H. Sedative effects on physiological and psychological measures in anxious patients. Psychological Medicine, 1974, 4, 374-380.

Borland, R.G., and Nicholson, A.N. Immediate effects on human performance of a 1,5-benzodiazepine (clobazam) compared with the 1,4 benzodiazepines, chlordiazepoxide hydrochloride and diazapam. British Journal of Clinical Pharmacology, 1974, 2, 215-221.

Brogden, R.N., Heel, R.C., Speight, T.M., and Avery, G.S. Clobazam: A review of its pharmacological properties and therapeutic use in anxiety. Drugs, 1980, 20, 161-178.

Caird, W.K., Sanderson, R.E., and Inglis. J. Cross-validation of a learning test for use with elderly psychiatric patients. Journal of Mental Science, 1962, 108, 368-370.

Church, M.W. and Johnson, L.C. Mood and performance in poor sleepers during repeated use of flurazepam. Psychopharmacology, 1979, 61, 309-312.

Claridge, G.S. Personality and arousal. Oxford: Pergamon, 1967.

Claridge, G.S. Drugs and human behaviour. London: Allen Lane, 1970.

Clayton, A.B. The effects of psychotropic drugs on driving-related skills. Human Factors, 1976, 18, 241-252.

DiMascio, A. and Barrett, J. Comparative effects of oxazepam in 'high' an 'low' anxious student volunteers. Psychosomatics, 1965, 6, 298-302.

Doongaji, D.R., Sheth, A., Apte, J.S., Lakdawala, P.D., Khare, C.B., and Thatte, S.S. Clobazam versus diazepam: a double-blind study in anxiety neurosis. British Journal of Clinical Pharmacology, 1979, 7, 119S. (Abstract).

Duceman, I., Malmgren, H. and Norrman, B. Comparison studies of clorazepate administered as a divided daily dose and as a single dose at night. Psychopharmacology, 1978, 57, 123-127.

Eysenck, H.J. Experiments with drugs. Oxford: Pergamon, 1963.

Farhoumand, N., Harrison, J., Pase, C.M.B., Turner, P and Wynn, S. The effects of high dose oxprenolol on stress induced physical and psychophysiological variables. Psychochopharmacology, 1979, 64, 365-369.

Fielding, S., and Hoffman, I. Pharmacology of anti-anxiety drugs with special reference to clobazam. British Journal of Clinical Pharmacology, 1979. 7, 7S-15S.

File, S.E. and Bond, A.J. Impaired performance and sedation after a single dose of lorazepam. Psychopharmacology, 1979, 66, 309-313.

Gilbert, L. Deciding upon a sample size. Unpublished Honours Research Methodology Notes, University of Cape Town, 1977a.

Gilbert, L. Issues and assumptions in the anova: unequal sample sizes. Unpublished Honours Research Methodology Notes, University of Cape Town 1977b.

Gilbert, L. Hotelling's T Squared. Unpublished Honours Research Methodology Notes, University of Cape Town, 1977c.

Goldstone, S. Critical Flicker Fusion measurements and anxiety level. Journal of experimental psychology, 1955, 49, 200-202.

Greenblatt. D.J., and Shader, R.I. Benzodiazepines in clinical practice. New York: Raven Press, 1974.

Hakkinen, S. Traffic accidents and psychomotor test performance. Modern Problems in pharmacopsychology, 1976, 11, 51-56.

Hamilton, M. The assessment of anxiety states by rating. British Journal of Medical Psychology, 1959, 32, 50-55.

Harper, C.R. and Kidera, G.J. Aviator performance and the use of hypnotic drugs. Aerospace Medicine, 1972, 43, 197-199.

Harry, T.V.A. and Richards, D.J. Lorazepam - a study in psychomotor depression. British Journal of Clinical Practice, 1972, 26, 371-373.

Hedges, A. Turner, P., and Harry T.V. Preliminary studies on the central effects of lorazepam a new benzodiazepine. Journal of Clinical Pharmacology, 1971, 11, 423-427.

Hesbacher, P.T., Richels, K., Hutchinson, J., Raab E., Sablosky, L., Whalen, E.M. and Phillips, F.J. Setting, patient, and doctor effects on drug response in neurotic patients. 2 Differential improvement. Psychopharmacologia, 1970, 18, 209-226.

Hindmarch, I. The Leeds psychomotor tester. Hounslow, Middlesex: Hoechst U.K. Lts., 1975a.

Hindmarch, I. The effects of psychoactive drugs on psychomotor integration and performance. Hounslow: Hoechst U.K. Ltd., 1975b.

Hindmarch, I., Hanks, G.W., and Hewett, A.J. Clobazam, a 1,5-benzodiazepine and car-driving ability. British Journal of Clinical Pharmacology, 1977, 4, 573-578.

Hindmarch, I. and Parrott, A.C. The effect of sub-chronic administration of three dose levels of a 1,5 benzodiazepine derivative, clobazam, on subjective assessments of sleep and aspects of psychomotor performance the morning following night time medication. Arzneimittel-Forschung/Drug Research, 1978, 28, 2169-2172.

Hindmarch, I. and Parrott, A.C. The effects of repeated noctunal doses of clobazam, dipotassium chlorazepate and placebo on subjective ratings at sleep and early morning behaviour and objective measures of arounsal, psychomotor performance and anxiety. British Journal of Clinical Pharmacology, 1979, 8, 325-329.

Hindmarch, I. A preliminary study of the effects of repeated doses of clobozam on aspects of performance, arousal and behaviour in a group of anxiety rated volunteers. European Journal of Clinical Pharmacology, 1979, 16, 17-21.

Hindmarch, I. Some aspects of the affects of clobazam on human psychomotor performance. British Journal of Clinical Pharmacology, 7, 77S-82S.

Hindmarch, I. Psychomotor Function and psychoactive drugs. British Journal of Clinical Pharmacology, 1980, 10, 189-209.

Hindmarch, I. and Gudgeon, A.C. The effects of clobozam and Lorazepam on aspects of psychomotor performance and car handling ability. British Journal of Clinical Pharmacology, 1980, 10, 145-150.

Hindmarch, I. and Parrott, A.C. The effects of combined sedative and anxiolytic preparation on subjective aspects of sleep and objective measures of arousal and performance the morning following nocturnal medication Part I: Acute doses. Arzneimittel-Forschung/Drug Research, 1980, 30, 1025-1028.

Hindmarch, I, and Parrott, A.C. The effects of combined sedative and anxiolytic preparations on subjective aspects of sleep and objective measures of arousal and performance the morning following nocturnal medication. Part II: Repeated doses. Arzneimittel-Forschung/Drug Research, 1980, 30, 1167-1170.

Hollister, L.E. Benzodiazepines - an overview. British Journal of Clinical Pharmacology, 1981, 11, 1175-1195.

Inglis, J. A paired-associate learning test for use with elderly psychiatric patients. Journal of Mental Science, 1959, 105, 440-443.

Kilbrich, E. and Smart, R. Psychotropic drug use and driving risk: a review and analysis. Journal of of safety research, 1970, 2, 73-85.

Kleinknecht, R.A., and Donaldson, D. A review of the effects of diazepam on cognitive and psychomotor performance. The Journal of Nervous and Mental Diseases, 1975, 161, 399-411.

Koeppen, D. Review of clinical studies on clobazam. British Journal of Clinical Pharmacology, 1979, 7, 139S-150S.

Lader, M. Anxiety reduction and sedation: psychophysiological theory. British Journal of Clinical Pharmacology, 1979, 7, 995-1055.

Lader, M., and Marks, I. Clinical Anxiety. London: William Heinemann, 1971.

Lewis, A. Problems presented by the ambiguous word "anxiety" as used in psychopathology. In: G.D. Burrows and B. Davies (Eds.). Handbook of studies of an anxiety. Amsterdam: Elsevier/North-Holland Biomedical Press, 1980.

Lewis, E.G., Fustman, R.E., and Beck, E.C. The effects of alcohol on sensory phenomena and cognitive and motor tasks. Quarterly Journal of Studies of Alcohol, 1969, 30 618-633.

Linniola, N., Erwin, L.W. and Logue, P.E. Efficiency and side-effects of flurazepam and a combination of amobarbital and secobarbital in insomniac patients. The Journal of Clinical Pharmacology, 1980, 20, 117-121.

Luria, R.E. The validity of the visual analogue mood scale. Journal of Psychiatric Research, 1975, 12, 51-57.

Malpas, A., Legg, N.J. and Scott, D.F. Effects of hypnotics on anxious patients. British Journal of Psychiatry, 1974, 124, 482-484.

Matarazzo, J.D. Wechsler's measurement and appraisal of adult intelligence. Baltimore: Williams and Wilkins, 1972, (Fifth Edition).

McCurdy, L. Lorazepam, a new benzodiazepine derivative, in the treatment of anxiety: a double-blind clinical evaluation. American Journal of Psychiatry. 1978, 136, 187-190.

McNair, D.M. Antianxiety drugs and human performance. Archives of General Psychiatry, 1973, 29, 611-617.

Michon, J.A. Human Information processing - with and without drugs. Clinical Neurology and Neurosurgery 1973, 76, 163-174.

Mirsky, A.F., and Kornetsky, C. On the dissimilar effects of drugs on the digit symbol substitution and continuous performance tests. Psychopharmacolgia, 1964, 5, 161-177.

Ogle, L.W., Turner, P. and Markomihelakis, H. The effects of high doses of oxprenolol end of propanolol on: pursuit rator performance, reaction time and critical flicker frequency. Psychopharmacology, 1976, 46, 295-299.

Paivio, A., Yuille, J.C., and Madigan, S.A. Concreteness, imagery and meanigfulness values for 925 nouns. Journal of Experimental Psychology. Monograph supplement, 1968, 78, 1-25.

Parrott, A.C. and Hindmarch, I. Arousal and performance - the ubiquitous inverted U relationships. Comparison of changes in response latency and arousal level in normal subjects indeed by CNS stimulants, sedatives and tranquillizers. IRCS Medical Science: Clinical Pharmacology and Therapeutics; Psychiatry and Clinical Psychology; Psychology, 1975a, 3, 176.

Parrott, A.C. and Hindmarch, I. Clobazam, a 1,5 benzodiazepine derivative: effects on anxiety, arousal and performance compared with those of CNS stimulants, sedatives and tranquilizers. IRCS Medical Science: Clinical Pharmacology and Therapeutics; Psychiatry and Clinical Psychology; Psychology, 1975b, 3, 177.

Parrott, A.C. and Hindmarch, I. Comparative effects of acute doses of three benzodiazepine derivatives - clobazam, nitrazepan and Flurazepam, upon psychomotor performance under different reinforcement conditions. IRCS Medical Science: Clinical Pharmacology and Therapeutics; Psychiatry and Clinical Psychology; 1977, 3, 166.

Parrott, A.C. and Hindmarch, I. The effects of repeated doses of a 1,5 benzodiazepine derivative, clobazam, on the Middlesex Hospital Questionnaire Scores of a group of high anxiety subjects. IRCS Medical Science: Clinical Pharmacology and Therapeutics; Psychiatry and Clinical Psychology; Psychology, 1978a, 6, 441.

Parrott, A.C. and Hindmarch, I. Clobazam: a 1,5 benzodiazepine derivative - its effects on human psychomotor performance under different levels of task reinforcement. Archives internationales de Pharmacodynamie et de Therapie, 1978b, 232, 261-267.

Plutchick, R. Foundations of Experimental Research. New York: Harper and Row, 1974.

Rickels, K., Clark, E.L., Etezady M.H., Sachs, T., Sapra, R.K. and Yee, R. Butabarbital sodium and chlordiazepoxide in anxious neurotic out-patients: a collabarative controlled study. Clinical Pharmacology and Theraeutics, 1970, 11, 538-550.

Rickels K., Downing R.W., and Howard, K., Predictors of chlordiazepoxide response in anxiety. Clinical Pharmacology and Therapeutics. 1971, 12, 263-273.

Rickels, K. Are benzodiazepines overused and abused? British Journal of Clinical Pharmacology, 1981, 11, 715-835.

Rosenthal, R. and Rosnow, R.L. The volunteer Subject. In: R. Rosenthal and R.L. Rosnow (Eds.). Artifact in Behavioural Research. New York: Academic Press, 1969.

Saario, I., Linnoila, M. and Mattila, M.J. Modification by diazepam or thioridazine of the psychomotor skills related to driving: a sub-acute trial in neurotic out-patients. British Journal of Clinical Pharmacology, 1976, 3, 843-848.

Salkind, M.R., Hanks, G.W., and Silverstone, J.T. Evaluation of the effects of clobazam, a 1,5 benzodiazepine, on mood and psychomotor performance in clinically anxious patients in general practice. British Journal of Clinical Pharmacology, 1979, 7, 113S-116S.

Salkind, M.R., and Silverstone, J.T. A clinical and psychometric evaluation of flurazepam. British Journal of Clinical Pharmacology, 1975, 2, 223-228.

Saxena, B., Singh, A.N., and Porter W.R. Clinical and experimental comparison of intramuscular lorazapam, and placebo psychometric tests and psychiatric rating scales in the assessment of benzodiazapines. Current Therapeutic Research, 1980, 28, 260-267.

Siassi, I., Mivart, T., and Vanov, S.K. Evaluation of the safety and therepeutic effects of lorazepam on long-term use. Current Therapeutic Research. Clinical and Experimental, 1975, 18, 163-171.

Silverstone, J.T. Lorazepam in Phobic disorders: a pilot study. Current Medical Research and Opinion, 1973, 1, 272-276.

Silverstone, T. Drugs and driving. British Journal of Clinical Pharmacology, 1974, 1, 451-454.

Smith, J.M., and Misiak, H. Critical Flicker Frequency (CFF) and psychotropic drugs in normal human subjects - A review. Psychopharmacology, 1976.

Taber, B. Proving new drugs: a guide to clinical trials. Los Altos: Geron-X, Inc., 1969.

Tansella, M., Zimmermann-Tansella, C., and Lader, M. The Residual effects of N-desmethyldiazepan in patients. Psychopharmacologia, 1974, 38, 81-90.

Teichner, W.H. and Krebs, M.J. Lewis of simple reaction time. Psychological Review, 1972, 79, 344-358.

Teichner, W.H. and Krebs, M.J. Laws of visual choice reaction time. Psychological Review, 1974, 81, 75-98.

The world Medical Association. Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects, 1975 revised version.

Tiffin, J. Purdue pegboard examiner manual. Chicago Science Research Associates, 1968, (third printing).

Turner, P. Clinical pharmacological studies on lorazepam. Current Medical Research and Opinion, 1973, 1, 262-264.

Uhlenhuth, E.H., Turner, O.A., Purchatzke, G., Gift, T. and Chassan, J. Intensive design in evaluating antrolytic drugs: Psychopharmacology, 1977, 52, 79-85.

Wittenborn, J.R. Effects of benzodiazepines on psychomotor performance. British Journal of Clinical Pharmacology. 1979, 7, 61S-67S.

Wittenborn, J.R., Flaherty, C.F., jr., McGough, W.E. and Nash, R.J. Psychomotor changes during initial day of benzodiazepine medication. British Journal of Clinical Pharmacology. 1979b, 7, 69S-76S.

Wittenborn, J.R. Behavioural toxicity of psychotropic drugs. The Journal of Nervous and Mental Disease. 1980, 168, 171-176.

Yerkes, R.M., and Dodson, J.D. The relation of strength of stimulus to rapidity of habit-formation. Journal of comparative and Neurological Psychology, 18, 459-482, 1908.

Zeally, A.K and Aitken, R.C. Measurement of Mood. Processings of the Royal Society of Medicine, 1969, 62, 993-996.

Zimmermann-Tansella, C., Tansella, M. and Lader, M. A comparison of the clinical and psychological effects of diazepam and amylobarbitone in anxious patients. British Journal of Clinical Pharmacology, 1979, 7, 605-611.

APPENDICES

1. Structural Formulas of lorazepam and clobazam.

2. Three alternative forms of the Inglis Paired-Associate Learning Test.

3. Informed Consent Form.

4. Hamilton Anxiety Rating Scale.

5. Visual analogue scale of anxiety.

6. Visual analogue scale of motivation.

7. Details of patients.

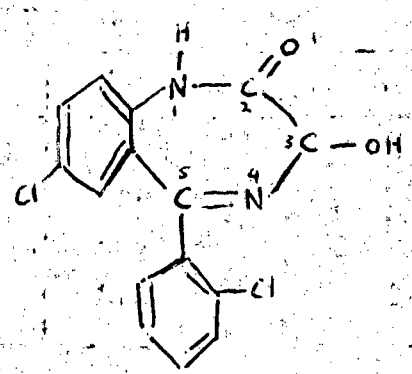
8. Raw data.

APPENDIX I

STRUCTURAL FORMULAS OF LORAZEPAM AND CLOBAZAM

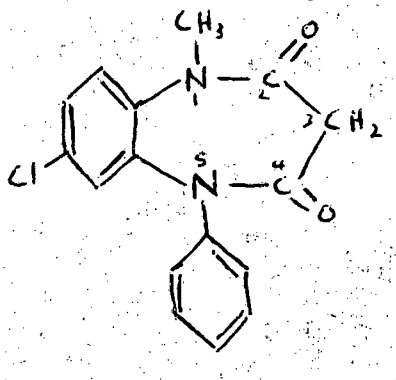
Lorazepam

(a I,4 - benzodiazepine)



Clobazam

(a I,5 - benzodiazepine)



APPENDIX 2

THREE ALTERNATIVE FORMS OF THE INGLIS PAIRED-ASSOCIATE LEARNING TEST

Form A		Form B	
Stimulus	Response	Stimulus	Response
cabbage	pen	flower	spark
knife	chimney	table	river
sponge	trumpet	bottle	comb

Form C	
Stimulus	Response
tree	fork
cloud	drum
kettle	book

(Devised by the investigator)

PATIENT CONSENT

I, _____, hereby declare that I have given my consent for the procedure and/or treatment stipulated below.

I have been fully informed by _____ about the possible beneficial effects and also the possible detrimental effects which may occur to me as a result of the undermentioned procedure and/or treatment.

I have also been fully informed by _____ that the undermentioned procedure and/or treatment constitutes a deviation from the normal procedure and/or treatment.

The nature of the procedure and/or treatment is: _____

_____

_____

The procedure and/or treatment shall be carried out by:

_____

My consent is granted voluntarily and I realise that I may at any time withdraw my consent.

SIGNED:

_____

Patient

_____

Person who informed Patient

_____

Person who will carry out procedure and/or treatment

GASTRO-INTESTINAL SYMTOMS

Difficulty in swallowing, wind, dyspepsia: pain before or after meals, burning sensations, fullness, waterbrach, nausea, vomiting, sinking feelings. Borborygmi, "working" in abdomen, looseness of bowels, loss of weight, constipation. ☐

GENITO-URINARY SYMPTOMS

Frequency of micturition, urgency of micturition, amenorrhoea, menorrhagia, development of frigidity, ejaculatio praecox, loss of erection, impotence. ☐

DEPRESSED MOOD

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing. ☐

GENERAL SOMATIC (Muscular)

Muscular pains and aches, muscular stiffness, muscular twitchings, clonic jerks, grinding of teeth, unsteady voice. ☐

GENERAL SOMATIC (Sensory)

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensations. ☐

CARDIOVASCULAR SYMPTOMS

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat. ☐

RESPIRATORY SYMPTOMS

Pressure or constriction in chest, choking feelings, sightings, dyspnoea. ☐

AUTONOMIC SYMPTOMS

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair. ☐

BEHAVIOUR AT INTERVIEW

Tense, not relaxed. Fidgeting, and restlessness: Hands, picking fingers. 

BEHAVIOUR PHYSIOLOGICAL

Tremor of hands, furrowed brow, strained face, facial pallor, swallowing, belching, sweating, eye-lid twitching. 

Name / Naam .....

Date / Datum .....

Ek voel baie kalm.

I feel very calm.

Ek voel baie angstig.

I feel very anxious.

APPENDIX 6

Name / Naam .....

Date / Datum .....

Ek het geen motivasie in my daaglikse bedrywighede.

I have absolutely no motivation in my daily activities.

Ek is deeglik gemotiveer in my daaglikse bedrywighede.

I am extremely motivated in my daily activities.

DETAILS OF PATIENTS

	Placebo		Clobazam		Lorazepam	
Patient Number	Age	School Standard Passed	Age	School Standard Passed	Age	School Standard Passed
1	40	6	38	5	25	4
2	25	4	45	1	55	5
3	42	4	30	3	38	5
4	36	8	35	3	31	5
5	52	4	27	5	32	5
6	40	5	19	7	22	5
7	33	7	30	5	26	8
8	43	5	41	4	42	5
9	50	5	46	1	45	3
10	20	4	28	5	21	6
11	42	1	32	2	20	6
12	24	5	20	9	27	3
13	32	5	42	3	20	4
14	63	5	18	5	37	5
15	26	5	51	8	42	6
16	34	3	44	4	36	6
17	45	2	24	6	21	8
18	18	7	37	3	23	5
19	20	6	44	6	38	7
20	25	6	39	6	57	2
21			51	6	21	3
22			38	3	40	3
23			43	7	38	7
24			21	4		
25			38	3		
26			27	2		
27			49	5		

RAW DATA[4]

Hamilton Anxiety Scale

	Placebo			Clobazam			Lorazepam		
Patient Number	Pre[1]	2[2]	9[3]	Pre	2	9	Pre	2	9
1	21	17	20	21	16	12	17	07	5
2	23	10	7	31	15	8	30	11	7
3	22	17	20	25	9	6	29	12	15
4	23	12	17	28	16	10	29	15	16
5	26	21	23	27	22	22	29	15	12
6	19	10	10	23	19	15	25	14	11
7	21	12	13	19	13	14	20	15	12
8	17	14	13	19	8	5	21	15	11
9	21	15	13	24	19	13	26	15	11
10	20	19	12	23	10	8	20	12	10
11	29	15	13	28	21	19	17	12	10
12	25	14	12	17	11	11	18	10	9
13	13	10	10	12	6	5	23	19	12
14	17	11	9	24	20	13	24	15	14
15	21	16	14	26	16	9	25	16	12
16	16	11	9	21	14	13	29	22	12
17	24	22	19	14	7	6	23	17	11
18	17	10	8	24	14	10	23	14	9
19	16	12	10	21	19	10	20	15	9
20	22	18	11	22	13	10	18	12	10
21				15	11	8	27	21	18
22				22	17	10	28	19	16
23				23	18	11	29	17	10
24				30	25	24			
25				27	19	19			
26				27	17	18			
27				21	12	17			

1. Pre-treatment assessment.
2. 2-day assessment.
3. 9-day assessment.
4. Raw data are presented in the format that was used for the 2-way anovas.

Visual Analogue Scale for Anxiety

	Placebo			Clobazam			Lorazepam		
Patient Number	Pre	2	9	Pre	2	9	Pre	2	9
1	83	49	43	88	90	67	98	2	2
2	71	21	2	91	57	41	93	48	13
3	94	31	43	85	5	3	78	26	36
4	88	14	2	77	38	21	74	24	21
5	98	100	100	72	70	50	76	48	9
6	2	2	4	23	2	2	82	31	24
7	52	29	18	95	78	72	75	46	75
8	74	80	71	73	25	2	75	22	9
9	75	28	7	97	80	37	97	22	10
10	71	83	47	81	4	3	90	63	13
11	84	19	3	96	60	58	98	98	0
12	95	28	21	73	48	38	98	3	10
13	85	2	5	32	20	12	86	56	21
14	76	39	17	100	100	1	85	0	30
15	92	54	51	99	45	1	96	34	24
16	87	55	10	95	81	37	100	82	43
17	80	87	66	59	3	4	87	37	33
18	63	30	9	98	1	2	70	2	3
19	60	33	14	79	91	4	62	25	3
20	98	69	8	99	83	2	85	70	6
21				41	38	13	95	80	58
22				95	97	20	99	62	45
23				99	93	2	100	65	42
24				100	96	97			
25				90	51	33			
26				94	57	41			
27				80	45	67			

Visual Analogue Scale for Motivation

Placebo				Clobazam			Lorazepam		
Patient Number	Pre	2	9	Pre	2	9	Pre	2	9
1	73	73	64	96	95	5	98	98	94
2	89	90	100	93	47	63	45	44	85
3	6	27	42	48	49	95	48	50	33
4	63	94	63	79	92	24	75	37	23
5	96	100	99	20	69	33	40	46	88
6	96	97	97	93	100	99	85	50	39
7	50	30	15	28	33	6	75	78	75
8	63	69	61	63	78	92	86	6	21
9	90	96	96	68	53	45	2	75	93
10	81	89	96	72	98	99	13	82	72
11	8	70	97	38	51	63	97	97	100
12	2	8	17	44	55	73	3	86	91
13	88	85	76	88	93	97	49	22	85
14	66	88	94	0	0	100	5	2	54
15	92	90	39	98	62	90	29	42	62
16	84	91	85	30	83	65	64	57	51
17	81	83	76	45	97	96	8	25	29
18	27	31	60	4	99	97	98	97	97
19	65	70	99	99	99	98	21	50	45
20	2	34	82	97	97	93	28	55	80
21				96	75	92	14	15	53
22				4	2	2	6	8	21
23				39	94	98	6	36	63
24				70	95	97			
25				32	73	81			
26				15	55	55			
27				9	78	89			

Drowsiness Rating

	Placebo		Clobazam		Lorazepam	
Patient Number	2	9	2	9	2	9
1	0	0	2	2	1	0
2	0	0	0	0	1	2
3	0	0	0	1	0	0
4	0	0	0	1	0	2
5	1	0	0	0	2	2
6	0	0	0	0	2	0
7	0	0	0	0	2	2
8	0	0	0	0	1	1
9	0	0	1	0	0	0
10	2	0	0	0	1	1
11	0	0	2	2	1	1
12	2	2	0	0	2	1
13	0	0	1	1	1	1
14	1	0	0	0	2	2
15	0	0	2	0	1	1
16	0	0	2	1	2	2
17	0	0	0	0	1	0
18	1	0	1	0	2	0
19	0	0	2	2	1	1
20	1	0	2	0	1	0
21			1	0	2	1
22			1	0	2	2
23			1	0	1	2
24			2	2		
25			0	1		
26			1	1		
27			1	1		

Digit Symbol Substitution Test

Patient Number	Placebo			Clobazam			Lorazepam		
	Pre	2	9	Pre	2	9	Pre	2	9
1	24,5	27	31,5	29	33	31	20,5	24	24
2	28	39	39	17	23,5	23	15,5	16,5	17,5
3	16	18,5	23,5	17,5	30	31	19	23	28
4	32,5	40	38	23	24,5	33	20,5	27,5	22,5
5	18,5	18	14	33,5	39	29,5	30,5	26,5	33
6	14	21	21,5	31	40	50	31	32,5	37,5
7	38	49	53	35,5	47,5	49,5	33,5	37	43,5
8	17	15	13	24	28	28	17	20	27
9	35	40	45	6	9,5	5	13	11,5	10
10	38	45	46	22.5	33,5	39,5	25	33,5	40
11	18,5	26	33,5	8,5	10	16	33	34	27,5
12	10	16	20,5	49	56	61	15	21	25
13	8,5	13	10	24,5	31,5	44	22	24	28
14	23,5	31,5	37,5	30	34	35	16,5	24,5	27
15	21,5	28	35,5	25,5	29	34,5	13	20	31
16	30	35	35,5	10,5	19	24	17	27,5	27,5
17	8	11	10	37,5	54,5	57	38	40	54
18	39	50,5	53,5	21	30	37,5	30	40	45,5
19	29	38,5	36	38,5	46	47,5	30,5	29,5	39,5
20	26,5	43,5	45,5	28	22,5	30,5	8	7,5	11,5
21				22	27,5	27,5	9	16	21
22				22,5	23,5	23	24	21,5	24
23				29	34,5	37,5	18	20	22,5
24				19,5	24	20,5			
25				19,5	24	24			
26				23,5	26,5	32			
27				24	36,5	37,5			

Critical Flicker Fusion Threshold

	Placebo			Clobazam			Lorazepam		
Patient Number	Pre	2	9	Pre	2	9	Pre	2	9
1	17,80	16,80	19,10	17,05	17,20	18,40	17,38	19,60	20,98
2	17,90	19,85	20,45	16,02	19,40	17,68	18,95	19,65	19,47
3	21,82	18,72	20,725	20,47	21,67	22,95	21,225	18,80	19,25
4	19,80	19,52	20,425	24,35	23,40	22,88	22,50	21,18	20,42
5	23,67	23,60	22,35	23,77	23,35	23,17	23,80	22,07	20,15
6	22,72	23,02	21,20	20,65	21,00	20,65	23,30	23,07	23,23
7	21,95	22,75	24,45	20,43	20,42	20,87	22,20	22,02	21,00
8	19,12	20.10	21,50	18,95	20,58	19,10	22,025	24,00	23,25
9	22,10	22,45	21,30	17,72	19,90	18,63	25,20	23,10	22,73
10	22,58	21,72	20,25	22,67	22,20	22,48	22,20	20,63	20,83
11	17,83	17,65	18,35	22,57	21,40	21,45	19,825	19,30	20,00
12	25,50	22,28	23,375	19,33	20,92	21,40	22,625	22,25	21,37
13	23,03	22,40	22,025	26,05	25,60	25,77	17,475	16,95	16,13

(Continued overleaf)

Critical Flicker Fusion Threshold (Continued)

	Placebo			Clobazam			Lorazepam		
Patient Number	Pre	2	9	Pre	2	9	Pre	2	9
14	22,40	21,00	22,425	22,50	22,15	21,45	25,50	25,25	21,97
15	23,58	25,23	25,625	21,30	21,00	20,22	21,10	22,20	19,90
16	21,98	22,25	22,90	21,18	19,48	21,10	18,75	19,40	17,57
17	17,93	17,30	17,55	26,03	23,20	21,05	20,15	18,93	19,85
18	17,12	17,40	18,80	19,88	20,35	18,70	24,975	23,45	22,43
19	25,87	24,77	23,05	23,23	22,85	21,60	21,675	24,23	25,03
20	22,80	20,93	18,725	21,65	22,45	23,4	17,325	18,15	17,10
21				20,42	20,12	18,78	23,75	25,63	23,85
22				20,02	19,10	20,28	22,225	20,12	21,82
23				19,20	18,67	19,47	18,475	18,12	18,87
24				23,60	23,73	23,60			
25				19,52	18,35	19,65			
26				21,83	20,40	23,82			
27				20,90	22,48	23,15			

Inglis Paired-Associate Learning Test

Patient Number	Placebo			Clobazam			Lorazepam		
	Pre	2	9	Pre	2	9	Pre	2	9
1	11	14	17	9	4	11	20	11	17
2	14	11	12	30	33	14	10	21	7
3	14	7	8	9	9	4	4	10	11
4	25	9	13	4	3	9	57	52	26
5	20	9	11	35	19	17	5	8	5
6	24	8	18	12	4	4	12	4	8
7	5	3	4	6	7	4	11	5	19
8	10	6	15	12	12	9	18	4	4
9	5	8	10	14	12	16	13	6	4
10	10	14	8	18	10	20	6	4	5
11	10	6	4	10	13	13	6	6	6
12	25	14	13	7	9	10	10	6	5
13	21	15	18	8	4	4	14	20	14
14	8	7	11	21	6	4	24	11	15
15	4	7	5	15	8	4	5	11	7
16	8	7	10	8	8	10	9	5	4
17	4	6	10	11	15	10	5	3	4
18	6	5	3	18	9	11	6	4	4
19	6	5	5	4	4	5	6	5	3
20	5	5	3	8	9	8	12	5	5
21				18	6	8	31	21	8
22				14	9	7	19	4	5
23				5	6	4	6	4	4
24				10	8	7			
25				5	8	6			
26				4	6	5			
27				7	5	6			

Purdue Pegboard Test - Preferred Hand Task

Patient Number	Placebo			Clobazam			Lorazepam		
	Pre	2	9	Pre	2	9	Pre	2	9
1	17	18	17	14	16	13	15	16	18
2	11	15	16	12	15	13	13	13	15
3	12	12	12	15	18	17	14	13	13
4	14	15	15	15	13	14	11	13	14
5	14	16	15	17	12	15	14	14	15
6	11	13	12	14	15	14	14	17	17
7	13	13	18	13	14	15	16	14	16
8	12	13	14	11	14	13	15	14	14
9	15	15	14	13	13	11	13	12	14
10	13	15	15	13	16	14	14	15	16
11	12	16	17	10	11	13	13	13	14
12	12	14	14	17	16	18	13	13	13
13	14	15	16	14	16	17	14	14	15
14	16	16	18	13	15	15	18	16	16
15	13	13	15	13	16	16	10	11	12
16	15	17	15	12	13	13	15	15	15
17	11	12	12	14	15	14	14	14	15
18	14	16	18	11	14	14	15	13	15
19	11	13	13	16	15	14	11	13	14
20	11	14	15	10	10	12	13	13	13
21				12	13	13	9	10	13
22				14	13	16	11	11	12
23				12	13	13	15	15	17
24				13	13	11			
25				11	12	11			
26				15	16	16			
27				15	16	15			

Purdue Pegboard Test - Both Hands Task

Patient Number	Placebo			Clobazam			Lorazepam		
	Pre	2	9	Pre	2	9	Pre	2	9
1	12	11	14	10	11	10	12	12	14
2	10	12	11	11	12	12	9	9	10
3	10	9	10	11	12	13	10	11	10
4	10	12	12	10	10	10	10	10	10
5	11	11	12	12	11	12	10	10	11
6	9	10	9	12	12	12	11	12	12
7	11	11	13	10	11	12	11	12	11
8	10	10	12	10	8	10	9	10	9
9	11	11	11	8	9	8	9	11	10
10	10	10	11	9	13	13	10	10	10
11	9	11	10	8	7	9	9	8	10
12	9	11	12	12	13	11	8	8	9
13	11	10	12	9	10	10	10	10	11
14	12	13	11	8	10	10	11	13	11
15	10	10	10	11	9	12	9	8	9
16	12	10	12	10	12	11	10	11	11
17	8	9	9	10	11	10	10	11	12
18	12	11	13	9	9	11	9	10	10
19	8	8	8	11	9	12	9	9	9
20	9	10	11	7	7	8	10	9	9
21				9	11	8	6	5	7
22				12	11	12	8	7	7
23				9	7	8	13	14	13
24				9	10	9			
25				8	8	9			
26				11	12	12			
27				10	10	10			

Purdue Pegboard Test - Assembly Test

Patient Number	Placebo			Clobazam			Lorazepam		
	Pre	2	9	Pre	2	9	Pre	2	9
1	37	44	52	36	48	44	36	52	58
2	57	59	65	36	40	46	42	38	44
3	27	28	42	48	52	48	34	35	32
4	50	54	50	51	52	48	36	36	46
5	42	36	44	52	52	41	44	46	50
6	36	42	42	52	52	56	48	56	54
7	44	52	54	48	48	58	50	50	52
8	48	50	38	38	41	48	42	44	46
9	44	50	52	28	40	34	40	40	44
10	54	58	54	32	50	52	50	50	60
11	40	48	42	36	38	34	52	46	46
12	44	44	46	56	54	56	42	34	42
13	34	36	44	44	52	48	38	38	44
14	52	56	58	44	48	54	42	40	39
15	46	54	44	41	44	46	34	35	40
16	46	46	50	42	44	46	44	46	58
17	34	30	38	56	58	58	48	44	56
18	56	54	49	32	46	48	42	44	48
19	36	48	50	46	50	50	40	46	52
20	44	52	52	44	32	36	32	34	38
21				40	54	44	20	21	20
22				44	46	44	32	30	36
23				36	42	42	48	46	54
24				36	42	38			
25				28	36	26			
26				48	46	52			
27				44	48	44			

Choice Reaction Time Test

	Placebo			Clobazam			Lorazepam		
Patient Number	Pre	2	9	Pre	2	9	Pre	2	9
1	0,698	0,618	0,618	0,769	0,729	0,787	0,798	0,655	0,672
2	0,712	0,760	0,598	0,643	0,642	0,619	0,607	0,710	0,606
3	0,754	0,712	0,637	0,657	0,630	0,614	0,642	0,605	0,624
4	0,577	0,556	0,563	0,552	0,573	0,545	0,684	0,592	0,604
5	0,742	0,669	0,637	0,602	0,586	0,648	0,631	0,731	0,632
6	0,734	0,650	0,680	0,528	0,551	0,589	0,588	0,572	0,592
7	0,650	0,644	0,600	0,807	0,755	0,727	0,665	0,679	0,620
8	0,650	0,670	0,615	0,611	0,619	0,597	0,714	0,767	0,767
9	0,654	0,642	0,555	0,620	0,638	0,639	0,660	0,593	0,570
10	0,746	0,640	0,586	0,819	0,619	0,593	0,748	0,638	0,579
11	0,532	0,533	0,486	0,746	0,717	0,793	0,643	0,717	0,591
12	0,682	0,635	0,618	0,685	0,668	0,624	0,806	0,735	0,679
13	0,680	0,680	0,660	0,592	0,535	0,529	0,715	0,708	0,578

(Continued overleaf)

Choice Reaction Time Test (Continued)

	Placebo			Clobazam			Lorazepam		
Patient Number	Pre	2	9	Pre	2	9	Pre	2	9
14	0,626	0,551	0,581	0,662	0,658	0,643	0,615	0,609	0,531
15	0,564	0,592	0,586	0,740	0,708	0,658	0,740	0,694	0,667
16	0,636	0,611	0,555	0,753	0,716	0,613	0,634	0,615	0,597
17	0,713	0,698	0,665	0,673	0,603	0,589	0,688	0,659	0,633
18	0.513	0,484	0,448	0,677	0,607	0,572	0,614	0,629	0,582
19	0,578	0,521	0,551	0,578	0,660	0,565	0,591	0,644	0,617
20	0,703	0,647	0,620	0,640	0,761	0,667	0,642	0,632	0,593
21				0,620	0,571	0,536	0,839	0,810	0,767
22				0,624	0,590	0,554	0,665	0,676	0,632
23				0,636	0,607	0,570	0,575	0,581	0,552
24				0,830	0,731	0,866			
25				0,662	0,657	0,611			
26				0,594	0,594	0,555			
27				0,669	0,618	0,584			