A PSYCHOPHYSIOLOGICAL INVESTIGATION OF THE EFFECTS OF A PSYCHOTROPIC AGENT (CLOZAPINE) UPON SLEEP PARAMETERS OF NORMAL YOUNG ADULTS

A thesis submitted to the Department of Psychology, University of Cape Town, in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Psychology

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Do but consider what an excellent thing sleep is: it is so inestimable a jewel that, if a tyrant would give his crown for an hour's slumber, it cannot be bought: of so beautiful a shape is it, that though a man lie with an Empress, his heart cannot beat quite till he leaves her embracements to be at rest with the other: yea, so greatly indebted are we to this Kinsman of death, that we owe the better tributary, half of our life to him: and there is good cause why we should do so: for sleep is the golden chain that ties health and our bodies together. Who complains of want? of wounds? of cares? of great men's oppressions? of captivity? whilst he sleepeth? Beggars in their beds take as much pleasure as kings: can we therefore surfeit on this delicate Ambrosia?

Thomas Dekker

PREFACE

Recent research has suggested that clozapine, a psychotropic agent, may have sleep inducing properties. However, no research has yet attempted to systematically determine the effects of low doses of clozapine (12,50mg-25mg) upon the sleep patterns and REM dream content of normal young adults. In addition, contradictory findings exist in the literature at present as to whether the administration of a placebo influences the sleep patterns of normal young adults.

The present study makes significant contributions to the field of psychopharmacology in that results suggest that clozapine may have important therapeutic implications for the treatment of insomnia as well as disorders of slow wave sleep.

Moreover, the experiments conducted indicate that the administration of a placebo has no significant effect upon the sleep patterns of normal young adults.

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Many hours of "burning the midnight oil" are required in a research program of this nature and all-night laboratory monitoring of electrophysiological apparatus was continued seven days a week for weeks on end. The physiological and psychological demands made on the human body by the continuous loss of sleep in a research program of this nature were extremely arduous. I would like to express my gratitude to James Reed who on many occasions afforded me the opportunity of repaying my sleep debt by deputising for me in the sleep laboratory. I would also like to thank Trevor Lubbe for assisting me in the REM Dream Recall Study.

Psychologists are prohibited by law to prescribe drugs and without stringent medical coverage this study would not have been possible. In this regard I would like to express my gratitude to Professor Gillis for providing the necessary medical coverage on Dr. Beumont's departure for Australia and Dr. Zabow for his assistance in the medical examination of subjects, the taking of blood and the prescribing of clozapine.

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This study was approved by the Pharmaceutical Advisory Committee of Groote Schuur Hospital, Observatory, South Africa, on the 20th June, 1974.

In conclusion, I am deeply grateful for the constant support of my parents and for the immense help of my wife, Wren, whose graphics, patience and overall support have greatly contributed to the completion of this work.

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SUMMARY

Hypnotic and sedative drugs have been regarded as the most expedient method for the treatment of insomnia in contemporary western culture and their prescription has increased dramatically (Karacan and Williams 1971; Oswald 1968). However, many of these drugs suppress REM sleep (Oswald 1968), cause death when taken in overdose (Johns 1975), produce dependence (Kales and Kales 1973), become relatively ineffective in the treatment of insomnia after chronic administration (Johns 1975) and the abrupt withdrawal after continuous administration may result in a drug withdrawal insomnia characterised by difficulty in falling asleep, an increased vividness in REM mentation as well as the occurrence of nightmares (Kales et al 1968(a)(b), 1969(a)(b)).

Recent research has suggested that clozapine, a psychotropic agent, may have pronounced sleep inducing properties (Hemphill et al 1975; Ruch et al 1976; Gross and Langner 1966,1969; Berzewski et al 1969). However, its role as an hypnotic agent has yet to be systematically investigated. In the present study, therefore, the effects of clozapine upon the sleep patterns of twenty normal young adults were investigated during both short- and long-term administration at two different dose rates (25mg and 12,50mg/night respectively). In addition, the short-term effects of 12,50mg clozapine/night upon REM dream content were also investigated. The present study required a total of 2190 hours of recording over a period of 219 nights.

The first major aim of the present study was to elucidate the effects of the short-term administration of 25mg clozapine upon

the sleep patterns of seven normal young adults. The experiment employed an additional group of seven control subjects. This research strategy permitted the use of a double blind cross-over design and, in addition, enabled the investigator to assess the effects of the short-term administration of placebo upon the sleep patterns of normal young adults. Contradictory evidence exists in the literature at present as to whether the administration of a placebo influences the sleep patterns of normal young adults (Davis and Hartmann 1973(a)(b); Zung 1973; Adam et al 1975,1976). The second major aim of the present study was, therefore, to determine the effects of the short-term administration of placebo upon the sleep patterns of normal young adults.

The subjects slept for nine consecutive nights in a sound attenuated, temperature regulated sleep laboratory while EEG's and EOG's were monitored continuously throughout the night. The first two nights served purely an adaptive purpose and no recordings were made. Baseline sleep patterns were obtained from nights three and four. On nights five, six and seven, subjects received 25mg clozapine or 25mg placebo. Nights eight and nine were used to assess any drug withdrawal effects. Measures of mood and performance, as well as a questionnaire concerning possible side-effects of drug administration, were administered each morning to the subjects in the laboratory fifteen minutes after awakening for the entire duration of the study.

The short-term administration of 25mg clozapine suppressed stage 4 sleep on the second and third nights of administration.

This finding suggests that clozapine may have important therapeutic implications for the treatment of disorders of slow wave sleep. The short-term administration of clozapine also appears to have important therapeutic implications for the treatment of insomnia. This conclusion is supported by the following findings: (i) Total sleep time was significantly increased on the first and second nights of clozapine administration, despite the attempt to control for the duration of time spent in bed. (ii) The number of body movements was significantly reduced on all three nights of clozapine administration. (iii) The number of body movements/minute of sleep was also significantly reduced on all three nights of clozapine administration. (iv) The short-term administration and withdrawal of 25mg clozapine/night had no significant effect upon stage REM sleep.

However, the indices of stage REM sleep were significantly affected. The mean burst length, the density/minute REM sleep and % motility were significantly increased on the third night of clozapine administration and this increase persisted on the first night of clozapine withdrawal. In addition, the total number of bursts and the number of bursts/REM period increased significantly on the first night of clozapine withdrawal. It is tentatively suggested that these findings may reflect the antipsychotic properties of clozapine (Blum and Girke 1974). Finally numerous psychological and physiological side-effects including the impairment of intellectual performance, nausea, difficulty in writing and talking, hypotension and drowsiness were reported and this finding may represent a major limitation in the possible use of clozapine as an hypnotic agent.

The administration of placebo had no systematic effect upon any of the monitored sleep parameters. This finding does not appear to hold true for psychological parameters as the administration of placebo resulted in a significant increase in the subjective estimation of drowsiness on the morning following the second night of administration.

The third major aim of the present study was an attempt to determine the effects of the long-term administration of 12,50mg clozapine upon the sleep patterns of six normal young adults, This investigation employed a 25 night single blind cross-over design. The subjects received 12,50mg placebo on the first and last five nights. On the intermediate fifteen nights, subjects received 12,50mg clozapine. Subjects reported to the laboratory on the third and fourth nights in order that baseline sleep recordings could be obtained. To determine the effects of 12,50mg clozapine on sleep patterns, subjects slept in the laboratory on the eighth, twelfth, sixteenth and twentieth nights. Nights twenty one and twenty five were used to determine whether the withdrawal of clozapine after fifteen consecutive nights of administration would result in an altered sleep pattern. Subjects completed a home log each morning throughout the twenty five days. Prior to the commencement of the study, subjects slept for two nights in the laboratory. This was done in order to adapt the subjects to the laboratory environment, experimenter and experimental routine.

The long-term administration of 12,50mg clozapine significantly reduced the number of minutes spent awake during the second three

hours of the record, the percentage of time spent in stage I sleep, the number of body movements during sleep as well as movement time. This evidence appears to suggest that clozapine may have sleep inducing properties. Additional support for the above assumption was provided by the finding that no rebound of stage REM sleep occurred, despite the fact that a small but significant reduction in stage REM sleep occurred during the administration of clozapine. This finding is in marked contrast to the effects of many hypnotics which produce a REM rebound on withdrawal characterised by difficulty in falling asleep, an increased vividness in REM mentation as well as the occurrence of nightmares (Kales et al 1968(a)(b), 1969(a)(b)).

However, numerous side-effects such as depression, apathy, tiredness, lack of vitality, resentfulness and lack of physical and mental energy were reported. In addition, the drug identification rating indicated that a rapid tolerance to clozapine may develop. These findings represent further limitations in the possible use of clozapine as an hypnotic agent over an extended period of time. Further research on insomniac subjects should therefore be carried out to determine whether the administration of 12,50mg clozapine will enhance sleep duration over an extended period of time.

The fourth major aim of the present study was to explore the effects of the short-term administration of 12,50mg clozapine upon the REM dream content of six normal young adults. This investigation comprised a four night single blind cross-over design, the subject being unaware of the experimental condition. Each subject

spent a total of four recording nights in the sleep laboratory each within the space of six days of one another. This intermediate period permitted the subjects to recover from the well documented REM rebound phenomenon incurred by repeated laboratory awakenings. Prior to the commencement of the study, the subjects were issued with coded tablets and were instructed to take specific tablets at home on the two nights preceding each of the four laboratory recording nights. In addition, the subjects were issued with a home log which they were asked to complete upon awakening on the two mornings prior to each laboratory recording night.

The first recording night was used to adapt the subjects to the laboratory environment, experimenter and laboratory routine. Only one laboratory night was effected, as all the subjects participating in this investigation had previously taken part in a sleep research program. Baseline REM dream reports were obtained on the second recording night. The third recording night was used to determine the effects of the short-term administration of 12,50mg clozapine upon REM dream content whereas the fourth recording night endeavoured to trace any possible withdrawal effects. The subjects were woken ten minutes into their second, third and fourth REM periods.

The short-term administration and withdrawal of 12,50mg clozapine had no systematic effect upon REM dream content. This finding is in marked contrast to the effects of many hypnotic agents which produce an increased vividness in REM mentation characterised by nightmares upon withdrawal (Kales et al 1969(b),1974;

Oswald and Priest 1965). This evidence provides additional support for the assumption that clozapine may have therapeutic implications for the treatment of insomnia.

The present study makes a number of significant contributions to the field of psychopharmacology, a rapidly developing discipline within the domain of psychology. The findings of the present study suggest that clozapine may have important therapeutic implications for the treatment of insomnia as well as disorders of slow wave sleep. However, further research should be carried out on insomniac subjects to extend and substantiate the present findings.

1.0 THE AIMS AND OBJECTIVES OF THE PRESENT INVESTIGATION

Insomnia is one of the most prevalent disorders encountered in general medicine today (Johns 1975) (see section 4.1) and is generally treated by the prescription of hypnotic and sedative drugs (see section 4.3). However, many of these drugs suppress REM sleep (Oswald 1968; Freemon 1972; King 1972), cause death when taken in overdose (Johns 1975), produce dependence (Kales and Kales 1973), and become relatively ineffective after chronic administration (Johns 1975). The abrupt withdrawal of an hypnotic after chronic administration usually results in a drug withdrawal insomnia characterised by difficulty in falling asleep and an increased vividness in REM mentation with the occurrence of nightmares (Kales et al 1968(b), 1969(b), 1970(e), 1974). These findings suggest that many of the hypnotic and sedative drugs prescribed at present produce numerous undesirable side-effects and that a definite need exists for the development of more effective and safer sleep inducing medications.

Clozapine (Leponex) is a psychotropic agent which has been used in many countries over the past five years. It appears to be effective in the treatment of a wide variety of psychiatric disorders including delusional states, schizophrenic affective disturbances, mutistic delusions, behaviour disorders, aggressiveness and affective inadequacy (Angst et al 1971). Clozapine, unlike the phenothiazines, does not cause extrapyramidal side-effects (Stille et al 1971). In addition, recent findings suggest that clozapine may have pronounced sleep inducing properties (Hemphill et al 1975; Ruch et al 1976;

Gross and Langner 1966, 1969; Berzewski et al 1969). However, its role as an hypnotic agent has yet to be systematically investigated. In the present study, therefore, the efficacy of low doses of clozapine (12,50mg-25mg/night) as a sleep inducing agent was examined by monitoring its effects upon sleep parameters of normal young adults in a rigorously controlled laboratory environment.

The investigation was carried out in three phases. The first experiment set out to determine the effects of the short-term administration of 25mg clozapine/night for three consecutive nights upon the sleep patterns of a group of seven normal young adults. Contradictory evidence exists in the literature, at present, as to whether the short-term administration of placebo affects the sleep parameters of normal healthy subjects (Zung 1973; Davis and Hartmann 1973; Adam et al 1975, 1976). The experiment thus employed an additional group of seven control subjects. This research strategy permitted the use of a double-blind cross-over design and, in addition, enabled the investigator to assess the short-term influence of a placebo upon sleep parameters. Psychological and physiological side-effects were also quantified.

The initial study demonstrated marked and significant effects of the 25mg/night dosage of clozapine upon stage 4 sleep and indices of stage REM sleep and the second experiment, therefore, investigated the effects of a lower dose of clozapine (12,50mg/night) employing a single-blind cross-over design in a group of six normal young adults. In addition, the long-term administration

of the lower dose was assessed over a period of fifteen consecutive nights in this experiment. Psychological and physiological side-effects were also assessed by means of a number of psychological tests.

The administration of many hypnotic agents results in a marked reduction of stage REM sleep, whereas their withdrawal often results in an increased vividness in REM mentation with the occurrence of nightmares (Kales et al 1968(b), 1969(b), 1970(e), 1974). The aims of the third experiment were therefore to assess the influence of the short-term administration and withdrawal of 12,50mg clozapine/night upon the REM dream content of six normal young adults.

2.0 THE NATURE OF SLEEP

2.1 The Initiation of Modern Sleep Research

The scientific investigation of sleep began a little more than a century ago. Burdach (1830), on the basis of his naturalistic observations, predicted that "...sleep is in its beginning deepest, in its continuation smooth and quiet, towards its end slightest" (Snyder and Scott 1972, p.646). The first systematic attempt to quantify the depth of sleep in human subjects was described by Fechner (1860) in his Elemente der Psychophysik but was credited to Kohlschutter, the founder of the experimental psychology of sleep (Fechner 1860; Snyder and Scott 1972; Williams et al 1974; Wohlisch 1957). Kohlschutter (1862) produced a sleep depth curve by plotting the figures for the intensities of sound required to awaken the sleeper at different times of the night. This curve was characterised by a substantial increase in threshold until the end of the first hour of sleep which was followed by a rapid and then gradual decrease. Michelson (1897) reported that the first hour of sleep was indeed the deepest but that the remaining hours of sleep were characterised by random fluctuations in the arousal threshold in contrast to the gradual decrease reported by Kohlschutter (1862). Johnson and Swan (1930) elucidated this discrepancy by pointing out major methodological pitfalls in Kohlschutter's design. Kohlschutter (1862) awakened his subjects as many as seventeen times per night which possibly explains why sleep was so light after the first few hours. He also fulfilled Fechner's expectation as to the smooth progression of the curve by

disregarding many of his calculations. Subsequent studies progressively altered the remainder of Kohlschutter's curve, having found the arousal threshold to be higher and less regular than Kohlschutter (1862) anticipated (Czerny 1891; De Sanctis and Neyroz 1902; Endres and Von Frey 1930; Hass 1923; Lambranzi 1900; Mullin et al 1937).

The continuous monitoring of the sleeping subject's brain was soon to replace the investigation of behavioural correlates of sleep such as the arousal threshold technique.

2.2 The Classification of Sleep into Sleep Stages

2.2.1 The Discovery of the Electroencephalogram (EEG)

Berger (1929) recorded the first human electroencephalogram (EEG) and at the time wondered whether "...one would be able to demonstrate a difference of the electroencephalogram in wakefulness from that of sleep" (Berger 1969, p.72). Subsequent studies have revealed that differences do exist between the awake and sleep EEG (Gibbs et al 1935; Loomis et al 1935(a)(b); Blake 1937; Knott et al 1939; Diaz-Guerrero et al 1946). Loomis et al (1937), on the basis of all night monitoring of the EEG and electro-oculogram (EOG), classified sleep into five different stages (A-E) thus dispelling the previously held notion that sleep was a homogeneous stage which only varied in depth (Johnson 1973). The authors reported that a continual shifting of sleep stages occurred during the night and attributed this to either exogenous or endogenous stimulation.

2.2.2 The Discovery of Rapid Eye Movement (REM) Sleep

In 1953 Eugene Aserinsky made a remarkable discovery which was to dramatically alter the future of sleep research (Aserinsky and Kleitman 1953). Aserinsky, while studying the sleep patterns of infants noted that there were periods when the eyelids were quiescent and times when they exhibited bursts of activity. Aserinsky and Kleitman (1953, 1955) attempted to systematically study this newly discovered phenomenon by monitoring the sleep EEG and EOG of adult subjects. They reported that jerky, binocularly conjugate rapid eye movements (REMS) occurred periodically every 90 minutes beneath the closed eyelids of the sleeping subjects. These REMS occurred in conjunction with a low voltage EEG. Aserinsky and Kleitman (1955) found that vivid dreams were frequently recalled when subjects were awakened in the midst of a REM period. This psychophysiological parallelism was anticipated by Ladd (1892) and Griesenger (1869) who remarked "...that with vivid dreaming movement of the eyes occur". (Snyder 1971, p.31).

Dement and Kleitman (1957), on the basis of the presence or absence of rapid eye movements, divided sleep into two distinct categories, rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep (Table 1). They further subdivided NREM sleep into four stages (stages 1-4).

Hartmann (1965) referred to waking sleep as W, NREM sleep as S and REM sleep as D. These capital letters W,S,D might depict the waking state; slow wave, synchronised or spindle sleep; and desynchronised or dreaming sleep. The W-S-D nomenclature

Table I The classification of sleep into sleep stages on the basis of the presence or absence of rapid eye movements as proposed by Dement and Kleitman (1957, p.675).

Sleep stage	Characteristics of sleep stage	Presence or absence of rapid eye movements	Type of sleep
1	This stage is characterised by the absolute lack of spindle activity, low voltage, relatively fast EEG activity corresponding to the B stage of Loomis et al (1937) and including what the Loomis group called the A or interrupted alpha stage.	The total absence of rapid eye movements.	NREM
2	This stage is characterised by the presence of sleep spindles and K complexes.	The total absence of rapid eye movements.	NREM
3	This is an intermediate stage containing 20% but less than 50% of high voltage slow wave activity (delta waves).	The total absence of rapid eye movements.	NREM
4	This stage is characterised by large voltage (100uv) slow wave activity (delta waves) which comprise more than 50% of the record.	The total absence of rapid eye movements.	NREM
REM	This stage resembles stage 1 but is characterised by the presence of rapid eye movements	The presence of rapid eye movements.	REM

system (Hartman 1965), despite its simple descriptive properties, has not been readily accepted by the scientific community (Freemon 1972).

The great proliferation of literature on sleep research in the late 1960's (Webb 1973) produced an array of terms for REM and NREM sleep. REM sleep was also referred to as paradoxical (Jouvet 1965), para-sleep (Iwamura et al 1967), rhombencephalic (Jouvet 1961, Buendia 1963), desynchronised (Dunlop and Waks 1965), LVF (Berger and Meier 1966), D (Hartmann 1965), activated (Dement 1958), active (Parmalee et al 1967), restless (Cadilhac et al 1961), irregular (Wolff 1959), light (Karacan et al 1970) and deep (Carli and Zanchetti 1965) whereas NREM sleep was often referred to as orthodox (Oswald 1970), orthodoxical (Jouvet 1965), slow wave (Jouvet 1967), ortho-sleep (Iwamura et al 1967), telencephalic (Jouvet 1961), high voltage (Buendia et al 1963), slow (Allison 1965), synchronised (Dunlop and Waks 1965), HVS (Berger and Meier 1966), ordinary (Dement 1958) quiet (Parmalee et al 1967, Cadilhac et al 1961), regular (Wolff 1959), deep (Karacan et al 1970), and light (Carli and Zanchetti (1965). This prompted a committee under the leadership of Rechtschaffen and Kales (1968) to develop a standardised terminology, technique and scoring system for human sleep stages (see section 5.4.1). This system was based on the findings of Loomis et al (1937) and Dement and Kleitman (1957).

Despite attempts to standardise terminology relating to sleep parameters (Clemente 1967, Rechtschaffen and Kales 1968), confusion still reigns as to the interchange of the physiological

concept of REM sleep with the psychological concept of dreaming, as can be seen from the following quotation: "Dreaming occurs most frequently during REM states, but it can also occur during NREM states of sleeping and even waking" (Freemon 1972, p.23). Malcolm (1959) has suggested that the label "dreaming" should only be used in a phenomenological context and it has so been employed in the present study.

2.3 Sleep Cycles

The architecture of a night's sleep is a well documented phenomenon (Dement and Kleitman 1957; Berger 1969; Feinberg et al 1967; Freemon 1972; Hartmann 1973(a); Foulkes 1966; Williams et al 1974; Oswald 1970(a); Webb 1968; Kamiya 1961; Snyder and Scott 1972). The cyclical fluctuations in cerebral and oculomotor activity during sleep implies that sleep is neither a homogeneous nor random state but a state characterised by the cyclical recurrence of distinct stages.

2.3.1 The Sleep Cycle of the Young Adult

The initial descent into stage 1 sleep from wakefulness is characterised by the disappearance of alpha activity in the EEG and the appearance of slow rolling eye movements in the EOG (Rechtschaffen and Kales 1968). The appearance of sleep spindles (see section 5.4.1) heralds the onset of stage 2 sleep. As sleep progresses, high voltage slow wave delta activity (0,5-2,0hz) becomes more prominent and the sleeper enters NREM stage 3 sleep. When the greater part of the EEG record is dominated by delta activity, the sleeper is said to be in NREM stage 4 sleep.

After approximately seventy minutes of predominantly stage 3 and 4 (slow wave) sleep, the first REM period generally occurs (Berger 1969(b)). The first REM period is usually preceded by a series of body movements and a brief return of the EEG to stage 2 activity. It can be distinguished from later REM periods by its short duration and fewer rapid eye movements (Feinberg et al 1967; Goodenough et al 1965; Verdone 1965). REM sleep is accompanied by a decrease in tonic chin muscle activity (Berger 1961).

The above sleep cycle is usually repeated four to six times during the night depending on the total time spent asleep (Foulkes 1966). The presence of stage 4 sleep diminishes and that of stage REM sleep increases as the night progresses (Dement 1965(b)). As a result, the latter sleep cycles do not contain stage 4 sleep and consist of an alternation of stage 2 and stage REM sleep (Johnson 1973). The duration of the sleep cycle is 90 minutes.

The young adult spends about six percent of his sleep in stage 1, fifty percent in stage 2, seven percent in stage 3, sixteen percent in stage 4 and twenty percent in stage REM; about one percent of his sleep is occupied by body movements (Johnson 1973). A decrease in slow wave sleep occurs with increasing age whereas REM sleep remains constant (Agnew et al 1967(a); Feinberg et al 1967; Williams et al 1974; Roffwarg et al 1964).

Numerous factors such as thirst (Bokert 1965; Koulack 1970), exercise (Hauri 1968, 1969; Baekeland and Lasky 1966; Horne and Porter 1975; Shapiro et al 1975), stressful films (Witkin

narcolepsy[1] (Dement and Guilleminault 1973; Dement et al 1966(b); Roth and Bruhova 1969; Mitler et al 1975; Fenton 1975; Shapiro 1975; Rechtschaffen et al 1963(c); Williams et al 1974; Rechtschaffen and Dement 1969; Zarcone 1973; Guilleminault et al 1974), in subjects deprived of REM sleep for prolonged periods (Dement et al 1973(a)) as well as in subjects placed on a 30-60 minute sleep-wakefulness schedule (Carskadon and Dement 1975; Dement et al 1972).

Foulkes and Vogel (1965), on the basis of EEG and EOG recordings, classified sleep onset into four consecutive periods: awake alpha rhythm with rapid eye movements, alpha rhythm with slow rolling eye movements, stage 1 and stage 2 sleep. They found that mental activity was elicited from 95 percent of awakenings from the four sleep onset periods and that on occasion this mental activity resembled that found during REM awakenings (Foulkes et al 1966; Vogel et al 1972(a)).

Mental activity showed an orderly progression across the four sleep onset periods changing from fragmentary visual material during the awake alpha rhythm to extended and more self-involved mentation during stage 2 sleep (Foulkes et al 1966). The authors reported that vast individual differences existed with regard to the occurrence and content of mental activity during sleep onset periods.

Foulkes (1966) concluded that mental activity at sleep onset was a "...temporary expedient adopted by the organism to allow it to pass, undisturbed and with its mental apparatus relatively

[1]Narcolepsy is a disease characterised by the uncontrollable desire to sleep.

intact, from wakefulness to sleep." (Foulkes 1966, p.137).

2.4.2 Mental Activity During NREM Sleep

Dement and Kleitman (1957) found that vivid dream reports were obtained 74 percent of the time when subjects were awakened during REM periods but only seven percent of the time during NREM awakenings. Subsequent studies have confirmed that the majority of REM awakenings produced vivid dream reports but failed to obtain consistent findings for NREM awakenings (Table 2).

Goodenough et al (1959) were able to elicit dream reports 53 percent of the time during NREM awakenings compared to the seven percent reported by Dement and Kleitman (1957). They attributed this finding to traces of mental experience which occurred in preceding REM periods. Subsequent studies, however, found that dream reports were elicited from NREM sleep prior to the commencement of a REM period thus dispelling the notion that NREM dream reports were the reminiscences of previous REM periods (Foulkes 1966, 1967; Rechtschaffen 1973).

Foulkes (1962) obtained 74 percent dream recall from NREM awakenings. He ascribed this finding to his broader categorisation of cognitive activities used to define dream reports. These cognitive activities included fragmentary reports of mental activity which resembled everyday thinking.

It has generally been established that NREM dream reports are less elaborate, more everydayish, shorter in duration, consist

Table 2 Percentage recall of dream reports following REM and NREM awakenings.

Authors	REM	NREM
Aserinsky and Kleitman (1955)	74	7
Dement (1955)	88	0
Dement and Kleitman (1957)	79	7
Wolpert and Trosman (1958)	85	0
Goodenough et al (1959)	69	34
Jouvet et al (1960)	60	3
Snyder (1960)	62	13
Wolpert (1960)	85	24
Kremen (1961)	75	12
Foulkes (1962)	82	74
Orlinsky (1962)	86	42
Kamiya (1962)	86	46
Rechtschaffen et al (1963(a))	86	23
Foulkes and Rechtschaffen (1964)	89	62
Goodenough et al (1965)	76	21
Hobson et al (1965)	76	14
Kales et al (1967)	81	7
Larson and Foulkes (1969)	74	58
Castaldo and Shevrin (1970)	95	81

of fewer characters other than the dreamer, are more conceptual and comprise more recent events from daily routine than REM dream reports (Foulkes and Rechtschaffen 1964; Goodenough et al 1965; Foulkes 1966; Rechtschaffen et al 1963(a)). Foulkes and Vogel (1974) reported that NREM dream reports were elicited less frequently than REM dream reports which were elicited on most awakenings. The authors also found that NREM dream reports, like REM dream reports, increased in vividness as the night progressed.

Goodenough et al (1965) investigated the effects of gradual versus abrupt awakenings to determine the extent to which NREM dream reports might be the product of awakening. They found that gradual awakenings resulted in "thinking" dream reports more often than did abrupt awakenings.

Rechtschaffen et al (1963) proposed that NREM mentation was incorporated into REM periods and that REM periods thus "...emerge as the most vivid and memorable part of a larger fabric of interwoven mental activity during sleep" (Rechtschaffen et al 1963, p.546). Some confirmation of this hypothesis has been provided by Foulkes (1962) who found that pre-REM stage 2 mentation comprised routine "everyday" topics as well as undistorted events which resembled Freud's concept of the day residue from which Freud presumed dreams to develop.

2.4.3 Mental Activity During REM Sleep

The world of dreams has fascinated mankind since antiquity:

> And Joseph dreamed a dream ..... For behold, we were binding sheaves in the field, and lo, my sheaf arose, and also stood upright; and, behold, your sheaves stood round about, and made obeisance to my sheaf. And his brethren said to him, shalt thou indeed reign over us?
>
> Genesis 37

It seems likely that it is REM sleep mentation that has been associated with vivid and distorted mental themes called dreams (Table 2). The sleep research community has yet to reach concensus on a definition of dreaming. "A meeting of psychologists attempted to formulate a definition of dreaming, but only reached the unhelpful consensus that each investigator should use his own definition" (Freemon 1972, p.23). Thus in the present study a REM dream report is defined as the "... mental activity which occurs during REM sleep and is sampled by waking the sleeper during the REM state and asking him what was going through his mind" (Freemon 1972, p.23).

Dement and Kleitman (1957(b)) found that the length of a REM dream report increased as the duration of the REM period increased prior to awakening. REM periods that occurred earlier in the night were found to have a lower profusion of rapid eye movements (Goodenough et al 1965; Aserinsky 1969, 1971) and dream reports elicited from these REM periods were found to be less perceptual, active and dramatic than those elicited from later REM periods (Domhoff and Kamiya 1964; Foulkes 1966, 1967; Shapiro et al 1963).

It was previously hypothesised that a psychophysiological parallelism existed between the profusion of rapid eye movements

during REM sleep and the visual imagery recalled upon awakening (Dement and Wolpert 1958; Dement and Kleitman 1957(b); Berger and Oswald 1962; Roffwarg et al 1962). This supposition, known as the "scanning hypothesis" (Firth and Oswald 1975), was supported by the finding that rapid eye movement profusion was positively related to various aspects of the REM dream report such as bizarreness (Goodenough et al 1965; Verdone 1965), emotionality (Karacan et al 1966; Verdone 1965), intensity (Pivik and Foulkes 1966) and vividness (Verdone 1965). Additional support for the "scanning hypothesis" was provided by the finding that congenitally blind people lacked visual imagery in their dreams and did not appear to produce rapid eye movements during REM sleep (Berger et al 1962; Offenkrantz and Wolpert 1963).

Recent research, however, has questioned the validity of the "scanning hypothesis". Recent studies have demonstrated the existence of rapid eye movements in congenitally blind subjects by the use of mechanical[1] rather than electrophysiological recording procedures (Amadeo and Gomez 1966; Gross et al 1965).

Further contradictions of the possible isomorphic relationship between rapid eye movement profusion and the visual imagery of dreams were provided by the findings that kittens which were reared in the dark (Fishbein et al 1966) as well as newborn infants (Delange et al 1962; Monod et al 1964; Weitzman et al 1965; Roffwarg et al 1966) produced rapid eye movements during REM sleep.

[1] The corneo-retinal potential has been found to be either diminished or absent in most blind subjects and the usual electrophysiological recording techniques would thus fail to detect eye movements.

The rate and distribution of rapid eye movement bursts (section 5.5.2) have been found to be constant within subjects from REM period to REM period and from night to night (Spreng et al 1968; Aserinsky and Cady 1967). Spreng et al (1968) reported that individual differences existed with regard to the direction of eye movements during REM sleep and that a consistent relationship existed between rapid eye movement bursts and autonomic activity. Thus it appears unlikely that the profusion of rapid eye movements during REM sleep are directly related to the visual imagery recalled upon awakening.

In view of the above contradictory evidence, the notion of a constant psychophysiological parallelism between rapid eye movements and visual imagery appears to be questionable (Firth 1973, 1974; Hauri and van de Castle 1973; Jacobs et al 1970; Koulack 1972; Moskowitz and Berger 1969). Koulack (1972) concluded; "The initial hypothesis of a constant isomorphic relationship between REM's and visual imagery seems to be untenable, although it is quite possible that from time to time eye movements and the visual imagery of dream might be related". (Koulack 1972, p.157). It has been suggested that a neurophysiological mechanism might be associated with the profusion of eye movements and autonomic changes which accompany REM sleep (Aserinsky 1965; Johnson 1973).

It has generally been established that visual, auditory and somesthetic stimuli become incorporated into ongoing REM mentation. Dement and Wolpert (1958) found that spraying water on exposed skin; sounding a tone or flashing a light during REM sleep resulted in the incorporation of these stimuli into

the REM dream report. Koulack (1969) stimulated the sleepers wrist with a mild electrical current during REM sleep and found a significant incorporation of this stimulus in the REM dream report. He obtained the highest incorporation when the stimulus was applied three minutes after the commencement of a REM sleep period and the sleeper awakened three minutes later. Castaldo and Holzman (1967, 1969) found that playing a tape recording of the sleeper's own voice during REM sleep produced a REM dream report in which the central character of the drama was active and dogmatic whereas the tape recording of another person's voice saying the same words produced a REM dream report in which the central character played an impassive role. Freud (1900) proposed that the incorporation of internal (bladder distention, stomach aches etc) as well as external stimuli into the ongoing dream process acted as a guardian of sleep by preventing the sleeping person from awakening.

Another notable finding has been the discovery that the gross body movements which occur during REM sleep, demarcate the REM dream report into several episodes (Wolpert and Trosman 1958; Dement and Wolpert 1958).

2.5 Physiological Characteristics of Sleep

Several studies have investigated the physiological concomitants of sleep and as a result "... we can now predict with a high degree of certainty that any virginal physiological activity will show distinct changes with the onset of REM sleep, compared with its level and pattern during NREM sleep" (Berger 1969(a) p.66). The transition from NREM to REM sleep and vice versa has been

found to be a gradual rather than an abrupt process (Shapiro 1967).

2.5.1 Electroencephalography

Modern technology has evolved techniques whereby it is now possible to record the activity of single neurons or the integrated activity of groups of neurons by means of microelectrodes. Berger (1969(a) reported that the rates of neural discharge during REM sleep resembled those during wakefulness. The groups of neurons however tended to fire simultaneously in synchronised patterns during NREM sleep in contrast to the asynchronous pattern of firing during wakefulness.

It has generally been established that the rate of firing of groups of neurons throughout most areas of the brain increased during REM sleep to levels found during wakefulness (Arduini et al 1963; Evarts 1962, 1964; Huttenlocher 1961; Benoit 1964; Bizzi et al 1964; Podvoll and Goodman 1967; Rougeul et al 1966).

This increase in neural activity during REM sleep is accompanied by an increase in cerebral blood flow (Kanzow et al 1962; Kety 1967, Reivich et al 1968) and by an increase in the temperature of the brain (Kawamura and Saywer 1965; Rechtschaffen et al 1965; Kawamura et al 1966). Kety (1967) reported that the blood flow to the cortex practically doubled during REM sleep in comparison to NREM sleep.

It had been previously thought that the increased brain temperature during REM sleep was the result of an increased metabolic

activity in the brain. Baker and Hayward (1967) have produced findings which have cast some doubt upon this assumption. They found that the rise in the brain temperature of the rabbit during REM sleep originated in a temperature rise in the cerebral arterial blood.

The EEG characteristics of the various stages of sleep have been discussed in sections 2.3.1 and 5.4.1.

2.5.2 Heart Rate, Blood Pressure, Respiration and Metabolic Activity

Heart rates, systolic blood pressure and respiration rates have been reported to be higher during REM than NREM sleep (Aserinsky and Kleitman 1953; Kamiya 1962). It has generally been established that with the onset of REM sleep the above vegetative activities became increasingly irregular (Johnson and Lubin 1967; Shapiro et al 1964; Snyder 1960; Snyder et al 1963, 1964; Khatri and Freis 1967; Richardson et al 1964).

Hobson et al (1965) reported that a correlation existed between the number of rapid eye movements and the respiration rate during REM sleep. Aserinsky and Houseknecht (1965) found that a decrease in the respiration amplitude was associated with REM bursts. This decrease in the respiration amplitude was associated with an increase in the frequency of respiration (Aserinsky 1965).

It has generally been established that a gradual decrease in oxygen consumption and body temperature occurs during sleep (Brebbia and Altshuler 1965; Kreider et al 1958). During REM

sleep, however, an increase in oxygen consumption and carbon dioxide production has been observed (Brebbia and Altshuler 1965). Aserinsky (1965) found that during intense bursts of rapid eye movements, the blood oxygen tension fell to extremely low levels.

Biochemical assessments have revealed that an increase in the osmolality of urine (Mandell et al 1966) as well as increases in the circulating levels of plasma 17-hydroxycorticoids and catecholamines (Mandell and Mandell 1965; Weitzmann et al 1966) occur during REM sleep. It thus appears that an activation of the anterior and posterior lobes of the hypophysis occurs during REM sleep (Mandell and Mandell 1965).

The evidence points overwhelmingly to the conclusion that REM sleep is accompanied by an increase in most autonomic parameters.

2.5.3 Electrodermal Phenomena

Slow wave sleep (stages 3 and 4) has usually been considered to be the least active stage of sleep during which "all functions are depressed and the lowest level of vigilance and alertness is reached" (Johnson and Lubin 1966, p.8). However, spontaneous galvanic skin responses are more prominent during stage 3 and stage 4 sleep than during REM sleep (Asahina 1962; Broughton et al 1965; Burch 1965; Johnson and Lubin 1967). This finding contrasts with the autonomic functions such as the finger plethysmograms and finger temperature (Johnson et al 1965), heart rate, blood pressure and respiration rate (Kamiya 1961; Snyder et al 1964) which have been reported to be elevated during REM and not NREM sleep.

Johnson and Lubin (1966) have attempted to provide an explanation for the contradictory finding that an increase in the spontaneous electrodermal activity occurred during the least active stage of sleep. They proposed that if a rhombencephalic electrodermal inhibitory centre existed, which was active during REM sleep but inactive during slow wave sleep, little or no electrodermal activity would occur during REM sleep.

2.5.4 Slow Eye Movement Activity

Dement (1964) reported that direct observation of sleeping subjects revealed that slow eye movements appeared as rhythmical, oscillating swings of the eyeball from one side of the orbit to the other. The greatest proportion of movement was found to occur in the horizontal plane. When these slow rolling eye movements are recorded polygraphically, they resemble a sine wave and have a maximum frequency of between ten and twenty cycles per minute. Slow rolling eye movements are most prominent at the onset of sleep (Foulkes 1966). Dement (1964) found that the slow eye movements preceded the discontinuity of the EEG alpha activity and were thus a more sensitive index of sleep onset. Slow eye movements also occur throughout the night immediately following gross body movements (Dement 1964). On occasion the slow eye movements precede the body movements by a few seconds.

Dement (1964) noted that slow eye movements resembling those at sleep onset occurred when a subject briefly awoke and returned to sleep during the night. The duration of these eye movements was however shorter than the duration at sleep onset.

2.5.5 Rapid Eye Movement Activity

Rapid eye movements are binocularly synchronous and resemble the waking eye movements of visual fixation in man (Dement 1964(b); Aserinsky and Kleitman 1953). They occur with similar speeds in all directions. Antrobus et al (1969) reported that the majority of rapid eye movements occurred in the horizontal plane. Spreng et al (1968) found that individual biases existed in the predominance of rapid eye movements in the horizontal or vertical plane.

The rapid eye movements occur in clusters or bursts for long periods of time, or are exceedingly sparse, in the same individual. (Dement and Kleitman 1957(b); Mouret and Jeannerod 1964; Aserinsky 1965; Spreng et al 1968; Snyder 1967). In man, the number of rapid eye movements have been found to be relatively constant from night to night (Spreng et al 1968). Aserinsky and Cady (1967) reported that the number of rapid eye movements per REM period increased with each successive REM period of the night.

2.5.6 Body Movement

Oswald et al (1963) found that gross body movements occurred during all stages of sleep. He reported that the highest incidence of gross body movements occurred during REM sleep and the lowest incidence during stages 3 and 4 sleep.

Several studies have reported the presence of irregular twitching and trembling movements of muscles of the face and hands in human subjects during REM sleep (Baldridge et al 1965;

Dement and Kleitman 1957(a); Stoyva 1965; Wolpert 1960). Newborn infants have been found to stretch, smile, frown and cry during stage REM sleep (Delange et al 1962; Roffwarg et al 1964).

2.5.7 Nocturnal Penile Tumescence

The periodic occurrence of penile erections during human sleep was reported by Ohlmeyer et al (1944, 1947). Aserinsky (1953) suggested that a temporal relationship existed between the sleep erection cycle and stage REM sleep. Oswald (1962) was unable to demonstrate the existence of this temporal relationship. However subsequent studies have confirmed the existence of a REM-tumescence correlation in human subjects (Morita 1975; Hursch et al 1972; Karacan 1965,1970; Karacan et al 1965,1966,1972(a)(b)(c), 1975; Fisher et al 1965; Jovanovic 1967, 1968; Kahn and Fisher 1969) as well as in monkeys (Karacan 1966; Karacan and Snyder 1966).

Karacan (1970) reported that the well known phenomenon of a penile erection upon awakening in the morning was not precipitated by bladder distention but was related to the occurrence of a REM period. He also found that less anxiety was evident in the REM dream reports which were obtained following awakenings from full erections than those obtained following awakenings from partial erections or in the absence of erections.

Karacan et al (1972(c)) proposed that nocturnal penile tumescence and stage REM sleep were related but not entirely interdependent phenomena. The evidence for this hypothesis has been provided

by the following findings: The authors found that REM sleep did not necessarily precede penile tumescence; penile tumescence occurred during NREM sleep; the first night effect (Agnew et al 1966) resulted in a decrement in stage REM sleep without influencing tumescent time; temporary sexual abstinence affected tumescence but failed to influence stage REM sleep; REM sleep deprivation did not totally inhibit tumescence.

Thus, the available evidence points to the conclusion that REM sleep usually precedes penile tumescence but that on occasion REM sleep or penile tumescence can occur independently of one another.

2.5.8 Growth Hormone Secretion

It has generally been established that slow wave sleep is often accompanied by a rise in the human growth hormone concentration in the plasma of most healthy individuals (Hunter and Bigal 1966; Quabbe et al 1969; Takahashi et al 1968; Honda et al 1969; Sassin et al 1969(a)(b); Underwood et al 1971; Beck et al 1975; Karacan et al 1971(a), 1973(a); Parker et al 1969).

Subsequent research has confirmed the assumption that an association between slow wave sleep and the human growth hormone concentration in the plasma exists. The deprivation of slow wave sleep was found to result in a significant but incomplete suppression of the plasma human growth hormone concentration shortly after sleep onset (Karacan et al 1971(a); Sassin et al 1969(a)). Karacan et al (1971(a)) found that the significant decrease in the human growth hormone plasma levels was restricted to the first third of the night when slow wave sleep would have

predominated if it had not been suppressed. Further confirmation for this assumption has been provided by the findings that acute fasting (Karacan et al 1973(a); Parker et al 1972) as well as the interruption of the sleep cycle (Beck et al 1975; Takahashi et al 1968) both resulted in an increase in slow wave sleep as well as an increase in the human growth hormone concentration in the plasma.

It has been suggested that slow wave sleep and human growth hormone may serve an anabolic restorative function (Beck et al 1975; Oswald 1970(a),(b); MacFayden et al 1973; Dunleavy et al 1974; Adamson et al 1974).

2.5.9 Tonic and Phasic Concomitants of REM Sleep

The physiological activities that occur during REM sleep have been divided into phasic and tonic events (Hartmann 1967(a); Moruzzi 1963; Molinari and Foulkes 1969). Tonic events are those physiological activities which persist for the entire duration of the REM period. Tonic events include an activated EEG, electromyogram suppression, an increase in brain temperature and the presence of hippocampal theta waves of five cycles per second (Grosser and Siegal 1971).

Phasic events are those physiological activities that are short lasting and do not persist for the entire duration of the REM period. Phasic events include the rapid eye movements (Aserinsky 1965), cardiovascular irregularities (Snyder et al 1964), myoclonic twitches and increased fine muscle activity (Baldridge et al 1965), changes in pupil diameter (Berlucchi et al 1964), fluctuations in

nocturnal penile tumescence (Fisher et al 1965; Karacan et al 1965, 1972(a)(b)(c), 1975; Jovanovic 1967, 1968; Morita 1975) and finally bursts of monophasic sharp waves[1] that are characteristic of the electrical activity of the pons, oculomotor nuclei, lateral geniculate nuclei and the occipital cortex (Brooks 1967; Brooks and Bizzi 1963; Michel et al 1964; Pompeiano 1967).

Dement et al (1970) proposed that the PGO spikes were the triggering mechanism for the commencement of phasic events during REM sleep, especially the rapid eye movements. These PGO spikes occur in the cat, squirrel monkey as well as the rhesus monkey but as yet have not been observed in man (Dement et al 1970). It has been suggested that the reason for this could be the result of the restricted use of implanted electrodes in man (Dement et al 1970). It has generally been suggested that the sawtooth waves (Berger et al 1962), seen in the EEG of human subjects during stage REM sleep, could be analogous to the PGO spikes seen in the cat (Dement et al 1970; Schwartz 1962).

The PGO spikes normally precede the commencement of a REM period. These spikes have been found to show a reduction in amplitude, a rise in frequency and an increased probability of occurring in clusters or bursts. During NREM sleep, the PGO spike has been reported to occur as a unitary, high amplitude discharge at equidistant intervals (Thomas and Benoit 1968; Dement et al 1970). The termination of a REM period is characterised by the cessation of spike activity.

[1] These monophasic sharp waves are known as PGO (pontine-geniculate-occipital) spikes. The PGO spikes occur at a fairly constant daily rate of ±14000 per day in the cat (Jouvet 1969). They always precede stage REM sleep by ±30 seconds and accompany bursts of rapid eye movements.

Delorme et al (1965) reported that tonic and phasic events could be dissociated from one another. They found that high doses of reserpine totally suppressed REM sleep in the cat without influencing the discharge of PGO spikes. On the basis of this finding, Dement et al (1970) have postulated that at least two distinct neurological mechanisms were responsible for the production of REM sleep.

2.5.10 REM SLEEP As An Activated State

REM sleep has been found to be accompanied by an increase in heart rate, blood pressure and respiration rate (section 2.5.2), an increased neural activity in the sensory and motor areas of the brain (section 2.5.1), an increased cerebral blood flow and brain temperature (section 2.5.1) as well as an increased activity in the anterior and posterior lobes of the hypophysis (section 2.5.2) whereas a decrease in the tonic chin muscle activity (Berger 1961), the number of spontaneous galvanic skin responses in relation to slow wave sleep (2.5.3), the spinal H reflex (Hodes and Dement 1964) as well as a reduced neural activity in the hippocampus (Mink et al 1967) and fibres of the corpus callosum (Berlucchi 1965) occur. In view of these findings "... the notion that there are active and quiet periods of sleep must be abandoned. Each state of sleep has its own unique pattern of physiological activity." (Johnson and Karpan 1968, p.444). Berger (1969) postulated that each sleep stage had a distinct function and as a result was characterised by a different conglomeration of physiological activities.

2.6 Sleep Deprivation

2.6.1 Total Sleep Deprivation

Several studies have investigated the psychological, neurological and biochemical effects of prolonged sleep deprivation in human subjects (Gulevich et al 1966; Ross 1965; Pasnau et al 1968; Kollar et al 1966; Tyler 1955 and Kupfer et al 1970(b)). The psychological investigations have revealed that extended sleep loss has resulted in dramatic behaviour such as fatigue, irritability, feelings of persecution and disorientation. Johnson (1973) reported that hallucinations could occur after extended sleep loss but that they would be primarily visual and tactile in contrast to the auditory hallucinations usually found in schizophrenic patients. However,subjects have also been found to perform adequately on performance tasks during extended sleep deprivation when the task had a high incentive value and was of short duration (Wilkinson 1964; Lubin 1967).

Neurological examination revealed that extended sleep loss resulted in the slurring of speech, inability to concentrate, loss of ocular convergence, immediate memory loss and episodes of disorientation to time (Ross 1965; Kollar et al 1968) as well as a decrease in alpha abundance (Johnson 1969; Freeman 1972). Biochemical changes such as a rise in serum creatinine phosphokinase (Kupfer et al 1970(b)) and circulating levels of glucose and cortisol (Kollar et al 1969) have been reported after sleep deprivation. Kuhn et al (1967) reported that a considerable decrease in plasma iron levels occurred as well as a moderate fall in plasma cholesterol. It has generally been

established that these neurological, psychological and biochemical changes are transient phenomena and disappear once the subject returns to his usual sleep habits (Freemon 1972).

In studies where psychotic behaviour has been reported following sleep deprivation (Brauchi and West 1959; Bliss et al 1959; Katz and Landis 1935; Luby et al 1960) some predisposition of the subject to psychotic or bizarre behaviour under conditions of stress were evident (Johnson 1969). Thus it would appear that each subject's response to sleep deprivation would depend on his age, premorbid personality, motivation, physical health and the expectation of the experimenters (Freemon 1972).

In view of the above findings, the previously held notion that extended sleep loss would result in a psychosis can now be dismissed (Johnson 1969).

The recovery from total sleep deprivation has been characterised by a dramatic increase in total sleep time on the first recovery night. This dramatic increase was associated with a marked increase in slow wave sleep as well as an increase in the arousal threshold during all sleep stages (Berger and Oswald 1962; Williams et al 1964(b)). Kales et al (1970(f)) reported that although REM sleep time increased on the first recovery night, the REM sleep percentage either remained unchanged or showed a slight increase. It is on the second recovery night that REM sleep has been found to show its greatest rebound (Dement 1965(a); Johnson 1969, Berger and Oswald 1962), although studies have reported the REM rebound to occur on the first recovery night as well (Gulevich et al 1966; Johnson et al 1965). The increase

in stage 4 and stage REM sleep during the recovery from sleep deprivation was found to be associated with a substantial decrease in stage 2 sleep (Freemon 1972).

2.6.2 Differential Sleep Deprivation

The question often asked is one of whether a specific sleep stage meets a particular need? (Johnson 1973). Shakespeare's Macbeth described sleep as "labour's bath, balm of hurt minds.....chief nourisher at life's feast". It has been suggested that slow wave sleep replenishes the body after labour (Backeland and Lasky 1966; Oswald 1970) and that REM sleep soothes hurt minds (Hartmann 1973(a)).

Differential sleep deprivation has been achieved by the prevention of a subject obtaining a particular stage of sleep but permitting all the other sleep stages (Webb 1969(b)). Stage 4 deprivation has not received as much attention as stage REM deprivation has amongst the sleep research community (Webb 1969(b); Johnson 1973).

Agnew et al (1964) reported that stage 4 deprivation was associated with a rebound of stage 4 during recovery sleep. In a subsequent investigation they found that no consistent performance differences existed between stage 4 and stage REM deprived subjects (Agnew et al 1967(b)). They did however find that stage 4 deprived subjects displayed hypochondriacal and depressive symptoms whereas stage REM deprived subjects showed an increase in irritability and emotional lability.

Lubin et al (1974) found that when performance was impaired by the complete loss of sleep, recovery sleep was found to be equally effective regardless of the quantity of stage 4 or stage REM sleep permitted during this period. Johnson et al (1974) deprived seven subjects of stage 4 sleep and seven subjects of stage REM sleep for three consecutive nights which were followed by one night of total sleep deprivation. They found that no changes in waking behaviour occurred in either the stage 4 or the stage REM deprived subjects.

The earlier REM deprivation investigations found that REM deprivation resulted in the occurrence of deleterious psychological abnormalities in human subjects (Dement and Fisher 1963; Sampson 1965). Subsequent studies have failed to replicate the above finding (Greenberg et al 1970; Vogel 1968; Kales et al 1964; Snyder 1963; Foulkes et al 1968). Recent studies have reported that REM deprivation may be of therapeutic value to some depressed patients (Vogel and Traub 1968(a)(b); Vogel et al 1968).

In view of the evidence against the deleterious psychological effects of REM sleep deprivation, Dement (1965(a) remarked that "...it seems likely that the psychological changes observed in the earlier studies were an artifact of the experimental procedures and the expectations of the experimenters" (Dement 1965(a) p.599). Vogel (1975) reported that the earlier studies had methodological inadequacies which would have had an influence on the results obtained. They failed to use NREM control awakenings, the subjects were aware of the experimental and control conditions, the researchers were not blind to the

experimental conditions and psychological assessment had in fact revealed that no consistent changes had taken place.

Does REM deprivation eliminate dreaming? Before the discovery that mental activity occurred throughout sleep (Foulkes 1962, 1966; Foulkes and Vogel 1965), REM sleep deprivation was considered to be synonomous with the elimination of dreaming. In view of the above finding, it was thought the only methodological procedure to eliminate NREM and REM dreaming would be total sleep deprivation. Recent research has indicated that this assumption may not be entirely valid (Foulkes and Scott 1973; Foulkes 1974).

Foulkes and Scott (1973) found that subjects frequently reported hallucinatory experiences during relaxed wakefulness which showed a marked resemblance to nocturnal dreaming. These hallucinatory experiences occurred without drugs or prior sleep deprivation. Vogel (1975) concluded that "...dreaming, similar to and often indistinguishable from REM reports, occurs in all other conventional natural states of consciousness that sleep researchers recognise, eg. wakefulness, sleep onset and NREM sleep". (Vogel 1975 Pp 753-754).

2.6.3 Partial Sleep Deprivation

Partial sleep deprivation has been achieved by preventing subjects from obtaining their normal quota of sleep within a twenty four hour period (Webb 1969). Webb and Agnew (1974) suggested that partial sleep deprivation may in fact be differential sleep deprivation because when sleep duration was reduced to as little as three hours per night, no reduction in stage 4 sleep occurred

(Webb and Agnew 1965; Dement and Greenberg 1966; Rush et al 1968). This occurred because stage 4 sleep predominates in the first third of the night and is thus insensitive to the restriction of sleep duration.

Several studies have investigated the effects of restricted sleep schedules on sleep stages and performance tasks (Sampson 1965; Dement and Greenberg 1966; Rush et al 1968; Webb and Agnew 1965, 1974; Wilkinson 1969; Frazier et al 1971; Johnson and Macleod 1973). The restriction of the duration of sleep resulted in little or no decrement in stage 4 sleep and some studies have even reported a slight increment in stage 4 sleep (Dement and Greenberg 1966; Webb and Agnew 1974; Rush et al 1968). The most surprising result was that of a stage 4 rebound during recovery sleep despite the fact that no stage 4 sleep decrement occurred during the restricted sleep schedule (Webb and Agnew 1965; Rush et al 1968).

REM sleep which occurs predominantly in the last third of the night was found to show a marked decrease during the restriction of sleep duration (Webb and Agnew 1965, 1974; Rush et al 1968). It did however show a compensatory response by occurring earlier in the night (Webb and Agnew 1974(b); Johnson and Macleod 1973).

Restricted sleep schedules were found to have little or no effect on performance tasks when they were of brief duration (Sampson 1965; Webb and Agnew 1965, 1974(b)). Prolonged vigilance tasks however resulted in a marked reduction in performance after partial deprivation of sleep (Sampson 1965; Frazier et al 1971).

The above-mentioned studies suffer from the limitation that the restricted sleep schedules were imposed for a limited time period (Webb 1969(b)). Recent studies have investigated the sleep patterns and personality traits of normal individuals who consistently sleep for long and short periods. They found that differences in sleep patterns existed between these two groups of individuals (Hartmann 1973(b); Hartmann et al 1971(a), 1972; Webb and Agnew 1968, 1970; Baekeland and Hartmann 1970, 1971; Webb and Friel 1971). Hartmann (1973(a)) reported that when sleep stages were expressed as percentages of total sleep time, short sleepers[1] had a greater percentage of stage slow wave sleep than long[2] sleepers. The percentage of time spent in stage REM sleep was the same for both groups of subjects. The long sleepers however had significantly greater REM densities and recalled more dreams at home than did the short sleepers (Hartmann 1973(a), Hartmann et al 1972).

Contradictory findings have been reported as to whether long and short sleepers differ from one another on psychological dimensions (Hartmann 1973(a); Webb and Agnew 1971(a)). Hartmann et al (1971(a)) reported that psychological test data indicated that long sleepers scored in a more pathological direction than short sleepers on most of the MMPI, CPI and Cornell Medical Index scales. In contrast Webb and Friel (1971) were unable to find any significant differences between long and short sleepers on personality, intellectual performance or medical measures. Taub (1972) has suggested that the above discrepancy could be attributed to inadequate sampling procedures.

[1]Short sleepers had a mean sleep duration of 5½ hours.
[2]Long sleepers had a mean sleep duration of 8 hours.

2.6.4 Chronic Sleep Deprivation

Recent research has indicated that living in contemporary society may result in a chronic loss of sleep. The majority of people go to sleep when they wish to, but wake up when they have to.

Webb (1969(a)) noted that 8-17 year old students in 1911 obtained an average of 1½ hours more sleep than similarly aged students in 1963. Kleitman et al (1937) using sleep diaries of six month's duration, noted that only one third of the subjects reported that they frequently awoke spontaneously and that half reported upon awakening that they had not had adequate amounts of sleep.

Agnew (1974) reported that in a questionnaire study involving one thousand students, less than a third reported that "...they typically wake up in the morning feeling fresh and rested" (Webb 1975, p.47). White (1975) carried out a study where 89 students kept sleep logs for fourteen consecutive days. He found that weekend sleep was an hour longer than their weekday sleep. This is consistent with the findings reported by Johns et al (1971(a)).

Webb and Agnew (1974(a)) placed 14 subjects on an ad lib sleep schedule for fourteen days in an environment which offered no cues as to the time of day. Prior to the commencement of the study, subjects indicated that they had a mean sleep duration of 7½ hours per night. The subjects all significantly exceeded their anticipated sleep durations by an hour each night. Webb and Agnew (1974(b)) placed subjects on a strictly controlled sleep schedule for ten days in which the lights were switched off at 11 pm and the subjects awakened promptly at 7 am. The subjects

had a mean sleep duration of seven hours and twenty four minutes per night. For the next ten nights subjects were permitted to sleep as long as they desired and under this experimental condition they had a mean sleep duration of eight hours and fifty one minutes.

More evidence as to the question of whether one is sleep deprived was provided by Webb and Agnew (1975(b)). Sixteen subjects slept in a sleep laboratory, in which all cues as to the time of day were eliminated, for four consecutive nights. On the first three nights subjects were put to bed at 11 pm and were woken promptly at 7 am. The mean sleep duration on the third night was found to be seven hours and thirty four minutes. On the fourth night subjects were unaware that they would be permitted to sleep until the EEG showed ten minutes of wakefulness in the morning. The subjects had a mean sleep duration of nine hours and forty minutes on this ad lib sleep duration night.

It has thus been generally established that when subjects are permitted to sleep in a time free environment, they significantly exceed their normal estimated sleep durations. Webb and Agnew (1975(b)) found that when sleep was experimentally restricted for a night, an increase similar to the amount restricted occurred on the following night. The authors concluded that "...as in the case of eating, given unlimited amounts of food, we will eat more than we need. Our regular sleep diets may be simply and sensibly keeping us from being 'sleepfat'" (Webb and Agnew 1975(b) p.48).

3.0 METHODOLOGICAL CONSIDERATIONS FOR SLEEP LABORATORY DRUG EVALUATION PROGRAMS

3.1 The Adaptation to The Sleep Laboratory Environment

3.1.1 The "first night" effect

Several studies have reported the existence of a "first night" adaptation effect in EEG sleep studies in normal subjects as well as in psychiatric outpatients (Agnew et al 1966; Schmidt and Kaelbling 1968, 1971; Rechtschaffen and Verdone 1964; Mendels and Hawkins 1967; Dement et al 1965; Antrobus 1962). The "first night" effect consists primarily of a decrease in stage REM sleep as well as an increase in total time spent awake (Agnew et al 1966; Hawkins and Mendels 1966; Scharf et al 1975; Antrobus 1962; Rechtschaffen and Verdone 1964). In addition, an increase in stage 4 and stage REM latency as well as an increase in the number of shifts in sleep stages occur (Agnew et al 1966; Hawkins and Mendels 1966).

Recent studies have questioned the existence of this well documented adaptation phenomenon in normal subjects as well as in psychiatric inpatients (Coble et al 1974; Kupfer et al 1974; Toner et al 1975; Niimi et al 1968; Globus 1970; Williams et al 1972; Clausen et al 1974).

Toner et al (1975) attempted to familiarise normal subjects to the experimental setting by taking them on an informal tour of the sleep laboratory. The subjects were also shown a documentary film which depicted the sleep stages as well as the procedure used to secure the various electrodes. Subjects were

also permitted to assist the experimenter in wiring up fellow subjects. However, this familarisation technique was unsuccessful in eliminating the "first night" effect.

Coble et al (1974) permitted subjects to sleep in private, comfortably furnished bedrooms. The subjects were allowed to use kitchen facilities and had free access to a "denlike" television area until they were required to go to sleep. This laboratory environment resembled a good hotel in the middle price bracket. In addition, the laboratory personnel were friendly and helpful and explained the operation of the equipment to the subjects. There was a significant decrease in stage REM latency from the first to the second night, but no changes in any of the other sleep parameters occurred.

Kupfer et al (1974) were unable to detect any significant "first night" effects in psychiatric inpatients. Mendels and Hawkins (1967) noted that depressed inpatients, with the exception of a decrease in stage 2 sleep, had similar sleep patterns on their first and second nights in the sleep laboratory. It has been suggested that the absence of an adaptation response shown by psychiatric inpatients may be a manifestation of a decreased ability to adapt to stressful situations (Kupfer et al 1974).

Contradictory evidence exists at present as to whether an initial adaptation night should be incorporated into sleep research designs. In conclusion, it seems advisable at present that sleep research designs involving normal human subjects should comprise an initial adaptation night as most sleep

laboratories do not resemble a good hotel in the middle price bracket.

3.1.2 Readaptation to The Sleep Laboratory

Scharf et al (1969) analysed the data of eight subjects who participated in a series of sleep research programs over a two year period to determine whether the first night effect persisted throughout the series. They concluded that "...regardless of the number of times previously adapted to the sleep laboratory, on a subsequent series there usually was a repeat adaptation or "first night" effect consisting of an increased sleep latency, and decreased percent sleep time and percent stage REM (Scharf et al 1969, p.263). The authors however failed to mention the time lapses between the successive series of experiments.

Scharf et al (1975) reported that a readaptation effect existed in insomniac subjects when they were re-recorded in the sleep laboratory after spending seven nights at home. The authors found that the readaptation effect was similar to that seen in the initial adaptation period and included a decrease in stage 4 and stage REM sleep as well as a decrease in the number of stage REM periods. These results should however be interpreted with caution as the adaptation effects appear to be confounded with drug effects.

3.2 The Reliability of Sleep Measures

Several studies have reported similar percentages (normative data) for the various sleep stages in normal young adult subjects (Williams et al 1964(a), 1972, 1974, Dement et al 1966;

Williams and Williams 1966; Agnew and Webb 1968; Niimi et al 1968; Brebbia et al 1969; Hori et al 1969; Moses et al 1972; Scott 1972; Johnson 1973; Clausen et al 1964)(section 2.3.1). However, it has been assumed that these values are consistent from one night to the next. Berger (1969(b)) reported that "...the pattern of sleep from night to night in a single individual remains relatively constant, except for the first night spent in the laboratory when the subject takes a longer time to fall asleep, tends to awaken more frequently and has less REM sleep than on subsequent nights" (Berger 1969(b) p.21).

Several studies have investigated the consistency and predictability of sleep parameters for groups of subjects over several nights (Williams et al 1964(a), 1966; Hartmann 1968(a), Weitzman et al 1970), but only a limited number of studies have attempted to assess whether the sleep parameters of individual subjects are reliable over several nights (Moses et al 1972; Feinberg 1974; Webb and Agnew 1969; Webb 1974; Clausen et al 1974). These studies differed from one another in that they employed different methodological techniques, variable sample sizes as well as subjects of different age groups. Despite these discrepancies the above studies arrived at similar conclusions as to the reliability of sleep parameters and these conclusions are discussed below.

Webb and Agnew (1969) investigated the reliability of sleep parameters in sixteen young adult subjects with an age range from 20-29 years. These subjects slept in the laboratory for four consecutive nights from 11 pm to 7 am in the morning. The data from the last three nights revealed that stage 4 and

stage 1 reliabilities were consistently higher than stage REM reliabilities. In addition, stage awake was found to have a consistently low reliability whereas the reliability of stage 3 sleep was found to be variable. The authors also found that stage 2 reliabilities were lower than those of stage 4 or stage 1 sleep but were greater than those of stage REM sleep. Thus the NREM sleep stages had consistently higher reliabilities over the three recorded nights than stage REM sleep.

Moses et al (1972) used twenty adolescent subjects with an age range from 17-21 years to determine whether sleep parameters were reliable. The subjects lived in the sleep laboratory for 11 days and were only permitted to sleep during specified hours. The data from the third and fourth nights were used to determine the reliability coefficients. Two subjects were only monitored for 390 minutes as a result of technical difficulties. The author's results resembled those of Webb and Agnew (1969), but in addition it was noted that the number of body movements and the number of sleep stage changes were consistent over the nights. Sassin and Johnson (1968) have previously reported that a relationship existed between body movements and sleep stage changes.

Webb (1974) reported the reliability coefficients of the sleep parameters of eight young adult subjects with an age range from 18-23 years. The subjects were studied under highly controlled environmental conditions for ten consecutive days. They lived in a 12x12 foot room that provided no external cues as to the time of day and they were permitted to sleep from 11 pm at night to 7 am in the morning. The results of this study resembled those obtained by Webb and Agnew (1969).

Feinberg (1974) attempted to determine the reliability of REM sleep across three consecutive nights in 38 normal subjects with an age range from 16-34 years. He permitted a greater degree of variability both within the between subjects in sleep duration. The mean within subject variability across the three nights was 49,6 minutes. REM reliability coefficients were determined for a variable sleep duration; the sleep length adjusted to each subjects shortest sleep duration and sleep duration limited to six hours and three minutes for all subjects. The author found REM sleep was consistent across nights and that the reliability coefficients were higher when the nights were equated for total sleep time than when total sleep time was permitted to vary. The reliability coefficients across the three nights for NREM sleep were consistently higher than those for REM sleep. High reliability coefficients also existed for rapid eye movement activity[1] as well as for rapid eye movement density[2] and were in accordance with the findings of de la Pena et al (1972). Clausen et al (1974) reported that rapid eye movement activity varied considerably amongst subjects but showed a consistent increase in individual subjects across four nights of study.

In summary, it thus appears that the inter-night reliability coefficients are higher for NREM sleep stages, especially stage 4 sleep, than for stage REM sleep (Webb and Agnew 1969; Webb 1974; Moses et al 1972; Clausen et al 1974; Feinberg 1974). The night to night variability of the sleep stages may be the result of inadequate scoring criteria. "We should not forget that the

[1]The number of 20 second epochs displaying rapid eye movements.

[2]Rapid eye movement activity per twenty second epoch.

stages of sleep are man made; devised by a committee based primarily upon an epiphenomenon of sleep, the EEG. These sleep stages, as defined have been useful and have provided an effective tool around which to orient our research. We should be careful not to reify these stages or to cast their rules in cement" (Johnson 1974, p.4).

3.3 The Selection of Subjects

It may seem peculiar to remunerate subjects for sleeping in the sleep laboratory. However "...although there is a small pool of interested volunteers, this pool is quite shallow, unreliable and dries up rapidly when subjects must be used over a number of successive nights or it is necessary to sharply modify their normal sleep routine" (Webb 1968, p.8).

Hartmann and Cravens (1973(a)) have reported the advantages of using the same pool of subjects in sleep research programs. The subjects become familiar with the laboratory, experimenter and experimental procedure and as a result become increasingly more cooperative and reliable.

Whitman et al (1963) reported that subjects have been noted to withhold personal dreams from the experimenter and Keith(1962) indicated that the presence of transference in the laboratory dream reports could not be ruled out. The subject may distort a dream in such a way as to avoid embarrassment. Orne (1962) has emphasised the extremes to which subjects will go in order to comply with the expectations of the experimenter.

Most sleep research programs require subjects to abstain from alcoholic beverages, hallucinogenic drugs, brief sleep periods during the day and may require subjects to take prescribed medication on specified nights. The failure to comply with these requests could result in an altered nocturnal sleep pattern.

Subjects should be selected within a narrow age range as slow wave sleep decreases with increasing age (Agnew et al 1967(a); Feinberg et al 1967; Feinberg 1969; Williams et al 1974). Female subjects should not be used in studies of extended duration due to the increase in stage REM sleep reported to occur prior to menstruation (Hartmann 1966(a); Sheldrake and Cormack 1974).

In view of the above findings, care should be exercised in the selection of subjects for sleep research programs and wherever possible subjects with previous sleep laboratory experience should be used.

3.4 The Nonindependence of Successive Nights

Several studies have reported the importance of studying drugs independently of one another in order to eliminate the carry over effects of one drug to another (Freemon 1972; Oswald 1968; Kales and Kales 1975; Kales et al 1975). If two different drugs are studied on consecutive nights, it becomes impossible to determine to what extent the drug administered on the first night would influence the one administered on the second.

3.5 The Control of Sleep Duration

It is a well documented phenomenon that stage REM sleep usually predominates in the early morning (Verdone 1968) and an extended sleep duration normally results in an increase in the number of minutes spent in stage REM sleep (Hartmann 1973(a)). The extended sleep duration may however have no influence on the percent of total sleep time spent in stage REM sleep (Hartmann 1973(a); Johnson 1975 (Personal communication). Thus a pharmacological agent which increased sleep duration without having a direct influence on specific sleep stages might be regarded as an agent which increased stage REM sleep activity if absolute values (minutes) were considered. However if stage REM sleep was expressed as a percentage of total sleep time then the agent would most likely be considered to have no effect on stage REM sleep.

In addition to expressing sleep stages as a percentage of total sleep time, several other methods such as curtailing all the records to a specified length or to the length of the shortest sleep duration have been used to control for sleep duration (Freemon 1972; Webb 1974).

3.6 The Analysis of Smaller Portions of the Night's Data

Many scientists presently involved in sleep research programs have recommended that portions of the night's sleep should be analysed in addition to the data for the entire night (Kales et al 1975; Freemon 1972; Hartmann and Cravens 1973(a)). This type of analysis is essential in determining whether sleep stage alterations occur both throughout the night as well as within

only certain portions of the night's sleep. Hartmann and Cravens (1973(a)) have suggested that data from the first three hours, second three hours, first six hours of the record as well as the data from the entire night should be scored and analysed. This system of data analysis has been carried out in the present study.

3.7 Summary

The costly nature of sleep laboratory research has often culminated in the development of research designs which have consisted of a limited number of nights and few subjects. The use of single subjects in the evaluation of the effects of drugs on sleep has not been an infrequent phenomenon in the sleep research literature (Green 1965; Knowles et al 1968; Wyatt et al 1969). Freemon (1972) reported that "...the incomparability of results from different laboratories has driven many clinical scientists to despair the entire field of sleep pharmacology and to ignore important clinical correlations" (Freemon 1972, p.96).

Many of the methodological inadequacies inherent in sleep laboratory drug evaluation studies have been reviewed in this chapter. The research designs employed in the present studies have been critically evaluated in terms of the above methodological inadequacies in sections 6.2.1, 7.2.1 and 8.2.1.

4.0 THE EFFECTS OF DRUGS ON SLEEP

4.1 Insomnia

Insomnia has usually been regarded as the inability to obtain an adequate night's sleep and has been found to be one of the most common disorders that exist in contemporary medical practice (Johns 1975). The prevalence rate of insomnia has been reported to be between five and ten percent in "healthy young adults" (Johns et al 1971), in twenty percent of patients treated at general hospitals (Johns et al 1970) and in excess of eighty percent in patients suffering from acute psychiatric illnesses (Ward 1968; Detre 1966). The incidence of insomnia increases with age and occurs more frequently in women than in men (Johns 1975).

Surveys taken in two Scottish cities revealed that about fifteen percent of the men and twenty five percent of the women over the age of 45 years, regularly took prescribed hypnotic medication. Karacan (1972) found that insomnia was evident in fourteen percent of the population of Aluchua County. A survey in an urban area of Melbourne revealed that 9,4 percent of a sample of the population reported suffering from moderate, severe or frequent insomnia. The phenomenal increment in the sale of hypnotics and tranquilisors in the United States during the last ten years has provided indirect information as to the widespread incidence of sleep disorders (U.S. Department of Health, Education and Welfare 1967).

Fenton (1975) reported that although insomnia was "...very real to the individual sufferer.....it was curiously difficult to define and evaluate clinically" (Fenton 1975, p.122). Rechtschaffen and Monroe (1969) indicated that the criteria which delineated the borderline between normality and insomnia were largely "guesswork". However insomniacs have been categorised into those individuals who experienced difficulty in falling asleep (sleep onset insomnia), those who frequently woke up during the night for extended periods of time (sleep maintenance insomnia) and those individuals who consistently awoke in the early hours of the morning (terminal insomnia) (Williams et al 1974). Various combinations of these disorders are evident in insomniacs.

Numerous factors such as noise (Johns 1975), climatic conditions (Johns 1975), high altitudes (Williams 1959), age (Feinberg and Carlson 1968, Feinberg 1969), psychiatric illness (Kupfer et al 1970(a); Takahashi and Gjessing 1972), left or right heart failure (Rohmer et al 1967), thyrotoxicosis (Oswald et al 1972), Cushing's syndrome (Krieger and Glick 1972), fever (Karacan et al 1968) and the last three months of pregnancy (Karacan et al 1969) have been clinically associated with insomnia. Insomnia thus appears to be symptomatic of a variety of physical or mental disorders and there has been considerable doubt as to whether insomnia exists as a distinct entity (Fenton 1975).

However, several sleep laboratory investigations have provided evidence in support of the existence of insomnia as an independent disturbance (Tanaka 1975; Hartmann 1967(a); Shimuzu et al 1970; Karacan et al 1971(b)). Monroe (1967) attempted to

determine whether healthy young adults who regarded themselves as good or poor sleepers would differ from one another on psychological as well as physiological dimensions. Poor sleepers had longer sleep onset latencies, more nocturnal awakenings, more stage 2 sleep and less stage REM sleep than good sleepers (Monroe 1967). They also exaggerated the time needed to fall asleep. The poor sleepers exhibited a high degree of arousal both before sleep onset and during sleep. This increased arousal was evident in higher heart rates, increased central body temperatures, and more frequent vasoconstrictions in their fingers during sleep (Monroe 1967), higher levels of adrenocortical activity during the day and night (Johns et al 1971(b)) as well as lower arousal thresholds to external stimulation during sleep (Zimmerman 1970).

Rechtschaffen and Monroe (1969) indicated that this elevation in physiological arousal in the poor sleepers should be regarded as a failure of the rest-inducing mechanisms rather than a continuation of the elevated presleep arousal levels. Support for this assumption has been provided by Hauri (1968) who found that exercise prior to sleep resulted in increased presleep levels of heart rate and rectal temperature which showed a rapid decline after sleep onset. The increased rectal temperature and heart rate in poor sleepers failed to show a similar decline after sleep onset.

Rechtschaffen and Monroe (1969) reported that psychological differences existed between good and poor sleepers: poor sleepers were more anxious, depressed and displayed more

"peculiarities of thought" than good sleepers. Williams et al (1974) reported that the differences between good and poor sleepers were remarkable since none of the poor sleepers considered themselves to be insomniacs and usually slept for four or five hours per night. They had no intention of seeking psychiatric assistance and did not take sleeping tablets.

Most of the research on poor sleep has been carried out on "healthy" subjects (Fenton 1975) and relatively few methodical studies of insomniac patients have appeared in the literature. This could be due to the absence of an adequate definition of insomnia. It has generally been established that insomniacs have an increased sleep latency, reduced total sleep time and longer latencies of arising (the time taken from awakening in the morning to getting out of bed) (Karacan et al 1971(b)), but were found to have normal quotas of stage REM sleep (Kales 1972; Snyder 1972). The night to night sleep patterns of insomniac patients revealed a great degree of variability and nights of poor sleep with reduced quantities of stage REM sleep were followed by nights of good sleep with increased quantities of stage REM sleep (Kales 1969; Karacan et al 1973(c); Fenton 1975).

Another important feature of the insomniacs sleep has been the discovery of abnormal EEG waveforms despite the occurrence of normal sleep patterns. These EEG waveforms consisted of intermingled alpha and delta activity (Hauri and Hawkins 1973; Karacan et al 1973(c)).

Insomnia should not be equated with a reduction in total sleep time because reduced sleep could represent either insufficient

sleep or a decreased need for sleep. Jones and Oswald (1968) reported that two individuals were recorded who only slept for three hours a day and yet lived healthy, content, productive lives. Insomniacs have been found to differ from these healthy short sleepers in having a high incidence of psychopathology such as mild depression, anxiety as well as psychosomatic symptomology (Fenton 1975). Several studies have found that insomniacs fear losing control over their aggressive or sexual feelings and this could be instrumental in their difficulty in falling asleep (Kales 1972; Hartmann 1973(b)).

Hypnotic and sedative drugs have been regarded as the most expedient method for the treatment of insomnia in contemporary culture and their prescription has increased dramatically (Karacan and Williams 1971; Oswald 1968). It has generally been established that these drugs have undesirable side effects such as drug dependence, self poisoning, changes in perceptual motor performance as well as mood changes (Oswald and Priest 1965; Hartmann 1972). Several studies have indicated that the chronic use of hypnotic drugs should be avoided because of their relative ineffectiveness and the danger of both physiological and psychological dependence (Kales and Kales 1973; Johns 1975). Most hypnotic drugs have been reported to suppress stage REM sleep and this suppression has been associated with a reduction in the intensity and vividness of REM mentation (Carrol et al 1969; Kales et al 1969(a)(b)). "... One thing we can declare, though, with incontrovertible certitude, is that the REM rebound following withdrawal of the chronic use of a drug is one of the commonest causes of sleep disturbance" (Freemon 1972, p.127).

Drug withdrawal insomnia is associated with a difficulty in falling asleep, an increased vividness in REM mentation as well as the occurrence of nightmares (Kales et al 1968(a)(b), 1969(a)(b).

Several studies have advocated non-pharmacological treatments for insomnia such as hypnosis (Hanley 1965; Fry 1963; Tiller 1967; Todd and Kelley 1970), muscle relaxation training (Kahn et al 1968; Jacobson 1938; Paul 1969; Wolpe 1969; Hinkle and Lutker 1972; Borkovec and Fowles 1973; Borkovec et al 1973; Weil and Goldfried 1973; French and Tupin 1974; Gershman and Clouser 1974), systematic desensitisation (Geer and Katkin 1966; Evans and Bond 1969; Borkovec et al 1973; Gershman and Clouser 1974), classical conditioning (Poser et al 1965; Evans and Bond 1969), biofeedback (Raskin et al 1973; Budzynski 1973), electrosleep[1] (Rosenthal and Wulfsohn 1970; Rosenthal 1972; Feighner et al 1973; Weiss 1973; Hearst et al 1974; Frankel et al 1973; Frankel 1974) as well as expectation[2] and attribution[3] (Nicholis and Silvestri 1967; Zaroslinski et al 1969; Storms and Nisbett 1970; Davison et al 1973).

In view of the many undesirable side effects produced by the administration of hypnotics, these non-pharmacological methods should play an ever increasing role in the overall management of insomnia.

[1] The transcranial application of a low intensity electrical current.

[2] The powerful effects of suggestion, therapist expectation and placebo administration (Montgomery et al 1975).

[3] Attribution "refers to the beliefs the subject has about the causes of his current physiological and psychological state" (Montgomery et al 1975, p.96).

4.2 The Effects of Placebo Administration on Sleep Parameters

Within the realm of clinical psychology and psychopharmacology the placebo effect has remained a poorly explained phenomenon and attempts at advancing a feasible rationale have been notably few (Rachman and Philips 1975).

The placebo has been defined as "...a preparation containing no medicine, employed with or without some ritual, but always with the suggestion or implication of its power or helpful properties", and the placebo reaction as "...the physiologic and psychologic reaction to the administration and acceptance of the placebo, this reaction can be positive and beneficial or it can be negative and detrimental" (Fischer and Dlin 1956, p.509; English and English 1958, p.393).

The administration of placebo has been found to be effective in the treatment of a variety of physiological and behavioural disorders such as headaches (Beecher 1955), seasickness (Beecher 1955), severe post-operative wound pain (Keats and Beecher 1950; Beecher 1955), anxiety and tension (Wolf and Pinsky 1954) and pain tolerance (Gelfland et al 1963), but as yet there has been little investigation into the direct effects of placebo on sleep patterns (Hartmann and Cravens 1973(a); Adam et al 1975). "The placebo effect is a much quoted but less often investigated assumption in sleep studies"(Adam et al 1975, p.84).

Placebo administration, in general, has been reported to produce positive as well as negative effects (Shader and Di Mascio 1970). Beecher (1955) reported that the administration of placebo

resulted in the occurrence of side-effects such as dry mouth, nausea, sensations of heaviness, headache, and difficulty in concentrating. Such findings have resulted in the widespread tendency to compare a drug to a similar appearing placebo whenever an attempt has been made to determine the pharmacological effect of the drug in contrast to its total effect on the subject (Hartmann and Cravens 1973(a)). The total effect of a drug has been reported to be its pharmacological effect as well as the placebo[1] effect (Stroebel 1972).

Davis and Hartmann (1973(a)(b)) investigated the effects of the short-term administration of placebo on the sleep patterns of male subjects with an age range of 21-35 years as well as female subjects with an age range of 45-60 years. The male subjects spent significantly more time awake whereas the female subjects spent significantly more time in stage 3 and stage slow wave sleep during placebo administration. Hartmann and Cravens (1973(a)) suggested that the discrepancy in the responses of male and female subjects to placebo administration should be evaluated in terms of the subjects' expectations of the medication. They indicated that the older women may have had a positive expectation that any medication evaluated in a sleep laboratory would have a beneficial effect whereas young male subjects may have regarded their normal sleep as adequate and that medication would do little to improve this.

Zung (1973) reported that the short-term administration of placebo resulted in an increase in stage 4 sleep and a decrease in stage REM sleep in five healthy subjects. These findings

[1]The expectation of the subjects (Sternbach 1966) and/or the experimenter (Rosenthal 1965).

should be interpreted with caution as a result of methodological inadequacies in research design such as the absence of an initial adaptation period (section 3.1.1) and the nonindependence of successive nights (section 3.4). Hartmann and Cravens (1973(a) found that the long-term administration and withdrawal of placebo resulted in a significant increase in stage REM sleep in normal young adult subjects.

Several more recent studies, however, have reported that the short-term administration of placebo exerted no significant effect on sleep stages, quality of sleep or mood (Adam et al 1975, 1976; Touyz et al 1975(b).

The evidence appears to favour the conclusion that the short-term administration of placebo does not markedly alter the sleep patterns of normal adult subjects (Adam et al 1975, 1976; Touyz et al 1975(b)), but Nicolis and Silvestri (1967) have indicated that this conclusion may not be applicable to insomniac subjects whose sleep improved under placebo administration. Additional research is also required to confirm the findings of Hartmann and Cravens (1973(a)) that the long-term administration and withdrawal of placebo resulted in a significant increase in stage REM sleep.

4.3 Sleep and Hypnotic Drugs

It has generally been established that many hypnotic drugs suppress REM sleep (Oswald 1968; King 1972; Freemon 1972), cause death when taken in overdose (Johns 1975), produce dependence (Kales and Kales 1973) and become relatively ineffective in the treatment of insomnia after chronic administration (Johns

1975). The abrupt withdrawal of an hypnotic after continuous administration may result in a drug withdrawal insomnia (Kales and Kales 1973). "It is ironic that insomnia should be caused frequently by the very drugs which have been prescribed to treat the sympton" (Johns 1975, p.464).

The recent advances in psychopharmacological sleep research have now made it possible for a more scientific approach to be adopted in the prescription of hypnotic agents in the treatment of sleep disturbance. The physician, provided with the information as to the exact problem of his patient, will now be able to prescribe a drug which has been scientifically shown to alleviate the specific sleep deficiency (Williams et al 1974). The trial and error method of prescribing hypnotic medication may soon be a phenomenon of the past.

4.3.1 Barbiturates

The barbiturates, which are powerful hypnotic agents (Sapeika 1972), have been frequently used and abused (Freemon 1972). Friend (1969) reported that secobarbital and pentobarbital were among the twenty most prescribed medications in the United States. The barbiturates are the most common chemical used to induce death by suicide (Oliver and Hetzel 1975; Berger 1967).

Sharpless (1970) reported that the barbiturates were rapidly absorbed from the gastrointestinal tract and were distributed throughout the body, having a profound depressant effect upon the entire central nervous system. Johns (1975) noted that the barbiturates were metabolised at an increased rate by the hepatic

microsomal enzymes after only a few days of administration and it has been suggested that this increased rate of metabolism has been responsible for the rapid development of tolerance (Remmer 1969; Sharpless 1970).

The barbiturates reduce the latency to sleep onset as well as the frequency and duration of nocturnal awakenings (Johns 1975). It has generally been established that barbiturate administration resulted in the suppression of stage REM sleep (Baekeland 1967; Hartmann 1968(b); Kales et al 1968(b), 1970(e); Oswald 1970(b); Oswald and Priest 1965; Evans and Lewis 1968; Haider 1969; Haider and Oswald 1971; Davison et al 1970). This reduction in stage REM sleep has been found on occasion to return to baseline levels (Evans and Lewis 1968; Kay et al 1972). The abrupt withdrawal of barbiturates after chronic administration results in a REM rebound (drug withdrawal insomnia) characterised by frequent nocturnal awakenings as a result of disturbing dreams and nightmares (Oswald and Priest 1965). Carroll et al (1969) found that the barbiturates influenced dream content making it more conceptual less perceptual, more "thought-like" and less "dream-like". Kales et al (1974) reported that the barbiturates have often been continued to be taken to avoid the symptoms produced by the drug withdrawal insomnia, but the resultant sleep was found to be no better than that during the preadministration period. Whitlock (1970) found that the dosage was often increased in an attempt to improve sleep and resulted in intoxication with tremor and confusion during the day and insomnia at night. Oswald and Priest (1965) have shown that it takes up to five weeks to "...escape the sleeping pill habit" after chronic administration (Oswald and Priest 1965, p.1093).

The barbiturates produce hangover effects on the day following administration (Johns 1975) as well as to impair performance tasks (Malpas et al 1974). Johns (1975) concluded that in view of the many side-effects produced by the administration of barbiturates they "...have ceased to have a legitimate role in the treatment of insomnia" (Johns 1975, p.467).

4.3.2 Benzodiazepines

The benzodiazepam derivative nitrazepam (5-10mg/night) is extensively used as an hypnotic in Australasia, Europe and the United Kingdom, whereas a related drug, flurazepam (15-30mg/night) has been extensively used in the United States (Johns 1975; Taws et al 1975). These drugs are as equally effective as the barbiturates (Haider 1968; Morgan et al 1970; Haider and Oswald 1971; Mathew et al 1969; Malpas et al 1970; Davies and Levine 1967; Fisher and Gal 1969; Bordeleau et al 1970; le Riche et al 1966; Jick et al 1966; Hartmann 1968(b); Andersen et al 1969) and non-barbiturates such as chloral hydrate (Jick 1967; Kales et al 1970(a)(b)),glutethimide (Jick 1967; Kales et al 1970(e))and methaqualone (Kales et al 1970(d)).

Low therapeutic doses of nitrazepam (5mg) and flurazepam (15mg) had an insignificant effect on stage 4, stage slow wave or stage REM sleep (Gastaut et al 1967; Johns and Masterton 1974). The administration of higher doses of these drugs, however, had a much more consistent suppressant effect on stage 4 than on stage REM sleep (Kales and Scharf 1973; Dement et al 1973(b); Kales et al 1970(d); Vogel et al 1972(b); Oswald et al 1973; Hartmann 1968(b)). Kales et al (1970(d)) reported that flurazepam suppressed stage slow wave sleep to a greater extent

than did nitrazepam whereas nitrazepam reduced stage REM sleep to a greater extent than did flurazepam. The withdrawal of nitrazepam after continuous administration resulted in a REM rebound which persisted for several weeks (Oswald and Priest 1965; Haider and Oswald 1971).

The benzadiazepines have distinct advantages over other traditional sleep inducing drugs in that they have been found to be innocuous when taken in suicidal or accidental overdose (Barraclough 1974; Mathew et al 1969), and have a low dependence lability (Isbell and Chrusciel 1970; Greenblatt and Shader 1974). Flurazepam is unique in that its hypnotic efficacy has been found to persist after several weeks of administration (Kales et al 1970(d); Greenblatt and Shader 1974). The benzodiazepines, however, produce hangover effects (Greenblatt and Shader 1974) as well as persistent psychomotor impairment (Malpas et al 1970; Bond and Lader 1972(a)(b); Salkind and Silverstone 1975)) but these effects are reportedly of a lesser degree than those of the barbiturates (Bond and Lader 1972(a)(b); Johns 1975).

In view of the above findings, it has been recommended that nitrazepam or flurazepam should be prescribed in preference to other hypnotics in situations where sleep inducing medication is indicated (Greenblatt and Shader 1974; Johns 1975).

4.3.3 Non-Barbiturate Hypnotics

Chloral hydrate is one of the oldest hypnotic agents and has been extensively used throughout the world (Hartmann and Cravens 1973(e); Johns 1975). It is an inexpensive and efficient

hypnotic agent for the short-term treatment of insomnia (Sapeika 1972; Johns 1975). Chloral hydrate has an unpleasant taste with a tendency to irritate the upper gastrointestinal tract and should be taken with milk or brandy (Johns 1975). It is metabolised to trichloroethanol which exerts the potent neural suppressant effect (Hartmann and Cravens 1973(e); Sapeika 1972; Johns 1975; Marshall and Owens 1954; Imboden and Lasagna 1956; Goodman and Gillman 1970). It has generally been established that the administration of chloral hydrate (500mg-1000mg) has no significant effect on sleep stages (Kales et al 1969(b); 1970(d); Hartmann and Cravens 1973(e). Chloral hydrate loses its hypnotic effect during long-term administration in insomniac subjects (Kales et al 1970(d)). Bare and Pepino (1961) found that chloral hydrate produced minimal hangover effects.

Glutethimide is a sedative and hypnotic agent (Sapeika 1972). The administration of glutethimide (500mg-1gm) results in a decrease in stage REM sleep (Rubin et al 1969; Williams and Agnew 1969; Kales et al 1969, 1970(a)(e)) and its withdrawal results in a REM rebound (Kales et al 1969, 1970(a)(e)). Johns (1975) reported that glutethimide has no advantages over the barbiturates either in its short-term or long-term use as it produces dependence and is toxic in overdose (Sapeika 1972; Kales et al 1970(b); Goldstein et al 1971).

Methyprylone is related chemically to glutethimide (Johns 1975). The administration of 300mg of methyprylone resulted in a decrement of stage REM sleep and a REM rebound occurred on withdrawal (Kales et al 1969(b), 1970(e)). Methyprylone produces dependence and is toxic in overdose (Rickels and Bass 1963; Kales et al (1970(b)).

Methaqualone, a synthetic non-barbiturate hypnotic, is a quinazolone derivative (Sapeika 1972). The administration of methaqualone has no effect on sleep stages (Williams and Agnew 1969; Davison et al 1970; Evans and Ogunremi 1970; Kales et al 1970(d)). Dunlop (1970) reported that non-fatal side-effects occur with methaqualone administration.

Carbromal is a brominated monoureide and has been regarded as a mild and relatively safe hypnotic (Johns 1975). Sharpless (1970) has warned that care should be exercised in the long-term administration of carbromal as its ingestion results in the release of free bromide which could cause bromism. As far as it could be ascertained, research has yet to be carried out to determine the effects of carbromal on sleep patterns.

4.3.4 Antidepressants

The tricyclic compounds and the monoamine oxidase inhibitors have been found to have a marked effect on the sleep patterns of normal subjects as well as in patients suffering from depression (Wyatt et al 1969, 1971(a); Zung 1969; Akindele et al 1970; Hartmann and Cravens 1973(c)). The tricyclic antidepressants imipramine, desipramine, clomipramine and amitriptyline increase total sleep time and reduce body movement activity (Johns 1975). It has generally been established, however, that these drugs have an initial inhibitory effect on stage REM sleep which results in a REM rebound on withdrawal (Hartmann and Cravens 1973(c); Toyoda 1964; Ritvo et al 1967; Chernik et al 1973(b)). The administration of iprindole and trimipramine however, did not inhibit stage REM sleep (Baxter and Glukman (1969).

The monoamine oxidase inhibitors suppress stage REM sleep within a few days of chronic administration and this suppression of stage REM sleep persists for the entire duration of administration (Okuma et al 1974; Johns 1975; Wyatt et al 1969; Cramer and Kuhlo 1967; Ryba et al 1966). Wyatt et al (1971(a)) indicated that a marked rebound of stage REM sleep occurs upon the cessation of administration of these drugs.

4.3.5 Phenothiazines

The phenothiazine drugs such as chlorpromazine have seldomly been prescribed for the treatment of insomnia in the absence of psychosis (Johns 1975). Hartmann and Cravens (1973(d)) reported that chlorpromazine was the most extensively used major tranquilisor in the world today.

Several studies have investigated the effects of the administration of chlorpromazine and related phenothiazines on the sleep patterns of normal volunteer subjects as well as of psychiatric patients (Toyoda 1964; Lester and Guerrero-Figueroa 1966; Feinberg et al 1969; Lewis and Evans 1969; Sagales et al 1969; Lester et al 1971; Kupfer et al 1971). The overall effect of chlorpromazine administration on sleep parameters was found to depend on the dosage administered. It has been established that low doses (25mg) increase stage REM activity (Lewis and Evans 1969), high doses (200mg) inhibit stage REM activity (Feinberg et al 1969) but increase total sleep time (Hartmann and Cravens 1973(d)) whereas intermediate doses (50mg) have no effect on sleep parameters (Hartmann and Cravens 1973(d)).

Research has yet to be carried out on other phenothiazines such as promethazine and trimeprazine to ascertain whether they have an effect on sleep parameters (Johns 1975).

4.3.6 Alcohol

Alcohol is the most frequently used "psychoactive" agent in contemporary Western culture (Freemon 1972). It increases total sleep time (Freemon 1972) and decreases stage REM activity (Gresham et al 1963; Yules et al 1967; Knowles et al 1968; Maclean and Cairns 1975; Greenberg and Pearlman 1967). The withdrawal of alcohol after chronic administration results in a marked rebound of stage REM sleep (Yules et al 1967; Knowles et al 1968; Gross et al 1966; Johnson et al 1970).

It has generally been established that the REM rebound which occurs following the withdrawal of alcohol, is more profound than following the withdrawal of barbiturates or any other drug (Freemon 1972). The hallucinatory experiences associated with delirium tremens[1] may be related to the mechanisms underlying the REM state.

4.3.7 Miscellaneous Drugs

The amphetamines decrease stage REM sleep as well as total sleep time (Rechtschaffen and Maron 1964; Baekeland 1967; Lewis 1970). It has been established that the withdrawal of amphetamines after chronic administration results in a rebound of stage REM sleep (Oswald 1969(a), Lewis 1970).

[1] delirium tremens is an acute delirium precipitated by alcohol and is characterised by great anxiety and tremors.

Lithium carbonate, used to treat patients suffering from depression, has also been found to reduce stage REM sleep (Kupfer et al 1970(c); Chernik and Mendels 1972, 1974; Mendels and Chernik 1973) and to increase slow wave sleep (Kupfer et al 1970(c); Chernik et al 1973(a); Chernik and Mendels 1974).

Tetrahydrocannabinol, the active ingredient of marihuana, suppresses stage REM sleep (Pivik et al 1972; Moreton and Davis 1973; Freemon 1974; Feinberg et al 1975).

On the other hand, a variety of drugs enhance stage REM sleep: these include reserpine (Hartmann 1966(b); Tissot 1965; Hoffman and Domino 1969; Coulter et al 1971; Hartmann and Cravens 1973(b)), lysergic acid diethylamide (Muzio et al 1966; Green 1965, 1969), tryptophan and 5-hydroxytryptophan (Evans and Oswald 1966; Oswald et al 1966; Hartmann 1967(c); Hartmann et al 1971(b); Wyatt et al 1971(b)).

4.3.8 Clozapine

Clozapine (leponex), a new and powerful psychotropic agent, became available in South Africa in 1974 (Hemphill et al 1974) (section 5.2.4). Recent research has indicated that clozapine may have sleep inducing properties (Hemphill et al 1974, 1975; Ruch et al 1976) but as yet only one investigation on the effects of clozapine on sleep patterns has been carried out (Blum and Girke 1974). The authors reported that the administration of clozapine resulted in a phenomenal increase in stage REM sleep in four neurotic and one psychotic patient. The reported increase in stage REM sleep was as high as 85% of total sleep

time. This result should however be interpreted with extreme caution as many methodological inadequacies are evident in the research design. These included the absence of an adaptation night; the administration of a variable dose of clozapine with a range of more than 300mg; the criteria as to what constituted stage REM sleep were not specified, but it was reported that REM sleep occurred at sleep onset and that muscle tension was frequently recorded; REM awakenings were effected but no mention was made on which night or nights this was done; no statistical analyses were attempted and the ages of the subjects were not specified. In view of the above findings, the remarkable increase in stage REM sleep reported appears to be questionable.

4.4 Summary and Conclusions

Insomnia is one of the most prevalent disorders encountered in general medicine today (Johns 1975) and attempts at advancing a feasible definition have largely been unsuccessful. However, insomniacs have been categorised into those individuals who experience difficulty in falling asleep (sleep onset insomnia), those who frequently wake up during the night for extended periods of time (sleep maintenance insomnia) and those individuals who consistently awake in the early morning (terminal insomnia). Williams et al (1974) reported that various combinations of these disorders were evident in insomniacs.

It has generally been established that insomniacs have an increased sleep latency, reduced total sleep time and have longer latencies of arising in the morning than normal subjects. Insomniacs were however found to have normal quotas of stage REM

sleep (Kales 1969(a); Kales 1972; Snyder 1972). The night to night sleep patterns were found to have a high degree of variability and nights of poor sleep with reduced quantities of stage REM sleep were followed by nights of good sleep with increased quantities of stage REM sleep (Kales 1969(a); Karacan et al 1973(c); Fenton 1975). Abnormal EEG waveforms comprising intermingled alpha and delta activity have been reported to occur in insomniac subjects (Hauri and Hawkins 1973; Karacan et al 1973(c)).

Hypnotic and sedative drugs have been regarded as the most expedient method of treatment of insomnia despite the fact that non-pharmacological treatments such as hypnosis, muscle relaxation, systematic desensitisation, biofeedback, classical conditioning, electrosleep as well as the powerful effects of suggestion and expectation have been advocated (section 4.1). Nicolis and Silvestri (1967) have indicated that placebo administration may enhance the sleep of insomniac patients(section 4.2).

Thus, sleep laboratory investigations of the effects of hypnotic drugs on sleep patterns have indicated that a "...potential and largely unrecognised danger lies in their use" (Kales and Kales 1970, p.2232). The intensely aggravating reactions associated with the withdrawal of many hypnotics after chronic administration have led to drug dependence (Kales and Kales 1969; Oswald and Priest 1965). Kales et al (1969(b)) proposed a number of recommendations for the treatment of drug dependent patients. The authors advocated that the drug should be withdrawn gradually, that the patient should be informed that psychological disturbances such as increased dreaming and nightmares may occur and

that these would be of physiological rather than a psychological origin, and finally where the total withdrawal of a drug was not feasible, the drug should be replaced by an hypnotic which has been found not to suppress stage REM sleep.

Freemon (1972) reported that the indiscriminate prescription of sleep inducing medication was the most "...common error in medicine today" (Freemon 1972, p.128).

Recent research in the United States has indicated that physicians and patients may be adopting a more responsible attitude to the use of hypnotic drugs and that "...in the great majority of cases the drugs are used for a relatively short period of time"... and "...of all adults in the general population who reported a major sleep problem in a recent calender year, only a small minority were treated with hypnotic drugs". (Balter and Bauer 1975, p.291).

The evidence favours the conclusion that hypnotic agents should be thoroughly investigated <u>prior</u> to being placed on the medical market. The investigations should include the following: the effects of the drug on sleep parameters, the short and long-term effectiveness of the drug as well as the side-effects produced.

5.0 METHODOLOGY

5.1 Subjects

The subjects in all phases of the present study comprised 20 paid student volunteers drawn from approximately the same socio-economic and educational background. They were all English speaking, registered students at the University of Cape Town and ranged in age from 18-24 years with a mean age of 20,65 years. Prior to the commencement of the study, subjects completed legal consent forms, which was a Groote Schuur Hospital prerequisite for research on human subjects, a questionnaire concerning their normal sleep and drug taking habits and an Eysenck Personality Inventory (EPI) (Form A). Subjects were also required to undergo a medical examination and in no instance was any obvious physical or mental abnormality found. The Neuroticism score on the EPI revealed a mean of 7,7 with a range of 4 - 16 whereas the Extroversion score was found to have a mean of 12,9 and a range of from 4 - 19. The mean Neuroticism and Extroversion scores thus fell well within the normal range. (Eysenck and Eysenck 1964).

The questionnaire concerning sleep and drug habits indicated that subjects normally had a mean sleep duration of 7,68 hours with a range of 7 - 9 hours per night, kept their sleep habits constant and were not habitual drug takers. Subjects were assured that they were free to withdraw from the study if they so desired; however the costly nature of sleep research with respect to time and money was pointed out to them. Subjects were paid on the completion of each investigation. The subjects were distributed across three separate investigations and some subjects took part in more than one investigation.

Subjects were permitted to take part in more than one investigation as the three investigations were carried out 3 months apart thus avoiding any possible contaminating effects of a drug upon subsequent drug periods (Hartmann and Cravens 1973(a)). The advantages of using the same pool of subjects clearly outweighed the disadvantages. The experimenter became familiar with subjects through repeated laboratory sessions and interviews. Likewise the subjects became familiar with the laboratory and experimental procedure and as a result became increasingly more cooperative and reliable (Hartmann and Cravens 1973(a)). As far as could be ascertained, there was no dishonesty regarding the taking of medication (i.e. subjects took the coded tablet on the required night). In no instance did any subject fail to arrive at the laboratory on a prescribed recording night.

5.1.1 Short-Term Clozapine Investigation

This group originally consisted of 15 subjects - 11 males and 4 females. The first male subject constituted a pilot study to test the intended dose of clozapine of 50mg per night. This dose was found to be unsuitable and was altered to 25mg per night. The initial intended dose was too strong to be of use as an hypnotic as it resulted in the subject sleeping for up to 14 hours. As a result, the data obtained for the above subject were excluded from the study. The remaining 14 subjects, 10 males and 4 females with a mean age of 21,20 years and an age range of from 18-24 years participated in this investigation. The female subjects commenced the investigation on the fourth day of their menstrual cycles in order to control for the increase in REM sleep reported to occur prior to menstruation (Hartmann 1966(a), Sheldrake and Cormack 1974).

The subjects were told that the aim of the study was to investigate the possible physiological and psychological concomitants of a new sleeping tablet. The majority of subjects were psychology students and were aware that placebos are often used in conjunction with sleep medication in drug trials of this nature.

Subjects were asked to abstain from all medications (with the exception of those prescribed by the experimenter), cannabis, hallucinogens, alcohol and caffeine (after midday) two days prior to and for the duration of the study. Subjects were not permitted to sleep during the day for the duration of the study.

All the subjects participated on a volunteer basis and were paid R45 on the completion of the investigation.

5.1.2 Long-Term Clozapine Investigation

This group comprised 6 male subjects with a mean age of 19,67 years and an age range of from 19-22 years. The duration of this investigation required the exclusion of female subjects because of the increase in REM sleep reported to occur prior to menstruation (Hartmann 1966(a); Sheldrake and Cormack 1974). Prior to the commencement of this investigation, blood was drawn by venepuncture from each subject and analysed by the Department of Haematology at Groote Schuur Hospital. This procedure was repeated on the completion of the investigation.

Subjects were asked to abstain from alcohol, cannabis, hallucinogens and caffeine (after midday) on the days of scheduled laboratory recordings. They were told that the aim of this study was

to investigate the possible psychological, physiological and biochemical concomitants of a new sleeping tablet over an extended period of time. The subjects were each paid R85 on the completion of the investigation.

5.1.3 REM Dream Recall Investigation

This group comprised 6 male subjects with a mean age of 19,83 years and an age range of from 19-22 years. Prior to the commencement of the study, subjects completed the Rotter Incomplete Sentences Blank Test in addition to the EPI and were found to have a mean score of 122,67 and a range of from 115 to 135[1]. The Rotter ISB provided additional information as to the normality of the subjects as studies have indicated the REM dream content in psychopathological states such as schizophrenia and depression differ from those of normal subjects (Kramer 1970). The subjects were told that the aim of the study was to investigate the possible effects of a new sleeping tablet on dream content. The subjects were all volunteers and were paid R20 on the completion of the investigation.

5.2 Apparatus

5.2.1 Sleep Laboratory

Subjects slept in a private, sound attenuated, temperature regulated sleep laboratory. The temperature was maintained at 74°F and approximately 50% humidity, thus approaching ideal sleep conditions (Holdstock and Verschoor 1974). A buzzer was provided with which the subject could call the experimenter monitoring the

[1] Rotter and Rafferty (1950) reported that "...a cutting score of 135 provided a very efficient separation of adjusted and maladjusted students" (Rotter and Rafferty 1950, p.10).

Figure 1 : The Sleep Laboratory.

dynograph in an adjacent electrically shielded monitoring room.

5.2.2 Electrophysiological Apparatus

A Beckman type R Dynograph multipurpose laboratory recorder equipped to record four channels of information was employed. It included 4 Type 481 B Preamplifiers, 2 Type 482 M8 Amplifiers and 4 Type AN 3057-6 Amphenol size 14 leads. In addition, it incorporated a vertical (paper) chart drive with 8 possible chart speeds ranging from 0,1 to 25cm per second. The write out medium consisted of ink on prefolded Beckman No. 344-206569 rectilinear paper.

Beckman silver chloride disc electrodes were used to monitor the EEG and EOG. They were attached to the scalp and outer canthi of the eyes by means of collodion adhesive. Collodion is a quick drying adhesive which can be easily dissolved with acetone. DB electrode paste was used as a conducting paste.

A Philips PM 3200 single beam oscilloscope with a frequency range of 0-10 MHz provided an additional monitor of the ongoing EEG activity. This monitor, as a result of the negligible electron mass, had the distinct advantage over the paper printout of being a more sensitive index of EEG activity (Doxey 1975). This was particularly useful in identifying background interference at the commencement of the recording which did not appear on the paper record.

5.2.3 Tape Recording Equipment

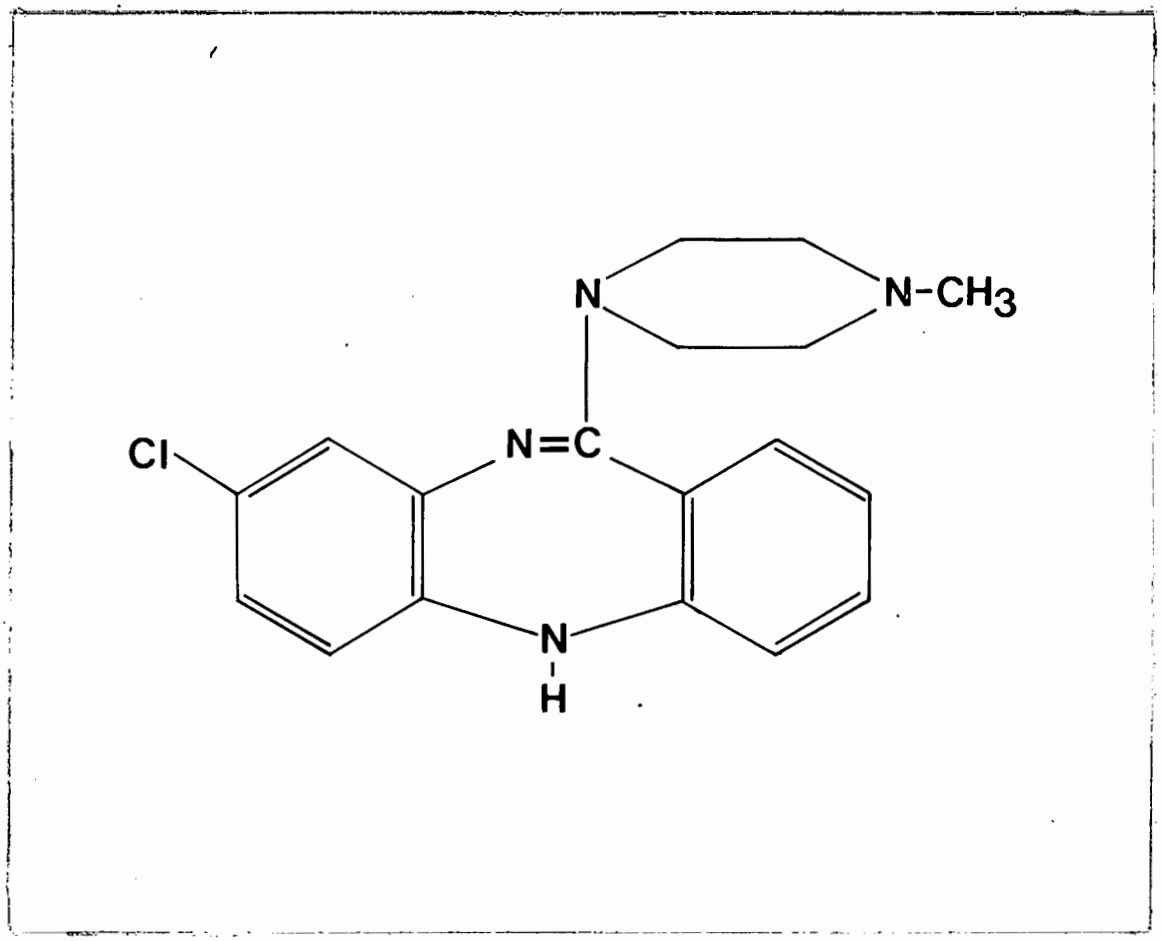
A JVC Type 1610 V Novico portable cassette taperecorder with a built in electret-condensor microphone was used to record the subjects' dreams.

5.2.4 Pharmacological Agents

Clozapine (Leponex): Clozapine differs in chemical structure from the major conventional tranquilisors such as the phenothiazines, thioxanthenes and butyrophenone derivatives. It is a tricyclic compound with an asymmetric 7-member central ring and is the first substance with a halogen in position 8 instead of position 2 (Figure 2).

Clozapine has been found to be void of cataleptogenic activity (Poldinger and Stille 1968) and is thus able to be clearly differentiated from antipsychotic agents which preferentially affect the extrapyramidal system. The extrapyramidal effects of known major tranquilisors are closely associated with their antipsychotic effects (Stille et al 1971).

Major tranquilisors increase the turnover of dopamine in the brain (Corrodi et al 1967; Roos 1965; Vogt 1965) and this increase has usually been associated with an increase in the homovanillic acid (hva) concentration in the corpus striatum (Anden et al 1963; Da Prada et al 1966; Laverty and Sharman 1965; Sharman 1966). Clozapine however, has not been found to cause an increase in the hva concentration of the corpus striatum (Stille et al 1971).



8-chloro-11-(4 methyl - 1-piperazinyl) - 5H-dibenzo (b,e) (1,4) diazepine.

CLOZAPINE

Figure 2 The biochemical structure of clozapine showing the halogen in position 8.

Clozapine has been characterised by the lack of extrapyramidal side effects, decreased vigilance, increased muscular relaxation and its strong dampening action of peripheral autonomic functions. (Stille et al 1971). Clinically clozapine can be regarded as an antipsychotic agent (Berzewski et al 1969; De Maio 1968; Gross and Langner 1966) and has been ranked among the major tranquilisors (Stille et al 1971). In the series of major tranquilisors ranging from haloperidol to thioridazine, clozapine has been placed below thioridazine (Table 3) because of the absence of activities such as cataleptogenesis and apomorphine antagonism.

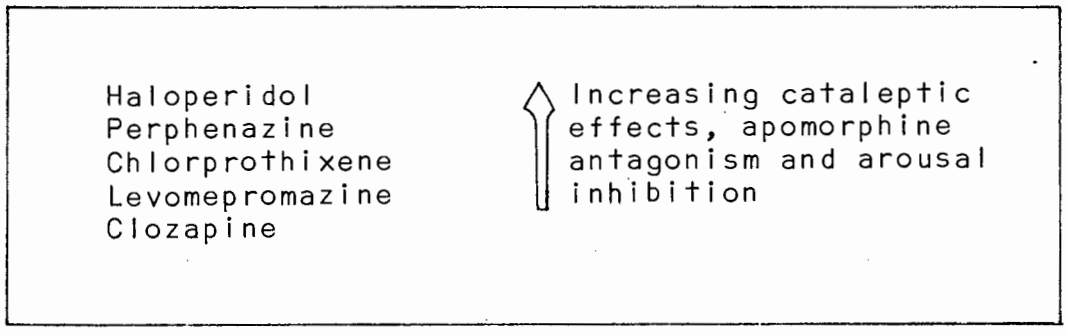


Table 3 Pharmacological classification of some major tranquilisors according to cataleptic effect, apomorphine antagonism and arousal inhibition (Stille et al 1971).

Clozapine Placebo: Clozapine placebo was manufactured by Sandoz Drug Company and was used in the long-term clozapine investigation. The tablet was identical in size, colour and taste to the clozapine tablets. The constituents of clozapine placebo are presented in Table 4.

Lactose Pulv.	134,31145
Corn Starch	6,4
Aerosil 200 (Degussa)	1,06
Talcum	5,7
Magnesium Stearate	1,06
Collidon 30 (BASF)	10,4
Ariavit Yellow 2.85 (Tartrazin) Water Soluble (Anstead)	2,85 0,00820
Ariavit Blue (Indigotin) Water soluble (Sandoz)	0,00035
Paraffin-Oil Sub Liquid	1,06

Table 4 The constituents of clozapine placebo in milligrams.

Ascorbic Acid: Ascorbic acid was used as a placebo in the short-term clozapine investigation as well as in the REM dream recall investigation. Ascorbic acid (vitamin C) possesses an asymmetrical C atom and is therefore optically active. L-ascorbic acid and L-dehydro ascorbic acid are the only known naturally occurring biologically active substances, the D component being inert (Harper 1971). Pure ascorbic acid is a white crystalline solid freely soluble in water. It is a powerful reducing agent giving up two hydrogen atoms to become dehydro-ascorbic acid. This oxidation is reversible in the body. It is present in all body fluids and tissues (Bell et al 1968; Harper 1971).

5.2.5 Psychological Test Apparatus

The Taylor Manifest Anxiety Scale (Taylor 1953) gives an indication of the subjects habitual level of general or residual anxiety and consists of 50 items thought to be indicative of "manifest anxiety" (Appendix I). The 50 items were selected from the MMPI and 175 "buffer items" were added. The normative data on the test, which is presented under the title of

"Biographical Inventory" were obtained on a sample of 229 psychology students. The mean score was about 12. Taylor (1953) reported a test - retest reliability of 0,88 when a group of 179 subjects were retested after a period of 4 weeks had elapsed. Anastasi (1961) reported that the validity of the above scale was sound and that favourable evidence had been obtained from studies that compared neurotic and psychotic patients with normal groups.

The Eysenck Personality Inventory (Eysenck and Eysenck 1964) measures two major dimensions of personality - extraversion and neuroticism. The EPI furthermore consists of two parallel forms thus making it possible to retest subjects after an experimental treatment without interference from memory factors (Form A and Form B). The means of the combined forms of the EPI obtained on a normal standardisation sample of 2000 subjects were as follows: approximately 27,5 for the "E" dimension and 9,1 for the "N" dimension. Eysenck and Eysenck (1964) have reported test retest reliabilities in the region of 0,84(N) and 0,94(E) for the combined forms and between 0,80(N) and 0,97(E) for separate forms of the test over a period of a year. The split half reliability of the combined scales was reported to be in the region of 0,85 to 0,95. Eysenck (1962) and Eysenck and Eysenck (1963) have shown on numerous occasions that when independent judges are asked to rate subjects in terms of "introversion" and "extroversion" or stability or lability, their ratings show a clear and predictable correspondence with the subjects' EPI scores.

The Activation Deactivation Adjective Check list (AD-ACL) (Thayer 1967, 1970 and 1971) measures transient levels of mood and consists of 21 activation - descriptive adjectives which were

integrated with 27 nonactivation mood descriptive adjectives previously used by Nowlis (1965) (Appendix 2). The non-activation adjectives were incorporated as a means of disguising the aims of the test. Subjects were asked to describe their present feelings with their first response to each word. A four point scale, with symbols indicating definitely feel (vv), feels slightly (v) cannot decide (?) and definitely do not feel (no) were used by the subjects as a rating scale for each adjective. The AD-ACL has been factor analysed (Thayer 1967, 1970,1971) and yielded four orthogonal dimensions; General Activation (peppy, energetic, vigorous, lively, activated, full of pep, active); High Activation (jittery, intense, stirred up, fearful, clutched up); Deactivation Sleep (sleepy, tired, drowsy); and General Deactivation (placid, leisurely, calm, at rest, still, quiet, quiescent). General Activation, High Activation and Deactivation Sleep have been found to be relatively stable factor analytic dimensions whereas General Deactivation has been found to be relatively unstable (Thayer 1971). The AD-ACL is purported to be reliable and that the mood factors are valid and sensitive indicators of transient levels of activation (Thayer 1967, 1970, 1971).

The Rotter Incomplete Sentences Blank (ISB)(College Form) method of sentence completion is a semi-structured projective technique in which the subject is asked to finish a sentence for which the first word or words are supplied. It is assumed that the subject reflects his own wishes, desires, fears and attitudes in the sentences he makes (Rotter and Rafferty 1950). The ISB consists of 40 items revised from a form developed by Rotter and Willerman (1947). This form was in turn a revision of blanks used by

Shor (1946), Hutt (1945) and Holzberg et al (1947). The ISB provides a technique for objectively screening experimental subjects as well as information regarding the diagnosis of "mental" disorders for treatment purposes. Rotter and Rafferty (1950) found a corrected split half reliability of 0,84 when the data were based on the records of 124 male college students and 0,83 when based on 71 female students. The scoring plan involved judgements and the matching of sentences against criterion sentences, so reliability of scoring was an important factor. Rotter and Rafferty (1950) reported an inter-rater reliability of 0,91 when based on 50 male records and 0,96 for 50 female records.

The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1973) comprises 18 symptom constructs which are rated on a seven point scale of severity which range from "not present" to "extremely severe" (Appendix 3). This scale was developed to provide a highly efficient, rapid assessment technique to evaluate change in psychiatric patients and provides a comprehensive description of the major symptom characteristics (Overall and Gorham 1962). The authors recommend an interview duration of eighteen minutes and provide a schedule to assist the interviewer. The eighteen minute schedule is subdivided into a three minute interval in which the interviewer establishes rapport with the patient, a ten minute period for non directive interaction and a five minute period for direct questioning. Overall and Gorham (1962) have indicated that this schedule should not be regarded as inflexible and can be modified wherever necessary. The BPRS has been reported to be reliable (Overall and Gorham 1962).

The Stanford Sleepiness Scale (Hoddes et al 1972,1973) is a self rating scale which is used to quantify subjective changes in sleepiness for any period of the day or night. The scale comprises seven statements (Appendix 4) which were selected on the following basis. Hoddes et al (1972) asked 95 subjects to sort 52 statements of sleepiness into 7 categories denoting increasing degrees of sleepiness. The final statements were selected using Thurston's method of equal appearing intervals (Thurstone and Chave 1929). An alternate form reliability check of the scale yielded an agreement of 0,88 for 10 subjects.

5.2.6 Visual Analogue Scales

It has been suggested that visual analogue scales may provide a sensitive index of feelings and mood, more so than category scales which fail to grasp nuances of feelings (Aitken 1969; Zeally and Aitken 1969); words or semantic phrases are sometimes inadequate media for descriptions of mood (Aitken 1969).

"Feelings are states of self and incorporate mood and sensations. Although a person may appreciate precisely his state on a selected dimension, words may fail to describe the exactness of the subjective experience" (Aitken 1969, p.989). Hayes and Paterson (1921) reported that lines with their boundaries clearly defined as the extremes of feeling, served as a useful index of mood and feelings. The analogue method is thus particularly useful for sensitive comparisons between different occasions in the same person. The visual analogue scale has been successfully employed in the measurement of mood changes in a number of clinical drug trials (Firth 1971; Bond and Lader 1975).

All the visual analogue scales used in this study consisted of 100mm lines and were scored to the nearest millimeter (Aitken 1969). Four visual analogue scales were employed in the short-term clozapine investigation :-

(i) depression (very depressed - not depressed at all)
(ii) anxiety (very anxious - not anxious at all)
(iii) drowsiness (very drowsy - not drowsy at all)
(iv) ability to concentrate (able to think clearly - not able to think clearly at all)

The following three analogue scales were used in the REM dream recall investigation :-

(i) quantity of dreaming (dreaming all the time - little or no dreaming)
(ii) quality of dreaming (very everydayish ordinary dreaming - very vivid, bizarre dreaming)
(iii) activity in dream (very active - very passive)

The Dream Activity - Passivity Scale: The development of this analogue scale was based on the finding of Berger and Oswald (1962) that there was a direct relationship between the eye movements depicted on the EOG and the visual content of one's dream. Berger and Oswald (1962) awakened 8 volunteers from periods of rapid eye movement sleep on 103 occasions during 37 nights. Dream recall occurred in 89 instances and was recorded on magnetic tape. The double blind procedure was adopted and an independent scorer who had never been present during the nocturnal recording sessions and who had never seen the relevant electroencephalographic or eye movement recordings classified the dream reports

as "active" or "passive". The dream reports were classified as "active" or "passive" according to the nature of the events described and especially if it was felt that such events would have been accompanied by many shifts of gaze, had they occurred in real life. The rapid eye movement periods were then classified as "active" or "passive" according to the frequency and size of the eye movements. Berger and Oswald (1962) found a significant association (x^2 = 16,18 $p<0,001$) between the nature of the dream content and the amount of movement of the eyes, thus confirming the hypothesis of Dement and Wolpert (1958) that eye movements during rapid eyemovement sleep were directional responses to the events of the dream. These criteria of "activity" and "passivity" appear quite generalised and the broad approach of rating dreams as either active or passive is questionable. Thus as a result of the above criticism, a visual analogue scale was developed in the present study to enable the rater to assess the "activity" or "passivity" of the dreams. This enabled raters to express their own nuances of judgement.

5.2.7 Dream Report Rating Scales

The Dream Report Rating Scales were selected on the basis of their previous use in sleep research programs of this nature (Carrol et al 1969, Firth 1974). These scales have not been published and are difficult to obtain and as a result the development and rationale of these tests has been covered in much detail below.

The Larson Interview Schedule (1969) comprises a series of questions which were used as a standard format for eliciting

dream recall throughout the experiment and consequently across all rating scales. A copy of this interview schedule appears in Appendix (5).

The Dreamlike Fantasy (DF) Scale (Foulkes, Spear and Symonds 1966) focuses on the formal properties of dreams such as the presence of visual imagery and hallucinatory quality and only secondarily considers content properties such as realistic or bizarre happenings. Foulkes and Vogel (1965) originally developed the DF scale to differentiate mental thought-like activity at sleep onset from pictorial, hallucinatory dreamlike imagery occurring during REM periods. The scale contains 8 points with assigned values from 0 - 7 (Foulkes 1970) (Appendix 6). Recall is defined as the mention of at least one item of specific content, for example not "I saw images" or "I had feelings" but "I saw a car" or "I felt sad" (Foulkes 1970).

Two special methodolological procedures should be taken into account when using this scale. Firstly the DF scale was designed to be used in conjunction with the Larson Interview Schedule (1969) and can probably only be used in this context (Foulkes 1970). Secondly the DF scale was constructed primarily to differentiate various stages of NREM sleep or to contrast NREM and REM mentation. It has a limited value for scaling REM mentation as most REM dreams are visual and hallucinatory. The use of the DF scale in the present study was restricted to its purported content properties, i.e. the progression from "thought-like" mentation to pictorial mentation to hallucinatory imagery was seen as providing an index of dream intensity. Intensity of dream experience was construed as a function of

distortion, dramatisation and vividness. Foulkes (1970) indicated the possibility of using the above scale in this particular way. Carrol et al (1969) and Firth (1974) have since used this scale in the above way. Pivik et al (1969) found the inter-rater reliability of the DF scale to be 0,94.

The Physical Aggression (PA) Scale (Foulkes and Rechtschaffen 1964) concentrates on overtly physically aggressive behaviour. The PA scale is a seven point ordinal scale (0 - 6) (Appendix 7). Each point on the scale is characterised in terms of one or more general classes of dream events. The PA scale should be used to rate individual dream reports and not a collection thereof and should be assigned the highest score that could be attributed to any particular part of the dream. Foulkes and Rechtschaffen (1964) applied the scale separately to physical aggression "need" (dreamer as agent) and physical aggression "press" (others as agents). A factor analytic study (Hauri et al 1967) revealed the usefulness of distinguishing between physical and verbal aggression but not between the "need - press" distinction. Foulkes et al (1969) have used the PA scale as a unitary entity without distinguishing whether the dreamer was the object, agent or bystander. The scale has been used in the above context in the present study. The inter-rater reliability of the PA scale, in evaluating REM dream reports, using a sample of 78 dreams obtained from 14 male adolescents was r = 0,91. Weisz and Foulkes (1970) rated 38 dream reports which were obtained from 12 male adults. Twenty dreams were obtained in the laboratory while eighteen were recorded at home. They reported an inter-rater reliability of 0,88.

The Manifest Sexuality Scale (Swanson and Foulkes 1968) focuses upon overt sexual behaviour and manifest sexual feeling. It is a seven point scale (0 - 6) and is assumed to be ordinal. Higher ratings are given to the self as a dream character than when similar events are seen in other dream characters. The Manifest Sexuality Scale is used to rate individual dream reports. Manifest sexuality is defined both in terms of physical intimacy as well as other forms of sexual interaction such as dating, joking and teasing. Physical intimacy receives the highest ratings whereas socialised sexual encounters receives intermediate ratings. Symbolic or suppressed sexual behaviour receive low ratings and where no sexual behaviour is present, a score of 0 is assigned, (Appendix 8). Only heterosexual behaviour is ever scored. Swanson and Foulkes (1968) have reported Pearson product moment inter-rater reliabilities coefficients of 0,71 (40 dreams), 0,79 (34 dreams), 0,51 (38 dreams) and 0,84 (39 dreams). All the dream protocols rated were obtained from laboratory REM awakenings. The above scale differs from the Sexuality-Interaction Scale (Hall and Van de Castle 1966) in the fact that it is ordinal rather than nominal, results in a single score per dream report and is less exclusively "physical" in its definition of sexuality.

The Active Participation Scale (Foulkes et al 1969) is a five point scale (1 - 5) and is assumed to be ordinal (Appendix 9). Each point on the scale is characterised by the degree of participation by the dreamer in his own dream. This scale should be applied to each individual dream rather than a collection of dreams. Foulkes et al (1969) reported an inter-rater reliability of 0,80 when 2 raters independently evaluated 78 laboratory monitored REM dream reports obtained from 14 male

adolescents. Weisz and Foulkes (1970) rated 38 dream reports which were obtained from 12 young male adults. They reported a Pearson Product moment correlation of 0,76.

The Verbal Aggression (VA) Scale (Foulkes and Rechtschaffen 1964) is a seven point ordinal scale (0 - 6) and centres around overt verbal aggressive behaviour (Appendix 10). Higher values are given to "more intense and explicitly malicious episodes of interpersonal derogation" and lower values are given to "teasing or other indirect forms of derogation of the person" (Foulkes and Rechtschaffen 1964). Verbal threats of physical aggression are regarded as physical aggression and not as verbal aggression. Hauri et al (1967) reported that factor analysis had revealed the fruitfulness of distinguishing between verbal and physical aggression but suggested that verbal aggression "need" (dreamer as agent) and verbal aggression "press" (others as agents) should be regarded as a unitary entity. Foulkes et al (1969) and Weisz and Foulkes (1970) have reported inter-rater reliabilities of 0,92 (n=78) and 0,97 (n=38) respectively.

The Hedonic Tone (unpleasantness) Scale (Foulkes Spear and Symonds 1966) was developed to quantify the distinction between "good" and "bad" dreams. The scale is a seven point ordinal scale (1 - 7) (Appendix 11). The lower portion of the scale (1 - 3) quantifies degrees of pleasantness whereas the upper portion quantifies degrees of unpleasantness (5 - 7). The middle position on the scale (4) is used to score hedonically neutral or unscorable dreams. Dreams are rated on their overall hedonic tone. When the dream consists of pleasant and unpleasant events (hedonically mixed dreams) a special adjustment procedure must be carried out.

The rater obtains the maximum P score and the maximum UP score when rating the dream. The UP score is then doubled and the P score is then added to this value. The total is now divided by 3 to obtain a weighted average. All fractions are rounded off to the next highest digit if it is over 5, and to the next lower digit if it is below 4, for example:-

Max. UP element	Max. P element	Weighted average	Scale value
7	1	5	5
7	2	5.3	6
6	3	5	5
5	1	3.7	3

When events depicted in the dream are either pleasant or unpleasant (hedonically unmixed dreams) the rater assigns the most extreme score that is given to any dream event, for example:-

1 + 2 + 3 = 1
5 + 6 + 7 = 7

These special weighting procedures are purported to increase the reliability of the scale with respect to raters assigning their own overall rating to the dream report. The scale relies on the rater's subjective judgement of what is pleasant and unpleasant and does not attempt to define the above terms. Foulkes et al (1966) and Weisz and Foulkes (1970) have reported inter-rater reliabilities of 0,78 (n=14) and 0,86 (n=38) respectively when rating dream reports obtained from REM dream awakenings and morning arousals respectively.

The Distortion Scale (Foulkes and Rechtschaffen 1970) was

originally developed to determine the subject's own subjective estimate of the degree of distortion and fantasy which occurred in the previous night's dreams. This is a six point scale (1 - 6) ranging from "not at all distorted" to "extremely distorted" (Appendix 12). The authors report that an inter-rater reliability of 0,85 was obtained when a sample of 127 REM dream reports were evaluated; however a low correlation of 0,44 was obtained when the ratings of the experimenters were compared to those of the subjects. Foulkes and Rechtschaffen (1970) express reservations concerning the value of self rating techniques when compared to other rater orientated techniques. With regard to the present study, the above scale, despite its "skimpy formal properties" provided a simple subjective estimate as to the quality of dreaming.

5.2.8 Sleep Logs

Sleep logs were used in each of the three studies as follows:

(i) Short-term investigation. A home sleep log developed by Hartmann and Cravens (1973(a)) was used as a laboratory sleep log in the present study. This log provided useful information regarding estimated sleeping time, events of the previous day which could have influenced the night's sleep, dreams recalled, naps taken and any unusual psychological or physiological feelings that occurred (Appendix 13).

(ii) Long-term investigation. The home sleep log of Hartmann and Cravens (1973(a)) used in the short-term study was adapted to meet the demands of the present study. It provided additional information with regard to side-effects and the identification of the nature of the medication. The Stanford Sleepiness Scale (described in section 5.2.5) formed part of this home log (Appendix 14).

(iii) REM Dream recall investigation. This home log comprised two visual analogue scales which provided information concerning the quantity

and quality of the subject's dreams (section 5.2.6). The Rechtschaffen and Foulkes Distortion Scale (1970) also formed a part of this home log (Appendix 15).

5.2.9 Mental Speed Test

A mental speed test comprising 258 simple addition problems derived from a table of random numbers (Edwards 1968) was constructed to assess the speed and accuracy of performance (Appendix 16).

5.3 Procedure

5.3.1 Electrophysiological Recording Procedure

Subjects reported to the laboratory one hour before their normal retiring times which were established on the basis of a questionnaire concerning their sleeping habits (section 5.1), completed before the commencement of the study. The subject then undressed and changed into his sleeping apparel. It was essential for subjects to do this as tight fitting clothing would either dislodge or totally remove the electrodes when taken off. The subject was then comfortably seated and the appropriate electrode attachment sites were thoroughly cleaned with cotton wool which had previously been immersed in alcohol. DB electrode paste was then rubbed into these electrode attachment sites to facilitate electrical conduction. Collodion adhesive paste was used to secure the Beckman silver chloride disc electrodes to the scalp and to the outer canthus of each eye. In addition, each electrode attached to the outer canthus of the eye was taped to the skin with No. 1530 micropore surgical tape. A ground electrode which was common to all transducers was placed on the

forehead. A blunted hypodermic needle attached to a syringe filled with DB paste was then inserted into the hole in the centre of the electrode. The scalp was gently scratched to remove dead hornified cells which were poor conductors and the electrode was then filled with DB conducting paste.

Electrode placements were kept constant for all subjects. Bipolar EEG recordings were obtained from the central and occipital areas. The C3 and C4 as well as the O1 and O2 positions (Jasper 10-20 system 1958) were used to record the EEG (Figure 3). The EOG recordings of horizontal eye movements were obtained from electrodes placed 1-2cm lateral to the outer canthus of each eye.

The dynograph settings were kept constant for all subjects. The time constant of the Type 9806 A A/C coupler was set at 0,3 and the high frequency filters at 3. For the EEG records, the Type 481 B Preamplifier setting was at 0,5 millivolts per centimeter whilst the setting for the Type 482 M 8 amplifier was at X0,1 (ie. 0,1X0,5 millivolts per centimeter) giving a net resultant amplification of 50 microvolts per centimeter on the recording paper. For the EOG recordings the Type 481 B Preamplifier setting was at 1 millivolt per cm whilst the setting for the Type 482 M 8 Amplifier was at 0,1 (ie. 1X0,1 millivolts per centimeter) giving a net resultant amplification of 100 microvolts per centimeter on the recording paper.

The subject then retired and once he was comfortable in bed, both the EEG and EOG electrodes were attached via electrically shielded input leads to the couplers of the dynograph situated in the

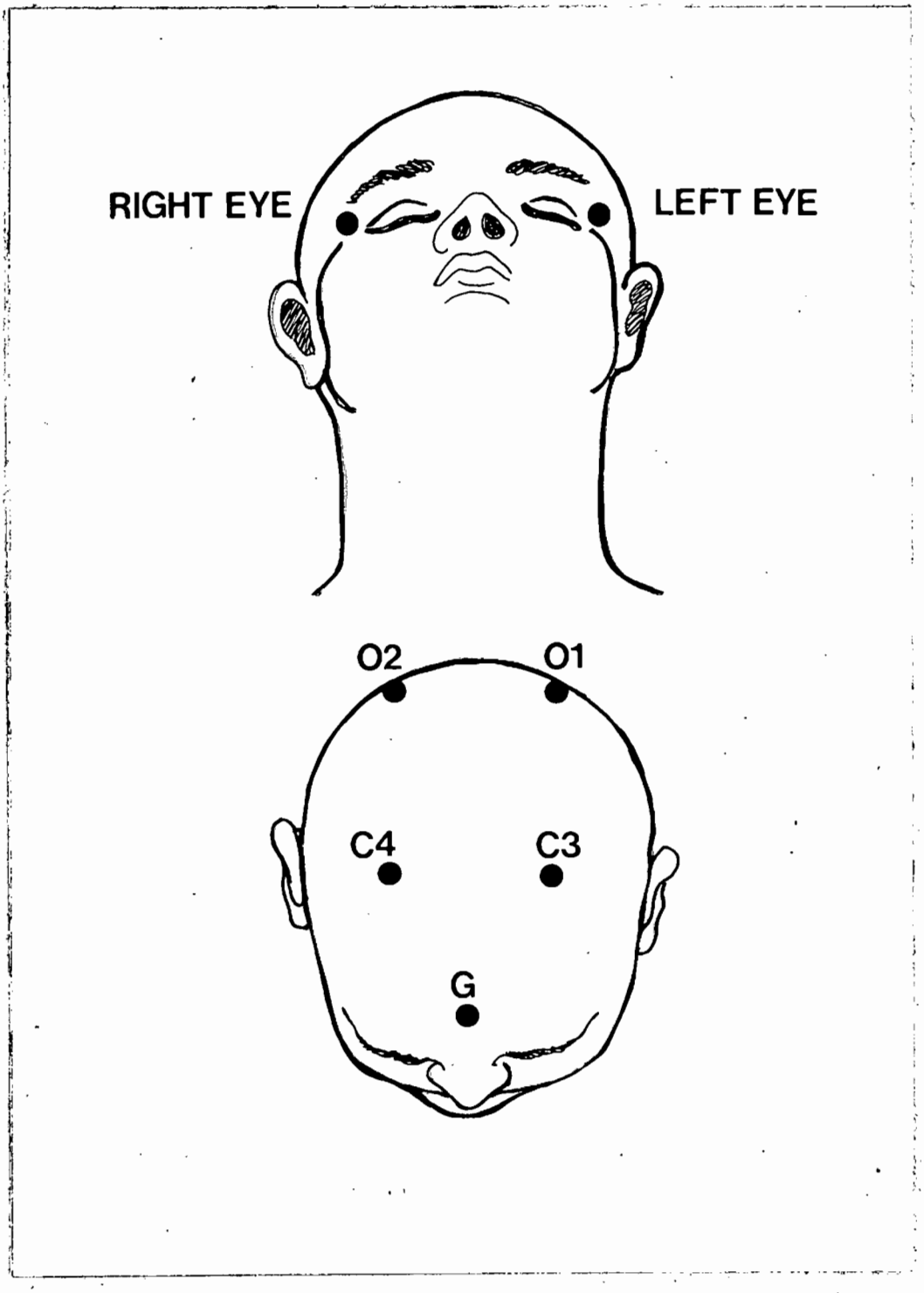


Figure 3 EEG and EOG Electrode Placement Sites.

adjacent monitoring room. The experimenter then thoroughly checked the EEG and EOG activity on the oscilloscope as well as on the recording paper and wherever necessary made adjustments to the electrodes or monitoring apparatus. It was essential to obtain artifact free recordings from the onset in order to avoid arousing a subject once the recording had commenced. The subject was then asked to look to his left and right to determine whether these eye movements would be detected by the EOG channel on the dynograph. The subject then received the coded tablet and the sleeping room lights were switched off. The interleading door was closed and the recording was terminated in the morning either by a spontaneous awakening or by the experimenter at a time specified by the subject's sleeping habits.

5.3.2 Short-Term Clozapine Investigation Procedure

This study comprised a nine consecutive night, double blind cross-over design (Touyz et al 1975(a))(Figure 4). The first two nights served a purely adaptive purpose to control for the "first night" effect (Agnew et al 1966; Hartmann 1967(b), Scharf et al 1969; Schmidt and Kaelbling 1971; Kupfer et al 1974; Coble et al 1974). It has been suggested that a first night adaptation might not be sufficient (Agnew et al 1966; Dement and Kleitman 1957; Rechtschaffen and Verdone 1964; Williams et al 1964, 1966) and as a result two nights were used for subjects to adapt themselves to the laboratory conditions. These two nights were also used to explain the workings of all the equipment which the subject would encounter during the course of the study. In addition an attempt was made to dispel any apparent fears or

EXPERIMENTAL CONDITION	ADAPTATION	BASELINE	DRUG ADMINISTRATION	DRUG WITHDRAWAL
CONSECUTIVE NIGHTS	1 and 2	3 and 4	5, 6 and 7	8 and 9
CLOZAPINE GROUP n=7	No Medication	No Medication	25mg	No Medication
PLACEBO GROUP n=7	No Medication	No Medication	25mg	No Medication

Figure 4 Experimental design for the short-term assessment of the effects of clozapine and placebo on human sleep.

misapprehensions subjects may have had concerning the experiment. Although the full electrophysiological recording procedure was carried out, (section 5.3.1) no all night recordings were made. Baseline sleep parameters were obtained from nights three and four. On nights five, six and seven, subjects received upon retiring, either 25mg clozapine or 25mg placebo (ascorbic acid) administered in tablet form. Nights eight and nine were used to assess any withdrawal effects. The double blind technique was employed as both the experimenter and subject were unaware of the drug condition. The sleep log (section 5.2.8), the visual analogue scales (section 5.2.6) as well as measures of mood (section 5.2.5) and performance (section 5.2.9) were administered to the subjects each morning fifteen minutes after awakening for the entire duration of the study.

5.3.3 Long-Term Clozapine Investigation Procedure

This study comprised a twenty five night, single blind cross-over design (Figure 5), the subject being unaware of the experimental condition. Subjects received 12,50mg clozapine placebo (section 5.2.4) on the first and last five nights. On the intermediate fifteen nights, subjects received 12,50mg clozapine (section 5.2.4). Subjects reported to the laboratory on the third and fourth nights in order that baseline sleep recordings could be obtained. To determine the effects of 12,50mg clozapine on sleep patterns, subjects slept in the laboratory on the eighth, twelfth, sixteenth and twentieth nights. Nights twenty one and twenty five were used to determine whether the withdrawal of clozapine after fifteen consecutive nights of administration would result in an altered sleep pattern.

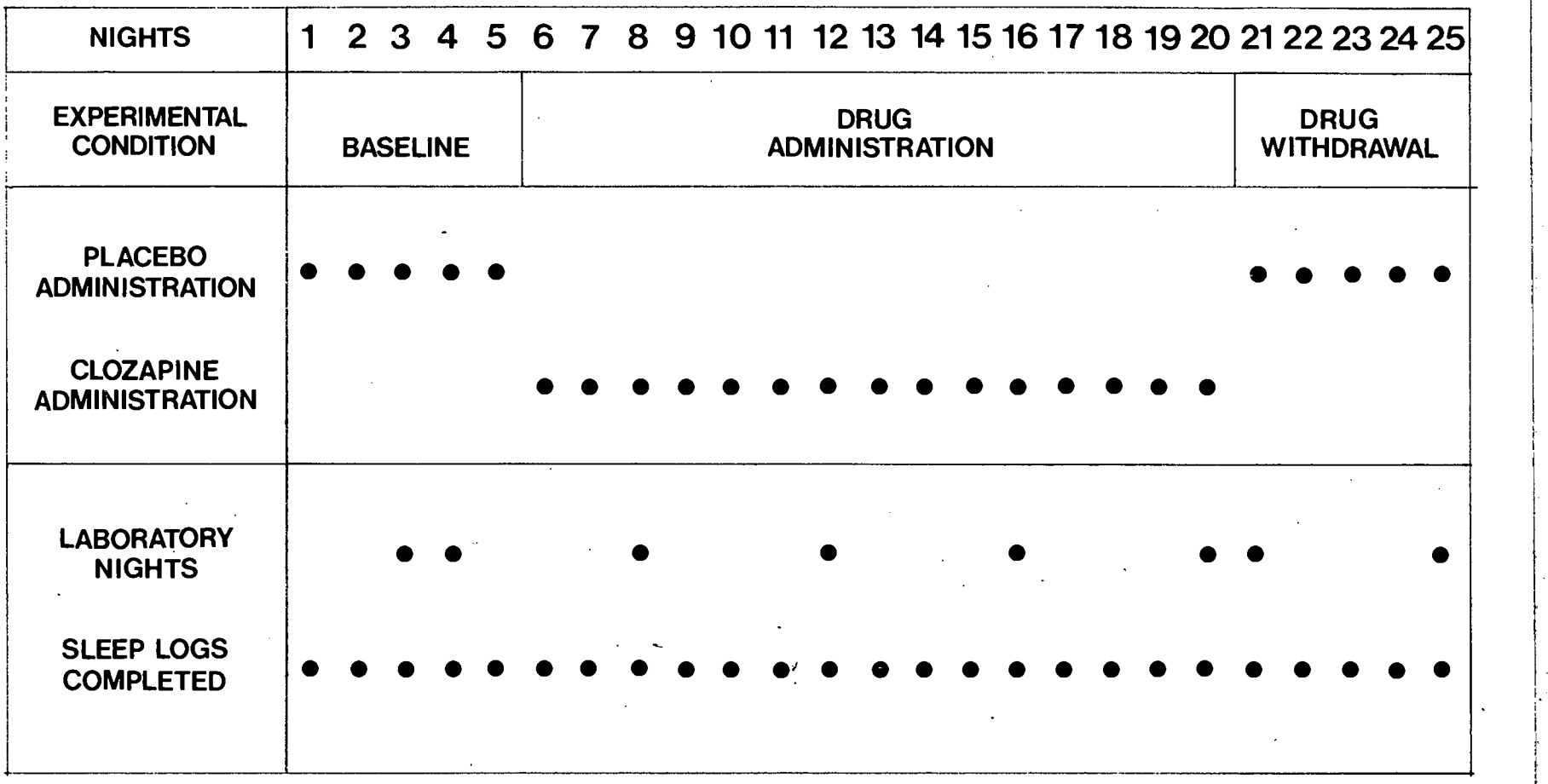


Figure 5 The single blind, cross-over design used in the long-term investigation.

Subjects completed a home log (section 5.2.8) each morning throughout the twenty five days.

Prior to the commencement of the study, subjects slept for two nights in the laboratory. This was done in order to adapt the subjects to the laboratory, experimenter and experimental routine (section 5.3.2). The electrophysiological recording procedure (section 5.3.1) was carried out with two exceptions; (i) subjects received no medication upon retiring and (ii) all-night monitoring was not carried out. On the morning prior to the commencement of the study, subjects reported to the laboratory, underwent a medical examination (section 5.3.8) and had 5cc's of blood taken (section 5.3.9). Subjects also completed the Taylor Manifest Anxiety Scale (section 5.2.5) and were rated on the Brief Psychiatric Rating Scale (section 5.2.5) by the experimenter. The subjects were then given their coded tablets, home logs and a calendar depicting the nights they were expected to report to the sleep laboratory. The entire electrophysiological recording procedure (section 5.3.1) was carried out on each recording night. On the final morning of the study,5cc's of blood were once again taken from each subject. Subjects once again completed the Taylor Manifest Anxiety Scale and were rated on the Brief Psychiatric Rating Scale by the experimenter.

5.3.4 REM Dream Recall Investigation Procedure

This study comprised a four night single blind, cross-over design (Figure 6), the subject being unaware of the experimental condition. Each subject spent a total of four recording nights in the sleep laboratory each within a space of six days of one

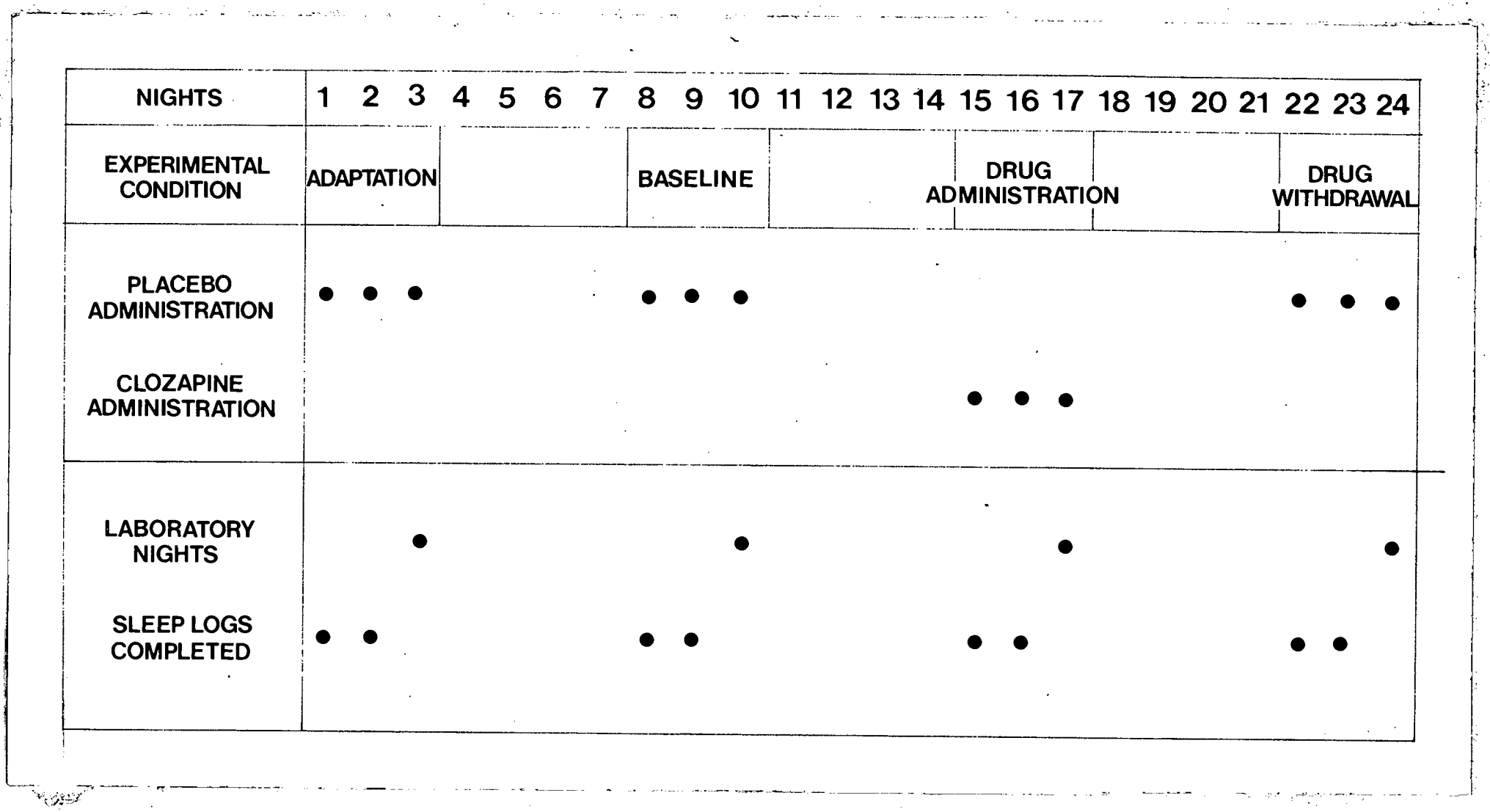


Figure 6 The single blind, cross-over design used in the REM dream recall investigation.

another. This intermediate period permitted the subjects to recover from the well documented REM rebound phenomenon incurred by repeated laboratory awakenings (Oswald 1970(c)). Prior to the commencement of the study, the subjects were issued with coded tablets and were instructed to take specific tablets at home on the two nights preceding each of the four laboratory recording nights. In addition, the subjects were issued with a home log (section 5.2.8) which they were asked to complete upon awakening on the two mornings prior to each laboratory recording night (Figure 6).

Placebo (12,50mg/night) was administered on the two nights prior to the first, second and fourth laboratory recording nights whereas clozapine (12,50mg/night was administered on the two nights prior to the third laboratory recording night. In addition, 12,50mg placebo was administered on the first, second and fourth recording nights whereas 12,50mg clozapine was administered on the third recording night. This design enabled the experimenter to determine the short-term effects of three consecutive nights of 12,50mg clozapine administration upon REM dream content.

The first recording night was used to adapt the subjects to the laboratory environment, experimenter and laboratory routine. Only one laboratory night was affected, as all the subjects participating in this study had previously taken part in a sleep research program. Baseline REM dream reports were obtained on the second recording night. The third recording night was used to determine the effects of the short-term administration of 12,50mg clozapine upon REM dream content whereas the fourth recording night endeavoured to trace any possible withdrawal effects.

5.3.5 REM Awakening Procedure

Subjects were briefed about the awakening procedure for each laboratory night to dispel any fears or misapprehensions they might have had concerning the possible detrimental effects often associated with REM sleep deprivation (Dement 1960; Kales et al 1964 and Clemes and Dement 1967). Awakenings were made by the experimenter calling the subject by name and/or gently touching his body. On all laboratory recording nights three awakenings were effected. Subjects were woken ten minutes into their second, third and fourth REM periods. The first REM period was excluded because of its short and variable duration (Feinberg et al 1967; Goodenough et al 1965: Verdone 1965). On the adaptation night three random awakenings were effected. A standard interview format, the Larson Interview Schedule (1969) was used to elicit dream reports (Appendix 5). The interviews were all tape-recorded for later transcription and analysis. Once the dream had been tape-recorded the subject was permitted to sleep again.

5.3.6 Mental Speed Test Procedure

This procedure commenced 15 minutes after the subject had woken up. The subject was seated in a comfortable chair and was given two minutes to complete as many problems as accurately as possible (section 5.2.9). The two minute duration was measured by the experimenter using a stopwatch accurate to a hundredth of a second.

5.3.7 AD - ACL, Visual Analogue and Sleep Log Procedure

The subject was given the AD-ACL check list (section 5.2.5), visual

analogue scales (section 5.2.6) and sleep log (section 5.2.8) to complete in his own time once the mental speed test procedure had been completed during the short-term clozapine investigation. The subjects completed the sleep logs (section 5.2.8) fifteen minutes after awakening during the long-term and REM dream recall investigations.

5.3.8 Medical Examination Procedure

All of the subjects who participated in each of the three studies underwent a medical examination at Groote Schuur Hospital. The medical examination was performed by a psychiatric registrar one day prior to the commencement of the study. In no instance was any obvious physical or mental abnormality found.

5.3.9 Venepuncture Procedure

In addition to their medical examination, the subjects participating in the long-term study, (section 5.1.2) had a sample of blood taken on the morning prior to the commencement of the study. This procedure was repeated on the final morning of the study. Five cc's of bloodwere taken from an upper limb vein and placed in a tube containing a standard anticoagulant. The blood sample was then coded and sent to the Department of Haematology, Groote Schuur Hospital for analysis. This procedure was necessitated by the fact that clozapine administration has been associated with the occurrence of agranulocytosis in clinical patients (Goodson 1976 - personal communication) and was carried out as a precautionary measure to ensure that the subjects participating in the study suffered no ill-effects from long-term drug administration. The occurrence of agranulocytosis has been rare and only when

exceptionally high doses have been administered for exceedingly long periods (Goodson 1976 - personal communication).

5.4 Scoring System

The epoch by epoch scoring procedure advocated by Rechtschaffen and Kales (1968) was strictly adhered to throughout the scoring of the data. The most convenient interval to use as an epoch was a page of recorded data, which in this case was 30cm. This interval had the additional benefit that at a paper speed of 1cm per second, each page would be the equivalent of 30 seconds. This epoch duration also falls within the Rechtschaffen and Kales (1968) recommendation. Each epoch however was not scored in total isolation but preceding and succeeding polygraphic features were taken into consideration when assigning a sleep stage to an epoch. In no instance were two epochs ever combined to create a new epoch as only one sleep stage score was permitted for each epoch. On occasion when more than one sleep stage was present in an epoch, the sleep stage which occupied the greatest portion of the epoch was assigned to the particular epoch. All the sleep stages as well as movement time were scored according to the criteria set out by Rechtschaffen and Kales (1968).

5.4.1 Criteria for Scoring Sleep Stages

(i) Stage awake. An epoch is scored as stage awake when more than half the epoch is characterised by alpha or low voltage mixed frequency activity. Some individuals termed "alpha producers" are able to generate virtually continuous streams of alpha activity whereas other subjects may show little or

no alpha activity in the waking record. This stage is frequently but not always accompanied by rapid eye movements and eye blinks in the EOG channel.

(ii) Stage I sleep. An epoch is scored as stage I when the alpha activity occupies less than half the epoch. The scoring of an epoch as stage I requires the complete absence of clearly defined K complexes[1] and sleep spindles[2]. Stage I, when it follows wakefulness is characterised by the appearance of slow rolling eye movements which are of several seconds duration. These slow eye movements have a wave-like appearance and are usually more conspicuous during the early portion of this stage. Prominent vertex sharp waves which may reach amplitudes of 200 microvolts also occur during this stage.

(iii) Stage 2 sleep. An epoch is scored as stage 2 by the presence of sleep spindles and/or K complexes and the absence of high amplitude, slow wave activity which constitute the presence of either stage 3 or stage 4. Sleep spindles and K complexes are transient phenomena and long periods of time may elapse between the occurrence of a sleep spindle and/or K complex. If this duration exceeds 3 minutes, without any indication of body movement activity, the interval is scored as stage I, but if the appearance of a sleep spindle and/or

[1] K complexes are defined as EEG waveforms which have a well delineated negative sharp wave which is immediately followed by a positive component. K complexes can occur as a result of endogenous stimulation in the absence of any detectable stimulus or in response to a sudden stimulus (Johnson and Karpan 1968).

[2] A sleep spindle is defined as 12 - 14 hz. activity of at least 0,5 seconds duration. The term spindle relates to a spindle-shaped envelope of this sigma paroxysm. Sleep spindles are characteristic of stage 2 sleep (Rechtschaffen and Kales 1968).

K complex occurs before 3 minutes, the interval is scored stage 2.

(iv) Stage 3 sleep. An epoch is scored as stage 3 sleep when at least 20% but not more than 50% of the epoch consists of waves of 2 hz.or slower. The amplitudes of these waves should be greater than 75 microvolts measured from peak to peak, (the distance between the extreme negative and positive points of the wave). Sleep spindles may or may not occur during this stage.

(v) Stage 4 sleep. An epoch is scored stage 4 sleep when half the epoch or more comprises waves of 2 hz.or slower which have amplitudes in excess of 75 microvolts peak to peak. Sleep spindles may or may not occur during stage 4 sleep. The apparent eye movement activity present in the electro-oculogram recording is merely a "spillover" of brain wave activity into the eye movement record (Foulkes 1966).

(vi) Stage REM. An epoch is scored as stage REM sleep when relatively low voltage mixed frequency EEG activity and episodic rapid eye movements predominate the EEG and EOG recordings respectively. Stage REM activity differs from stage I activity in the following ways. Firstly the vertex sharp waves which occur in stage I are not as conspicuous in stage REM. Secondly in stage REM distinct "sawtooth" waves (Berger et al 1962) frequently but not always appear in conjunction with rapid eye movements. Alpha activity is more pronounced during stage REM than during stage I and is characteristically I - 2 hz.slower than during wakefulness (Johnson et al 1967). Stage REM

is also characterised by a total absence of sleep spindles and K complexes. An exception to the rule however is the occasional appearance of sleep spindles during the first REM period of the night.

5.4.2 Criteria for Scoring Body Movements Indices During Sleep

(i) Body movements. The following criteria had to be met before muscle activity appearing on the EEG or EOG records was scored as body movement (Rechtschaffen et al 1963). (i) Fast muscle potential of at least 30 microvolts had to be present in one of the EEG channels as well as on the EOG channel. (ii) The burst of muscle potential had to be at least 4 seconds in duration. (iii) Amplifier blocking of 1 second or longer on at least one of the channels was required. (iv) Periods of muscle tension artifact which were separated by at least 4 seconds of EEG record containing no trace of muscle tension artifact were counted as separate body movements. (v) Periods of muscle tension and amplifier blocking which occurred prior to and upon awakening were counted as body movements occurring during sleep.

(ii) Movement time (MT). The score "MT" was assigned to epochs in which the EEG and EOG tracings were obscured in more than half the epoch as a result of muscle tension and/or amplifier blocking caused by the movement of the subject. Whenever an epoch was obscured by muscle tension and/or amplifier blocking artifacts but was immediately preceded and followed by wakefulness, the epoch was scored as stage awake rather than MT (Rechtschaffen and Kales 1968).

5.4.3 Procedure for Scoring Dream Rating Scales

The dreams were all transcribed and coded before they were given to raters who were unaware of the aims of the experiment. The raters were all psychologists involved in the scientific study of dreams.

5.4.4 Procedure for Scoring Sleep Records

The names of the subjects, the dates of the recordings as well as the experimental conditions were systematically deleted from all of the sleep records which were then coded. The recordings were then scored "blind" as the experimenter was unaware as to whether the records were of baseline, drug administration or withdrawal origin.

Several prominent sleep researchers have recommended that the sleep record should be evaluated for smaller portions of the night as well as for the entire night (Kales et al 1975; Hartmann and Cravens 1973(a); Freemon 1972). In addition to the total night's analyses, the major sleep stages (section 5.4.1) as well as indices of body movement activity (section 5.4.2) were analysed for the first three hours, the second three hours as well as the first six hours of the record as recommended by Hartmann and Cravens (1973(a)).

5.4.5 Procedure for Scoring Sleep Logs

The short-term clozapine investigation: This sleep log consisted of eleven questions of which the answers to questions six, seven, nine and ten were evaluated for each day of the study (see

appendix 13). These questions referred to the subject's subjective estimation of the quality and quantity of the previous night's sleep as well as any physiological or psychological side-effects experienced shortly after awakening.

The long-term clozapine investigation: This sleep log consisted of sixteen questions as well as the Stanford Sleepiness Scale (see appendix 14). These questions referred to the subject's estimation of the quantity and quality of the previous night's sleep as well as any physiological or psychological side-effects experienced shortly after awakening. In addition, the sleep log assessed the subject's ability of correctly identifying the nature of the previous night's medication i.e. clozapine or placebo. The answers to questions five, six, seven, ten and thirteen as well as the Stanford Sleepiness Scale were evaluated.

The duration of the long-term clozapine investigation was twenty five nights and was divided into 5 five night periods to facilitate statistical analyses. These included an initial baseline period, a first, second and third clozapine administration period as well as a clozapine withdrawal period. Mean scores of the answers to the questions of each 5 five night period were subjected to statistical analyses. The psychological side-effects (question twelve) were listed for each 5 five night period.

The REM dream recall investigation: The subjects completed home logs on the two mornings prior to each laboratory recording night (Figure 6). Mean scores were thus obtained for the baseline, clozapine administration and withdrawal conditions on

all of the visual analogue scales (section 5.2.6) as well as of the Distortion Scale (section 5.2.7).

5.5 Definitions and Terminology

A standardised system for the scoring of human sleep stages has been formulated by a number of prominent sleep research workers (Rechtschaffen and Kales 1968). Wherever possible the definitions and terminology developed by this committee have been strictly adhered to. However many other additional indices of sleep parameters have been included in this study and are defined below.

5.5.1 Sleep Stage Activity

(i) Total recording time (TRT). The time from when the subject was comfortable in bed with the electrodes attached and the lights switched off, till the recording was terminated in the morning. This included the time taken for the subject to fall asleep as well as the time he lay awake in bed in the morning before he buzzed the experimenter to terminate the recording.

(ii) Total waking time (TWT). The total time in minutes subjects spent awake from the time of drug administration (recording commencement) until awakening the next morning.

(iii) Total sleep time (TST). The total time in minutes during which recordings were made minus the total waking time.

(iv) Percent stage awake. The total waking time expressed as a percentage of total recording time.

(v) Percent stage 1 sleep. The total number of minutes of stage 1 sleep expressed as a percentage of TST.

(vi) Percent stage 2 sleep. The total number of minutes of stage 2 sleep expressed as a percentage of TST.

(vii) Percent stage 3 sleep. The total number of minutes of stage 3 sleep expressed as a percentage of TST.

(viii) Percent stage 4 sleep. The total number of minutes of stage 4 sleep expressed as a percentage of TST.

(ix) Percent stage slow wave sleep. The total number of minutes of stage 3 and stage 4 sleep expressed as a percentage of TST.

(x) Percent stage REM sleep. The total number of minutes of stage REM sleep expressed as a percentage of TST.

5.5.2 REM Indices

(i) Mean REM duration. The total time in minutes spent in REM sleep divided by the number of REM periods.

(ii) REM burst. A REM burst is defined as one or more rapid eye movements in which two successive eye movements are separated by less than 8 seconds (Aserinsky 1971).

(iii) Total number of REM bursts. The total number of REM bursts occurring throughout all REM periods.

(iv) The number of bursts per REM period. The total number of REM bursts divided by the number of REM periods.

(v) Burst length. The distance from the first to the last rapid eye movement of each burst measured to the nearest second (Aserinsky 1971).

(vi) Total burst length. The duration in seconds of all burst lengths occurring throughout all the REM periods.

(vii) Mean burst length. The total burst length divided by the number of REM periods.

(viii) REM density. The total number of rapid eye movements that occur during the total time spent in REM sleep. The criterion for a rapid eye movement was an out of phase deflection of at least 60 microvolts.

(ix) Density/min.REM sleep. REM density divided by the number of minutes of REM sleep.

(x) % Motility. % motility is defined as the percentage of REM periods occupied by REM bursts (Aserinsky 1971).

5.5.3 Sleep Stage Latencies

(i) Stage 1 latency. The number of minutes from the commencement of recording to the appearance of the first stage 1 period leading to stage 2 activity.

(ii) Stage 2 latency. The number of minutes from the commencement of recording to the appearance of the first sleep spindle.

(iii) Stage 4 latency. The number of minutes from the onset of sleep to the appearance of the first stage 4 activity.

(iv) Latency to 1st REM period. The number of minutes from the onset of sleep to the appearance of the first stage REM period.

(v) Latency to 2nd REM period. The number of minutes from the onset of sleep to the appearance of the second stage REM period.

(vi) Latency to 3rd REM period. The number of minutes from the onset of sleep to the appearance of the third stage REM period.

5.5.4 Sleep Stage Incidence

(i) Number of awakenings. The total number of times the subject awakened after sleep onset but excluding the final awakening.

(ii) Number of stage 4 periods. The total number of stage 4 periods, each period being separated by at least 15 minutes from preceding stage 4 activity.

(iii) Number of stage REM periods. The total number of stage REM periods, each period being separated by at least 15 minutes from the preceding REM period.

5.5.5 Sleep Cycle Durations

(i) 1st cycle. The number of minutes from the end of the first REM period to the end of the second REM period (Hartmann and Cravens 1973(a)).

(ii) 2nd cycle. The number of minutes from the end of the

second REM period to the end of the third REM period (Hartmann and Cravens 1973(a)).

5.5.6 Body Movement Activity

(i) Total number of body movements. The total number of body movements occurring during sleep.

(ii) Body movements/minute sleep. The total number of body movements divided by TST.

(iii) Movement time. The total number of 30 second epochs of MT occurring during sleep.

5.5.7 Blood Parameters

The following blood parameters were defined according to Ganong (1969).

(i) White blood cells. In man there are normally 4000 - 11000 white blood cells per cu.mm.of blood. Of these the granulocytes or polymorphonuclear leukocytes are the most numerous. Fifty to seventy percent of the granulocytes are neutrophils, 1-4% are eosinophils and 0,1% are basophils. Lymphocytes (20 - 40%) and monocytes (2 - 8%) are also normally found in the peripheral blood.

(ii) Red blood cells. The red blood cells or erythrocytes carry haemoglobin in the circulation. They are biconcave discs that are manufactured in the bone marrow. The mean "normal" red blood cell count is 5.4×10^3/cu.cm.in men and 4.8×10^3/cu.cm.in women.

(iii) Haemoglobin. Haemoglobin is the red oxygen carrying pigment in the red blood cells. It has a molecular weight of approximately 68000. Haemoglobin is a globular molecule made up of 4 subunits and each subunit contains a heme moiety conjugated to a polypeptide.

(iv) Haematocrit. Haematocrit is the percentage of the volume of blood occupied by red blood cells.

(v) Mean corpuscular volume (MCV). The volume of a red blood corpuscle expressed in cubic microns.

(vi) Mean corpuscular haemoglobin (MCH). The amount of haemoglobin per red blood corpuscle expressed in mmg's.

(vii) Mean corpuscular haemoglobin concentration (MCHC). The concentration of haemoglobin per red blood corpuscle.

5.6 Statistical Methods

The data were analysed according to the statistical procedures outlined in Roscoe (1969), Winer (1962) and Kirk (1968) and processed by a Hewlett Packard (HP2114B) computer. The following statistical procedures were carried out :

(i) one way analysis of variance with repeated measures (Winer 1962, Roscoe 1968).

(ii) two way analysis of variance (Winer 1962, Roscoe 1968).

(iii) two way analysis of variance with repeated measures on one factor (Winer 1962, Roscoe 1969).

(iv) Pearson Product Moment Correlation (Roscoe 1968).

(v) Dependent t test (Roscoe 1968).

The experimental design employed in the short-term clozapine and

placebo investigation involved the comparison of the two groups of subjects on baseline, drug administration and withdrawal conditions on a given variable. This required a two factor design where the subjects were recorded on seven consecutive nights. The appropriate statistical analysis employed was the two factor analysis of variance with repeated measures on one factor (Winer 1962).

The experimental designs employed in the long-term clozapine and REM dream recall investigations involved the comparison of one group of subjects on baseline, clozapine administration and withdrawal conditions on a given variable. These were one factor designs where the subjects were monitored repeatedly, and the appropriate analysis employed was the one way analysis of variance with repeated measures (Winer 1962).

Wherever the two way analysis of variance revealed significant interaction effects, simple main effects analyses were carried out (Kirk 1968, p.263) before comparisons between means were attempted. This procedure provided useful information regarding those levels of factors where such comparisons would prove to be fruitful. Finally, significant simple main effects analyses were followed up by comparisons between cell means using the Tukey HSD procedure (Kirk 1968, p.292). The F Max test was used to determine the homogeneity of variance.

5.6.1 Z Score Transformations

It was decided to transform the visual analogue scores to normalised scores using a Z score transformation computer program which

was developed by Gilbert (1976 - personal communication) for this purpose (see Appendix 16 for details of the computer program). This was done in order that each subject's data would receive equal statistical weight. This was necessitated by the fact that some subjects rated themselves on a very narrow range on the 100 mm analogue scales (i.e. between 40mm and 60mm) whereas others rated themselves using the extremities (i.e. between 0mm and 100mm). The formula for Z score transformations which formed the basis of the computer program was as follows:

$$Z = \frac{X - \overline{X}}{SD}$$

Where Z = Z score

X = raw score

$\overline{X}$ = arbitrary mean of 50

SD = arbitrary standard deviation of 10

The Z score transformation removed individual differences and as a result analysis of variance with repeated measures was not the appropriate statistical procedure to be employed in the analysis of the visual analogue scales (Gilbert 1976 - personal communication). The one and two way analyses of variance without repeated measures were employed in the analysis of the visual analogue scales.

5.7 Interscorer Reliability

5.7.1 Major Sleep Stage Interscorer Reliability

All of the sleep records were coded and then scored by the experimenter according to the recommendations of Rechtschaffen and Kales (1968). In order to assess the reliability of scoring the sleep stages, six records were scored independently by a

second experienced sleep researcher and the results were compared by the Pearson product moment coefficient of correlation. The correlation coefficients and means of the major sleep stages scored by the two researchers are shown in Table 5. There were no systematic differences between the means.

Table 5 Estimates the agreement in the scoring of the major sleep stages in human subjects by two experienced sleep researchers according to the criterion of Rechtschaffen and Kales (1968) (6 records).

Researcher	I	II	
	x mean(minutes)	y mean(minutes)	r
stage awake	12,92	14,33	0,99
stage 1	40,67	40,25	0,99
stage 2	198,00	192,67	0,56
stage 3	39,08	45,42	0,84
stage 4	71,33	67,75	0,74
stage REM	88,42	89,25	0,97

5.7.2 Interscorer Reliability for the Dream Report Rating Scales

All the dream rating scales were evaluated independently by two experienced dream researchers. The Pearson product moment coefficient of correlation was used to assess the interscorer reliability. The correlation of coefficients and means of the various dream rating scales are shown in Table 6.

Table 6 Estimates of agreement in the scoring of the dream report rating scales by two experienced dream researchers according to specified criteria (45 REM dream reports).

Researcher	I	II	
	x mean	y mean	r
Dreamlike Fantasy Scale	5,02	3,98	0,81
Physical Aggression Scale	0,47	0,76	0,67
Verbal Aggression Scale	1,07	0,58	0,80
Activity-Passivity Scale	5,00	5,40	0,71
Manifest Sexuality Scale	0,78	0,40	0,76
Hedonic Tone Scale	4,71	4,64	0,88
Active Participation Scale	3,44	3,13	0,76

There were no systematic differences between the means.

5.7.3 Interscorer Reliability for the REM Indices

In order to assess the reliability of the experimenter in scoring the indices of REM sleep, 10 five minute periods of REM sleep were scored independently by a second experienced sleep researcher and the results were compared by the Pearson product moment coefficient of correlation. The correlation coefficients and means of the REM indices scored by the two researchers are shown in Table 7. The agreement between the scorers was exceptionally high. All of the correlation coefficients were above 0,95 and there were no systematic differences between the means.

Table 7 Estimates of agreement in the scoring of the REM indices in human subjects by two experienced sleep researchers according to specified criteria.

Researcher	I x mean	II y mean	r
Number of bursts	5,60	5,90	0,95
Mean burst length (seconds)	9,17	8,27	0,99
Number of rapid eye movements	21,30	28,00	0,98

5.7.4 Interscorer Reliability for the Body Movement Indices

In order to assess the reliability of the experimenter in scoring the body movement indices, 10 fifteen minute periods of a sleep record were scored independently by a second experienced sleep researcher and the results were compared by the Pearson product moment coefficient of correlation. The correlation coefficients and means of the body movement indices scored by the two researchers are shown in Table 8.

Table 8 Estimates of agreement in the scoring of body movement indices in human subjects by two experienced sleep researchers according to specified criteria (10, fifteen minute periods of a sleep record).

Researcher	I x mean	II y mean	r
Movement Time (number of 30 second epochs)	0,40	0,50	0,95
Number of body movements	0,80	0,90	0,76

6.0 THE SHORT-TERM CLOZAPINE INVESTIGATION

6.1 Results

The short-term, long-term and REM dream recall investigations required a total of 2190 hours of electrophysiological recording over a total of 219 nights. One hundred and twenty six analyses of variance were carried out to analyse the data. The data of the major sleep stages and body movement indices were analysed for the first three hours, second three hours and first six hours of the record in addition to the analysis of the data of the entire night. This procedure generated a very large number of statistical summary tables, and in the interests of concision only the data for the entire night are presented in the tables. In all other cases, the F ratios, degrees of freedom and p values are indicated in the text.

The convention used to indicate the two way analysis of variance interaction effect was as follows: F(AXB). Means and standard errors are tabulated throughout the thesis.

6.1.1 Total Sleep Time

The effects of the administration of clozapine and placebo upon the duration of total sleep time are presented in Table 9 and significant findings are illustrated in Figure 7 ($F(AXB) = 3,42$; df 6,72; $p<0,01$). Closer examination of the data through simple main effects analysis revealed a significant difference between the clozapine and placebo groups on the first night of drug administration ($F = 5,54$; df 1,84; $p<0,05$) and a significant

Table 9. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean sleep stage percentages of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
Mean total sleep time (minutes)										
clozapine group	449,14±9,41	447,36±8,20	487,50±15,67	473,93±8,89	450,57±7,36	442,29±9,66	428,50±11,20			
placebo group	453,86±8,67	459,71±8,35	456,64±10,89	450,43±9,11	454,43±7,65	461,64±4,93	453,79± 4,07	6,72	3,42	<0,01
Mean time spent in stage awake expressed as a percentage of total recording time										
clozapine group	2,76±1,01	1,68±0,46	1,88± 0,53	1,26±0,50	2,73±1,14	2,70±1,65	2,55± 0,91			
placebo group	2,80±1,13	3,06±0,95	2,11± 0,87	2,73±1,08	1,48±0,57	1,48±0,46	2,37± 1,06	6,72	1,23	>0,25
Mean time spent in stage 1 sleep expressed as a percentage of total sleep time										
clozapine group	12,14±1,22	11,34±2,65	13,26± 2,83	12,60±2,59	13,18±3,84	10,61±1,25	9,95± 1,63			
placebo group	8,82±1,50	7,23±1,89	6,58± 1,75	9,30±2,72	8,91±2,22	7,12±1,74	5,55± 1,51	6,72	0,25	>0,25
Mean time spent in stage 2 sleep expressed as a percentage of total sleep time										
clozapine group	43,88±1,51	44,04±1,84	52,45± 2,93	52,02±2,61	50,45±2,92	47,29±3,45	49,38± 2,35			
placebo group	49,25±2,80	47,43±3,55	47,49± 1,72	47,67±3,21	46,40±4,21	49,25±3,47	52,72± 2,97	6,72	1,96	<0,10
Mean time spent in stage 3 sleep expressed as a percentage of total sleep time										
clozapine group	6,72±0,87	5,66±0,60	7,21± 1,53	6,10±1,43	7,18±1,67	7,55±2,26	6,22± 1,45			
placebo group	7,26±0,90	10,21±1,22	8,47± 1,83	8,78±1,13	7,81±1,12	7,92±1,53	7,42± 1,51	6,72	0,72	>0,25
Mean time spent in stage 4 sleep expressed as a percentage of total sleep time										
clozapine group	15,96±1,63	15,30±1,35	10,56± 2,11	8,37±1,37	9,40±1,50	10,84±1,38	11,76± 2,15			
placebo group	11,31±1,21	10,52±2,28	13,07± 1,51	12,91±1,70	11,27±2,58	10,68±1,02	11,07± 2,24	6,72	3,27	<0,01
Mean time spent in stage slow wave sleep expressed as a percentage of total sleep time										
clozapine group	22,68±2,26	20,96±1,28	17,77± 2,70	14,46±1,51	16,58±2,81	18,40±2,65	17,98± 2,38			
placebo group	18,57±1,66	20,65±2,49	21,51± 2,24	21,68±1,27	19,08±2,40	18,60±1,74	18,22± 2,99	6,72	1,96	<0,10
Mean time spent in stage REM sleep expressed as a percentage of total sleep time										
clozapine group	21,04±1,49	22,87±1,11	16,50± 1,06	21,37±1,17	19,87±1,78	23,72±1,73	22,71± 1,35			
placebo group	23,37±2,16	24,57±1,59	24,46± 1,15	21,78±1,25	25,61±1,99	25,02±1,90	23,27± 2,63	6,72	1,90	<0,10

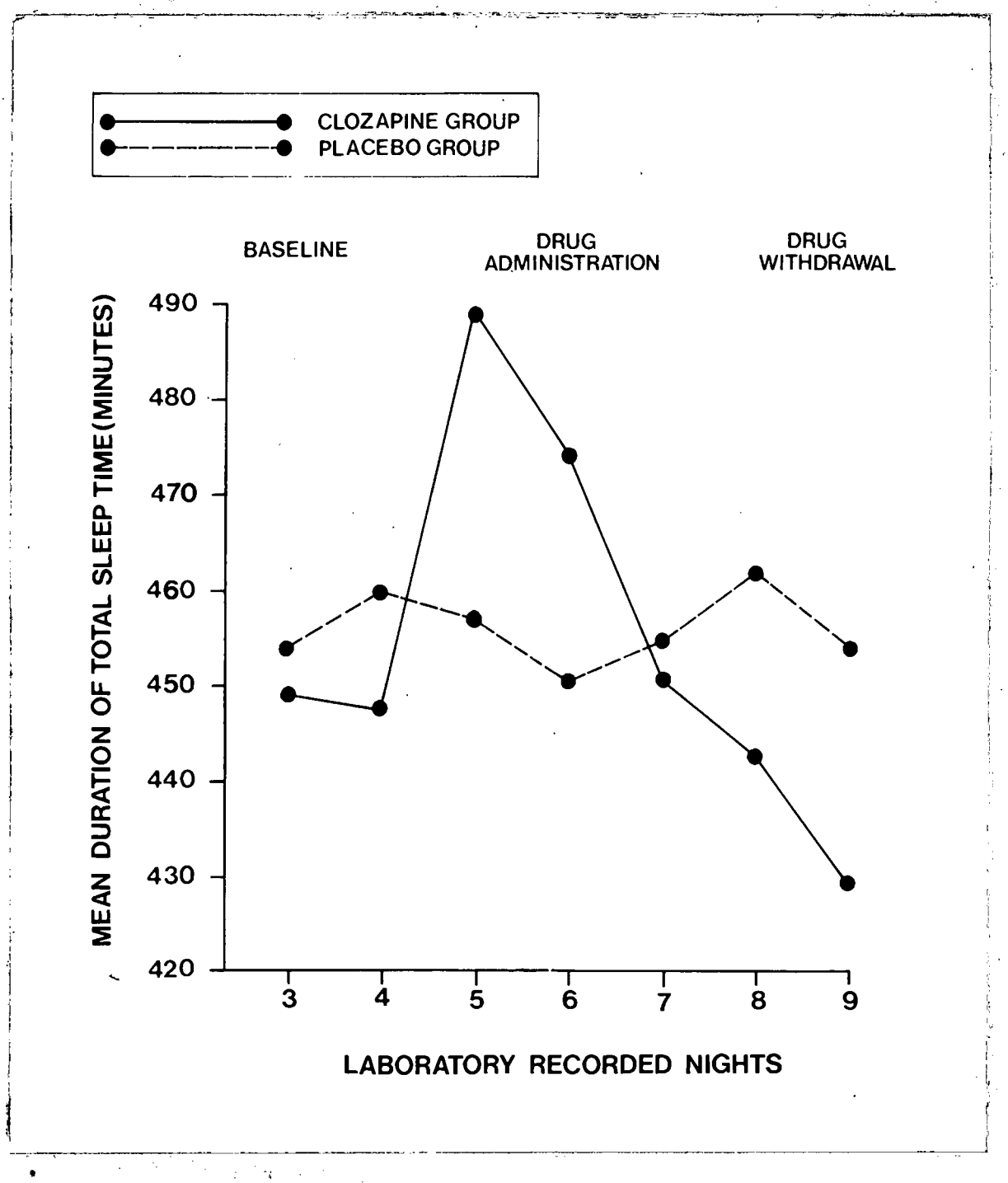


Figure 7. The mean duration of total sleep time (minutes) for the clozapine and placebo groups over the laboratory recorded nights. Total sleep time was significantly increased on the first and second nights of clozapine administration. The administration of placebo had no significant effect. Nights 3-4 and nights 8-9 were baseline and withdrawal conditions respectively.

difference over the laboratory recorded nights for the clozapine group ($F = 6,07$; df 6,41; $p<0,001$),but not for the placebo group ($F = 0,22$; df 6,41; $p>0,25$).

The Tukey HSD comparisons indicated that sleep duration was markedly increased on the first night of clozapine administration (Figure 7). The mean sleep duration on the first night of clozapine administration was longer than on either the first ($p<0,05$) or second ($p<0,05$) baseline nights as well as the third night of clozapine administration ($p<0,05$). The mean sleep duration on the first night of clozapine administration was also significantly longer than the means of the first ($p<0,01$) and second ($p<0,01$) withdrawal nights. Finally, the mean sleep duration on the second clozapine administration night was longer than the second night of withdrawal ($p<0,01$).

6.1.2 Major Sleep Stages

As previously described (section 5.5.4) the major sleep stages were analysed for the first three hours, the second three hours, the first six hours of the record as well as for the entire night, expressed as a percentage of total sleep time. Stage awake was expressed as a percentage of total recording time (section 5.4.1).

Stage Awake. The administration of clozapine and placebo had no significant effect upon the percentage of time spent awake ($F(AXB) = 1,23$; df 6,72; $p>0,25$) (Table 9). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 1,92$; df 6,72; $p<0,10$), the second

three hours ($F(AXB) = 0,51$; df 6,72; $p>0,25$) as well as the first six hours ($F(AXB) = 1,54$; df 6,72; $p<0,25$) of the record.

Stage 1. The administration of clozapine and placebo had no significant effect upon the percentage of time spent in stage 1 sleep ($F(AXB) = 0,25$; df 6,72; $p>0,25$) (Table 9). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 0,41$; df 6,72; $p>0,25$), the second three hours ($F(AXB) = 0,29$; df 6,72; $p>0,25$) as well as the first six hours ($F(AXB) = 0,10$; df 6,72; $p>0,25$) of the record.

Stage 2. The administration of clozapine and placebo had no significant effect upon the percentage of time spent in stage 2 sleep ($F(AXB) = 1,96$; df 6,72; $p<0,10$) (Table 9). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 1,14$; df 6,72; $p>0,25$), the second three hours ($F(AXB) = 1,47$; df 6,72; $p<0,25$) as well as the first six hours ($F(AXB) = 0,94$; df 6,72; $p>0,25$) of the record.

Stage 3. The administration of clozapine and placebo had no significant effect upon the percentage of time spent in stage 3 sleep ($F(AXB) = 0,72$; df 6,72; $p>0,25$) (Table 9). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 0,65$; df 6,72; $p>0,25$), the second three hours ($F(AXB) = 0,69$; df 6,72; $p>0,25$) as well as the first six hours ($F(AXB) = 0,83$; df 6,72; $p>0,25$) of the record.

Stage 4. The effects of the administration of clozapine and placebo upon the percentage of time spent in stage 4 sleep are presented in Table 9 and significant findings are illustrated in Figure 8 ($F(AXB) = 3,27$; df 6,72; $p<0,01$). Closer examination

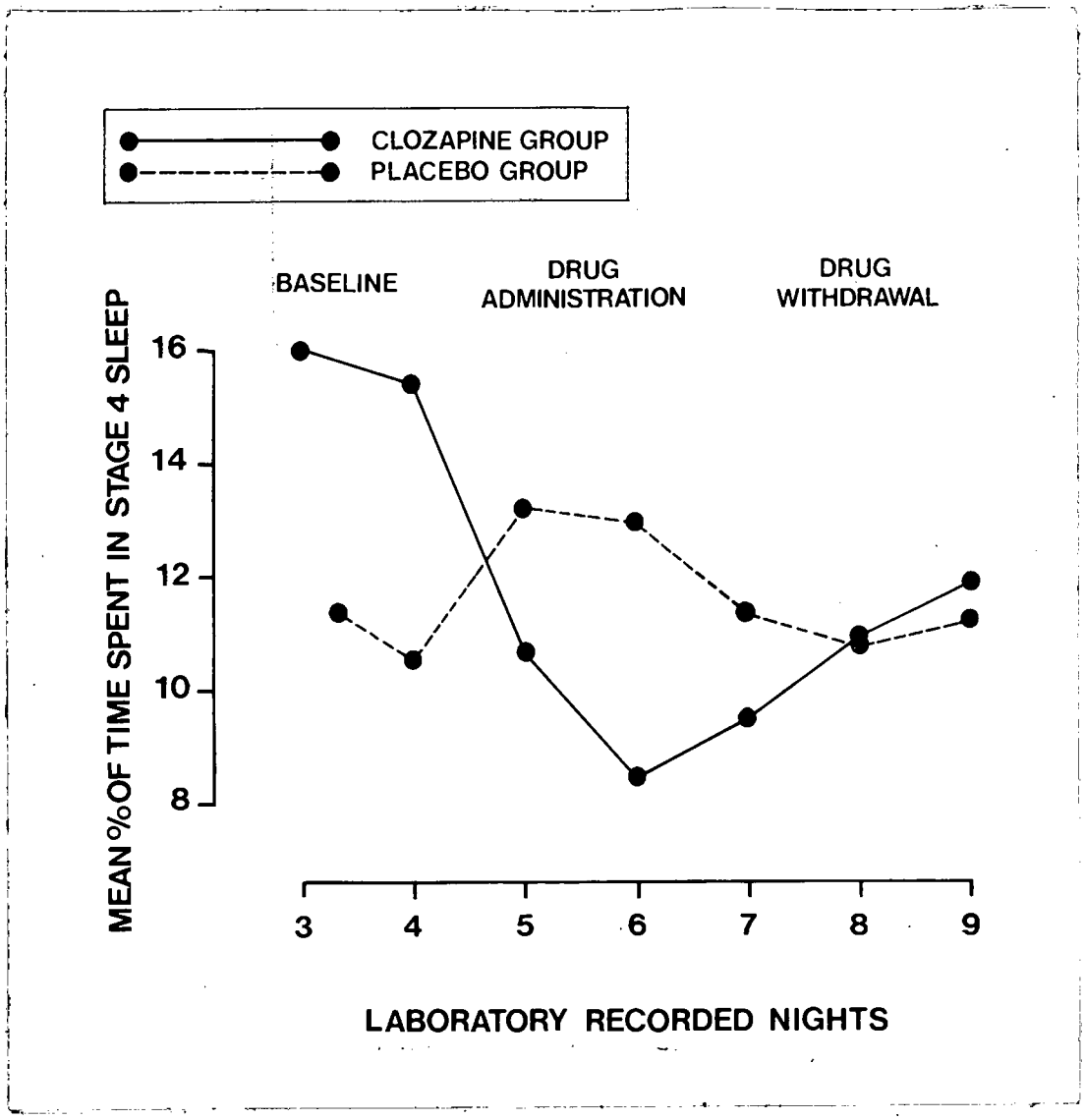


Figure 8 The mean percentage of time spent in stage 4 sleep for the clozapine and placebo groups over the laboratory recorded nights. Stage 4 sleep was significantly suppressed on the second and third nights of clozapine administration. The administration and withdrawal of placebo had no significant effect. Nights 3-4 and nights 8-9 were baseline and withdrawal conditions respectively.

of the data through simple main effects analysis revealed a significant difference over the laboratory recorded nights for the clozapine group ($F = 4,31$; df 6,41; $p<0,01$), but not for the placebo group ($F = 0,55$; df 6,41; $p>0,25$).

The Tukey HSD comparisons indicated that stage 4 sleep was markedly suppressed on the second and third nights of clozapine administration (Figure 8). The mean percentage of time spent in stage 4 sleep on the second night of clozapine administration was lower than on either the first ($p<0,01$) or second ($p<0,01$) baseline nights. The mean percentage of time spent in stage 4 sleep on the third night of clozapine administration was also lower than on the first baseline night ($p<0,05$).

The within-night analyses revealed no significant differences for the first three hours ($F(AXB) = 1,78$; df 6,72; $p<0,25$) and second three hours ($F(AXB) = 1,96$; df 6,72; $p<0,10$) of the record. The analysis of variance of the first six hours of the record yielded a significant variance ratio ($F(AXB) = 3,18$; df 6,72; $p<0,01$). Closer examination through simple main effects analysis revealed a significant difference over the laboratory recorded nights for the clozapine group ($F = 3,58$; df 6,41; $p<0,01$), but not for the placebo group ($F = 0,63$; df 6,41, $p>0,25$).

The Tukey HSD comparisons indicated that stage 4 sleep was markedly suppressed during the <u>first six hours</u> of the second and third nights of clozapine administration and remained at low levels during the first six hours of the first night of drug withdrawal. The mean stage 4 duration during the first six hours of the second

night of clozapine administration was significantly lower than on either the first ($p<0,01$) or second ($p<0,01$) baseline nights. In addition, the mean stage 4 duration during the first six hours of the third night of clozapine administration was also significantly lower than on either the first ($p<0,01$) or second ($p<0,01$) baseline nights. Finally, the mean stage 4 duration during the first six hours of the first night of clozapine withdrawal was significantly lower than on the first baseline night ($p<0,05$).

Stage Slow Wave. The administration of clozapine and placebo had no significant effect upon the percentage of time spent in stage slow wave sleep ($F(AXB) = 1,96$; df 6,72; $p<0,10$) (Table 9). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 1,37$; df 6,72; $p<0,25$), the second three hours ($F(AXB) = 1,09$; df 6,72; $p>0,25$) as well as the first six hours ($F(AXB) = 1,80$; df 6,72; $p<0,25$) of the record.

Stage REM. The administration of clozapine and placebo had no significant effect upon the percentage of time spent in stage REM sleep ($F(AXB) = 1,90$; df 6,72; $p<0,10$) (Table 9). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 1,21$; df 6,72; $p>0,25$), the second three hours ($F(AXB) = 0,66$; df 6,72; $p>0,25$) as well as the first six hours ($F(AXB) = 0,89$; df 6,72; $p>0,25$) of the record.

6.1.3 REM Indices

The effects of the short-term administration of 25mg clozapine and placebo upon the mean indices of stage REM sleep over the

laboratory recorded nights are illustrated in Figure 9.

Mean REM Duration. The administration of clozapine and placebo had no significant effect upon the mean duration of stage REM sleep ($F(AXB) = 1,35$; df 6,72; $p<0,25$) (Table 10).

Total Number of Bursts. The effects of the administration of clozapine and placebo upon the total number of bursts are presented in Table 10 and significant findings are illustrated in Figure 9 ($F(AXB) = 2,64$; df 6,72; $p<0,05$). Closer examination of the data through simple main effects analysis revealed a significant difference between the clozapine and placebo groups on the first night of drug administration ($F = 12,11$; df 1,84; $p<0,001$) and a significant difference over the laboratory recorded nights for the clozapine group ($F = 5,33$; df 6,41; $p<0,001$), but not for the placebo group ($F = 0,31$; df 6,41; $p>0,25$).

The Tukey HSD comparisons indicated that the total number of bursts increased markedly on the first night of clozapine withdrawal (Figure 9). The first night of clozapine withdrawal contained significantly more bursts than either the first baseline ($p<0,01$) or first ($p<0,01$) and third ($p<0,05$) clozapine administration nights. The second night of clozapine withdrawal contained significantly more bursts than the first night of clozapine administration ($p<0,05$).

Number of Bursts per REM period. The effects of the administration of clozapine and placebo upon the number of bursts per REM period are presented in Table 10 and significant findings are illustrated in Figure 9 ($F(AXB) = 2,60$; df 6,72; $p<0,05$). Closer examination of the data through simple main effects

Table 10. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean REM indices of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
Mean REM duration (minutes)										
clozapine group	22,43± 2,19	24,31±1,61	18,44±1,09	21,51±2,91	20,43±1,85	23,23±1,58	22,94± 1,27	6,72	1,35	<0,25
placebo group	22,46± 1,74	25,64±1,61	26,19±3,51	22,77±2,16	26,78±2,46	25,64±3,24	24,20± 3,08			
Mean (total) number of bursts										
clozapine group	85,71± 6,76	95,71±6,92	71,43±3,03	95,29±6,75	91,14±6,99	124,29±7,48	102,00±12,54	6,72	2,64	<0,05
placebo group	106,29±11,52	107,86±9,72	111,86±8,11	101,57±7,17	109,71±5,01	111,57±9,12	112,43± 8,86			
Mean number of bursts per REM period										
clozapine group	19,91± 1,95	22,65±1,59	16,26±1,22	21,99±2,50	21,01±1,95	27,80±2,28	23,36± 2,62	6,72	2,60	<0,05
placebo group	22,51± 2,12	25,37±2,54	25,70±2,84	23,24±1,77	25,70±2,50	24,60±1,58	25,68± 2,28			
Mean burst length (seconds)										
clozapine group	7,35± 0,96	7,49±0,90	7,76±1,78	10,65±1,99	12,98±3,04	10,88±1,09	8,93± 1,38	6,72	2,63	<0,05
placebo group	11,70± 1,81	13,17±1,39	8,97±0,74	10,85±1,29	11,17±1,49	9,53±0,74	9,86± 1,09			
Mean density per minute REM sleep										
clozapine group	4,40± 0,75	4,21±0,64	4,38±0,25	5,62±1,09	8,36±1,27	8,37±1,11	5,73± 0,56	6,72	5,10	<0,001
placebo group	7,14± 1,05	8,08±1,03	6,43±0,77	7,36±1,13	7,08±1,26	6,14±0,75	6,53± 0,66			
Mean % motility										
clozapine group	12,32± 2,04	12,26±1,87	11,38±1,31	18,31±2,90	23,53±3,57	23,89±2,95	16,75± 2,25	6,72	4,90	<0,001
placebo group	20,29± 3,10	23,43±2,07	18,18±1,93	21,68±3,11	20,09±3,05	18,03±2,10	19,64± 1,35			

analysis revealed a significant difference between the clozapine and placebo groups on the first night of drug administration ($F = 9,40$; df 1,84; $p<0,01$) and a significant difference over the laboratory recorded nights for the clozapine group ($F = 4,46$; df 6,41; $p<0,01$), but not for the placebo group ($F = 0,62$; df 6,41; $p>0,25$).

The Tukey HSD comparisons revealed that the number of bursts per REM period increased markedly on the first night of clozapine withdrawal (Table 10). The first night of clozapine withdrawal contained significantly more bursts per REM period than either the first baseline ($p<0,05$) or the first night of clozapine administration ($p<0,01$). The second night of clozapine withdrawal also contained significantly more bursts per REM period than the first night of clozapine administration ($p<0,05$).

Mean Burst Length. The effects of the administration of clozapine and placebo upon the mean burst length are presented in Table 10 and significant findings are illustrated in Figure 9 ($F(AXB) = 2,63$; df 6,72; $p<0,05$). Closer examination of the data through simple main effects analysis revealed significant differences between the clozapine and placebo groups on the first ($F = 4,80$; df 1,84; $p<0,05$) as well as the second ($F = 8,19$; df 1,84; $p<0,01$) baseline nights and a significant difference over the laboratory recorded nights for the clozapine group ($F = 3,09$; df 6,41; $p<0,05$), but not for the placebo group ($F = 1,40$; df 6,41; $p<0,25$).

The Tukey HSD comparisons indicated that the mean burst length increased significantly on the third night of clozapine

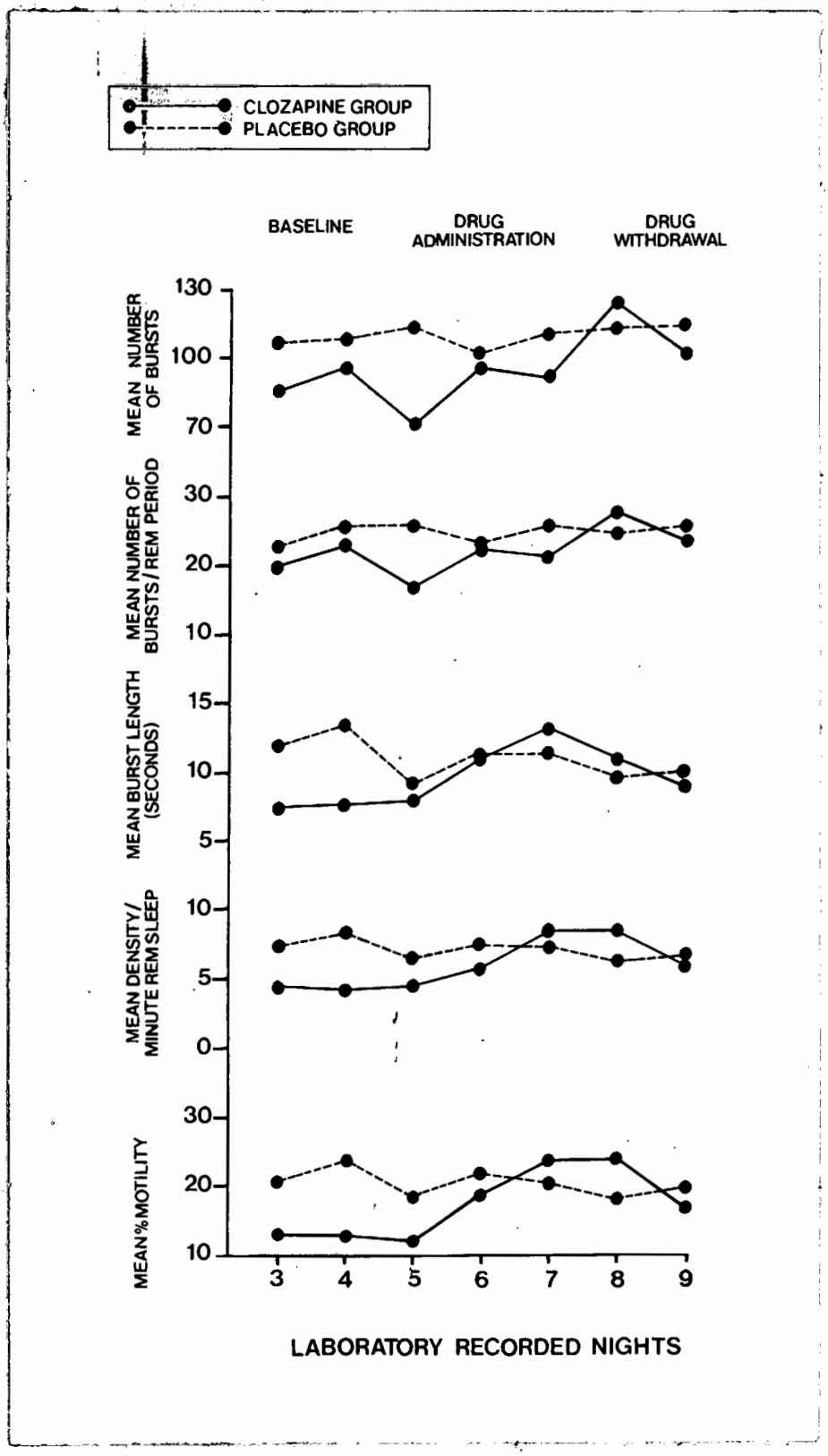


Figure 9 The effects of the short-term administration of 25mg clozapine and placebo upon the mean indices of stage REM sleep over the laboratory recorded nights. The density/minute REM sleep, the mean burst length and % motility increased significantly on the third night of clozapine administration and this increased activity persisted on the first night of clozapine withdrawal. In addition, the total number of bursts and the number of bursts/REM period increased dramatically on the first night of clozapine withdrawal. The administration of placebo had no significant effect. Nights 3-4 and nights 8-9 were baseline and withdrawal conditions respectively.

administration. The mean burst length on the third night of clozapine administration was significantly longer than on either the first ($p<0,05$) and second ($p<0,05$) baseline nights as well as the first night of clozapine administration ($p<0,05$).

Density per Minute REM sleep. The effects of the administration of clozapine and placebo upon the density per minute REM sleep are presented in Table 10 and significant findings are illustrated in Figure 9 ($F(AXB) = 5,10$; df 6,72; $p<0,001$). Closer examination of the data through simple main effects analysis revealed significant differences between the clozapine and placebo groups on the first ($F = 4,36$; df 1,84; $p<0,05$) as well as the second ($F = 8,72$; df 1,84; $p<0,01$) baseline nights and a significant difference over the laboratory recorded nights for the clozapine group ($F = 7,03$; df 6,41; $p<0,001$), but not for the placebo group ($F = 0,93$; df 6,41; $p>0,25$).

The Tukey HSD comparisons indicated that the density per minute REM sleep increased significantly on the third night of clozapine administration and persisted on the first night of clozapine withdrawal. The mean density per minute REM sleep on the third night of clozapine administration was significantly greater than on either the first ($p<0,01$) and second ($p<0,01$) baseline nights as well as the first night of clozapine administration. In addition, the mean density per minute REM sleep on the first night of clozapine withdrawal was significantly greater than on either the first ($p<0,01$) and second ($p<0,01$) baseline nights as well as the first night of clozapine administration ($p<0,01$).

% Motility. The effects of the administration of clozapine and placebo upon % motility are presented in Table 10 and

significant findings are illustrated in Figure 9 (F(AXB) = 4,90; df 6,72; p<0,001). Closer examination of the data through simple main effects analysis revealed significant differences between the clozapine and placebo groups on the first (F = 5,09; df 1,84; p<0,05) as well as the second (F = 10,01; df 1,84; p<0,01) baseline nights and a significant difference over the laboratory recorded nights for the clozapine group (F = 7,29; df 6,41; p<0,001), but not for the placebo group (F = 0,94; df 6,41; p>0,25).

The Tukey HSD comparisons indicated that % motility increased significantly on the third night of clozapine administration and that this increase persisted on the first night of clozapine withdrawal. The mean % motility on the third night of clozapine administration was significantly greater than on either the first (p<0,01) and second (p<0,01) baseline nights as well as on the first night of clozapine administration (p<0,01). In addition, the mean % motility on the first night of clozapine withdrawal was significantly greater than on either the first (p<0,01) and second (p<0,01) baseline nights as well as on the first night of clozapine administration (p<0,01).

6.1.4 Sleep Stage Latencies

Stage 1 Latency. The administration of clozapine and placebo had no significant effect upon the latency to stage 1 sleep (F(AXB) = 1,77; df 6,72; p<0,25) (Table 11).

Stage 2 Latency. The administration of clozapine and placebo had no significant effect upon the latency to stage 2 sleep (F(AXB) = 2,09; df 6,72; p<0,10) (Table 11).

Table II. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean sleep latencies of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
Mean stage 1 latency (minutes)										
clozapine group	5,93± 1,52	6,86± 2,77	6,64± 1,79	5,93± 2,51	10,00± 5,03	13,00± 8,34	10,43± 4,12	6,72	1,77	<0,25
placebo group	8,64± 3,84	13,43± 5,05	9,93± 4,47	8,14± 3,77	5,00± 2,22	5,50± 2,28	8,71± 4,11			
Mean stage 2 latency (minutes)										
clozapine group	18,71± 3,21	14,50± 3,18	15,71± 1,85	18,36± 4,08	21,79± 4,65	19,00± 4,47	25,50± 5,92	6,72	2,09	<0,10
placebo group	18,86± 5,36	19,64± 5,75	17,64± 5,13	13,71± 3,71	12,57± 2,96	13,86± 2,71	13,71± 4,05			
Mean stage 4 latency (minutes)										
clozapine group	32,43± 4,77	29,50± 3,43	32,93± 4,16	37,36± 4,15	41,00± 4,63	29,50± 3,71	36,71± 8,74	6,72	0,91	>0,25
placebo group	27,14± 2,07	27,21± 3,11	23,93± 2,31	26,07± 1,04	26,07± 3,43	29,57± 4,39	27,64± 2,29			
Mean latency to the first REM period (minutes)										
clozapine group	97,14±15,64	91,00±10,45	97,57± 7,23	76,07± 3,56	74,71± 6,72	70,57± 7,03	78,86± 6,61	6,72	0,85	>0,25
placebo group	96,00±15,27	87,29±14,37	96,57±13,95	96,64±15,16	91,14±13,58	100,50±12,44	85,50± 6,37			
Mean latency to the second REM period (minutes)										
clozapine group	188,14±15,10	185,57±12,74	199,29±12,64	159,93± 8,49	172,21±10,76	170,79± 9,98	175,79±11,14	6,72	1,01	>0,25
placebo group	179,64±18,94	180,86± 9,84	179,07±14,77	191,57±12,54	178,07±16,68	171,86±12,81	169,57± 7,97			
Mean latency to the third REM period (minutes)										
clozapine group	270,71±17,86	249,43±13,44	293,29±16,64	238,71±11,04	250,00±10,80	238,36±10,53	243,93±12,90	6,72	1,44	<0,25
placebo group	245,71±17,61	266,79± 6,12	260,93±20,52	260,36±11,37	244,71±16,00	249,86±14,37	240,64± 6,96			

Stage 4 Latency. The administration of clozapine and placebo had no significant effect upon the latency to stage 4 sleep ($F(AXB) = 0,91$; df 6,72; $p>0,25$) (Table 11).

Latency to the First REM Period. The administration of clozapine and placebo had no significant effect upon the latency to the first REM period ($F(AXB) = 0,85$; df 6,72; $p>0,25$) (Table 11).

Latency to the Second REM Period. The administration of clozapine and placebo had no significant effect upon the latency to the second REM period ($F(AXB) = 1,01$; df 6,72; $p>0,25$) (Table 11).

Latency to the Third REM Period. The administration of clozapine and placebo had no significant effect upon the latency to the third REM period ($F(AXB) = 1,44$; df 6,72; $p<0,25$) (Table 11).

6.1.5 Sleep Stage Incidence

Number of Awakenings. The administration of clozapine and placebo had no significant effect upon the number of awakenings during sleep ($F(AXB) = 0,56$; df 6,72; $p>0,25$) (Table 12).

Number of Stage 4 Periods. The administration of clozapine and placebo had no significant effect upon the number of stage 4 periods during sleep ($F(AXB) = 1,31$; df 6,72; $p>0,25$) (Table 12).

Number of Stage REM Periods. The administration of clozapine and placebo had no significant effect upon the number of stage REM periods during sleep ($F(AXB) = 0,17$; df 6,72; $p>0,25$).

Table 12. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean sleep stage incidence of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
	Mean number of awakenings									
clozapine group	1,29±0,36	0,43±0,30	0,43± 0,30	0,14±0,14	0,43±0,43	0,14±0,14	0,71±0,42	6,72	0,56	>0,25
placebo group	1,00±0,31	0,86±0,40	0,86± 0,34	0,86±0,34	0,86±0,46	0,86±0,26	1,00±0,44			
	Mean number of stage 4 periods									
clozapine group	3,14±0,26	3,29±0,68	2,43± 0,30	2,00±0,22	2,43±0,30	2,14±0,26	2,71±0,36	6,72	1,31	>0,25
placebo group	2,57±0,43	3,00±0,38	3,14± 0,40	2,86±0,34	2,43±0,37	2,71±0,29	2,71±0,18			
	Mean number of stage REM periods									
clozapine group	4,43±0,43	4,29±0,29	4,43± 0,37	4,57±0,37	4,43±0,30	4,57±0,30	4,29±0,29	6,72	0,17	>0,25
placebo group	4,71±0,29	4,43±0,20	4,57± 0,43	4,43±0,30	4,43±0,30	4,71±0,36	4,43±0,20			

6.1.6 Sleep Cycle Duration

Duration of the First Sleep Cycle. The administration of clozapine and placebo had no significant effect upon the duration of the first sleep cycle ($F(AXB) = 1,80$; df 6,72; $p<0,25$) (Table 13).

Duration of the Second Sleep Cycle. The analysis of variance yielded a significant variance ratio ($F(AXB) = 2,82$; df 6,72; $p<0,05$) (Table 13) as well as a significant F max.ratio ($F = 2,26$; df 2,36; $p<0,05$). In view of the significant F max. test of homogeneity of variance, no further statistical analysis was carried out.

6.1.7 Body Movement Activity

As previously described (section 5.5.4) the indices of body movement activity have been analysed for the first three hours, the second three hours, the first six hours of the record as well as for the entire night.

Number of Body Movements. The effects of the administration of clozapine and placebo upon the number of body movements are presented in Table 14 ($F(AXB) = 4,03$; df 6,72; $p<0,01$). Closer examination of the data through simple main effects analysis revealed a significant difference between the clozapine and placebo groups on the third night of drug administration ($F = 5,92$; df 1,84; $p<0,05$) and a significant difference over the laboratory recorded nights for the clozapine group ($F = 5,19$; df 6,41; $p<0,001$), but not for the placebo group ($F = 1,13$; df 6,41; $p>0,25$).

The Tukey HSD comparisons indicated that the number of body

Table 13. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean duration of the first and second sleep cycles of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
	Mean duration of the first sleep cycle (minutes)									
clozapine group	103,64± 5,72	111,71± 7,93	113,07±10,38	99,00± 8,75	105,43±9,57	113,64±11,00	113,29± 8,24	6,72	1,80	<0,25
placebo group	100,86± 5,69	108,14± 7,52	113,00±10,96	115,29± 4,69	102,50±5,55	89,86± 7,47	95,14± 2,64			
	Mean duration of the second sleep cycle (minutes)									
clozapine group	107,93± 7,27	91;64± 6,30	115,43±10,31	101,64± 7,26	104,93±5,15	91,64± 7,06	92,86± 3,64	6,72	2,82	<0,05
placebo group	87,43±10,06	121,29± 7,97	105,79±11,22	101,21±11,23	105,93±7,44	124,50±12,00	109,00±13,18			

Table 14. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean body movement indices of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
	Mean number of body movements									
clozapine group	75,00±8,11	72,29± 7,95	51,29± 5,71	53,14± 4,91	47,00± 5,95	50,57± 4,65	61,14± 7,53	6,72	4,03	<0,01
placebo group	65,00±8,13	77,14±11,60	75,43±11,76	66,14± 8,34	77,00±11,11	74,86±11,25	69,29±10,12			
	Mean number of body movements per minute of sleep									
clozapine group	0,17±0,02	0,16± 0,02	0,11± 0,01	0,11± 0,01	0,10± 0,01	0,12± 0,01	0,14± 0,02	6,72	4,90	<0,001
placebo group	0,14±0,02	0,17± 0,03	0,17± 0,02	0,15± 0,02	0,17± 0,02	0,16± 0,02	0,15± 0,02			
	Mean number of 30 second epochs spent in movement time									
clozapine group	10,86±0,96	12,86± 2,15	5,00± 0,75	6,29± 2,12	5,29± 0,92	7,00± 0,75	8,29± 1,06	6,72	1,31	>0,25
placebo group	15,00±3,23	17,29± 3,35	14,71± 1,46	13,00± 2,50	16,29± 3,50	13,00± 2,50	13,57± 1,75			

Tukey HSD comparisons indicated that the number of body movements was significantly reduced during the second three hours of the three nights of clozapine administration as well as during the second three hours of the first night of clozapine withdrawal (Table 15(a)).

The analysis of variance of the first six hours of the record yielded a significant variance ratio ($F(AXB) = 3,49$; df 6,72; $p<0,001$). Closer examination through simple main effects analysis revealed a significant difference over the laboratory recorded nights for the clozapine group ($F = 5,49$; df 6,41; $p<0,001$), but not for the placebo group ($F = 0,64$; df 6,41; $p>0,25$). The Tukey HSD comparisons indicated that the number of body movements were significantly reduced during the first six hours on the first and third nights of clozapine administration as well as on the first night of clozapine withdrawal (Table 15(b)).

Number of Body Movements per Minute of Sleep. The effects of the administration of clozapine and placebo upon the number of body movements/minute of sleep are presented in Table 14 and significant findings are illustrated in Figure 10 ($F(AXB) = 4,90$; df 6,72; $p<0,001$). Closer examination of the data through simple main effects analysis revealed significant differences between the clozapine and placebo groups on the first ($F = 5,16$; df 1,84; $p<0,05$) and third ($F = 6,19$; df 6,72; $p<0,05$) nights of drug administration and a significant difference over the laboratory recorded nights for the clozapine group ($F = 6,57$; df 6,41; $p<0,001$), but not for the placebo group ($F = 1,09$; df 6,41; $p>0,25$).

Table 15(a) Tukey HSD comparisons+ of the means of the seven laboratory recorded nights for the second three hours of the record on the number of body movements (clozapine group).

Experimental Condition	Baseline		Clozapine administration			Withdrawal	
Nights	3	4	5	6	7	8	9
3	-	0,83	7,03**	5,60**	7,63**	6,02**	3,99
4		-	6,20**	4,77*	6,79**	5,18*	3,16
5			-	1,43	0,60	1,01	3,04
6				-	2,03	0,42	1,61
7					-	1,61	3,63
8						-	2,03
9							-

+ DF = 7,72 for all comparisons

* $p<0,05$

** $p<0,01$

Table 15(b) Tukey HSD comparisons+ of the means of the seven laboratory recorded nights for the first six hours of the record on the number of body movements (clozapine group).

Experimental Condition	Baseline		Clozapine administration			Withdrawal	
Nights	3	4	5	6	7	8	9
3	-	0,03	4,98*	4,05	5,36**	4,94*	2,33
4		-	5,01**	4,09	5,39**	4,98*	2,37
5			-	0,93	0,38	0,03	2,64
6				-	1,30	0,89	1,72
7					-	0,41	3,02
8						-	2,61
9							-

+ DF = 7,72 for all comparisons

* $p<0,05$

** $p<0,01$

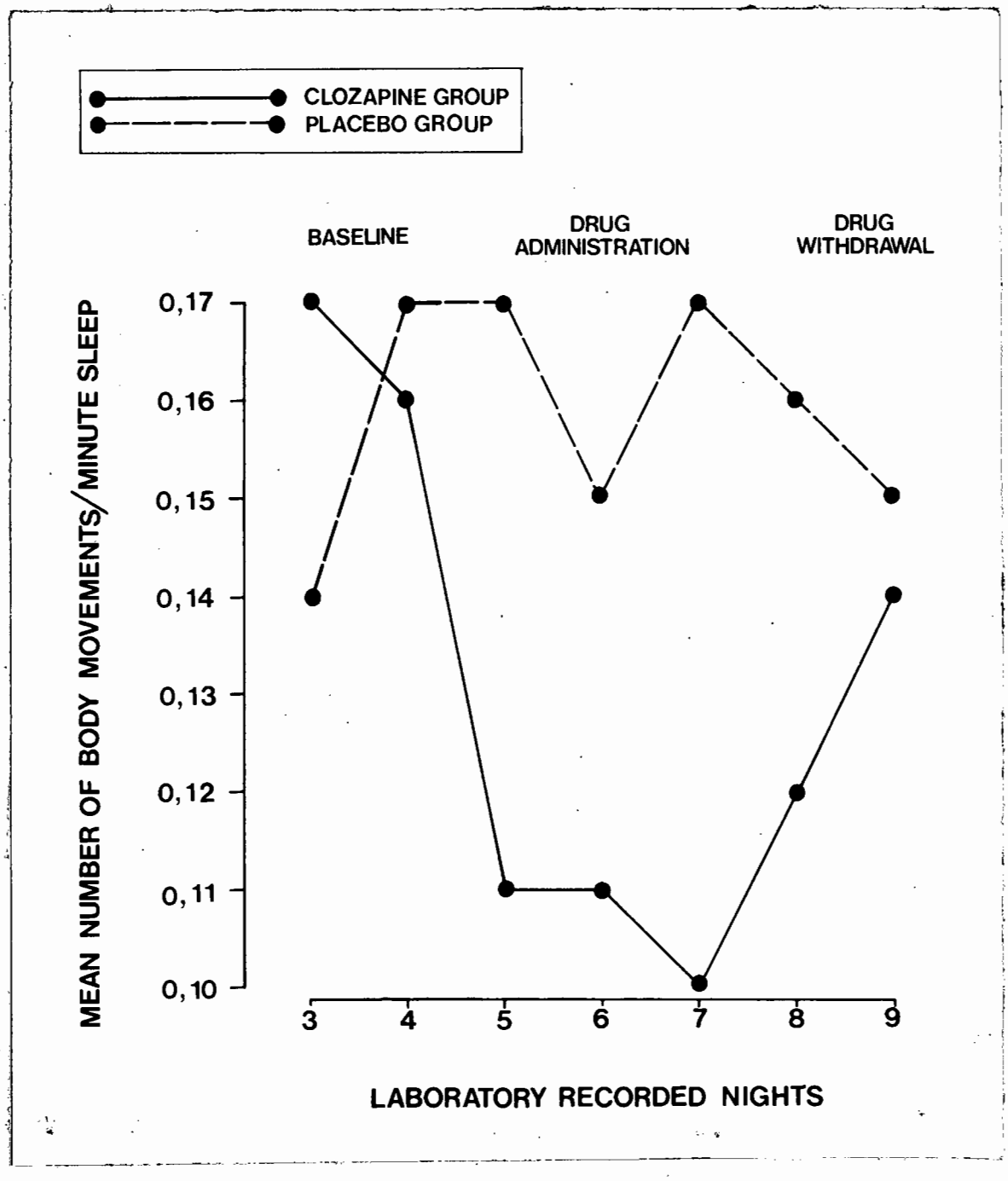


Figure 10 The mean number of body movements/minute of sleep for the clozapine and placebo groups over the laboratory recorded nights. The mean number of body movements/minute of sleep were markedly reduced during the administration of clozapine and values remained at low levels on the first night of clozapine withdrawal. Nights 3-4 and nights 8-9 were baseline and withdrawal conditions respectively.

The Tukey HSD comparisons indicated that the number of body movements/minute of sleep was markedly reduced during the administration of clozapine and values remained at low levels on the first night of clozapine withdrawal (Figure 10). The mean number of body movements/minute of sleep on the first night of clozapine administration was significantly lower than on either the first ($p<0,01$) or second ($p<0,01$) baseline nights. The mean number of body movements/minute of sleep on the second night of clozapine administration was significantly lower than on either the first ($p<0,01$) or second ($p<0,05$) baseline nights whereas the mean number on the third night of clozapine administration was also significantly lower than on the first ($p<0,01$) or second ($p<0,01$) baseline nights. Finally, the mean number of body movements/minute of sleep on the first night of clozapine withdrawal was significantly lower than on the first baseline night ($p<0,05$).

Movement Time. The administration of clozapine and placebo had no significant effect upon movement time ($F(AXB) = 1,31$; df 6,72; $p>0,25$) (Table 14). The within-night analyses also revealed no significant differences for the first three hours ($F(AXB) = 0,78$; df 6,72; $p>0,25$), the second three hours ($F(AXB) = 0,66$; df 6,72; $p>0,25$) as well as the first six hours ($F(AXB) = 1,02$; df 6,72; $p>0,25$) of the record.

6.1.8 Visual Analogue Scales

The visual analogue scales (depression, anxiety, drowsiness and concentration ability) provided a sensitive index of transient feelings and moods (section 5.2.6). The subjects completed the above visual analogue scales in the morning approximately fifteen

minutes after awakening (section 5.3.7). As previously described (section 5.6.1), the visual analogue data were transformed to normalised data using a Z score transformation procedure. The visual analogue data are presented in Table 16.

Depression. The administration of clozapine and placebo had no significant effect upon depression ($F(AXB) = 0,83$; df 6,84; $p>0,25$) (Table 16).

Anxiety. The administration of clozapine and placebo had no significant effect upon anxiety ($F(AXB) = 1,74$; df 6,84; $p<0,25$).

Drowsiness. The effects of the administration of clozapine and placebo upon drowsiness are presented in Table 16 ($F(AXB) = 4,85$; df 6,84; $p<0,001$). Closer examination of the data through simple main effects analysis revealed significant differences between the clozapine and placebo groups on the first morning following drug administration ($F = 14,995$; df 1,84; $p<0,001$) and on the first morning following drug withdrawal ($F = 11,65$; df 1,84; $p<0,001$),and a significant difference over the laboratory recorded nights for both the clozapine ($F = 10,44$; df 6,84; $p<0,001$) and placebo ($F = 3,04$; df 6,84; $p<0,01$) groups.

The Tukey HSD comparisons indicated that the administration of clozapine significantly increased the degree of drowsiness on the mornings following the first and second nights of administration whereas the administration of placebo significantly increased the degree of drowsiness on the morning following the second night of placebo administration. The mean value was significantly greater on the morning following the first night of clozapine administration than on the mornings following either the first ($p<0,01$) or second

Table 16. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the subjective estimates of depression, anxiety, drowsiness and concentration ability as measured by visual analogue scales in 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
Mean depression index										
clozapine group	49,25±3,78	49,38±3,75	52,78±4,30	58,00±4,18	51,20±3,14	44,88±1,52	44,52±1,25	6,84	0,83	>0,25
placebo group	43,35±1,75	47,39±2,69	51,99±3,74	55,15±4,82	50,92±3,51	50,65±2,80	50,55±4,27			
Mean anxiety index										
clozapine group	51,76±4,79	50,46±2,87	56,34±4,21	52,39±3,16	49,42±3,08	43,05±1,31	46,47±3,36	6,84	1,74	<0,25
placebo group	44,96±3,39	50,10±4,44	46,40±2,12	55,82±2,81	51,50±3,00	49,46±3,54	51,77±2,72			
Mean drowsiness index										
clozapine group	44,67±1,28	43,85±1,34	65,64±1,92	55,42±1,92	54,23±2,95	41,59±1,11	44,49±1,45	6,84	4,85	<0,001
placebo group	43,37±1,79	45,00±2,56	50,88±2,92	56,31±4,19	50,75±4,68	54,60±3,20	48,95±3,20			
Mean concentration ability index										
clozapine group	53,33±1,18	53,62±2,15	36,45±3,71	48,13±3,08	50,69±2,65	55,42±2,95	52,36±3,70	6,84	2,56	<0,05
placebo group	49,60±3,63	47,17±3,10	51,29±2,88	48,16±4,92	54,97±3,76	50,23±3,46	48,43±3,54			

($p<0,01$) baseline nights, the third night of clozapine administration ($p<0,05$) as well as the first ($p<0,01$) and second ($p<0,01$) nights of clozapine withdrawal. In addition, the mean value on the morning following the second night of clozapine administration was significantly greater than the mean values on the mornings following the second baseline night ($p<0,05$) and the first night of clozapine withdrawal ($p<0,01$). The mean value on the morning following the third night of clozapine administration was significantly greater than the mean value on the morning following the first night of clozapine withdrawal ($p<0,05$). Finally, the mean value on the morning following the second night of placebo administration was significantly greater than the mean value on the morning following the first baseline night ($p<0,05$).

Concentration Ability. The effects of the administration of clozapine and placebo upon concentration ability are presented in Table 16 ($F(AXB) = 2,56$; df 6,84; $p<0,05$). Closer examination of the data through simple main effects analysis revealed a significant difference between the clozapine and placebo groups on the morning following the first night of drug administration ($F = 10,13$; df 1,84; $p<0,01$) and a significant difference over the laboratory recorded nights for the clozapine group ($F = 3,79$; df 6,84; $p<0,01$), but not for the placebo group ($F = 0,62$; df 6,84; $p>0,25$).

The Tukey HSD comparisons indicated that the ability to concentrate was markedly reduced on the morning following the first night of clozapine administration. The mean value on the morning following the first night of clozapine administration was significantly lower than the mean values on the mornings following the

first ($p<0,01$) and second ($p<0,01$) baseline nights, the third night of clozapine administration ($p<0,05$) as well as the first ($p<0,01$) and second ($p<0,05$) nights of clozapine withdrawal.

6.1.9 Sleep Log

The sleep log provided information regarding the quality of the night's sleep, the mood shortly after awakening as well as psychological and physiological side-effects (section 5.2.8). The subjects completed the sleep log in the morning approximately fifteen minutes after awakening (section 5.3.7). The sleep log data are presented in Table 17.

Quality of Sleep (Question six). The administration of clozapine and placebo had no significant effect upon the quality of sleep ($F(AXB) = 1,33$; df 6,72; $p>0,25$) (Table 17).

Mood Shortly After Awakening (Question seven). The administration of clozapine and placebo had no significant effect upon the mood shortly after awakening ($F(AXB) = 2,07$; df 6,72; $p<0,10$) (Table 17).

Psychological and Physiological Side-Effects. The clozapine group reported numerous physiological side-effects such as nausea, difficulty in writing and speaking on the mornings following the three nights of clozapine administration but failed to report any psychological side-effects (Table 17). No side-effects were reported on the mornings following the baseline or drug withdrawal conditions. The placebo group failed to report any psychological or physiological side-effects.

Table 17. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the sleep log indices (quality of sleep and psychological and physiological side-effects) of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication				
Experimental Condition	Baseline		Drug Administration			Withdrawal		Degrees of Freedom	F Ratio (AXB)	P
Laboratory Recorded Nights	3	4	5	6	7	8	9			
	How well do you sleep compared to the way you usually sleep? (Question Six) (Mean score)									
clozapine group	2,57±0,20	2,86±0,14	4,14±0,26	3,29±0,42	3,71±0,29	3,14±0,34	3,14±0,34	6,72	1,33	>0,25
placebo group	3,14±0,14	3,43±0,20	3,57±0,37	3,29±0,18	3,71±0,36	3,43±0,20	3,29±0,18			
	How do you feel this morning? (Question Seven) (Mean score)									
clozapine group	3,00±0,00	3,14±0,14	2,00±0,38	2,14±0,26	2,43±0,20	3,43±0,30	3,43±0,37	6,72	2,07	<0,10
placebo group	3,29±0,18	3,29±0,18	3,14±0,34	2,71±0,29	2,86±0,14	3,29±0,29	3,00±0,22			
	Physiological side-effects reported. (Number in bracket indicates the frequency of occurrence)									
clozapine group	none	none	(i) slurring of speech(5) (ii) difficulty in writing(2) (iii) nausea(3) (iv) lethargic(2) (v) physically weak(2) (vi) hypotensive(3)	(i) mouth very dry(3) (ii) sleepy(3) (iii) hypotensive(1) (iv) nausea(1) (v) physically weak(1)	(i) slurring of speech(2) (ii) lethargic(4) (iii) nausea(1)	none	none			
placebo group	none	none	none	none	none	none	none			
	Psychological side-effects reported.									
clozapine group	none	none	none	none	none	none	none			
placebo group	none	none	none	none	none	none	none			

6.1.10 Mental Speed Test

The mental speed test assessed the speed and accuracy of performance (section 5.2.9). The subjects completed the mental speed test fifteen minutes after awakening (section 5.3.6).

Number of Errors. The administration of clozapine and placebo had no significant effect upon the number of errors produced on the mental speed test ($F(AXB) = 0,63$; df 6,72; $p>0,25$) (Table 18).

Number of Problems Attempted. The effects of the administration of clozapine and placebo upon the number of problems attempted are presented in Table 18 ($F(AXB) = 6,12$; df 6,72; $p<0,001$). Closer examination of the data through simple main effects analysis revealed significant differences between the clozapine and placebo groups on the mornings following the first ($F = 4,57$; df 1,84; $p<0,05$), second ($F = 4,25$; df 1,84; $p<0,05$) and third ($F = 4,21$; df 1,84; $p<0,05$) nights of drug administration and a significant difference over the laboratory recorded nights for both the clozapine ($F = 12,54$; df 6,41; $p<0,001$) and placebo ($F = 3,31$; df 6,41; $p<0,01$) groups.

The Tukey HSD comparisons indicated that the number of problems attempted were dramatically reduced on the mornings following the three nights of clozapine administration. An increased number of problems were attempted on the mornings following the nights of placebo administration. The mean number of problems attempted on the morning following the first night of clozapine administration was significantly less than on the mornings following the first ($p<0,01$) and second ($p<0,01$) baseline nights

Table 18. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the mean mental speed test performance of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
	Mean number of errors									
clozapine group	2,14± 0,63	2,00± 0,69	2,29± 0,42	2,14± 0,59	2,86± 1,22	2,71± 1,02	2,00± 0,75	6,72	0,63	>0,25
placebo group	0,86± 0,40	0,86± 0,26	0,86± 0,46	0,14± 0,38	0,43± 0,20	0,86± 0,26	1,00± 0,44			
	Mean number of problems attempted									
clozapine group	118,14±11,08	120,57±10,82	104,00±11,10	105,14±10,45	109,71±12,09	124,14±12,06	122,57±11,53	6,72	6,12	<0,001
placebo group	132,57± 9,49	133,00±10,06	136,00± 7,71	136,00± 9,18	140,43±10,82	142,00±10,18	143,43±10,52			

as well as the first ($p<0,01$) and second ($p<0,01$) withdrawal nights. In addition, the mean number of problems attempted on the morning following the second night of clozapine administration was significantly less than on the mornings following the first ($p<0,01$) and second ($p<0,01$) baseline nights as well as the first ($p<0,01$) and second ($p<0,01$) withdrawal nights. Finally, the mean number of problems attempted on the morning following the third night of clozapine administration was significantly less than on the mornings following the second baseline night ($p<0,05$) as well as the first ($p<0,01$) and second ($p<0,01$) withdrawal nights.

The mean number of problems attempted on the morning following the second night of placebo withdrawal was significantly greater than those on the mornings following the first ($p<0,05$) and second ($p<0,05$) baseline nights.

6.1.11 The Activation Deactivation Adjective Check List

The Activation Deactivation Adjective Check List measured transient levels of mood (section 5.2.5). The subjects completed the above check list in the morning approximately fifteen minutes after awakening (section 5.3.7). The check list data are presented in Table 19.

General Activation. The effects of the administration of clozapine and placebo upon General Activation are presented in Table 19 ($F(AXB) = 3,80$; df 6,72; $p<0,01$). Closer examination of the data through simple main effects analysis revealed a significant difference between the clozapine and placebo groups

Table 19. The effects of the short-term administration of 25mg clozapine and 25mg placebo upon the Activation Deactivation Adjective Check List (AD-ACL) of 14 normal young adults (Means ± S.E.)

Medication Administered	No Medication		25mg clozapine or 25mg placebo			No Medication		Degrees of Freedom	F Ratio (AXB)	P
Experimental Condition	Baseline		Drug Administration			Withdrawal				
Laboratory Recorded Nights	3	4	5	6	7	8	9			
	Mean General Activation index									
clozapine group	15,86±3,33	14,29±2,38	7,43±0,43	10,29±1,81	10,00±1,62	18,43±2,09	13,43±2,29	6,72	3,80	<0,01
placebo group	12,29±1,19	12,43±1,93	12,00±1,90	10,43±1,19	9,57±1,41	9,86±1,80	11,29±1,78			
	Mean High Activation index									
clozapine group	5,14±0,14	5,29±0,29	6,00±0,58	5,29±0,18	5,29±0,18	5,00±0,00	5,29±0,29	6,72	1,74	<0,25
placebo group	5,71±0,71	7,00±0,95	5,71±0,71	6,71±0,89	7,00±0,84	6,29±0,84	6,29±0,71			
	Mean Deactivation Sleep index									
clozapine group	6,57±1,11	6,71±0,84	11,43±0,20	10,00±0,79	9,00±1,23	4,00±0,72	6,86±1,16	6,72	2,86	<0,05
placebo group	7,71±0,71	6,29±1,13	7,43±1,17	7,86±1,31	7,43±0,72	5,57±0,99	6,29±1,34			
	Mean General Deactivation index									
clozapine group	19,57±2,02	20,00±2,16	18,86±1,93	18,86±1,35	20,71±1,92	18,00±1,90	19,43±2,12	6,72	0,28	>0,25
placebo group	21,00±1,19	19,86±2,01	20,29±1,68	18,57±1,85	19,57±1,54	18,71±1,15	19,86±1,50			

on the morning following the first night of drug withdrawal ($F = 10,05$; df 1,84; $p<0,01$) and a significant difference over the laboratory recorded nights for the clozapine group ($F = 6,91$; df 6,41; $p<0,001$), but not for the placebo group ($F = 0,67$; df 6,41; $p>0,25$).

The Tukey HSD comparisons indicated that General Activation was markedly reduced on the morning following the first night of clozapine administration (Table 19). The mean General Activation index on the morning following the first night of clozapine administration was significantly lower than on the mornings following the first ($p<0,01$) and second ($p<0,05$) baseline nights as well as the first night of clozapine withdrawal ($p<0,01$). In addition, the mean General Activation index on the morning following the first night of clozapine withdrawal was significantly greater than on the mornings following the second ($p<0,01$) and third ($p<0,01$) nights of clozapine administration.

High Activation. The administration of clozapine and placebo had no significant effect upon High Activation ($F(AXB) = 1,74$; df 6,72; $p<0,25$) (Table 19).

Deactivation Sleep. The effects of the administration of clozapine and placebo upon Deactivation Sleep are presented in Table 19 ($F(AXB) = 2,86$; df 6,72; $p<0,05$). Closer examination of the data through simple main effects analysis revealed a significant difference between the clozapine and placebo groups on the morning following the first night of drug administration ($F = 7,89$; df 1,84; $p<0,01$) and a significant difference over the laboratory recorded nights for the clozapine group ($F = 9,66$;

df 6,41; p<0,001), but not for the placebo group (F = 1,20; df 6,41; p>0,25).

The Tukey HSD comparisons indicated that Deactivation sleep was significantly increased on the mornings following the first and second nights of clozapine administration. The mean Deactivation Sleep index on the morning following the first night of clozapine administration was significantly greater than on the mornings following the first (p<0,01) and second (p<0,01) baseline nights as well as the first (p<0,01) and second (p<0,01) nights of clozapine withdrawal. In addition, the mean Deactivation Sleep index on the morning following the second night of clozapine administration was significantly greater than on the mornings following the first baseline night (p<0,05) and first night of clozapine withdrawal (p<0,01). Finally, the mean Deactivation Sleep index on the morning following the third night of clozapine administration was significantly greater than on the morning following the first night of clozapine withdrawal (p<0,01).

General Deactivation. The administration of clozapine and placebo had no significant effect upon General Deactivation (F(AXB) = 0,28; df 6,72; p>0,25) (Table 19).

6.2 Discussion

6.2.1 Research Strategy

The nine consecutive night, double blind cross-over design employed in the present study was developed in order to determine the effects of the short-term administration of 25mg clozapine and placebo upon the sleep patterns of normal young adults (Touyz et al 1975(a)). Many methodological inadequacies are inherent in contemporary sleep research designs (section 3.0) and the present study therefore employed the following strategies:

(i) Two adaptation nights were used to ensure that the subjects were adequately adapted to the sleep laboratory environment as the "first night" effect (section 3.1.1) has been associated with a decrease in stage REM sleep and increases in total waking time, the number of stage shifts and the latencies to stage 4 and stage REM sleep (Agnew et al 1966; Mendels and Hawkins 1966).

(ii) The effects of clozapine and placebo were evaluated independently of one another thus providing additional information as to the effects of placebo upon sleep parameters.

(iii) The double blind procedure was employed in order to eliminate the experimenter effect (Orne 1962; Rosenthal 1965) as both the experimenter and subject were unaware as to whether clozapine or placebo had been administered (section 3.3).

(iv) The duration of time which the subject was permitted to spend in bed was controlled in order to eliminate the increase in stage REM sleep which accompanies extended sleep in the morning (Hartmann 1973(b); Johnson 1975(b)-personal communication) (section 3.5).

(v) The subjects were of a similar age group and were medically healthy as slow wave sleep decreases with increasing age (Agnew et al 1967(a); Feinberg 1969; Williams et al 1974) (section 3.3).

(vi) The female subjects commenced the study on the fourth day of their menstrual cycles to control for the increase in stage REM sleep reported to occur prior to menstruation (Hartmann 1966(a); Sheldrake and Cormack 1974) (section 3.3).

(vii) Smaller portions of the night's data were analysed to ensure that all sleep stage alterations were detected (Kales et al 1976; Freemon 1972; Hartmann and Cravens 1973(a)) (section 3.6).

A limitation of the present study was the use of a limited number of subjects. This was necessitated by the exorbitant cost of sleep research. However, the number of subjects used in the present investigation was well within the average number used in most sleep research programs.

6.2.2 Total Sleep Time

The short-term administration of 25mg clozapine resulted in a marked increase in the duration of total sleep time on the first, and, to a much lesser extent, on the second night of administration (Figure 7). Clozapine administration, however, did not reduce the latency to stage 1 sleep (sleep onset) or the frequency and duration of awakenings during the night. The evidence therefore suggests that the administration of clozapine did not result in the subjects falling asleep more rapidly. Neither did the clozapine group wake up on fewer occasions or for shorter durations during the

night. However, they did sleep for more prolonged periods of time. It is of interest to note that an attempt was made to control for the length of time the subjects spent in bed (section 5.3.1), but attempts to awaken the subjects at the specified time on the first and second mornings after clozapine administration proved to be unsuccessful.

It is not surprising that the administration of clozapine had no significant effect upon the latency to stage I sleep as the subjects who participated in the present study were selected on the basis of their healthy sleeping habits. The mean latency to stage I sleep, during the baseline condition, was found to be only 6,40 minutes and was well below the mean value of 18 minutes reported for normal subjects of a similar age group by Williams et al (1974). The subjects fell asleep rapidly without the administration of medication and the effectiveness of clozapine in reducing the latency to sleep onset should thus be investigated in subjects suffering from sleep onset insomnia. This type of insomnia is characterised by sleep onset latencies of exceptionally long durations (Williams et al 1974).

It appears that the subjects developed a rapid tolerance to the drug since the duration of sleep returned to the pre-drug administration baseline levels by the third night of clozapine administration.

In general, therefore, the data showed that the short-term administration of 25mg clozapine resulted in an initial prolongation of sleep duration and that subjects developed a rapid

tolerance to the drug. The finding that clozapine enhanced the duration of sleep is in accordance with the assumption that clozapine may have sleep inducing properties (Ruch et al 1976; Hemphill et al 1974, 1975; Gross and Langner 1966, 1969; Angst et al 1971; Berzewski et al 1969).

The administration of 25mg placebo had no significant effect upon total sleep time. This result is in harmony with the findings of Adam et al (1975, 1976).

6.2.3 Major Sleep Stages

The short-term administration of 25mg clozapine resulted in a marked decrease in stage 4 sleep on the second and third nights of administration (Figure 8). The within-night analyses revealed that stage 4 sleep was suppressed during the first six hours of the record on both these nights as well as on the first night of clozapine withdrawal. These results are largely in agreement with earlier reports concerning the effects of benzodiazepines on sleep patterns. Benzodiazepines have been found to suppress stage 4 sleep much more consistently than stage REM sleep (Kales and Scharf 1973; Dement et al 1973(b); Kales et al 1970(d); Vogel et al 1972(b); Oswald et al 1973). The finding that the administration of 25mg clozapine significantly reduced stage 4 sleep may have important therapeutic implications for the treatment of disorders of slow wave sleep. Enuresis and somnambulism have been found to occur primarily, though not exclusively during slow wave sleep (Gastaut and Broughton 1964; Hawkins et al 1965; Pierce et al 1961; Ritvo et al 1967; Jacobson et al 1965;

Jacobson and Kales 1967),whereas night terrors (pavor nocturnus) are known to occur exclusively during stage 4 sleep (Gastaut and Broughton 1964).

Indeed, the benzodiazepines have been used in the treatment of disorders associated with slow wave sleep. Glick et al (1971) successfully treated seven children, suffering from combinations of enuresis, somnambulism and pavor nocturnus, with diazepam (2,50-5,0mg/night). Moreover, Fisher et al (1973) reported that seven patients suffering from pavor nocturnus, showed a marked clinical improvement when treated with diazepam (5,0-20mg/night). It thus appears that clozapine may play an important role in the treatment of disorders associated with slow wave sleep. However, since the long-term effects of the suppression of slow wave sleep have not yet been determined, such therapeutic intervention should be approached with caution.

In sharp contrast to the marked suppression of stage 4 sleep, the short-term administration of 25mg clozapine had no significant effect upon stage REM sleep (Table 9). Many of the hypnotic drugs, which are presently prescribed for the treatment of insomnia, have been reported to suppress stage REM sleep (Oswald 1968; Freemon 1972; King 1972). The withdrawal of these drugs after continuous administration, results in a rebound of stage REM sleep. This rebound has been associated with an increased vividness in REM mentation with the subsequent occurrence of nightmares (Kales et al 1968(a), 1969(b), 1974, 1975), a phenomenon that has often resulted in drug dependence. The finding that clozapine administration had no significant effect upon

stage REM sleep appears therefore to have additional therapeutic implications for the treatment of insomnia.

The short-term administration of 25mg placebo had no significant effect upon any of the major sleep stages (Table 9). This finding is in accordance with earlier reports that the administration of placebo did not influence sleep parameters in normal subjects (Adam et al 1975, 1976). The present study employed the double blind procedure as well as in depth statistical analyses and has thus provided convincing evidence for the notion that the short-term administration of placebo has no effect upon the sleep parameters of normal young adults. This finding may not be applicable to insomniac subjects whose sleep has been reported to improve following the administration of a placebo (Nicolis and Silvestri 1967).

6.2.4 REM Indices

The indices of stage REM sleep (section 5.4.2) have not been readily accepted by the sleep research community and have appeared infrequently in the published literature. A possible explanation for this tendency may be the large individual differences evident in many of these indices. Clausen et al (1974) reported that the number of eye movements during REM sleep "...varied considerably among subjects, as indicated by the large individual ranges, large SD's and significant concordance across individuals.....our data imply that number of eye movements may more strongly reflect individual characteristics" (Clausen et al 1974, p.515). Large individual differences are evident in the present study resulting in the clozapine and placebo groups differing significantly from

one another on the first and second baseline nights on the indices of mean burst length, density/minute of REM sleep and % motility (Table 10).

However, the administration of clozapine significantly increased the density/minute of REM sleep, the mean burst length and % motility on the third night of administration. This increased activity persisted on the first night of clozapine withdrawal. In addition, the total number of bursts and the number of bursts/ REM period increased dramatically on the first night of clozapine withdrawal despite the fact that no significant reduction occurred during the administration of clozapine (Figure 9).

The implications of these findings are difficult to assess as the function of stage REM sleep has yet to be conclusively determined. Dement et al (1970) commented that "...never before in the history of biology has so much been known about a phenomenon from the descriptive point of view while at the same time knowing so little about its function - its raison d'etre" (Dement et al 1970, p.72). It has been tentatively suggested that the increased rapid eye movement activity may be associated with the remission of symptoms in psychotic patients (Blum and Girke 1973). The authors commented that "...although no systematic investigations have been carried out, the general clinical impression is that a remission of psychotic symptoms coincides with.....the intensified dream activity" (Blum and Girke 1973, p.80).

The validity of the possible isomorphic relationship between the profusion of rapid eye movements and visual imagery (scanning

hypothesis) appears to be questionable (Firth 1973, 1974; Hauri and van de Castle 1973; Jacobs et al 1970; Koulack 1972; Moskowitz and Berger 1969). Recent research, however, has indicated that an increase in the profusion of rapid eye movements is associated "...with experiences in which the dreamer is an active participant, rather than thinking, reflecting, or passively observing events" (Firth 1974, p.547). The evidence from the present study therefore suggests that the REM dream content became more active on the third night of clozapine administration and that this effect persisted on the first night of clozapine withdrawal. This finding was responsible for eliciting REM dream reports on the third night of clozapine administration during the REM dream recall investigation. Previous studies have not attempted to determine the effects of placebo administration upon REM indices such as those employed in the present study. The present finding that the administration of placebo had no significant effect upon the indices of stage REM sleep is in accordance with the assumption that placebo administration does not influence sleep parameters (Adam et al 1975, 1976).

6.2.5 Sleep Stage Latencies

The short-term administration of 25mg clozapine and placebo had no significant effect upon the latencies to stage 1, stage 2 and stage 4 sleep as well as the latencies to the first, second and third REM periods.

The finding that the administration of clozapine did not significantly reduce the latency to stage 1 or stage 2 sleep implies that the subjects did not fall asleep more rapidly (section 6.2.2).

This is not surprising as the mean latency to stage 1 sleep, during the baseline condition, was well below the mean value reported by Williams et al (1974). The latencies to both stage 1 and stage 2 sleep were statistically analysed as it has been suggested that stage 2 may be a more reliable index of sleep onset than stage 1 sleep (Johnson 1975(a)).

The administration of clozapine markedly suppressed stage 4 sleep but had no effect upon its onset latency. The evidence therefore suggests that the onset of stage 4 sleep was not delayed but that it was consistently suppressed throughout the night. Confirmation of this assumption has been provided by the finding that the within-night analyses revealed that stage 4 sleep was in fact suppressed throughout the first six hours of the record. The administration of clozapine had no significant effect upon the percentage of time spent in stage REM sleep and is therefore not surprising that the latencies to the REM periods were not significantly affected (Table 11).

The finding that the administration of placebo had no significant effect upon the latencies to sleep stages as well as the latencies to REM periods provides further confirmation of the assumption that placebo administration does not influence sleep parameters (Adam et al 1975, 1976).

6.2.6 Sleep Stage Incidence

The short-term administration of 25mg clozapine had no significant effect upon either the number of awakenings or the number of stage 4 or stage REM periods (Table 12). The finding that the

administration of clozapine did not significantly reduce the number of stage 4 periods provides further confirmation for the finding that stage 4 sleep was consistently suppressed throughout the first six hours of the record, since the number of stage 4 periods remained constant and the reduction in stage 4 sleep was therefore not due to the suppression of one or more specific stage 4 periods.

The administration of placebo had no significant effect upon the incidence of sleep stages and thus provides further confirmation of the assumption that placebo administration does not influence sleep parameters (Adam et al 1975, 1976).

6.2.7 Sleep Cycle Duration

The "90-minute sleep-dream cycle" is relatively stable and with a few exceptions "...no pharmacological agent and no illness or hormonal condition we have studied, produce a systematic change in cycle length" (Hartman 1968(a)). The administration of clozapine and placebo had no significant effect upon the duration of the first or second sleep cycles (Table 13). This evidence suggests that the administration of clozapine did not have a disruptive effect upon the infrastructure of the night's sleep as the duration from the end of one REM period to the end of the next remained constant.

6.2.8 Body Movement Activity

The short-term administration of 25mg clozapine significantly reduced the number of body movements which occurred on all three

nights of administration and this effect persisted on the first night of clozapine withdrawal (Table 14). The within-night analyses revealed that the number of body movements was predominantly reduced during the second three hours of the record. The number of body movements per minute of sleep, an index which adjusted for sleep duration, was significantly reduced on the three nights of clozapine administration as well as on the first night of clozapine withdrawal (Figure 10). Movement time was also reduced during the administration of clozapine but this effect failed to reach statistical significance.

In general, therefore, the data showed that the administration of clozapine resulted in a significant reduction in body movement activity. This finding may have important therapeutic implications for the treatment of insomnia, since it suggests that sleep was more restful (Oswald 1970(c)).

The administration of placebo had no significant effect upon the body movement indices and is in accordance with the assumption that placebo administration has no effect upon sleep parameters (Adam et al 1975, 1976).

6.2.9 Psychological and Physiological Side-Effects

Psychological Side-Effects

"The ideal hypnotic agent would rapidly induce physiological sleep but produce no unwanted drowsiness or heavy-headedness upon awakening" (Greenblatt and Shader 1974, p.189).

The short-term administration of 25mg clozapine resulted in a significant increase in drowsiness on the first, second and third mornings following administration (Table 16). This increase in drowsiness was accompanied by a significant impairment of performance in a test of intellectual function on the three mornings following the administration of clozapine. General Activation as well as the subjective index of concentration ability were significantly reduced on the first morning following the administration of clozapine. In addition, Deactivation Sleep was significantly increased on the first and second mornings following administration (Table 19). In general, therefore, the data showed that the administration of 25mg clozapine resulted in specific "morning after" effects such as drowsiness and sleepiness as well as an impairment of intellectual performance. This evidence appears to suggest that clozapine does not meet the criteria of an ideal hypnotic (Greenblatt and Shader 1974).

However, most hypnotic agents, including the barbiturates and benzodiazepines, produce "morning after" side-effects such as drowsiness, heavy-headedness and the impairment of intellectual motor function (Greenblatt and Shader 1974) and clozapine appears to be no exception to the rule. Confirmation of the finding that clozapine produces "morning after" effects has been provided by an extensive clinical trial of the drug in the treatment of psychotic patients (Hemphill et al 1975). The authors remarked that "...because of the side-effects, especially sleepiness, it would be unwise to prescribe clozapine, in the doses[1] we have used, for outpatients until after one week's trial in hospital

[1]The doses varied from between 100mg to 300mg per day.

or under the supervision of a reliable person at home. Under no circumstances should the patient be allowed to drive a car, look after children, or have responsibilities at home that carry risks until continued tolerance has been demonstrated" (Hemphill et al 1975, p.2123). It should be emphasised, however, that the "morning after" drowsiness noted in the present study was of a less intense nature than that of the above study as a result of the low dose used.

The short-term administration of 25mg placebo resulted in a significant increase in drowsiness on the second morning following administration. This finding is in harmony with Beecher (1955) who reported numerous side-effects following the administration of placebo. This increase in drowsiness was reported despite the fact that no change in any of the sleep parameters were observed. The subjective ratings showed no change in anxiety or the quality of sleep and is in accordance with the findings of Adam et al (1975, 1976).

Physiological Side-Effects

Many, non-specific side-effects such as slurring of speech, difficulty in writing, nausea, physical weakness and dryness of mouth were reported following the short-term administration of 25mg clozapine (Table 17). These side-effects disappeared on the first morning following the withdrawal of clozapine. The above side-effects resulted in a lower dose of clozapine (12,50mg/night) being used in the remaining series of experiments.

The short-term administration of 25mg placebo produced no

physiological side-effects. The evidence points overwhelmingly in favour of the conclusion that the short-term administration of placebo has no significant effect upon sleep parameters and produces only minimal side-effects. Only one measure, namely the subjective estimation of drowsiness, increased significantly on the morning following the second night of placebo administration.

In summary, the evidence suggests that the short-term administration of clozapine may have therapeutic implications for the treatment of insomnia and disorders of slow wave sleep. This conclusion was supported by the following findings: (1) Stage 4 sleep was significantly suppressed on the second and third nights of clozapine administration (2) Total sleep time was significantly increased on the first and second nights of clozapine administration despite the attempt to control for the duration of time spent in bed (3) The number of body movements was significantly reduced on all three nights of clozapine administration (4) The number of body movements/minute of sleep was also significantly reduced on all three nights of clozapine administration (5) The short-term administration and withdrawal of 25mg clozapine/night had no significant effect upon stage REM sleep. However, the indices of stage REM sleep were significantly affected. The mean burst length, the density/minute REM sleep and % motility were significantly increased on the third night of clozapine administration and persisted on the first night of clozapine withdrawal. In addition, the total number of bursts and the number of bursts/REM period increased significantly on the first night of clozapine withdrawal despite the fact that no significant reduction occurred during the administration of clozapine. Finally, psychological

and physiological side-effects were reported and it thus appears that clozapine does not meet the criteria for an ideal hypnotic agent. However, further research on insomniac patients should be carried out to validate and extend the above findings.

The short-term administration of 25mg placebo had no significant effect upon any of the sleep parameters and this result is in harmony with the findings of Adam et al (1975, 1976). The administration of placebo resulted in a significant increase in only one index, namely the subjective estimation of drowsiness on the second morning following administration.

7.0 THE LONG-TERM CLOZAPINE INVESTIGATION

7.1 Results

The statistical procedures employed in this investigation involved the comparison of one group of subjects on baseline, clozapine administration and withdrawal conditions on a given variable. These were one factor designs where the subjects were monitored repeatedly and the appropriate analysis employed was the one way analysis of variance with repeated measures (Winer 1962). This one way analysis of variance was followed up by comparisons between cell means using the Tukey HSD procedure which identified the direction of significant findings. However, where the overall test of significance barely yielded a probability value of 0,05, the conservatively large confidence intervals employed by the pairwise comparison test (Tukey HSD) yielded probability values greater than 0,05 and hence non significance.

7.1.1 Total Sleep Time

The administration of clozapine had no significant effect upon the duration of total sleep time ($F = 0,41$; df 7,35; $p>0,25$) (Table 20).

7.1.2 Major Sleep Stages

As previously described (section 5.5.4), the major sleep stages were analysed for the first three hours, the second three hours, the first six hours of the record as well as for the entire night, expressed as a percentage of total sleep time. Stage awake was expressed as a percentage of total recording time.

Stage Awake. The administration of clozapine had no significant effect upon the percentage of time spent awake ($F = 0,67$; df 7,35; $p>0,25$) (Table 20).

The within-night analyses also revealed no significant differences for the first three hours ($F = 1,42$; df 7,35; $p<0,25$) and the first six hours ($F = 1,00$; df 7,35; $p>0,25$) of the record.

However, the administration of clozapine had a significant effect upon the second three hours of the record ($F = 2,33$; df 7,35; $p<0,05$). The Tukey HSD comparisons indicated that the mean number of minutes spent awake during the second three hours of the third (night 8)($p<0,05$) and eleventh (night 16)($p<0,05$) nights of clozapine administration was significantly lower than the mean number during the second three hours of the second baseline night (night 4). The administration of clozapine thus reduced the number of minutes spent awake during the second three hours of the recording on the third and eleventh nights of administration.

Stage 1. The effects of the administration of clozapine upon the percentage of time spent in stage 1 sleep are presented in Table 20 ($F = 2,37$; df 7,35; $p<0,05$). The Tukey HSD comparisons revealed that the mean percentage of time spent in stage 1 sleep was significantly lower on the third night of clozapine administration (night 8) than the mean on the second baseline night (night 4)($p<0,05$).

The within-night analyses revealed no significant differences for the first three hours of the record ($F = 1,50$; df 7,35; $p<0,25$). However, the administration of clozapine had a significant effect

Table 20. The effects of the long-term administration of 12,50mg clozapine upon the mean sleep stage percentages of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo			25mg clozapine			12,5mg placebo		Degrees of Freedom	F Ratio	P
Experimental Condition	Baseline			Clozapine Administration			Withdrawal				
Laboratory Recorded Nights	3	4	8	12	16	20	21	25			
	Mean total sleep time (minutes)										
clozapine group	450,42±7,86	449,17±9,39	440,75±5,37	446,42±11,10	437,50±9,77	437,42±13,03	445,92±5,19	434,25±17,30	7,35	0,41	>0,25
	Mean time spent in stage awake expressed as a percentage of total recording time										
clozapine group	1,42±0,35	2,12±0,72	1,73±0,56	3,45± 1,49	3,11±1,33	3,69± 1,42	2,84±1,61	1,70± 0,52	7,35	0,67	>0,25
	Mean time spent in stage 1 sleep expressed as a percentage of total sleep time										
clozapine group	3,22±0,45	5,05±0,98	1,70±0,41	3,57± 1,29	2,38±0,38	3,48± 0,99	4,18±0,99	3,06± 0,83	7,35	2,37	<0,05
	Mean time spent in stage 2 sleep expressed as a percentage of total sleep time										
clozapine group	55,14±1,01	54,92±1,33	56,63±1,35	56,90± 2,12	57,23±2,45	53,37± 3,08	51,81±3,52	52,11± 3,41	7,35	1,12	>0,25
	Mean time spent in stage 3 sleep expressed as a percentage of total sleep time										
clozapine group	5,41±0,42	5,37±1,06	8,09±1,03	6,46± 1,92	6,87±1,21	5,47± 0,63	5,58±0,22	6,29± 1,32	7,35	1,52	<0,25
	Mean time spent in stage 4 sleep expressed as a percentage of total sleep time										
clozapine group	15,28±1,11	14,50±1,46	16,37±1,57	14,31± 2,50	14,48±2,06	18,72± 2,71	15,86±2,87	14,83± 2,86	7,35	0,96	>0,25
	Mean time spent in stage slow wave sleep expressed as a percentage of total sleep time										
clozapine group	20,68±1,01	19,86±2,02	24,46±1,47	20,77± 2,32	21,36±1,77	24,19± 2,58	21,44±2,86	21,12± 2,72	7,35	1,08	>0,25
	Mean time spent in stage REM sleep expressed as a percentage of total sleep time										
clozapine group	20,94±0,58	20,17±1,32	17,20±0,83	18,76± 0,94	19,04±1,43	18,96± 1,29	22,57±1,86	23,71± 1,69	7,35	2,64	<0,05

upon the second three hours ($F = 3,91$; df 7,35; $p<0,01$) and first six hours ($F = 2,87$; df 7,35; $p<0,05$) of the record.

The Tukey HSD comparisons indicated that the mean number of minutes spent in stage I sleep during the second three hours of the first baseline night (night 3)($p<0,05$) and third (night 8) ($p<0,01$), seventh (night 12)($p<0,01$) and eleventh (night 16) ($p<0,01$)nights of clozapine administration was significantly lower than those during the second three hours of the second baseline night (night 4).

The Tukey HSD comparisons indicated that the mean number of minutes spent in stage I sleep during the first six hours of the third night (night 8)($p<0,01$) of clozapine administration and the fifth night (night 25)($p<0,05$) of clozapine withdrawal was significantly lower than those during the first six hours of the second baseline night (night 4).

Stage 2. The administration of clozapine had no significant effect upon the percentage of time spent in stage 2 sleep ($F = 1,12$; df 7,35; $p>0,25$)(Table 20).

The within-night analyses also revealed no significant differences for the first three ($F = 1,77$; df 7,35; $p<0,25$) and six ($F = 0,61$; df 7,35; $p>0,25$) hours of the record. However, the administration of clozapine had a significant effect upon the second three hours of the record ($F = 2,67$; df 7,35; $p<0,05$).

The Tukey HSD comparisons indicated that the mean number of minutes spent in stage 2 sleep during the second three hours of

the eleventh night (night 16) of clozapine administration was significantly greater than those during the second three hours of the fifth night (night 25) of clozapine withdrawal ($p<0,05$).

Stage 3. The administration of clozapine had no significant effect upon the percentage of time spent in stage 3 sleep ($F = 1,52$; df 7,35; $p<0,25$)(Table 20). The within-night analyses also revealed no significant differences for the first three hours ($F = 2,15$; df 7,35; $p<0,10$), the second three hours ($F = 0,55$; df 7,35; $p>0,25$) and first six hours ($F = 1,28$; df 7,35; $p>0,25$) of the record.

Stage 4. The administration of clozapine had no significant effect upon the percentage of time spent in stage 4 sleep ($F = 0,96$; df 7,35; $p>0,25$)(Table 20). The within-night analyses also revealed no significant differences for the first three hours ($F = 1,20$; df 7,35; $p>0,25$), the second three hours ($F = 1,23$; df 7,35; $p>0,25$) and first six hours ($F = 1,04$; df 7,35; $p>0,25$) of the record.

Stage Slow Wave. The administration of clozapine had no significant effect upon the percentage of time spent in stage slow wave sleep ($F = 1,08$; df 7,35; $p>0,25$)(Table 20). The within-night analyses also revealed no significant differences for the first three hours ($F = 1,41$; df 7,35; $p<0,25$), the second three hours ($F = 0,71$; df 7,35; $p>0,25$) and first six hours ($F = 0,76$; df 7,35; $p>0,25$) of the record.

Stage REM. The effects of the administration of clozapine upon the percentage of time spent in stage REM sleep are presented in Table 20 and significant findings are illustrated in Figure 11

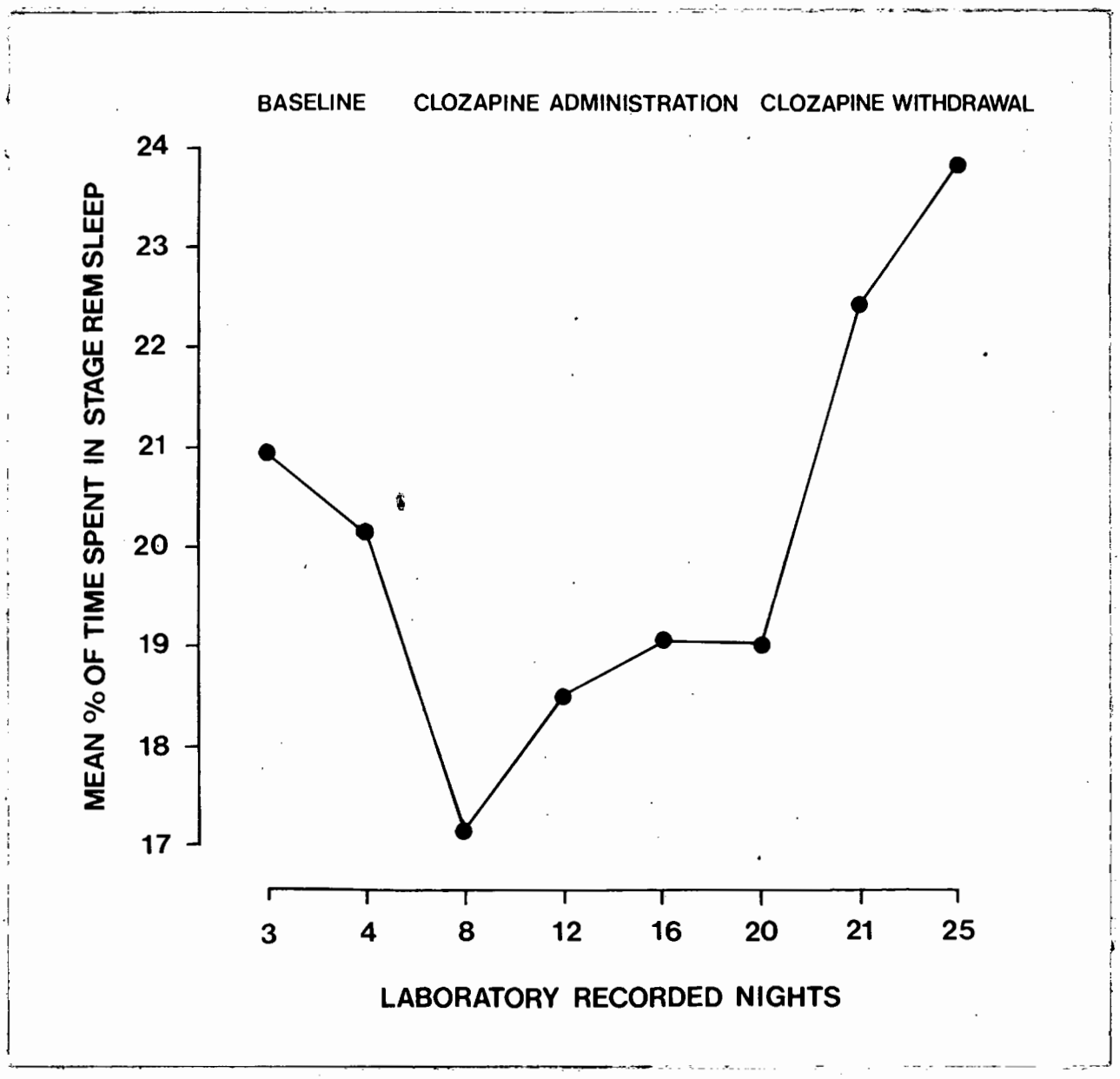


Figure 11. The effects of the long-term administration of 12,50mg clozapine upon the mean percentage of time spent in stage REM sleep over the laboratory recorded nights.

(F = 2,64; df 7,35; p<0,05). The Tukey HSD comparisons failed to identify the direction of this finding. Inspection of the data showed that stage REM sleep was reduced during the administration of clozapine (Figure 11)(Table 20).

The within-night analyses revealed no significant differences for the first three hours (F = 0,56; df 7,35; p>0,25), the second three hours (F = 1,56; df 7,35; p<0,25) and first six hours (F = 1,66; df 7,35; p<0,25) of the record.

7.1.3 REM Indices

Mean REM Duration. The administration of clozapine had no significant effect upon the mean duration of REM sleep (F = 0,90; df 7,35; p>0,25)(Table 21).

Total Number of Bursts. The administration of clozapine had no significant effect upon the total number of bursts (F = 0,89; df 7,35; p>0,25)(Table 21).

Number of Bursts per REM Period. The administration of clozapine had no significant effect upon the number of bursts/REM period (F = 0,48; df 7,35; p>0,25)(Table 21).

Mean Burst Length. The administration of clozapine had no significant effect upon the mean burst length (F = 1,05; df 7,35; p>0,25)(Table 21).

Density per Minute REM Sleep. The administration of clozapine had no significant effect upon the density/minute REM sleep (F = 2,23; df 7,35; p<0,10)(Table 21).

Table 21. The effects of the long-term administration of 12,50mg clozapine upon the mean REM indices of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo			12,5mg clozapine			12,5mg placebo				
Experimental Condition	Baseline			Clozapine Administration			Withdrawal		Degrees of Freedom	F Ratio	P
Laboratory Recorded Nights	3	4	8	12	16	20	21	25			
	Mean REM duration (minutes)										
clozapine group	30,04± 1,22	25,35± 2,11	26,60± 3,59	23,12± 1,47	25,16± 1,90	26,23± 1,47	24,95± 3,29	27,19± 2,15	7,35	0,90	>0,25
	Mean (total) number of bursts										
clozapine group	90,33±12,09	78,67±11,82	81,67± 5,24	96,33± 5,29	93,83± 6,53	87,33± 9,22	102,50±23,44	96,67±10,03	7,35	0,89	>0,25
	Mean number of bursts per REM period										
clozapine group	29,21± 4,49	23,64± 3,61	26,06± 2,01	26,88± 2,46	28,49± 2,32	27,32± 1,64	25,30± 3,21	25,43± 2,29	7,35	0,48	>0,25
	Mean burst length (seconds)										
clozapine group	6,42± 0,91	6,36± 1,24	7,50± 2,13	8,04± 0,58	8,59± 1,19	9,00± 1,55	7,46± 1,35	6,86± 0,97	7,35	1,05	>0,25
	Mean density per minute REM sleep										
clozapine group	3,99± 1,09	4,69± 1,22	4,69± 1,02	5,68± 0,87	5,89± 0,98	7,32± 2,02	5,35± 1,35	3,67± 0,95	7,35	2,23	<0,10
	Mean % motility										
clozapine group	12,76± 3,29	13,95± 3,56	17,37± 3,84	19,19± 2,82	19,19± 3,05	19,37± 3,49	17,22± 4,31	12,04± 2,59	7,35	2,58	<0,05

% Motility. The effects of clozapine administration upon % motility are presented in Table 21 ($F = 2,58$; df 7,35; $p<0,05$). The Tukey HSD comparisons failed to identify the direction of this significant finding.

7.1.4 Sleep Stage Latencies

Stage 1 Latency. The administration of clozapine had no significant effect upon the latency to stage 1 sleep ($F = 1,15$; df 7,35; $p>0,25$)(Table 22).

Stage 2 Latency. The administration of clozapine had no significant effect upon the latency to stage 2 sleep ($F = 0,95$; df 7,35; $p>0,25$).

Stage 4 Latency. The effects of the administration of clozapine upon the latency to stage 4 sleep are presented in Table 22 ($F = 2,96$; df 7,35; $p<0,05$). The Tukey HSD comparisons indicated that the mean latency to stage 4 sleep was significantly longer on the first night of clozapine withdrawal (night 21) than those on either the third (night 8)($p<0,05$) or fifteenth (night 20)($p<0,01$) nights of clozapine administration as well as on the fifth night (night 25) of clozapine withdrawal ($p<0,05$).

Latency to the First REM Period. The administration of clozapine had no significant effect upon the latency to the first REM period ($F = 1,18$; df 7,35; $p>0,25$) (Table 22).

Latency to the Second REM Period. The administration of clozapine had no significant effect upon the latency to the second REM period ($F = 1,46$; df 7,35; $p<0,25$)(Table 22).

Table 22. The effects of the long-term administration of 12,50mg clozapine upon the mean sleep latencies of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo		12,5mg clozapine				12,5mg placebo		Degrees of Freedom	F Ratio	P
Experimental Condition	Baseline		Clozapine Administration				Withdrawal				
Laboratory Recorded Nights	3	4	8	12	16	20	21	25			
	Mean stage 1 latency (minutes)										
clozapine group	5,08± 1,29	5,58± 1,27	8,25± 2,89	16,75± 7,33	14,00± 6,44	14,00± 6,64	6,67± 1,73	7,08± 2,80	7,35	1,15	>0,25
	Mean stage 2 latency (minutes)										
clozapine group	10,25± 1,34	9,75± 1,08	13,08± 2,97	20,50± 8,41	19,08± 6,50	17,00± 6,89	11,58± 0,55	8,67± 2,58	7,35	0,95	>0,25
	Mean stage 4 latency (minutes)										
clozapine group	19,83± 2,05	18,25± 0,80	17,75± 2,04	19,67± 2,47	22,50± 1,45	15,83± 1,53	25,17± 4,45	17,25± 1,91	7,35	2,96	<0,05
	Mean latency to the first REM period (minutes)										
clozapine group	146,08±19,38	117,33±21,95	153,25±20,37	147,00±24,13	107,33±16,65	130,75±14,54	100,17±18,79	126,33±24,77	7,35	1,18	>0,25
	Mean latency to the second REM period (minutes)										
clozapine group	271,00±23	225,00±27,29	275,08±32,43	246,83±21,84	227,33±19,85	248,25±16,90	190,75±21,20	230,17±26,13	7,35	1,46	<0,25
	Mean latency to the third REM period (minutes)										
clozapine group	392,00±25,13	331,20±23,19	359,00±17,94	332,20±20,26	353,10±18,95	355,00±10,56	298,90±27,17	312,70±33,02	7,28*	1,73	<0,25

* 5 subjects as one subject failed to have a third REM period on one of the recording nights.

Latency to the Third REM Period. The administration of clozapine had no significant effect upon the latency to the third REM period ($F = 1,73$; df 7,28; $p<0,25$).

7.1.5 Sleep Stage Incidence

Number of Awakenings. The administration of clozapine had no significant effect upon the number of awakenings during sleep ($F = 1,04$; df 7,35; $p>0,25$)(Table 23).

Number of Stage 4 Periods. The administration of clozapine had no significant effect upon the number of stage 4 periods during sleep ($F = 1,33$; df 7,35; $p>0,25$)(Table 23).

Number of Stage REM Periods. The effects of the administration of clozapine upon the number of stage REM periods during sleep are presented in Table 23 ($F = 2,41$; df 7,35; $p<0,05$). The Tukey HSD comparisons failed to reveal the direction of this significant finding.

7.1.6 Sleep Cycle Duration

Duration of the First Sleep Cycle. The administration of clozapine had no significant effect upon the duration of the first sleep cycle ($F = 0,85$; df 7,35; $p>0,25$)(Table 24).

Duration of the Second Sleep Cycle. The administration of clozapine had no significant effect upon the duration of the second sleep cycle ($F = 0,68$; df 7,28; $p>0,25$)(Table 24).

7.1.7 Body Movement Activity

As previously described (section 5.5.4), the indices of body

Table 23. The effects of the long-term administration of 12,50mg clozapine upon the mean sleep stage incidence of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo		12,5mg clozapine				12,5mg placebo		Degrees of Freedom	F Ratio	P
Experimental Condition	Baseline		Clozapine Administration				Withdrawal				
Laboratory Recorded Nights	3	4	8	12	16	20	21	25			
	Mean number of awakenings										
clozapine group	0,67±0,33	1,0 ±0,52	0,17±0,17	0,67±0,49	0,17±0,17	0,67±0,49	0,33±0,33	1,0 ±0,63	7,35	1,04	>0,25
	Mean number of stage 4 periods										
clozapine group	3,33±0,33	3,17±0,48	2,50±0,34	2,67±0,42	2,50±0,43	2,0 ±0,26	2,83±0,48	2,33±0,33	7,35	1,33	>0,25
	Mean number of stage REM periods										
clozapine group	3,17±0,17	3,67±0,33	3,17±0,17	3,67±0,21	3,33±0,21	3,17±0,17	4,16±0,75	3,83±0,31	7,35	2,41	<0,05

Table 24. The effects of the long-term administration of 12,50mg clozapine upon the mean duration of the first and second sleep cycles of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo		12,5mg clozapine				12,5mg placebo		Degrees of Freedom	F Ratio	P
Experimental Condition	Baseline		Clozapine Administration				Withdrawal				
Laboratory Recorded Nights	3	4	8	12	16	20	21	25			
	Mean duration of the first sleep cycle (minutes)										
clozapine group	125,83±11,74	110,08±13,54	124,67±13,44	111,08±13,71	128,17±11,80	129,83±13,95	101,58± 5,48	108,00± 8,00	7,35	0,85	>0,25
	Mean duration of the second sleep cycle (minutes)										
clozapine group	107,90± 9,35	113,90±20,83	104,70±22,17	103,20± 9,28	129,80±17,76	132,00±21,11	130,30±15,47	105,50±16,04	7,28*	0,68	>0,25

* 5 subjects as one subject failed to complete the second sleep cycle on one of the recording nights.

movement activity have been analysed for the first three hours, the second three hours, the first six hours of the record as well as for the entire night.

Number of Body Movements. The effects of the administration of clozapine upon the number of body movements are presented in Table 25 ($F = 2,42$; df 7,35; $p<0,05$). The Tukey HSD comparisons failed to reveal the direction of this significant finding.

The within-night analyses revealed no significant differences for the first three hours ($F = 1,94$; df 7,35; $p<0,10$), the second three hours ($F = 1,50$; df 7,35; $p<0,25$) as well as the first six hours ($F = 1,81$; df 7,35; $p<0,10$) of the record.

Number of Body Movements per Minute of Sleep. The effects of the administration of clozapine upon the number of body movements/minute of sleep are presented in Table 25 and significant findings are illustrated in Figure 12 ($F = 2,50$; df 7,35; $p<0,05$). The Tukey HSD comparisons failed to reveal the direction of this significant finding.

Movement Time. The effects of the administration of clozapine upon movement time are presented in Table 25 ($F = 3,19$; df 7,35; $p<0,05$). The Tukey HSD comparisons failed to reveal the direction of this significant finding.

The within-night analyses also revealed significant differences for the first three hours, second three hours as well as the first six hours of the record. The within-night analysis of the first three hours yielded a significant variance ratio ($F = 2,31$; df 7,35; $p<0,01$). However, the Tukey HSD comparisons failed

Table 25. The effects of the long-term administration of 12,50mg clozapine upon the mean body movement indices of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo		12,5mg clozapine				12,5mg placebo		Degrees of Freedom	F Ratio	P
Experimental Condition	Baseline		Clozapine Administration				Withdrawal				
Laboratory Recorded Nights	3	4	8	12	16	20	21	25			
	Mean number of body movements										
clozapine group	68,17±8,57	65,17±12,25	44,17±5,92	50,17±7,72	45,00±4,88	53,17±4,15	66,17±9,10	64,33±3,27	7,35	2,42	<0,05
	Mean number of body movements per minute of sleep										
clozapine group	0,15±0,02	0,15± 0,02	0,10±0,01	0,11±0,02	0,10±0,01	0,12±0,01	0,15±0,02	0,15±0,01	7,35	2,50	<0,05
	Mean number of 30 second epochs spent in movement time										
clozapine group	9,50±2,08	9,00± 3,53	3,83±1,11	6,67±1,98	4,33±1,78	4,00±1,55	10,50±2,36	9,83±1,42	7,35	3,19	<0,05

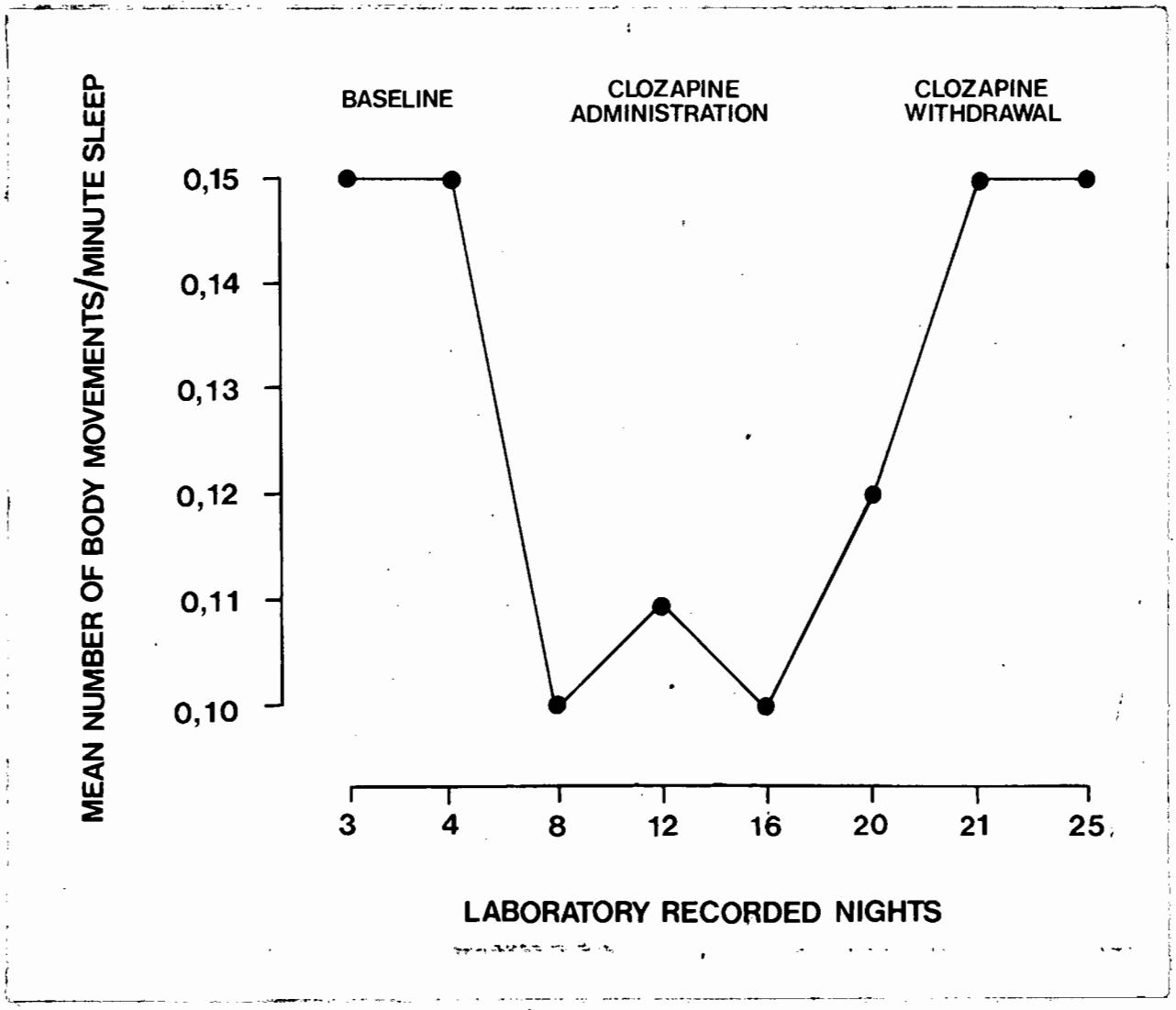


Figure 12 The effects of the long-term administration of 12,50mg clozapine upon the mean number of body movements/minute of sleep over the laboratory recorded nights.

to reveal the direction of this significant finding.

The within-night analysis of the second three hours yielded a significant variance ratio ($F = 3,06$; df 7,35; $p<0,05$). The Tukey HSD comparisons indicated that the mean movement time on the third night (night 8) of clozapine administration was significantly lower than the mean on the first night (night 21) of clozapine withdrawal ($p<0,05$).

The within-night analysis of the first six hours yielded a significant variance ratio ($F = 2,49$; df 7,35; $p<0,05$). However, the Tukey HSD comparisons failed to reveal the direction of this significant finding.

7.1.8 Sleep Log

The sleep log provided information regarding the quantity and quality of the night's sleep, the mood shortly after awakening, psychological and physiological side-effects as well as the subjective assessment of the nature of the medication administered (Appendix 14). The procedure for scoring the sleep log is described in section 5.5.5. The sleep log data are presented in Tables 26, 27 and 28.

Estimated Duration of Sleep Length (Question five). The effects of the administration of clozapine upon the estimated sleep duration are presented in Table 26 and significant findings are illustrated in Figure 13 ($F = 3,01$; df 4,20; $p<0,05$). The Tukey HSD comparisons indicated that the mean estimated sleep duration was significantly shorter on the five night period of

Table 26. The effects of the long-term administration of 12,50mg clozapine upon the sleep log indices (quality and quantity of sleep as well as psychological and physiological side-effects) of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo	12,5mg clozapine			12,5mg placebo	Degrees of Freedom	F Ratio	P
Experimental Condition	Baseline	Clozapine Administration			Withdrawal			
Nights	1 - 5	6 - 10	11 - 15	16 - 20	21 - 25			
	Mean estimated duration of sleep length in minutes (Question Five)							
clozapine group	447,07±11,08	453,33±13,86	459,57±16,40	455,83±13,04	409,83±15,91	4,20	3,01	<0,05
	How well did you sleep compared to the way you usually sleep? (Question Six) (Mean score)							
clozapine group	16,83± 0,75	18,33± 0,92	16,67± 0,49	16,17± 0,48	15,33± 0,76	4,20	2,62	<0,10
	How do you feel this morning? (Question Seven) (Mean score)							
clozapine group	13,83± 0,48	11,33± 0,56	12,83± 1,08	12,33± 0,71	13,00± 0,73	4,20	2,03	<0,25
	Mean number of side-effects reported (Question Ten)							
clozapine group	5,17± 2,41	14,17± 2,27	8,33± 2,91	7,83± 1,99	6,33± 1,94	4,20	5,26	<0,01
	Do you think you had a sleeping tablet or a placebo last night? (Question Thirteen) (Mean score)							
clozapine group	2,00± 0,93	6,17± 0,79	3,83± 1,25	4,33± 0,84	1,17± 0,48	4,20	5,86	<0,01
	Stanford Sleepiness Scale (Mean score)							
clozapine group	16,50± 1,23	20,67± 0,61	17,17± 1,54	18,67± 1,54	17,33± 1,87	4,20	2,39	<0,10

clozapine withdrawal than on the second five night period of clozapine administration ($p<0,05$).

Quality of Sleep (Question six). The administration of clozapine had no significant effect upon the quality of sleep ($F = 2,62$; df 4,20; $p<0,10$)(Table 26).

Mood Shortly After Awakening (Question seven). The administration of clozapine had no significant effect upon the mood shortly after awakening ($F = 2,03$; df 4,20; $p<0,25$) (Table 26).

Number of Side-Effects (Question ten). The effects of the administration of clozapine upon the number of side-effects reported are presented in Table 26 and significant findings are illustrated in Figure 14 ($F = 5,26$; df 4,20; $p<0,01$).

The Tukey HSD comparisons indicated that the number of side-effects reported increased dramatically on the mornings following the first five night period of clozapine administration and was followed by a progressive decline to baseline and withdrawal levels (Figure 14). The mean number of side-effects on the mornings following the first five night period of clozapine administration was significantly greater than the mean number on the baseline ($p<0,01$), third five night period of clozapine administration ($p<0,05$) and withdrawal condition ($p<0,01$).

The frequency of occurrence of individual side-effects are presented in Table 27. Side-effects such as tiredness, drowsiness and wanting to go back to sleep were reported on baseline and withdrawal conditions but increased markedly on the first five

Table 27 The frequency of occurrence of individual side-effects during the long-term administration of 12,50mg clozapine.

Experimental Condition	Base-line	Clozapine Administration			Clozapine Withdrawal
Side-Effects Reported	Nights 1-5	Nights 6-10	Nights 11-15	Nights 16-20	Nights 21-25
Dizzy	0	4	2	1	1
Nauseous	0	0	1	0	0
Tired	10	19	14	13	12
Drowsy	10	17	15	12	13
Exhausted	0	7	3	4	5
Feeling Faint	0	3	1	0	0
Difficulty in writing	0	0	0	1	0
Difficulty in talking	0	1	1	0	0
Mouth very dry	1	9	1	3	1
Mouth very moist	1	3	1	3	0
Want to go back to sleep	9	20	11	9	6
Felt dizzy but fine when I lay down	0	1	0	0	0
Felt dizzy even when lying down	0	2	0	1	0

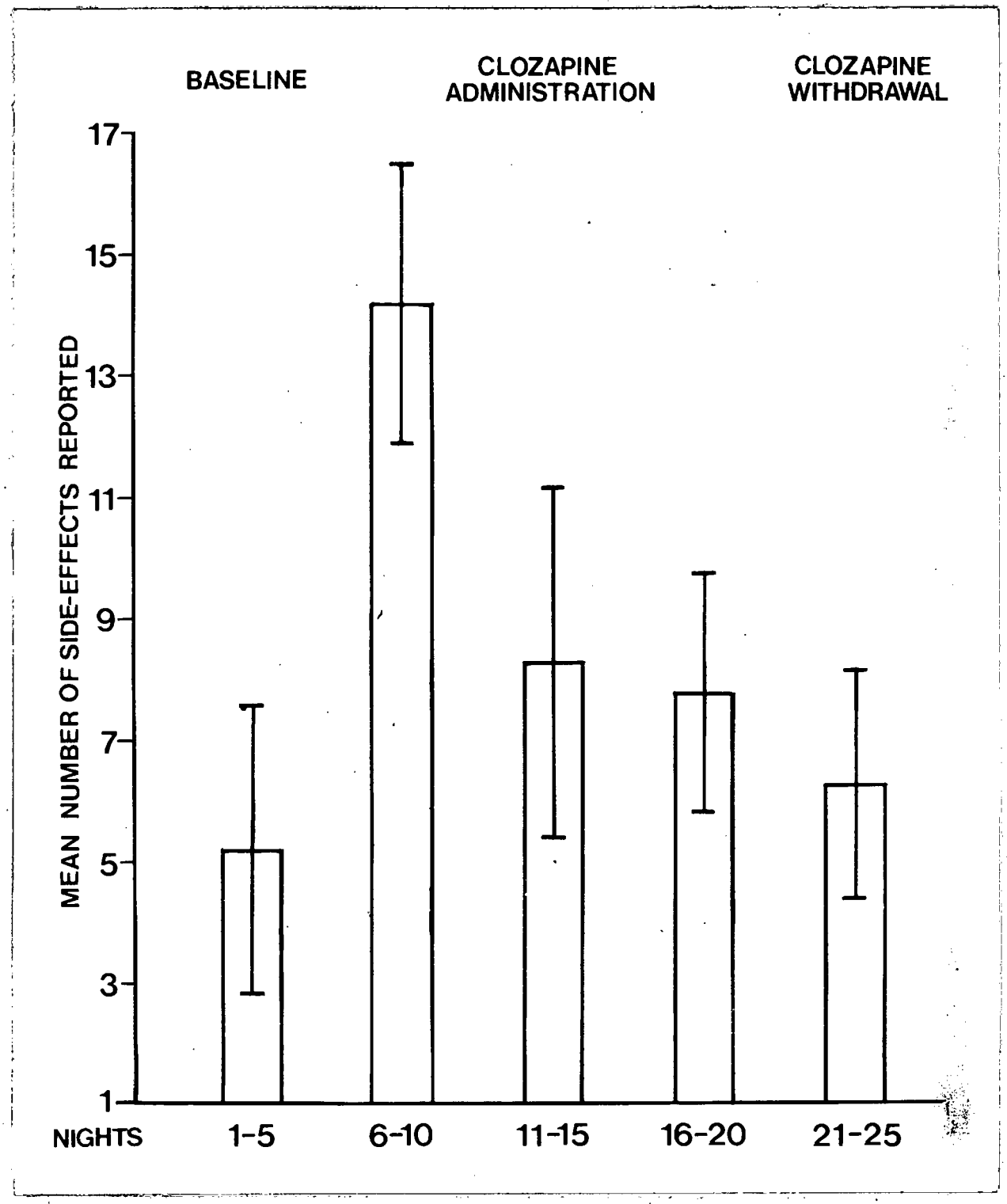


Figure 14 The effects of the long-term administration of 12,50mg clozapine upon the mean number of side-effects reported. The mean number of side-effects reported significantly increased on the first five night period (nights 6-10) of clozapine administration.

night period of clozapine administration.

Psychological Side-Effects (Question twelve). The subjects reported side-effects such as depression, apathy, tiredness, lack of vitality, resentfulness and the lack of mental and physical energy during the administration of clozapine (Table 28).

Drug Identification Rating (Question thirteen). The effects of the administration of clozapine upon the drug identification rating scale are presented in Table 26 and significant findings are illustrated in Figure 15 ($F = 5,86$; df 4,20; $p<0,01$).

The Tukey HSD comparisons indicated that the drug identification rating increased markedly on the mornings following the first five night period of clozapine administration. The values on the mornings following the second and third five night periods of clozapine administration remained elevated although not significantly so. There was a dramatic reduction in the drug identification rating when clozapine was withdrawn. The mean drug identification rating on the first five night period of clozapine administration was significantly greater than on the baseline ($p<0,05$) or clozapine withdrawal ($p<0,01$) periods.

Stanford Sleepiness Scale. The administration of clozapine had no significant effect upon the Stanford Sleepiness Scale ($F = 2,39$; df 4,20; $p<0,10$)(Table 26).

7.1.9 Psychological Assessment

The Brief Psychiatric Rating Scale. The administration of clozapine had no significant effect upon the Brief Psychiatric

Table 28. Psychological side-effects reported following the long-term administration of 12,50mg clozapine (Means ± S.E.)

Medication Administered	12,5mg placebo	12,5mg clozapine			12,5mg placebo
Experimental Condition	Baseline	Clozapine Administration			Withdrawal
Nights	1 - 5	6 - 10	11 - 15	16 - 20	21 - 25
	extremely relaxed and happy(1)*	depressed(2)	very apathetic and listless(3)	apathetic and listless(2)	depressed(1)
		frustrated(1)	tired of being tired(1)	lack of vitality(2)	withdrawn(1)
		absolutely buggered(1)	depressed (1)	depressed(1)	
		easy to argue(2)	irritable(2)		

* Number in brackets indicates frequency of occurrence

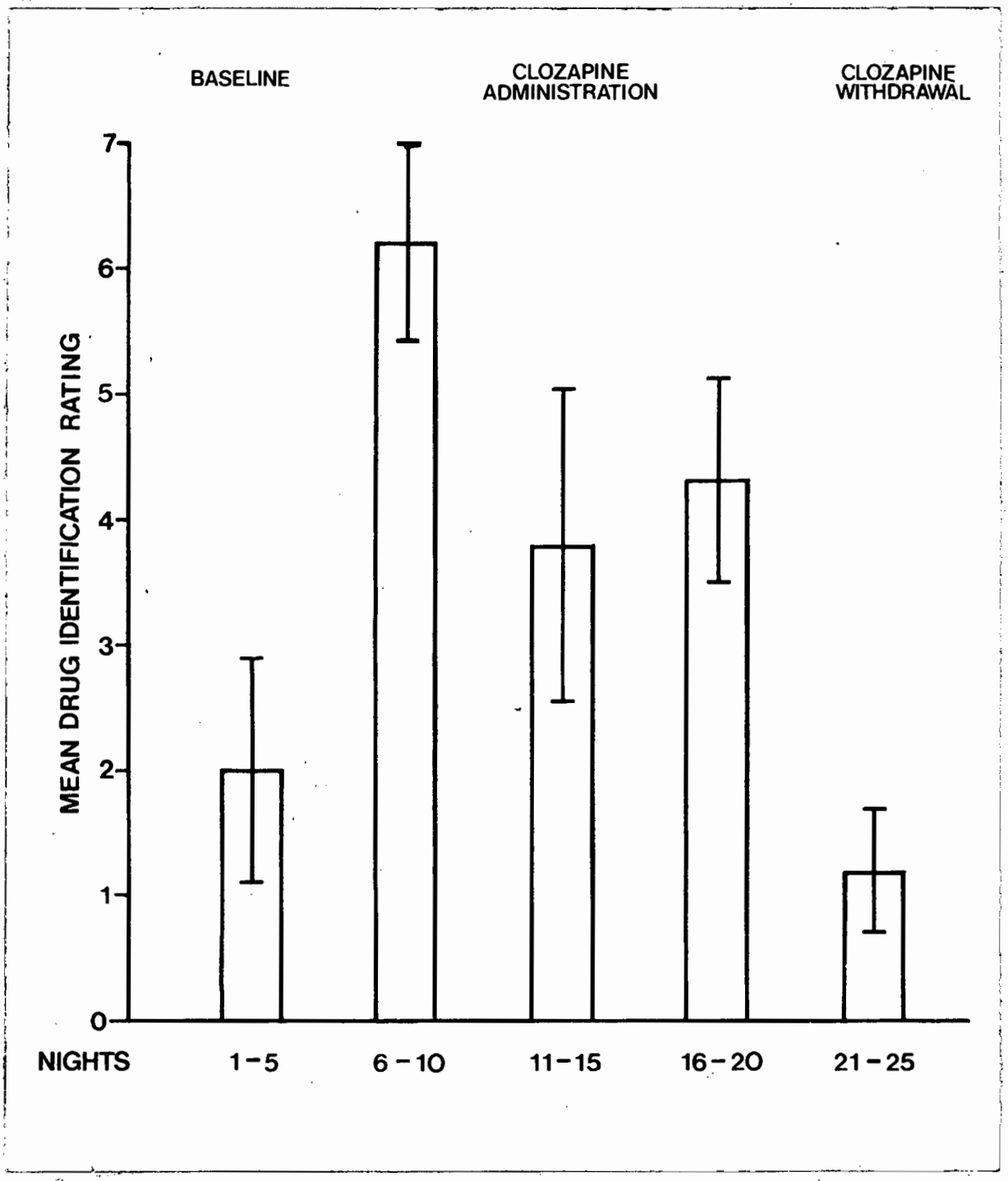


Figure 15 The effects of the long-term administration of 12,50mg clozapine upon the mean drug identification rating. The mean rating significantly increased on the first five night period (nights 6-10) of clozapine administration.

Rating Scale (Table 29). The dependent t test analysis failed to identify a significant difference ($t = -0,42$; $df\ 5$; $p > 0,05$).

The Taylor Manifest Anxiety Scale. The administration of clozapine had no significant effect upon the Taylor Manifest Anxiety Scale (Table 29). The dependent t test analysis failed to identify a significant difference ($t = -1,41$; $df\ 5$; $p > 0,05$).

7.1.10 Blood Parameters

The administration of clozapine had no significant effect on the blood parameters monitored (Table 30).

Table 29 The psychological assessment of the effects of the long-term administration of 12,50mg clozapine of 6 normal young adults (Means ± S.E.)

	Pre-Experimental Condition	Post-Experimental Condition	t	Degrees of Freedom	P
Brief Psychiatric Rating Scale (mean score)					
clozapine group	18,67±0,33	18,83±0,54	-0,42	5	>0,05
Taylor Manifest Anxiety Scale (mean score)					
clozapine group	12,50±0,85	14,33±1,71	-1,41	5	>0,05

Table 30 The effects of the long-term administration of 12,50mg clozapine upon the mean blood parameters of 6 normal young adults (Means ± S.E.)

	Pre-Experimental Condition	Post-Experimental Condition	t	Degrees of Freedom	P
Mean number of white blood cells X 10^3/cubic millimeter					
clozapine group	7,73±1,12	7,68±2,74	0,04	5	>0,05
Mean number of red blood cells X 10^3/cubic centimeter					
clozapine group	5,20±0,20	5,25±0,19	-0,28	5	>0,05
Mean number of grams of haemoglobin					
clozapine group	15,07±0,55	15,70±0,55	-1,05	5	>0,05
Mean haematocrit (%)					
clozapine group	44,97±1,98	45,82±2,15	-0,48	5	>0,05
Mean corpuscular volume (cubic microns)					
clozapine group	86,67±1,41	85,50±2,08	0,76	5	>0,05
Mean corpuscular haemoglobin (mmg's)					
clozapine group	28,83±0,40	29,98±0,77	-3,52	5	>0,05
Mean corpuscular haemoglobin concentration (gm/100ml)					
clozapine group	33,08±0,69	34,28±0,73	-5,72	5	>0,05

7.2 Discussion

7.2.1 Research Strategy

The twenty five night single blind cross-over design employed in this second phase of the investigation was developed in order to determine the effects of the long-term administration of 12,50mg clozapine upon the sleep patterns of normal young adults. As a result of the many methodological inadequacies inherent in sleep research designs (section 3.0), the present study:

(i) comprised two adaptation nights to ensure that the subjects were adequately adapted to the sleep laboratory environment as well as to the experimental routine (section 3.1.1).

(ii) enabled the long-term effects of clozapine to be evaluated independently of any other drug thus avoiding any possible carry-over effects from one drug to the other (section 3.4).

(iii) employed the single blind procedure as the experimenter was aware of the nature of the medication administered on each night of the investigation.

(iv) was designed in such a way as to permit the comparison between the effects of 25mg clozapine after three consecutive nights of administration with the effects of 12,50mg clozapine after the same duration of administration.

(v) used subjects of a similar age group who were medically healthy (section 3.3).

(vi) employed precautionary measures such as blood analysis before the commencement and after the completion of the

investigation to ensure that the subjects participating in the study suffered no ill effects after the long-term administration of 12,50mg clozapine.

(vii) controlled for the duration of time which the subject was permitted to spend in bed and

(viii) analysed smaller portions of the night's data (section 3.6). This procedure enabled changes in sleep patterns to be identified which would otherwise have remained undetected if only conventional analysis had been used. The within-night analyses of the first and second three hours of the record, however, often produced non systematic and inconsistent data which resulted in difficulties in interpretation.

A limitation of the present study was once again the use of a relatively small number of subjects. This was necessitated by the exorbitant cost of sleep research. However, the number of subjects used in the present investigation was well within the average number used in most sleep research programs.

7.2.2 Total Sleep Time

The long-term administration of 12,50mg clozapine had no significant effect upon the duration of total sleep time (Table 20). This finding is in marked contrast to the significant increase in total sleep time which occurred on the first and second nights of clozapine administration during the short-term investigation. This comparison should however be interpreted with caution as the first laboratory monitored night to be carried out in the present study, to determine the effects of clozapine upon sleep

parameters, was carried out on the third night of clozapine administration. The evidence from the two studies combined suggests that the effect of clozapine administration upon sleep duration may be dose related. Research has yet to be carried out to ascertain whether the administration of 12,50mg clozapine will enhance the sleep duration of insomniac subjects.

Hartmann and Cravens (1973c-f) reported that the long-term administration (60 days) of four drugs (amitriptyline 50mg/day, chlorpromazine 50mg/day, chloral hydrate 50mg/day and chlordiazepoxide 50mg/day) significantly increased total sleep time in fourteen young healthy male adults despite the fact that an attempt was made to maintain a regular sleep schedule. The increases in total sleep time failed to reach statistical significance after three to four weeks of administration. This finding suggests that the body developed a tolerance to these drugs after chronic administration. Similarly the increase in total sleep time during the short-term administration of clozapine returned to baseline levels by the third night of administration. It should be noted, however, that the doses used in the Hartmann and Cravens (1973c-f) studies were double those used in the short-term clozapine investigation.

7.2.3 Major Sleep Stages

Although the long-term administration of 12,50mg clozapine had no significant effect upon the percentage time spent awake, the within-night analyses of the second three hours of the record revealed that the number of minutes spent awake was significantly reduced on the third and eleventh nights of clozapine

administration. This evidence provides some confirmation of the assumption that clozapine has sleep inducing properties (Ruch et al 1976; Hemphill et al 1974, 1975).

The analysis of the data of the entire night as well as the within-night analyses of the second three hours and first six hours of the record revealed that the administration of clozapine significantly reduced stage 1 sleep (section 7.1.2). Stage 1 sleep has been reported to occur "...most often in the transition from wakefulness to other sleep stages or following body movements during sleep" (Rechtschaffen and Kales 1968, p.5). It is tentatively suggested that the significant reduction in wakefulness and body movement activity resulted in the significant decrement in stage 1 sleep. The large individual differences, inherent in the within-night analyses data, resulted in the first and second baseline nights differing significantly from one another during the second three hours of the record.

Although the long-term administration of 12,50mg clozapine had no significant effect upon the percentage time spent in stage 2 sleep, the within-night analysis of the second three hours of the record revealed that the number of minutes spent in stage 2 sleep was significantly increased on the eleventh night of clozapine administration. A tentative explanation for this finding appears to be that the increase in stage 2 sleep during the second three hours of the eleventh night of clozapine administration occurred as a compensatory response for the decrease in stage awake and stage 1 sleep on the same night. Stage 2 forms the bulk of sleep and it is therefore not surprising that stage 2 sleep

compensated for the decrease in stage awake and stage I sleep.

Two results in this investigation require particular attention: the first, the finding that the administration of 12,50mg clozapine had no significant effect upon stage 4 sleep; the second, the absence of a REM rebound despite the fact that a significant reduction in stage REM sleep occurred.

In sharp contrast to the marked decrease in stage 4 sleep during the short-term administration of 25mg clozapine (Figure 8), the long-term administration of 12,50mg clozapine was found to have no significant effect upon stage 4 sleep. This long-term investigation included a laboratory recording night on the third night of clozapine administration so as to enable a comparison with the short-term investigation to be made. The evidence from the two studies combined suggests that the effects of clozapine upon sleep parameters are dose related. Evidence for this assumption is provided by the finding that low doses of chlorpromazine increased REM sleep, high doses suppressed REM sleep and intermediate doses had no significant effect (Lewis and Evans 1969).

The second important point raised by the present investigation was a significant reduction in stage REM sleep during the long-term administration of clozapine. This effect, however, barely reached statistical significance (Table 20). Moreover, the Tukey HSD comparisons failed to identify the direction of this finding (section 7.12). In addition, the abrupt withdrawal of clozapine, after fifteen nights of consecutive administration, failed to result in a significant rebound of stage REM sleep.

However, there was a slight tendency for the percentage of time spent in stage REM sleep to be elevated above baseline levels (Figure 11),but these values were well below the normal values associated with the rebound of stage REM sleep[1] (Oswald 1970(c)). These findings have important therapeutic implications for the treatment of insomnia as many of the hypnotic agents presently prescribed have been found to produce a REM rebound upon withdrawal after chronic administration (section 4.3). These include the barbiturates (Oswald and Priest 1965), nitrazepam (Oswald and Priest 1965; Haider and Oswald 1971), glutethimide and methyprylone (Kales et al 1970(e)), tricyclic antidepressants (Hartmann and Cravens 1973(c); Toyoda 1964; Ritvo et al 1967; Chernik et al 1973(b)) and the monoamine oxidase inhibitors (Wyatt et al 1969). Freemon (1972) reported that the "...REM rebound following the chronic use of a drug is one of the commonest causes of sleep disturbance" (Freemon 1972, p.127). This REM rebound is often accompanied by difficulty in falling asleep, an increased vividness in REM mentation as well as the occurrence of nightmares.

7.2.4 REM Indices

The long-term administration of 12,50mg clozapine significantly increased % motility ($p<0,05$)(Table 21), but had no systematic effect upon any of the other REM indices. This finding is in sharp contrast to the marked increase in % motility ($p<0,001$) and the density/minute of REM sleep ($p<0,001$) as well as the increase in burst length ($p<0,05$) during the short-term administration of 25mg clozapine (Table 10). Two explanations for this

[1] The percentage of time spent in stage REM sleep during the night increases from 20-25% to 45-50%.

finding are possible.

The long-term administration of 12,50mg clozapine significantly reduced the percentage of time spent in stage REM sleep (Table 20) but had no effect upon the mean burst length. The duration of burst activity thus occupied a greater proportion of stage REM sleep and hence an increased % motility[1]. An alternative explanation, for the limited effect of the administration of 12,50mg clozapine upon indices of stage REM sleep, may be that clozapine no longer exerted an antipsychotic effect at this dosage. It has been suggested that the remission of psychotic symptoms during the administration of clozapine appear to be associated with an increase in rapid eye movement activity (Blum and Girke 1973). The evidence suggests that the administration of low doses of clozapine (12,50mg/night) has little or no effect upon rapid eye movement activity (Table 21).

7.2.5 Sleep Stage Latencies

The finding that the long-term administration of 12,50mg clozapine did not significantly reduce the latency to stage 1 or stage 2 sleep indicates that the administration of clozapine did not result in subjects falling asleep more rapidly. This finding is not surprising as the subjects had exceptionally short stage 1 (5,33 minutes) and stage 2 (10 minutes) latencies under baseline conditions.

However, Hartmann and Cravens (1973(b)(e)) reported that the long-term administration of 50mg chloral hydrate and 0,5mg reserpine

[1] % motility is defined as the percentage of REM periods occupied by bursts (Aserinsky 1971).

significantly reduced the latency to stage I sleep in normal young adults. It should be noted, however, that the baseline latency to stage I sleep was eleven minutes in the Hartmann and Cravens' (1973(b)(e)) study compared to the 5,33 minutes in the present study. There was thus a greater probability of a significant reduction of stage I latency in the Hartmann and Cravens' study than in the present investigation. The higher dose used in the Hartmann and Cravens' study may also have been partly responsible for the significant reduction in the latency to stage I sleep.

The finding that the latency to stage 4 sleep was significantly increased on the first night of clozapine withdrawal is more difficult to interpret. It is tentatively suggested that an increase in the duration of the first stage I, stage 2 or stage 3 period occurred or alternatively minor increases in all three sleep stages culminated in a significant increase in the latency to stage 4 sleep. The absence of statistical confirmation raises some doubt as to the validity of this explanation.

7.2.6 Sleep Stage Incidence

The long-term administration of 12,50mg clozapine had no significant effect upon the number of awakenings and stage 4 periods. This finding is in harmony with those of Hartmann and Cravens (1973(b)(c) who reported that the long-term administration of 50mg amitriptyline and 0,5mg reserpine had no systematic effect upon the number of awakenings in normal young adults. However, the long-term administration of clozapine had a significant effect upon the number of stage REM periods ($p<0,05$)(Table 23).

The Tukey HSD comparisons failed to identify the direction of this finding. There was a tendency, however, for the number of stage REM periods to increase on the first night of clozapine withdrawal (Table 23). It appears likely therefore that this increase in the number of stage REM periods upon the withdrawal of clozapine may be some manifestation of the REM rebound phenomenon as there was a significant decrease in the percentage of time spent in stage REM sleep during the administration of clozapine (Figure 11). The significance of this finding is questionable as no significant increase in stage REM sleep (rebound) occurred during the withdrawal of clozapine. Hartmann and Cravens (1973(b)(e) reported that the long-term administration of chloral hydrate had no systematic effect upon the number of stage REM periods whereas reserpine significantly increased the number of stage REM periods during drug administration.

7.2.7 Sleep Cycle Duration

The long-term administration of 12,50mg clozapine appears to have had little or no effect upon the organisation of laboratory sleep as the duration from the end of one REM period to the end of the next remained constant. Clozapine thus appears to resemble chloral hydrate in this respect as the long-term administration of chloral hydrate had no systematic effect upon the duration of the sleep cycles in normal young adults (Hartmann and Cravens 1973(e). The long-term administration of amitriptyline increases (Hartmann and Cravens (1973(c)), whereas reserpine decreases (Hartmann and Cravens (1973(b)) the duration of the sleep cycles.

7.2.8 Body Movement Activity

The long-term administration of 12,50mg clozapine significantly reduced the number of body movements ($p<0,05$), the number of body movements/minute of sleep ($p<0,05$)(Figure 12) as well as movement time ($p<0,05$)(Table 25). This effect was not as dramatic as the marked decrease in the number of body movements ($p<0,01$) and the number of body movements/minute of sleep ($p<0,001$) which occurred during the short-term administration of 25mg clozapine. The evidence from the two studies combined provides further support for the assumption that the effects of clozapine upon sleep parameters are dose related. The administration of clozapine thus reduces the number of body movements during sleep. This finding may have important therapeutic implications for the treatment of insomnia, since it implies that sleep was more restful (Oswald 1970(c); Hartmann and Cravens 1973(b)).

Clozapine thus appears to have a similar effect upon body movement activity as chlordiazepoxide (50mg/night) which significantly reduced the number of body movements during long-term administration in normal young adults (Hartmann and Cravens 1973(f)). The long-term administration of 50mg amitriptyline and chloral hydrate have no systematic effect upon the number of body movements during sleep and clozapine and chlordiazepoxide thus appear to be superior to these drugs in that they appear to produce a more restful sleep (Oswald 1970(c); Hartmann and Cravens 1973(b)).

7.2.9 Blood Parameters

The analyses of blood parameters were carried out as a precautionary

measure as the administration of large doses of clozapine has been associated with the occurrence of agranulocytosis in clinical patients (Goodson 1976-personal communication)(section 5.3.9). The long-term administration of 12,50mg clozapine had no significant effect upon any of the blood parameters monitored.

7.2.10 Psychological Assessment

Sleep Log. The long-term administration of 12,50mg clozapine had no systematic effect upon the estimated duration of sleep length (Table 26). The estimated duration of sleep length was, however, significantly reduced on the five night period of clozapine withdrawal (Figure 13). This finding appears to be consistent with the findings of Hartmann and Cravens (1973(a)) who reported that in a study of a similar nature "...the nights after discontinuation of medication, especially several nights thereafter, were sometimes associated with feeling better, with feeling they were 'over the hump', and nearing the end of one more drug study period" (Hartmann and Cravens 1973(a) p.165). Thus here, the decrease in the estimation of sleep duration could have been associated with the excitement of completing the sleep research program and receiving the substantial monetary compensation.

The number of side-effects reported increased markedly on the morning following the first five night period of clozapine administration (Figure 14). The most prominent side-effects to be reported were those which characterised sleepiness such as tiredness, drowsiness, exhaustion and wanting to go back to sleep (Table 27). This finding appears to be consistent with the

finding of Hemphill et al (1975) that "...sleepiness coloured the patient's response to the drug[1] for the first few days and masked other effects" (Hemphill et al 1975, p.2122). It is of interest to note that although the Stanford Sleepiness Scale revealed an increase in sleepiness during the first five night period of clozapine administration (Table 26), this finding did not reach statistical significance. It appears liekly therefore that the Stanford Sleepiness Scale was a less sensitive index of sleepiness than the sleep log.

The subjects also reported side-effects such as depression, apathy, tiredness, lack of vitality, resentfulness and the lack of physical and mental energy (Table 28). Having drawn attention to these side-effects, it should be noted that 12,50mg clozapine was administered to normal subjects with healthy sleeping habits for fifteen consecutive nights. Hartmann and Cravens (1973(a)) reported that "...our studies convinced us that normal human subjects cannot tolerate a higher[2] dose on a continuing basis... ....although 50mg/day[2] is a low dose in clinical terms, it is apparently the maximum dose tolerable for continued use by normal subjects" (Hartmann and Cravens 1973(a) p.161). The evidence suggests that the side-effects reported in the present study may not occur in insomniac subjects as these subjects have peculiar sleeping habits. However, further research on insomniac subjects is required to provide the necessary confirmation of this hypothesis.

The drug identification rating increased markedly on the first five night period of clozapine administration (Figure 15). This

[1]The dosage of clozapine varied between 100mg-300mg/day.
[2]chlorpromazine (50mg/day).

finding indicated that the subjects were able to correctly assess the nature of the medication (i.e.clozapine) on these five nights. The data, however, indicated that the subjects were far less accurate in their assessment of the nature of the medication on the second and third five night periods of clozapine administration (Table 26). This finding is consistent with the finding of Hemphill et al (1975) that "...tolerance and normal sleep patterns were established after a week" (Hemphill et al 1975 p.2122). The evidence favours the conclusion that a rapid tolerance to clozapine may develop. This finding may turn out to be the major limitation in the use of clozapine as an hypnotic agent over an extended period of time. Many hypnotic drugs have been found to become relatively ineffective after chronic administration (Johns 1975; Kales and Kales 1973) and the present finding appears to indicate that further research on insomniac subjects is required to determine whether the administration of 12,50mg clozapine will enhance sleep duration over an extended period of time.

Psychological Assessment

The long-term administration of 12,50mg clozapine had no significant effect upon the Brief Psychiatric Rating or the Taylor Manifest Anxiety scales and its effect was thus restricted to its sleep inducing properties. This finding is consistent with the finding that "...there was no evidence in any case that clozapine had a thymoleptic effect, or was a mood elevator or a direct psychostimulant" (Hemphill et al 1975 p.2123).

In summary, the evidence suggests that the long-term administration

of 12,50mg clozapine may have important therapeutic implications for the treatment of insomnia. This conclusion was supported by the following findings: (i) The number of minutes spent awake during the second three hours of the record on the third and eleventh nights of clozapine administration was significantly reduced. (ii) The percentage of time spent in stage I sleep was significantly reduced. (iii) The number of body movements which occurred during sleep was significantly reduced. (iv) The number of body movements/minute of sleep was significantly reduced. (v) Movement time was significantly decreased and (vi) There was no evidence of a stage REM rebound, despite the fact that a small but significant reduction in the percentage of time spent in stage REM sleep occurred, during the administration of clozapine. The finding that a rapid tolerance to clozapine may develop, may turn out to be the major limitation in the possible use of clozapine as an hypnotic agent over an extended period of time. Further research on insomniac subjects should however be carried out to determine whether the administration of 12,50mg clozapine will enhance sleep duration over an extended period of time.

8.0 THE REM DREAM RECALL INVESTIGATION

8.1 Results

8.1.1 Dream Report Rating Scales

The effects of the administration of clozapine and placebo upon the dream report rating scales are presented in Table 31. In all but one instance (Active Participation), no significant differences were obtained.

The analysis of variance of the Active Participation Scale yielded a significant variance ratio ($F = 8,16$; df 2,10; $p<0,01$). The Tukey HSD comparisons indicated that the Active Participation rating decreased on the withdrawal of clozapine. The mean Active Participation rating was significantly lower on the recorded clozapine withdrawal night (night 24) than the mean on the recorded baseline night (night 10)($p<0,05$) and the recorded clozapine administration night (night 17)($p<0,05$).

8.1.2 Sleep Log Indices

The administration of clozapine and placebo had no significant effect upon the sleep log indices (Table 32).

Table 31. The effects of the short-term administration of 12,50mg clozapine and 12,5mg placebo upon the mean dream rating scale indices of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo	12,5mg clozapine	12,5mg placebo			
Experimental Condition	Baseline	Clozapine Administration	Withdrawal	Degrees of Freedom	F Ratio	P
Laboratory Recorded Nights	10	17	24			
DREAM RATING SCALES						
Mean Dreamlike Fantasy rating	5,39±0,50	5,03±0,12	4,33±1,74	2,10	1,35	>0,25
Mean Physical Aggression rating	0,11±0,07	0,69±0,34	0,47±0,27	2,10	2,76	<0,25
Mean Verbal Aggression rating	0,50±0,28	1,08±0,60	0,0 ±0,0	2,10	2,06	<0,25
Mean Manifest Sexuality rating	0,78±0,37	0,78±0,37	0,69±0,53	2,10	0,01	>0,25
Mean Active Participation rating	3,83±0,29	3,75±0,36	2,56±0,46	2,10	8,16	<0,01
Mean Activity-Passivity rating	5,14±0,44	5,36±0,32	4,47±0,91	2,10	0,63	>0,25
Mean Hedonic Tone rating	4,28±0,26	5,06±0,30	4,44±0,44	2,10	3,78	<0,10

Table 32. The effects of the short-term administration of 12,50mg clozapine and 12,5mg placebo upon the sleep log indices (quality and quantity of dreaming) of 6 normal young adults (Means ± S.E.)

Medication Administered	12,5mg placebo	12,5mg clozapine	12,5mg placebo			
Experimental Condition	Baseline	Clozapine Administration	Withdrawal	Degrees of Freedom	F Ratio	P
Laboratory Recorded Nights	8 and 9	15 and 16	22 and 23			
SLEEP LOG INDICES						
Quality of dreaming (mean score)	51,77±2,77	50,05±0,88	54,94±4,22	2,10	0,59	>0,25
Quantity of dreaming (mean score)	47,72±2,67	49,68±2,40	48,43±3,80	2,10	0,12	>0,25
Mean Distortion rating	2,40±0,37	2,30±0,46	2,60±0,48	2,8 *	0,38	>0,25

* 5 subjects as one subject failed to complete this scale.

8.2 Discussion

8.2.1 Research Strategy

This study comprised a four night single blind, cross-over design. Each of the four recording nights were within a space of six days of one another. This intermediate period permitted the subjects to recover from any possible REM rebound incurred by laboratory awakenings (Hartmann and Cravens 1973(a). The major limitation of the present study was that any immediate withdrawal effect, which might have occurred within the space of five days, would have remained undetected. It appears likely however that only limited withdrawal effects occurred as the administration of 12,50mg clozapine had no systematic effect upon REM dream content as measured by the standard rating scales used (Table 31).

Only one adaptation night was effected as all of the subjects participating in the present phase of the investigation, had taken part in a previous sleep study in this series of experiments.

8.2.2 Dream Rating Scales

The short-term administration of 12,50mg clozapine had no systematic effect upon REM dream content. This finding appears to be consistent with the previous finding that the administration of 12,50mg clozapine had no systematic effect upon the indices of stage REM sleep (Table 21).

> "There is evidence that even if individual EM's do not represent the dreamer 'scanning' his world, profusion of EM's is associated with experiences in which the dreamer is an active participant, rather than thinking, reflecting, or passively observing events"
>
> (Firth 1974 p.547).

The present finding appears to be in marked contrast to most hypnotic agents which have been found to produce an increased vividness in REM mentation on withdrawal characterised by the occurrence of nightmares (Kales et al 1969(b), 1974; Oswald and Priest 1965). This evidence further indicates that clozapine (12,50mg) may have an important role to play in the treatment of insomnia, but again, further research on insomniac subjects is necessary to substantiate this hypothesis.

8.2.3 Sleep Log Indices

The short-term administration of 12,50mg clozapine had no significant effect upon the quality and quantity of the subject's dream experiences recalled upon awakening at home. This additional information proved to be invaluable as discrepancies between laboratory REM dream reports and dream experiences recalled at home, have been reported to occur (Weisz and Foulkes 1970). Hall and Van de Castle (1966) concluded that:

> Dreams reported at home differed in content from dreams reported after REM period awakenings in the laboratory. The major difference was that of dramatic quality. Home dreams tended to be more dramatic, laboratory dreams more prosaic.
>
> (Hall and Van de Castle 1966 p.48).

Thus, in the present study two lines of evidence, namely the laboratory REM dream reports and dream experiences recalled at home, have been brought together to determine the effects of the short-term administration of 12,50mg clozapine upon dream content. The findings of the present study thus provide further confirmation for the conclusion that the short-term administration of 12,50mg clozapine has no significant effect upon the REM dream content.

9.0 CONCLUSIONS

The findings of the short-term, long-term and REM dream recall investigations have been discussed in the relevant sections and in this section the major findings are highlighted again and the results from the numerous indices are synthesised.

A major aim of the present study was an attempt to assess the effects of the short-term administration of 25mg clozapine upon the sleep patterns of normal young adults. This investigation revealed that the short-term administration of clozapine markedly suppressed stage 4 sleep which remained at low levels even when clozapine had been withdrawn. It is tentatively suggested that the decrease in stage 4 sleep was produced in such a manner as not to permit homeostatic restoration within the first two days of clozapine withdrawal. The significant reduction in stage 4 sleep appears to have important therapeutic implications for the treatment of disorders of slow wave sleep.

In addition, the short-term administration of 25mg clozapine appears to have important therapeutic implications for the treatment of insomnia. This conclusion was supported by the following findings: (i) Total sleep time was significantly increased on the first and second nights of administration despite the fact that an attempt was made to control for the time spent in bed. (ii) The number of body movements was significantly reduced on all three nights of clozapine administration. (iii) The number of body movements/minute of sleep was significantly reduced on all three nights of clozapine administration. (iv) The short-term

administration and withdrawal of 25mg clozapine/night had no significant effect upon stage REM sleep.

However, the indices of stage REM sleep were significantly affected. The mean burst length, the density/minute REM sleep and % motility were significantly increased on the third night of clozapine administration and this increase persisted on the first night of clozapine withdrawal. In addition, the total number of bursts and the number of bursts/REM period increased significantly on the first night of clozapine withdrawal. It was tentatively suggested that these findings may have reflected the antipsychotic properties of clozapine (Blum and Girke 1974). Finally, numerous psychological and physiological side-effects were reported and these findings may represent a major limitation of the possible use of clozapine as an hypnotic agent.

The second major aim of the present study was an attempt to determine the effects of the short-term administration of a placebo upon the sleep patterns of normal young adults. Controversy exists in the literature at present as to whether the administration of placebo influences sleep parameters (Davis and Hartmann 1973 (a)(b); Zung 1973; Adam et al 1975, 1976). The present investigation revealed that the administration of placebo had no systematic effect upon any of the monitored sleep parameters. This finding, however, does not appear to hold true for psychological parameters as the administration of placebo significantly increased the subjective estimation of drowsiness on the morning following the second night of administration.

The third major aim of the present study was to determine the effects of the long-term administration of 12,50mg clozapine upon the sleep patterns of normal young adults. The evidence from this experiment suggested that clozapine may have important therapeutic implications for the treatment of insomnia. This conclusion was supported by the following findings: (i) The number of minutes spent awake during the second three hours of the record on the third and eleventh nights of clozapine administration was significantly reduced. (ii) The percentage of time spent in stage 1 sleep was significantly reduced. (iii) The number of body movements which occurred during sleep was significantly reduced. (iv) The number of body movements/minute of sleep was significantly reduced. (v) Movement time was significantly decreased and (vi) There was no evidence of a stage REM rebound, despite the fact that a small but significant reduction in the percentage of time spent in stage REM sleep occurred during the administration of clozapine.

There was some evidence, however, that indicated that a rapid tolerance to clozapine may develop. This finding may prove to be the major limitation in the possible use of clozapine as an hypnotic agent over an extended period of time as many hypnotic drugs have been found to become relatively ineffective after chronic administration (Johns 1975, Kales and Kales 1973). The present findings should be validated and extended on insomniac subjects to determine whether the administration of 12,50mg clozapine would enhance sleep duration over an extended period of time.

The fourth major aim of the present study was an attempt to explore the effects of the short-term administration of 12,50mg clozapine

upon REM dream content. The withdrawal of 12,50mg clozapine after three nights of consecutive administration was found to have no systematic effect upon the REM dream content. This finding was in marked contrast to most hypnotic agents which have been found to produce an increased vividness in REM mentation upon withdrawal (Kales et al 1973). This increased vividness has often been associated with the occurrence of nightmares (Kales et al 1969(b), 1974; Oswald and Priest 1965; Hartmann 1973(a)). This finding provides further confirmation of the previous assumption that clozapine may have important therapeutic implications for the treatment of insomnia.

In the present study a start has been made in an attempt to determine the effects of clozapine upon the sleep patterns and REM dream content of normal young adults. Kales and Kales (1975) have aptly portrayed the importance of rigorous research strategies in the evaluation of hypnotic drugs before they are placed on the medical market.

> "Insomnia is one of the most common symptoms treated by the physician, and pharmacologic agents are the most frequent method of treatment. Because of a number of shortcomings in the evaluation and promotion of hypnotic drugs, the physician is often provided insufficient and misleading information resulting in a general misuse of these drugs".
>
> (Kales and Kales 1975 p.826).

The present study employed a multiplicity of measures including sleep stage percentages, indices of stage REM sleep, sleep stage incidence, sleep stage latencies, sleep cycle duration, body movement indices as well as the assessment of psychological and physiological side-effects. This study required a total of

2190 hours of recording over a total of 219 nights. This comprehensive assessment of the effects of clozapine upon the sleep patterns of normal young adults indicates that clozapine, in addition to its proposed wide variety of uses, may be of use in the treatment of one of the most prevalent of disorders namely insomnia.

APPENDICES

APPENDIX I

TAYLOR MANIFEST ANXIETY SCALE

		T	F
1	I do not tire quickly	...	...
2	I am troubled by attacks of nausea	...	...
3	I believe I am more nervous than most others	...	...
4	I have very few headaches	...	...
5	I work under a great deal of tension	...	...
6	I cannot keep my mind on one thing	...	...
7	I worry over money and business	...	...
8	I frequently notice my hand shakes when I try to do something	...	...
9	I blush no more often than others	...	...
10	I have diarrhoea once a month or more	...	...
11	I worry quite a bit over possible misfortunes	...	...
12	I practically never blush	...	...
13	I am often afraid that I am going to blush	...	...
14	I have nightmares every few nights	...	...
15	My hands and feet are usually warm enough	...	...
16	I sweat very easily even on cool days	...	...
17	Sometimes when embarrassed, I break out in a sweat which annoys me greatly	...	...
18	I hardly ever notice my heart pounding and I am seldom short of breath	...	...
19	I feel hungry almost all the time	...	...
20	I am very seldom troubled by constipation	...	...
21	I have a great deal of stomach trouble	...	...
22	I have had periods in which I lost sleep over worry	...	...
23	My sleep is fitful and disturbed	...	...
24	I dream frequently about things that are best kept to myself	...	...
25	I am easily embarrassed	...	...
26	I am more sensitive than most other people	...	...
27	I frequently find myself worrying about something	...	...
28	I wish I could be as happy as others seem to be	...	...
29	I am usually calm and not easily upset	...	...
30	I cry easily	...	...
31	I feel anxiety about something or someone almost all the time	...	...

		T	F
32	I am happy most of the time	...	...
33	It makes me nervous to have to wait	...	...
34	I have periods of such great restlessness that I cannot sit long in a chair	...	...
35	Sometimes I become so excited that I find it hard to get to sleep	...	...
36	I have sometimes felt that difficulties were piling up so high that I could not overcome them	...	...
37	I must admit that I have at times been worried beyond reason over something that really did not matter	...	...
38	I have very few fears compared to my friends	...	...
39	I have been afraid of things or people that I know could not hurt me	...	...
40	I certainly feel useless at times	...	...
41	I find it hard to keep my mind on a task or job	...	...
42	I am usually self-conscious	...	...
43	I am inclined to take things hard	...	...
44	I am a high-strung person	...	...
45	Life is a strain for me much of the time	...	...
46	At times I think I am no good at all	...	...
47	I am certainly lacking in self-confidence	...	...
48	I sometimes feel that I am about to go to pieces	...	...
49	I shrink from facing a crisis of difficulty	...	...
50	I am entirely self-confident	...	...

APPENDIX 2

ACTIVATION DEACTIVATION ADJECTIVE CHECKLIST

Name _____ Date and Time _____
(Please include A.M. or P.M.)

Each of the words on the next sheet describes feelings or mood. Please use the list to describe your feelings at this moment.

If the word definitely describes how you feel at the moment you read it, circle the double check (vv) to the right of the word. For example, if the word is, relaxed, and you are definitely feeling relaxed at the moment, circle the double vv as follows:
relaxed (vv) v ? no.
This means you definitely feel relaxed at the moment.

If the word only slightly applies to your feelings at the moment, circle the single check as follows:
relaxed vv (v) ? no.
This means you feel slightly relaxed at the moment.

If the word is not clear to you or you cannot decide whether or not it applies to your feelings at the moment, circle the question mark as follows: relaxed vv v (?) no.
This means you cannot decide whether you are relaxed or not.

If you clearly decide the word does not apply to your feelings at the moment, circle the no as follows:
relaxed vv v ? (no).
This means you are definitely not relaxed at the moment.

Work rapidly. Your first reaction is best. Work down the first column, then go on to the next. Please mark all words. This should take only a few minutes.

-Now please turn the page and begin working-

(vv) v ? no : definitely feel
vv (v) ? no : feel slightly
vv v (?) no : cannot decide
vv v ? (no) : definitely do not feel

---

carefree vv v ? no
serious vv v ? no
peppy vv v ? no
pleased vv v ? no
placid vv v ? no
leisurely vv v ? no
sleepy vv v ? no
jittery vv v ? no
intense vv v ? no
grouchy vv v ? no
energetic vv v ? no
egotistic vv v ? no
calm vv v ? no
suspicious vv v ? no
tired vv v ? no
regretful vv v ? no
stirred up vv v ? no
warm-hearted vv v ? no
vigorous vv v ? no
engaged-in-thought vv v ? no
at rest vv v ? no
elated vv v ? no
drowsy vv v ? no
witty vv v ? no

aroused vv v ? no
fearful vv v ? no
lively vv v ? no
still vv v ? no
self-centered vv v ? no
wide-awake vv v ? no
skeptical vv v ? no
activated vv v ? no
sad vv v ? no
full-of-pep vv v ? no
affectionate vv v ? no
quiet vv v ? no
concentrating vv v ? no
sluggish vv v ? no
overjoyed vv v ? no
quick vv v ? no
nonchalant vv v ? no
quiescent vv v ? no
clutched-up vv v ? no
Wakeful vv v ? no
rebellious vv v ? no
active vv v ? no
blue vv v ? no
defiant vv v ? no

APPENDIX 3

BRIEF PSYCHIATRIC RATING SCALE
(Overall and Gorham)

INSTRUCTIONS : Insert General Scoring Sheet and Code 01 under Sheet Number.

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

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

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

0 = Not assessed
1 = Not present
2 = Very Mild
3 = Mild
4 = Moderate
5 = Moderately severe
6 = Severe
7 = Extremely severe

Mark on right half of scoring sheet on row specified		Row No.
1.SOMATIC CONCERN	Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	1
2.ANXIETY	Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	2
3.EMOTIONAL WITHDRAWAL	Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.	3
4.CONCEPTUAL DISORGANIZATION	Degree to which the thought processes are confused, disconnected or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	4

5. GUILT FEELINGS	Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	5
6. TENSION	Physical and motor manifestations of tension, "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	6
7. MANNERISMS AND POSTURING	Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	7
8. GRANDIOSITY	Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	8
9. DEPRESSIVE MOOD	Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.	9
10. HOSTILITY	Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety nor somatic complaints. (Rate attitude toward interviewer under "uncooperativeness".)	10
11. SUSPICIOUSNESS	Belief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.	11
12. HALLUCINATORY BEHAVIOR	Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.	12

APPENDIX 4

STANFORD SLEEPINESS SCALE

Please record the scale value of the statement which best describes your state of sleepiness.

1. Feeling active and vital; alert, wide awake.
2. Functioning at a high level, but not at peak; able to concentrate.
3. Relaxed; awake; not at full alertness; responsive.
4. A little foggy; not at peak; let down.
5. Fogginess; beginning to lose interest in remaining awake; slowed down.
6. Sleepiness; prefer to be lying down; fighting sleep; woozy.
7. Almost in reverie; sleep onset soon; lost struggle to remain awake.

RECORDED VALUE:

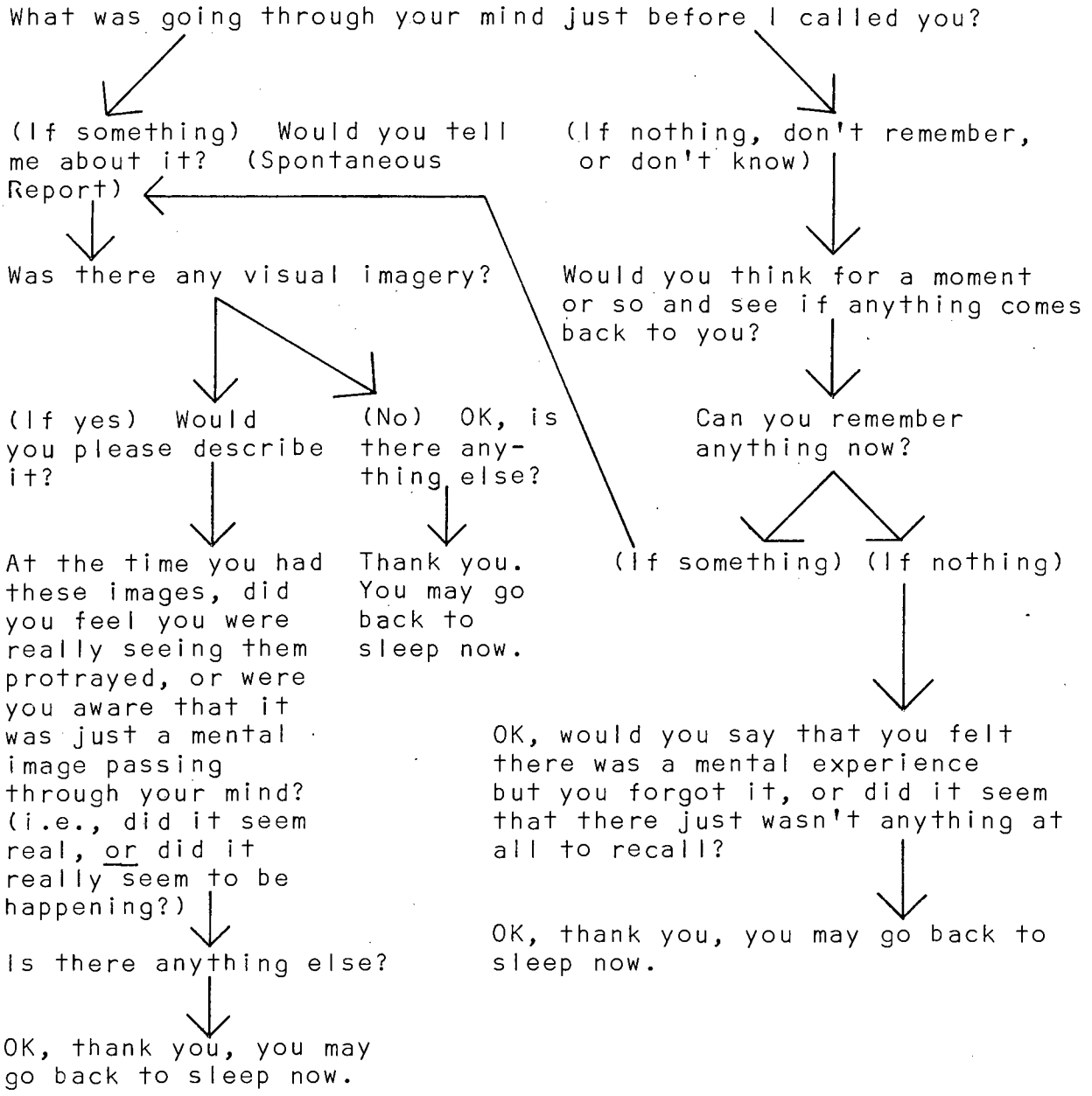
SURNAME:

DATE:

TIME:

APPENDIX 5

LARSON INTERVIEW SCHEDULE



APPENDIX 6

DREAMLIKE FANTASY SCALE

0 -- No recall	Feels mind was blank.
1 -- No recall	Feels he was experiencing something, but forgets what.
2 -- Recall	Conceptual (no sensory imagery), everydayish content.
3 -- Recall	Conceptual, bizarre content.
4 -- Recall	Perceptual (sensory imagery), non-hallucinatory (didn't believe experience was real), everydayish content.
5 -- Recall	Perceptual, nonhallucinatory, bizarre content.
6 -- Recall	Perceptual, hallucinatory (believed events he imagined were really happening), everydayish content.
7 -- Recall	Perceptual, hallucinatory, bizarre content.

APPENDIX 7

PHYSICAL AGGRESSION SCALE

0 none

1 hitting in fun, like hard slap on back

trivial property destruction

any case where actions not ostensibly involving aggression seem to you to involve it

2 threats and counterthreats by gesture, posture, word

carrying a weapon, being in war, if no specific agg. cited

accidental and extensive damage of property of others

one isolated bit of defensive behavior--one action of restraint (press: being apprehended for purposes of restraint, confinement only)

**perception but denial of vague, unspecified threats--he might do something bad or something bad might happen to him

3 perception of hostile threat, but minimization or denial of same. Ex**"You might think that he'd hit her but..." or (press) "You might think he'd be in danger but..."

or *accidental killing or injury to other, not S-caused is scored as need for S if it is indicated that he is guilty about it

mild type episode--e.g., one slap

or contemplation of accidental death or terminal illness of another person or self

or accidental non-fatal injury to others/self

or defensive role in aggressive sequence--more than 1 isolated act

or intentional and extensive destruction of property of others/self

4 perception of possibility of 6 act, but denial. Ex**"You might think that he would kill her, but he is actually..."etc.

or attack upon others: intentional, offensive, violent, though some provocation has been offered

or accidental killing of other or self (press includes being "killed" by disease and natural forces as well as being killed by another person by accident)

5 contemplation of or threat of committing an act listed as 6

or any major incident of aggression which seems quite unprovoked

particularly violent episode, sustained in character

6 killing another person, intentionally, whether described in gory detail or not (includes suicide)

APPENDIX 8

MANIFEST SEXUALITY SCALE

The Manifest Sexuality Scale

Instructions to judges:

1. Since extremely overt sexual behavior (petting, intercourse) is rare in dreams, liberal interpretations are to be made of sexual "behavior", so that scores of 3-6 will be moderately frequent for any set of dreams from normal subjects.

2. Where several scores apply, give the highest score except when a dream appears to be highly symbolic overall, but has, in addition to the symbolism, some casual sexual interaction (e.g., boy talking to girl). Here, give a score on the basis of the symbolism (1-2) rather than on the basis of the overt behavior (3-4).

The scale.

0 = none

1 = sexual feeling, interest, concern, ascribed to others with no overt sexual behavior OR

symbolic sexual behavior protrayed in others. A representative but not inclusive list of sexual symbols follows. Score if these or other symbols can be considered, on the basis of dream context, as "probably" sexual in any particular case.

(Male symbols	Female symbols	Interactional symbols
pole, key, pen, rifle, gun, sword, cigarette, cigar, pipe, snake, horse, dog, tree, conical or erect figures, etc.	enclosure, containers--such as box, door, window, vase, glass, pot--, kitten, flower, round open figures, openings, etc.	staircase activity--up/down, elevator up/down, playing instrument, any back and forth repetitive motion, wild/crazy driving in car as when out of control, bumping, contact symbols; soil, infect; shoot with gun, etc.)

2 = sexual feeling, interest, concern ascribed to self with no overt sexual behavior OR

symbolic sexual behavior portrayed in self...

3 = mild "erotic" behavior (dating, flirting, teasing, being with--in other than strict businesslike setting--, playing with, joking with, having fun or pleasurable casual social interaction with, member of opposite sex of approximately equivalent age) ascribed to others

4 = mild "erotic" behavior (...) ascribed to self

5 = strongly "erotic" behavior (spending night with, sleeping (with), having intercourse with, petting, kissing, fondling, grabbing, touching, bumping, or having any bodily contact with, going to bed with, in bedroom or sleeping quarters of, member of opposite sex of approximately equivalent age; pregnancy; implicitly or explicitly having babies or marrying (but not necessarily being a parent or being married)) ascribed to others

Note: sleeping in experiment is not counted, unless some erotic touch is added to the typical laboratory situation

6 = strongly "erotic" behavior (...) ascribed to self

APPENDIX 9

ACTIVE PARTICIPATION SCALE

1 - Dreamer is not present in dream; seems to be exerting no control over its action; is not on scene even as passive spectator.

2 - Dreamer is present in dream only to extent of being passive spectator.

3 - Dreamer is present as participating character but his role is entirely or almost entirely passive (recipient of others' actions rather than initiator).

4 - Dreamer is present as participating character in moderately active role; not the overriding determiner of dream events, however.

5 - Dreamer is present in active role and seems to be determining the character of dream events to a major degree.

APPENDIX 10

THE VERBAL AGGRESSION SCALE

0 none

1 mild teasing mocking or you sense some hostile-type tension in conversation with other

2 derogation of objects associated with person Ex**"Your car is a mess". (Some objects, e.g., clothing, may be so much a part of the self that an attack on them is more properly considered an attack on the person wearing them).

3 derogation of persons associated with a person. Ex**"Your mother is a dope"

4 direct derogation of behavior or beliefs of other. In one-sided form, "criticisms", etc. In two-sided form, "arguments", etc.

Score 5, if extended, particularly violent, etc.
Score 3, if incident is mild, without any apparent ill-will etc.

5 milder than 6 but stronger than 4, in that abusiveness is still evident as is focus of attack on other as a person

6 Extreme derogation of other as person: abusive, malicious

APPENDIX II

THE HEDONIC TONE SCALE

1 - very pleasant

2 - moderately pleasant

3 - slightly pleasant

4 - neither pleasant nor unpleasant; can't tell

5 - slightly unpleasant

6 - moderately unpleasant

7 - very unpleasant

APPENDIX 12

DISTORTION SCALE

How distorted or fantastic was it (that is, to what degree were you thinking or were you, or other people, or objects behaving in ways which would seem strange if they occurred in waking life)?

1 extremely distorted
2 quite distorted
3 fairly distorted
4 somewhat distorted
5 a little bit distorted
6 not at all distorted

This becomes a six point distortion scale by reversing the numbers preceding the response alternative (1 = not at all distorted, 6 = extremely distorted), and employing these reversed numbers as weights.

APPENDIX 13

THE SHORT-TERM INVESTIGATION SLEEP LOG

For Each Night of Sleep
Lab. Night 1 2 3 4 5 6 7 8 9

Day and Date
(Evening)

Questions 1 - 3 refer to day before sleep period. (Date above).

(1) Any Naps? Alcohol? Medication of any kind (except for this study)? If YES please describe.

(2) Any unusual activities or occurrences that might have influenced your sleep (e.g. physical exercise, upsetting news, sexual intercourse, exams, major changes in daily routine etc.)?

(3) Time to bed.

(4) Time you got up this morning?

(5) How much sleep do you think you had?

For Questions 6 and 7 use the following rating system:

5 = much better
4 = a little better
3 = same as usual
2 = a little worse
1 = much worse than usual

(6) How well did you sleep compared to the way you usually sleep?

(7) How do you feel this morning?

(8) Did you dream at all last night? If yes, please describe briefly including mood in dream and any unusual features.

(9) Do you feel sick in any way whatever?
Any unusual physical feelings? If YES please describe.

(10) Any unusual psychological feelings this morning or during the past day?
More or Less depressed, anxious, or angry than usual?
If YES please describe.

<u>Question 11 to be answered from night 5 only</u>.

(11) If you answered YES to questions 9 or 10, do you think that it may be due to the sleeping pill you are taking or is it explainable in other ways?

APPENDIX 14

THE LONG-TERM INVESTIGATION SLEEP LOG

S L E E P S T U D Y

Thank you once again for taking part in this study. You are being paid R85.00 for your participation. The reason for this is that I would like you to be as co-operative and honest as possible. It is essential for you to take your sleeping pill each night. Just keep in mind that a great deal of time, effort and money has been put into this study and your co-operation will result in its success. The most vital aspects on your part is to take your pill each night, complete the sleep log every morning, and to arrive at the laboratory on time on the required nights. Should you require any additional information please contact me:

Psychology Department Tel: 698531 ext. 532
Home: 447221

Steve Touyz
Department of Psychology.

HOME SLEEP LOG

INSTRUCTIONS

Read the questions carefully and answer them to the best of your ability.
Be quite sure not to leave any out.
Complete this log shortly after you have woken up.

Department of Psychology,
University of Cape Town.

SURNAME:

INITIALS:

DATE LAST NIGHT:

Day of week yesterday:

Code No. of pill:

Did you take your pill last night?

What time did you take your pill?

What is the time now?

Last night was the ..... night I have taken a pill.

.....
Signature.

Questions 1 - 3 refer to day before sleep period. (Date on front page).

(1) Any Naps? Alcohol? Medication of any kind (except for this study)? If YES please describe.

(2) Any unusual activities or occurrences that might have influenced your sleep (e.g. physical exercise, sexual intercourse, upsetting news, exams, changes in daily routine etc.)?

(3) Time to bed?

(4) Time you got up this morning?

(5) How much sleep do you think you had (hours)?

For Questions 6 and 7 use the following rating system:

5 = much better

4 = a little better

3 = same as usual

2 = a little worse

1 = much worse than usual

(6) How well did you sleep compared to the way you usually sleep?

(7) How do you feel this morning? (please elaborate if possible).

(8) Did you dream at all last night? If YES please describe your dream from beginning to end in as much detail as possible, including mood or any unusual features. If you only remember parts of your dream then write these down. How many dreams did you have? Include any drawings you might wish to make.

(9) Do you feel sick in any way?
Please describe. This is an important aspect of the study and it would be appreciated if you would write down any unusual physical feelings. If you answered yes, do you think it may be due to the sleeping pill you are taking or is it explainable in other ways?

(10) Are any of the symptoms listed below relevant to your present state? Answer YES, NO, or NOT APPLICABLE. Please complete all the categories. If you answered YES to any category, do you think it may be due to the sleeping pill you are taking or is it explainable in other ways.

(i) dizzy
(ii) nauseous
(iii) tired
(iv) drowsy
(v) exhausted
(vi) feeling faint
(vii) difficulty in writing
(viii) difficulty in talking
(ix) mouth very dry
(x) mouth very moist
(xi) want to go back to sleep
(xii) felt dizzy but fine when I lay down
(xiii) felt dizzy even when lying down

(11) If you answered yes to any category in question (10) please elaborate and explain if possible what could have caused it? Also if any feeling not listed, describe.

(12) Any unusual psychological feelings this morning or during the past day? More or less depressed, anxious, or angry than usual? If Yes please describe.

For Question 13 use the following rating system:

2 = sleeping tablet

1 = cannot decide

0 = placebo

(13) Do you think you had a sleeping tablet or a placebo (inert compound) last night?

(14) In as much detail as possible describe how you arrived at your decision in question 13.

(15) Judging by the way you slept last night and feel this morning, would you recommend the sleeping tablet you took last night to a friend? Describe.

(16) Any information you feel that could be relevant to the present study (not yet discussed).

APPENDIX 15

THE REM DREAM RECALL INVESTIGATION SLEEP LOG

HOME LOG

(To be completed each morning upon waking)

1. DATE NAME

2. Please indicate by a mark on the following line the amount or quantity of your last night's dreaming. An average night should mean a mark in the centre

   Dreaming all the time ——————————— Little or no dreaming

3. Please indicate by a mark on the following line the quality of your last night's dreaming. An average night should mean a mark in the centre

   Very everydayish, ordinary dreaming ——————————— Very vivid, bizarre dreaming

4. How distorted or fantastic was your dreaming last night, that is, to what degree were you thinking, or were you, or other people or objects behaving in ways which would seem strange if they occurred in waking life

   1. extremely distorted
   2. quite distorted
   3. fairly distorted
   4. somewhat distorted
   5. a little bit distorted
   6. not at all distorted

APPENDIX 16

MENTAL SPEED TEST

SURNAME:

NIGHT IN LAB: 1 2 3 4 5 6 7 8 9

DATE:

Complete as many of the problems as accurately as possible in the given time.

5+7 =	1+7 =	3+2 =	5+4 =	3+4 =	5+4 =
4+4 =	4+1 =	9+3 =	3+2 =	9+5 =	1+6 =
7+1 =	9+3 =	5+5 =	2+2 =	1+3 =	2+3 =
7+6 =	4+3 =	6+9 =	4+3 =	5+0 =	7+4 =
1+2 =	3+9 =	4+1 =	5+8 =	3+6 =	3+4 =
4+2 =	4+6 =	5+2 =	7+7 =	7+1 =	8+3 =
6+1 =	6+7 =	6+3 =	4+5 =	8+0 =	6+9 =
4+0 =	3+3 =	3+1 =	6+7 =	2+0 =	5+1 =
6+8 =	5+1 =	9+0 =	8+9 =	4+7 =	8+5 =
9+2 =	9+1 =	3+0 =	3+5 =	9+3 =	0+3 =
5+2 =	9+7 =	5+2 =	6+2 =	1+9 =	5+7 =
4+8 =	9+9 =	5+6 =	3+5 =	5+4 =	5+2 =
4+3 =	7+7 =	3+5 =	2+2 =	5+0 =	8+8 =
5+7 =	6+3 =	9+5 =	9+5 =	8+7 =	3+2 =
3+2 =	9+2 =	4+5 =	7+1 =	6+9 =	6+4 =
2+1 =	8+1 =	3+5 =	9+9 =	6+7 =	9+9 =
3+9 =	2+7 =	7+4 =	2+2 =	7+8 =	9+1 =
6+6 =	8+9 =	8+0 =	8+8 =	6+1 =	2+5 =
4+3 =	1+1 =	7+0 =	8+4 =	8+3 =	6+5 =
2+2 =	5+4 =	8+3 =	6+5 =	4+3 =	5+8 =
5+9 =	5+5 =	9+0 =	4+6 =	4+5 =	5+6 =
4+3 =	7+4 =	2+5 =	3+6 =	3+6 =	1+6 =
5+1 =	6+1 =	3+3 =	2+1 =	2+1 =	3+7 =
1+8 =	6+9 =	1+8 =	8+0 =	8+0 =	3+6 =
8+1 =	2+8 =	2+9 =	7+1 =	7+1 =	8+8 =
5+9 =	1+3 =	6+8 =	1+0 =	1+0 =	5+4 =
7+8 =	7+2 =	4+5 =	7+4 =	0+6 =	2+4 =
8+1 =	5+7 =	1+6 =	5+2 =	7+4 =	6+4 =
3+3 =	8+3 =	9+5 =	8+3 =	5+2 =	1+0 =
9+2 =	8+6 =	7+6 =	4+5 =	0+9 =	7+1 =
8+1 =	4+4 =	5+6 =	9+4 =	8+3 =	6+0 =
9+9 =	3+5 =	7+5 =	4+6 =	4+5 =	3+7 =
2+6 =	5+9 =	8+2 =	8+6 =	9+4 =	4+7 =
1+8 =	1+1 =	6+6 =	3+2 =	4+6 =	3+8 =
2+5 =	7+4 =	5+9 =	2+7 =	8+6 =	7+3 =
7+4 =	8+5 =	3+7 =	6+1 =	3+2 =	3+2 =
9+2 =	9+7 =	5+4 =	4+4 =	2+7 =	9+7 =
1+9 =	8+8 =	4+5 =	5+8 =	6+1 =	7+4 =
3+1 =	3+1 =	5+2 =	1+9 =	4+4 =	5+6 =
2+3 =	5+4 =	9+7 =	2+3 =	5+8 =	4+9 =
1+5 =	7+6 =	9+5 =	1+6 =	1+9 =	4+3 =
3+4 =	7+8 =	1+0 =	5+4 =	2+3 =	1+6 =
9+8 =	9+4 =	1+1 =	4+3 =	1+6 =	4+8 =

APPENDIX 17

PRINTOUT OF THE Z SCORE TRANSFORMATION PROGRAM

```
LIST
100  DIM X[20]
110  PRINT
120  PRINT " Z SCORE TRANSFORMATIOMS"
130  PRINT
140  PRINT
150  PRINT "NO OF SCORES(MAX=20)"
160  INPUT N
170  PRINT "NEW MEAN,SDEV"
180  INPUT M1,S1
190  PRINT "INPUT DATA"
200  PRINT
202  LET M2=S2=0
210  FOR I1=1 TO N
220  INPUT X[I1]
230  LET M2=M2+X[I1]
240  LET S2=S2+X[I1]↑2
250  NEXT I1
260  LET S2=SQR((S2-M2↑2/N)/(N-1))
270  LET M2=M2/N
280  PRINT "OLD MEAN=";M2;"OLD SDEV=";S2
290  PRINT
300  PRINT "Z SCORES & NEW SCORES"
310  FOR I1=1 TO N
315  IF S2=0 THEN 335
320  LET Z=(X[I1]-M2)/S2
330  LET Y=S1*Z+M1
331  GOTO 340
335  LET Z=0
336  LET Y=M1
340  PRINT Z,Y
350  NEXT I1
360  PRINT
370  GOTO 190
380  END

READY
```

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