THE ALCOHOL WITHDRAWAL SYNDROME: CHARACTERISATION, PREDICTORS OF SEVERITY, AND RELATIONSHIP TO RELAPSE

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by

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ABSTRACT

Investigations of withdrawal over the last 50 years have established that there is a syndrome that occurs with abstinence from alcohol, and that it is characterised by certain signs and symptoms. However, there is a paucity of information on symptom intensity and duration, predictors of withdrawal severity, and relationship of withdrawal severity to relapse.

Characterisation of the alcohol withdrawal syndrome was a major aspect of this study and involved mapping the intensity and duration of a range of withdrawal symptoms in humans. Physical symptoms of withdrawal were assessed by means of recently developed ambulatory monitors that provided objective twenty four hour recordings of skin temperature, sweating, and activity, all of which are disturbed by alcohol withdrawal. Activity levels during the night were indicative of the quality of sleep, and activity levels during the day reflected symptoms of restlessness and agitation. A significant proportion of this study was dedicated toward validation and calibration of the monitors. Psychiatric and health disturbances were assessed using standardised questionnaires. The BDI was used to assess depression, the STAI was used to assess anxiety, the POMS was used to assess general mood change, and the SF-36 was used to assess health. Assessments of withdrawal symptoms were made at during days 2, 3 & 4 of abstinence, and at two, six and ten weeks of abstinence.

Results from the monitors and questionnaires provided objective, standardised recordings of withdrawal during the first ten weeks of abstinence. Acute withdrawal (days 2, 3 & 4) was characterised by disruptions to diurnal temperature rhythms, periods of hyperthermia, severe sweating during the night persisting into the morning, sleep restlessness, disruption to diurnal activity rhythms, severe anxiety and depression, general mood disturbance, and poor physical and mental health. Protracted withdrawal after two weeks of abstinence was characterised by the same symptoms as during the acute phase. Protracted symptoms of hyperthermia, sleep restlessness, disrupted diurnal activity rhythms, anxiety, and physical and mental health disturbances were evident at six weeks. Symptoms of anxiety, sleep restlessness, disruption to diurnal activity rhythms and compromised mental health were present at ten weeks of abstinence.

The second major area of investigation was concerned with identifying predictors of alcohol withdrawal severity, including the global withdrawal syndrome as a whole, and also predictors of the severity of the global physical component of the withdrawal syndrome. Drinking history, kindling, and complications concomitant to withdrawal were investigated as predictors. Objective biological markers of hazardous alcohol intake were also investigated as potential predictors of withdrawal severity (gamma glutamyl transferase GGT, mean corpuscle volume MCV, carbohydrate deficient transferrin CDT). Two of the

components of drinking history (length of most recent drinking bout, and daily intake) appeared to predict the severity of the withdrawal syndrome as a whole. The concomitant complications of co-morbid illness and prescribed medication usage affected the severity of the global physical component of the withdrawal syndrome. The biological marker carbohydrate deficient transferrin was predictive of the global physical component of withdrawal severity.

The final major area of investigation concerned determining predictors of relapse using survival analysis. The main focus was on acute and protracted withdrawal severity as a predictor, and its relationship to other predictors of relapse. The other potential predictors of relapse that were incorporated into the survival analysis included several social factors (employment, residency, social support), and antecedents of withdrawal severity (drinking history, kindling, concomitant complications). The withdrawal syndrome as a whole, both acute and protracted, was not predictive of relapse, nor were any of the individual symptoms of withdrawal predictive of relapse. Of the antecedents of withdrawal severity, the concomitant complication of polydrug use was predictive of relapse, and increased the risk of relapse by approximately six times. The lack of availability of social support was also predictive of relapse, and increased the risk of relapse by approximately five times.

DECLARATION

I declare this thesis to be based on original data obtained while I was enrolled as a PhD candidate in the Department of Clinical and Experimental Pharmacology at the University of Adelaide. To the best of my knowledge this thesis contains no material which has previously been accepted for the award of any degree or diploma at any university, nor any material previously published by any person, except where due reference is cited in the text. The author consents to the thesis being made available for loan or photocopying.

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PRESENTATIONS TO LEARNED SOCIETIES

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ABBREVIATIONS AND DEFINITIONS

Abbreviations

A	amperes
AWS	Alcohol Withdrawal Scale
BAC	blood alcohol concentration
BDI	Beck Depression Inventory
BZD	benzodiazepine
°C	degrees Celsius
CDT	carbohydrate deficient transferrin
CNS	central nervous system
CIWA-A	Clinical Institute Withdrawal Assessment for Alcohol
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol – revised edition
cpm	counts per minute
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalogram
g	grams
µg	micrograms
GABA	gamma-aminobutyric-acid
GABA-A	gamma-aminobutyric-acid-A type receptor
GGT	gamma glutamyl transferase
Hz	Hertz
L	litres
µl	microlitres
MCV	erythrocyte mean cell (or corpuscle) volume
mg	milligrams
ml	millilitres
mV	millivolts
NMDA	N-methyl-D-aspartate
POMS	Profile Of Mood States
REM	rapid eye movement
%RH	percent relative humidity
SEM	standard error of the mean
SF-36	Short Form 36 question health survey
SSA	Selected Severity Assessment scale

STAI	State Trait Anxiety Inventory
TSA	Total Severity Assessment scale
U/l or U/L	units per litre
V	volts
W	watts

Definitions

The term 'clinician' has been used to denote any professional involved in the treatment of persons with alcohol problems, particularly alcohol withdrawal. This includes medical practitioners, psychiatrists, nurses, psychologists and support workers. The term physician is used interchangeably with the term medical practitioner.

The terms 'patient', 'subject', 'client', 'alcoholic' and 'drinkers' are used somewhat interchangeably. While not wishing to stigmatise, the terms 'alcoholic' and 'patient' are sometimes used as a more fluid way of expressing a term for 'alcohol-dependent person'.

CHAPTER 1

1. INTRODUCTION AND LITERATURE REVIEW

1.1 Foreward

Over the last fifty years the symptoms that comprise alcohol withdrawal have been well documented, although there remain unknown aspects of the syndrome. Edwards (1990) has outlined several areas that require further investigation. These include mapping the intensity and duration of the separate elements that comprise the withdrawal syndrome, drinking schedules and their effect on withdrawal intensity and duration, and consideration of the relationship between the intensity of withdrawal and its potential to affect the likelihood of relapse.

Characterisation of the intensity and duration of the withdrawal syndrome was a major aspect of the present study. This involved mapping a range of symptoms, encompassing health disturbances, and several physical and psychiatric manifestations that comprise the withdrawal syndrome. Moreover, it included characterisation of acute withdrawal, and a protracted withdrawal phase of ten weeks duration following cessation of consumption. Symptom characterisation was enhanced by the use of equipment specifically designed to objectively assess physical withdrawal symptomatology, while psychiatric and health disturbances were assessed using standardised questionnaires.

The second major area of investigation was concerned with individual differences in withdrawal severity, and the reasons for this variability. That is, the aim was to determine predictors of withdrawal severity. This study investigated the predictive potential of drinking history, and several other variables, to affect the intensity of acute withdrawal.

The third major area of investigation concerned determination of predictors of relapse drinking. That is, what are the particular variables that result in resumption of drinking once a person has decided to stop? Of particular interest was withdrawal severity as a predictor, both the syndrome as a whole, and also the potential of separate elements within the syndrome to affect relapse. Further, how does withdrawal severity as a predictor relate to other predictors of relapse?

Furthering knowledge in the above mentioned areas will significantly benefit detoxification services and addiction research. In the first instance it will provide a better understanding of the intensity and duration of a range of alcohol withdrawal symptoms, thereby improving the knowledge base of treatment services. Moreover, isolating predictors of withdrawal severity may help detoxification services to determine which patients will require in-patient medical detoxification, and those who could safely detoxify as an outpatient. Finally, early detection of those patients most likely to relapse will facilitate improvement of out-patient services, reducing the risk of further drinking and multiple presentations to detoxification services.

This chapter reviews the literature on the known characteristics of the alcohol withdrawal syndrome, the neuropharmacological mechanisms that mediate symptoms of withdrawal, the development of alcoholism to a point where a person will experience withdrawal upon cessation of drinking, the physiological effects associated with chronic alcohol use, factors that affect the severity of withdrawal, the protracted withdrawal syndrome, factors affecting relapse, current clinical assessment tools of alcohol withdrawal, and the experimental rationale and aims of the thesis.

1.2 Characteristics of the alcohol withdrawal syndrome

The alcohol withdrawal syndrome arises upon the reduction or cessation of prolonged heavy ingestion of alcohol use, where drinking has occurred for a period of several or more days (American Psychiatric Association, 1994; 291.8). The withdrawal syndrome follows a continuum of severity, ranging from mild to severe. Over the last fifty or so years many observations have been made of the alcohol withdrawal syndrome, using a range of standards and assessment tools. The result of these studies and observations have revealed that there is a body of frequently occurring symptoms that constitute alcohol withdrawal (Victor & Adams, 1953; Wellman, 1954; Isbell et al., 1955; Wellman 1955; Flaherty et al., 1955; Kissin et al., 1959; Mendelson & La Dou, 1964; Gross et al., 1966; Gross & Lewis, 1973; Gross et al., 1973; Feuerlein, 1974; Gross et al., 1974; Edwards & Gross, 1976; Sellers & Kalant, 1976; Hershon, 1977; Kissin, 1979; Clark & Friedman, 1985; Brown et al., 1991; O'Connor et al., 1991; Romach & Sellers, 1991; Hemmeter et al., 1993; Murphy & Hoffman, 1993; Schuckit et al., 1995; Le Bon et al., 1997). While these studies report the presence of specific symptoms, in many of the studies the degree of symptom intensity is either not measured, or determined via a scale

developed specifically for that study. Some investigations have used objective and standardised measures, particularly those measuring sleep disturbance, where electroencephalogram (EEG) recordings are commonly employed. Additionally, the investigations of psychiatric disturbances during withdrawal sometimes have utilised standardised tools of assessment. However, many studies, particularly those investigating a wide range of symptoms, usually derive their information from formal and informal interviews and clinical observations of patients.

The symptom of tremor is an important component of the alcohol withdrawal syndrome (Edwards & Gross, 1976; American Psychiatric Association, 1987). This may include whole-body shakes, course tremor of hands, tongue or eyelids. Tremor is one of the first symptoms of the syndrome to be manifested, usually within hours after cessation of drinking, and appears to last between three and seven days depending on the severity of the withdrawal (Victor & Adams, 1953; Sellers & Kalant, 1976; Romach & Sellers, 1991). Patients may have experienced degrees of transient tremor during their drinking history ranging from mild, to severe and incapacitating. For some alcohol-dependent subjects, tremor may be worse in the morning due to a drop in blood alcohol concentrations (BAC) overnight.

Autonomic hyperactivity is readily observed in alcohol withdrawal, and usually occurs within a few hours after alcohol consumption has ceased (Gross et al., 1973; Gross et al., 1974; Hershon, 1977; Clark & Friedman, 1985; King et al., 1991; Romach & Sellers, 1991). Manifestations of autonomic hyperactivity include hyperthermia, pupillary dilation, tachycardia and elevated blood pressure. If the withdrawal is severe, the patient may experience cardiac arrhythmias. Paroxysmal sweats commonly occur as a result of autonomic hyperactivity, and may vary in intensity from clammy hands to drenching sweats. Anecdotal reports from patients suggest that sweating is most severe during the night.

Alcohol withdrawal is also characterised by the presence of gastrointestinal disturbances which may take the form of anorexic behaviour, nausea, vomiting and diarrhea (Gross et al., 1973; Feuerlein, 1974; Edwards & Gross, 1976). Most patients will have experienced nausea and vomiting during the course of their drinking history, particularly following periods of sleep, (usually the morning) where their BAC has fallen overnight.

Sleep disturbances are an integral and frequently occurring aspect of the alcohol withdrawal syndrome (Gross et al., 1966; Johnson et al., 1970; Allen et al., 1971; Kissin et al., 1973; Gross et al., 1973; Lester et al., 1973; Gross et al., 1974; Gross and Hastey, 1977; Wagman & Allen, 1977; Gillin et al., 1990; Hemmeter et al., 1993; Le Bon et al., 1997). The sleep pattern in alcohol withdrawal is characterised by long periods before sleep onset, frequent awakenings, frequent movement and restlessness, sleep apnoea and increased frequency of changes between stages of sleep. Slow wave sleep is particularly affected and is markedly diminished or absent during withdrawal. REM sleep is also disturbed, more fragmented, and may occur with increased frequency. Vivid dreams, nightmares and 'night terrors' often form part of the withdrawal syndrome and may compound disturbed sleep (Victor & Adams, 1953; Gross et al., 1966; Gross et al., 1973).

Psychiatric disturbances may also be manifested during alcohol withdrawal, including disordered sense perception, the presence of hallucinations or illusions, and schizophrenic behaviour (Victor & Adams, 1953; Gross et al., 1966; Gross et al., 1973; Gross et al., 1974; Hershon, 1977). Patients may experience unnatural nightmarish episodes and find it difficult to separate fantasy from reality. Hallucinations are predominantly visual in nature, although auditory, tactile, olfactory hallucinations, or a combination of these, may also occur. Time of onset ranges from 1 to 96 hours after the cessation of drinking has occurred, although hallucinations predominantly occur between 7 and 48 hours following cessation of drinking.

In mild and uncomplicated withdrawal, hallucinations are transient and poorly formed, lasting for a few minutes. They may be especially common at night when the patient attempts to sleep. In severe withdrawal the hallucinations experienced are continuous, and may appear threatening to the patient. In such cases patients may react to the hallucinations as if they are real. Generally, these hallucinations are unpleasant and disturbing. If the hallucination has an auditory component, the voices may address the person directly, but more often they discuss the patient in the third person. Further schizophrenic behaviour such as delusions, mania, incongruent thoughts and emotions, may also appear in the alcohol withdrawal syndrome (Victor & Adams, 1953; Gross et al., 1966; Gross et al., 1973; Gross et al., 1974; Hershon, 1977).

Psychiatric manifestations of disturbances of mood are also commonly observed in the withdrawal syndrome and may include depression, anxiety, irritability and agitation, ranging from mild

to severe in intensity (Gross et al., 1973; Edwards & Gross, 1976; Hershon, 1977). The patient may report feeling "on edge" or "nervy", or may feel an overwhelming sense of distress, panic, sadness or futility. They may experience an exaggerated startle response, including feeling hypersensitive to noise and touch. An irritable or agitated patient will appear restless and fidgety, unable to sit quietly. In severe cases the patient constantly paces back and forth and thrashes around. This type of restless behaviour may also interfere with sleep.

Disorientation and clouding of the sensorium may also occur as a component of disordered sense perception where, in the worst case, the patient is disoriented for time, place and person, and is unable to perform simple arithmetic computations (Victor & Adams, 1953; Gross et al., 1973). This may be accompanied by poor insight, in which patients may find it difficult to understand the relationship between their excessive drinking and their present state of acute illness. Poor quality of contact may also be observed, in which the patient experiences detachment from their surroundings, and is unaware of their surrounding environment.

Seizures or convulsions may also be present in alcohol withdrawal, and in the past were termed "alcoholic epilepsy" or "rum fits" (Victor & Adams, 1953; Isbell et al., 1955; Victor & Brausch, 1967). Seizures may occur as single events, but more often occur as a burst of several seizures. Generally the seizures are of the grand mal type, where there is a loss of motor control and consciousness. Seizures tend to occur in the first two to four days after cessation of drinking.

In addition to tremor and gastric disturbances, malaise and weakness are some of the first symptoms to appear. These can be likened to the feeling of hangover, or pre-flu symptoms and commonly include headache and general fatigue (Mendelson & La Dou, 1964; Gross et al., 1973; Hershon, 1977). Additionally, the patient may experience muscular pain, cramps, and weakness, paraesthesia, pruritus and hyper-reflexia. Other miscellaneous symptoms that have been reported as occurring during alcohol withdrawal include tinnitus, hyper-reflexia, nystagmus, and chest pains (Mendelson & La Dou, 1964; Gross et al., 1973; Hershon, 1977).

Alcohol withdrawal delirium, or delirium tremens (DT's) may occur in severe withdrawal (Hare, 1915; Victor & Adams, 1953; Isbell et al., 1955). Although delirium tremens is considered a medical emergency its occurrence is not common, particularly with the improvement of treatment services. Delirium tremens usually occurs after at least 5 to 15 years of heavy drinking. The essential features

include confusion, disorientation, disordered sense perception, disorganised thinking, reduced level of consciousness and exaggerated autonomic and psychomotor function. The patient may also display an inability to maintain a coherent stream of thought, and cognitive processes become fragmented and disjointed. Inappropriate and excessive motor activity may also be observed in which the patient is restless and agitated and displays repetitious and inappropriate movements such as continually picking at the bedclothes, or reaching for objects that don't exist. Perceptual disturbances such as hallucinations and delusions are common, and the patient may react to them. Autonomic hyperactivity may also be present in alcohol withdrawal delirium, including pupillary dilation, tachycardia, hyperthermia and drenching sweats.

Alcohol withdrawal delirium commonly occurs within the second to fourth day after the cessation of drinking, and usually lasts less than three days, although there have been some documented cases of it lasting up to thirty days (Victor & Adams, 1953). Both its onset and termination are normally quite abrupt following which the patient will have no memory of the delirious period.

A more detailed review of studies of alcohol withdrawal symptomatology can be found in Chapter 4.

1.3 Neuropharmacological mechanisms of alcohol withdrawal

Abnormalities at a cellular level have been demonstrated following acute and chronic exposure to alcohol, and also during alcohol withdrawal. Since high doses of alcohol are a depressant, chronic excessive alcohol consumption results in inhibition, or depression, of central nervous system (CNS) activity. Chronic exposure to high levels of alcohol results in the central nervous system deploying several compensatory mechanisms in order to maintain homeostasis, and to adjust to the persistent presence of a depressant. In brief, the compensatory mechanisms comprise several structural and/or functional changes that result in an overall reduction in the activity of CNS inhibitory systems, and an increase in the activity of excitatory systems. However, when the depressant is removed, that is a reduction or cessation of alcohol consumption, the structural and/or functional changes that have previously been developed remain in place. Consequently, the fine balance between inhibitory and excitatory systems of the central nervous system is disrupted, resulting

in overall excitation. This rebound hyperexcitability is presumably the cause of many symptoms of withdrawal.

While the exact compensatory mechanisms are complex and not completely understood, three main systems have been proposed. These include changes to neuronal membranes, GABA, and glutamate systems (Buck & Harris, 1991). Other neurotransmitter systems in the CNS that are affected by alcohol and may be involved in mediating symptoms of withdrawal include dopamine, noradrenaline, serotonin and opioid systems (Pohorecky and Brick, 1988; Glue & Nutt, 1990; Nutt & Glue, 1990). It is also thought that calcium channels may play a role in mediating some of the effects of alcohol (Wu et. al., 1987; Whittington et. al., 1991) and withdrawal (Airaksinen & Peura, 1987; Glue & Nutt, 1990; Nutt & Glue, 1990).

1.3.1 Neuronal membranes

Alcohol has a widespread action on cell membranes, including neuronal membranes. Cell membranes are part lipid, part protein, and alcohol is able to change the consistency, or fluidity, of the membrane via perturbation of hydrophobic neuronal membrane lipids. This is a general action which affects all neurons with a surrounding membrane, and is potentially disruptive to normal cell function such as ion transport, enzyme activities, receptor binding and transmitter release (Deitrich et. al., 1989; Littleton, 1989; Little, 1991). Thus, exposure to alcohol increases the fluidity of the membrane, altering the membrane's protein conformation and function. In order to compensate for chronic alcohol consumption and increased membrane fluidity, the membrane undergoes structural changes or "defluidisation", in order to maintain homeostasis. The structural and/or functional changes are thought to occur at specific sensitive sites of the membrane. These changes remain, even when exposure to alcohol has decreased. Consequently, normal cell function is disrupted, and this may mediate subsequent symptoms of withdrawal (Airaksinen & Peura, 1987). However, it is not completely clear to what extent defluidisation has an effect on withdrawal. It appears that large concentrations of alcohol are required to fluidise the membrane, and it is not certain that the levels of alcohol achieved during intoxication are sufficient to produce changes in membrane fluidity and function (Hunt, 1985).

1.3.2 GABA

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. The receptors for this transmitter attenuate the activity of the neurons on which they are located. The GABA-A receptor is the most well characterised of the GABA receptors, and is a heterogeneous complex with a binding site for the inhibitory neurotransmitter GABA, a chloride ion channel, and also several other binding sites (Simmonds, 1983; Stephenson, 1988; Leidenheimer et al., 1991; Sivilotti et al., 1991). GABA mediates its inhibitory effect on the central nervous system by binding to GABA-A receptors which results in an influx in chloride ions through the chloride ion channel.

Other sites on the GABA-A complex include those that mediate the effects of sedative-hypnotic/anxiolytic drugs, including barbiturates and benzodiazepines (Simmonds, 1983; Stephenson, 1988; Leidenheimer et al., 1991; Sivilotti & Nistri, 1991). Barbiturates, such as pentobarbitone and thiopentone, have anxiolytic and hypnotic effects, although are not used commonly in current medical practice due to their narrow therapeutic index. The benzodiazepines, including diazepam (®Valium, ®Ducene, ®Pro-Pam), temazepam (®Normison) and nitrazepam (®Mogadon), have largely replaced barbiturates, because they have a very wide therapeutic index. Barbiturates and benzodiazepines enhance the action of GABA at the GABA-A receptor, by increasing chloride flux and consequently CNS inhibition. There is strong evidence that alcohol mediates some of its effects through the GABA-A receptor (Liljequist & Engel, 1982; Martz et al., 1983; Becker, 1988), and it has been suggested that there may be a site on the GABA-A receptor at which alcohol produces enhancement of GABA action (Deitrich et. al., 1989; Littleton, 1989; Little, 1991). However, a site for alcohol on GABA-A receptors is a debated issue and it has also been suggested that a site does not exist, but that alcohol affects the chloride channel directly (Allan & Harris, 1987). Many of the effects of alcohol may be mediated through this receptor-complex, and are similar to the effects produced by benzodiazepines including decreased anxiety, relaxation, motor incoordination and general sedation. Accordingly, the cross tolerance between benzodiazepines and alcohol makes benzodiazepines invaluable for treatment of alcohol withdrawal (Chan et al., 1991).

Molecular biology has shown that GABA-A chloride channels are comprised of complex subunits, which may contribute to their pharmacological diversity, and also their sensitivity to alcohol. Some subunits (α1, α2 & α4), have been shown to be particularly sensitive to chronic alcohol

exposure, undergoing structural and functional changes and thereby altering the function of the GABA-A receptor (Ticku & Kulkarni, 1988; Gonzales & Hoffman, 1991). Chronic excessive alcohol administration results in a decrease in GABA-A activity that compensates for the chronic depressant actions of alcohol. Activity is attenuated via decreased affinity of GABA binding sites on low affinity GABA-A receptors following chronic exposure to alcohol, but not following acute exposure to alcohol (Ticku & Burch, 1980; Volicer & Biagioni, 1982). The low affinity binding sites are thought to be involved in the physiological effects of GABA (Little, 1991). When exposure to alcohol is decreased, the balance between inhibition provided by alcohol, and excitation produced by a dampening of GABA-A activity is disrupted, resulting in an overall excitatory state. The hyperexcitability caused by the changes to GABA-A mediate alcohol withdrawal symptomatology (Airaksinen & Peura, 1987; Glue & Nutt, 1990; Nutt & Glue, 1990; Buck & Harris, 1991).

1.3.3 Glutamate

Glutamate is a major excitatory amino acid neurotransmitter and acts on several different types of receptors, one of which is the NMDA (N-methyl-D-aspartate) receptor. Activation of the NMDA receptor by either glutamate or NMDA results in an influx of calcium ions and excitation of cells. This contrasts with the action of GABA that inhibits the activity of cells. Alcohol affects the NMDA receptor by preventing the influx of NMDA-mediated calcium ions into the cell, thereby reducing overall central nervous system excitability (Deitrich et. al., 1989; Hoffman et al., 1989; Lovinger et. al., 1989). The actions of ethanol mediated through this receptor are thought to be anxiolytic, muscle relaxant, sedative and anticonvulsant. Chronic exposure to alcohol results in a compensatory increase in NMDA activity, in order to maintain a state of homeostasis. The mechanism for this is thought to be due to an increase in the number of NMDA receptor/ionophore binding sites (Grant et al., 1990; Iorio et al., 1992). Consequently, a reduction or cessation in alcohol consumption results in an overall excitatory state and withdrawal symptomatology, in particular seizure activity (Glue & Nutt, 1990; Grant et al., 1990; Nutt & Glue, 1990).

1.4 Development and progression of alcoholism and physical dependence

Kissin (1979) summarised the steps in the development and progression of alcoholism. An individual may be predisposed to alcoholism for a variety of biological and environmental reasons. Psychological dependence to alcohol is probably initiated prior to full dependence, due to the positive and reinforcing effects of alcohol (Edwards & Gross, 1976; Kissin, 1979). These effects include euphoria, behavioural stimulation or excitation, loss of inhibitions, sedation, relaxation, a dulling of memory and a reduction in anxiety and depression (Little, 1991). Such effects may be extremely salient to some individuals and may lead to an intense craving for alcohol and uncontrolled drinking. Tolerance to alcohol is an important factor in the development of alcoholism and can develop within the first few hours of alcohol consumption. Repeated exposure to increased doses of alcohol result in clinical dependence on alcohol. Clinical dependence may progress to the point of physical dependence on alcohol, in which withdrawal symptomatology will be manifested upon cessation of drinking. Predisposing factors, tolerance and dependence are outlined in more detail below.

1.4.1 Predisposing Factors

Human and animal studies demonstrate a genetic role in predisposition toward heavy drinking. Animal studies have shown differences in frequencies of self administration of alcohol, and that alcohol tolerance develops more rapidly and is more persistent in these alcohol-preferring rodents, than in their alcohol non-preferring counterparts (Li et al., 1987). In addition, there is growing evidence based on human studies that there is a genetic component to alcoholism. (Alterman & Tarter, 1986; Agarwal & Goedde, 1990; Blum et al., 1990; Devor et al., 1991; Goedde et al., 1992; Devor, 1993; Devor, 1994; Goldman et al., 1994). This includes recent work by Noble and colleagues who have repeatedly demonstrated that variants of the D2 dopamine receptor (DRD2) significantly contributes to the risk for alcoholism in humans (Noble, 1998; Noble et al., 1998).

Other human examples include family studies showing that there is a high frequency of alcoholism and alcohol-related disorders in the relatives of alcoholics, where the incidence of alcoholism is more frequent among close compared with distant relatives. While this is not sufficient evidence alone for heritable alcoholism, sons of alcohol dependent fathers who have been adopted

out, have an increased frequency of alcohol-dependence despite being raised by non alcohol dependent foster parents (Raphael, 1994).

Further, alcoholism may result as a secondary effect of genetic predisposition towards other pathological states such as anxiety, depression, poor impulse control and antisocial personality disorder (Hartka et al., 1991; Sconfeld & Dupree, 1991; Raphael, 1994). For example, the effects of alcohol may be particularly salient to a person with chronic depression, resulting in excessive alcohol consumption in order to attempt to find some relief from depressive symptomatology.

There are many environmental, or non-biological factors thought to affect the predisposition of alcoholism, including laws, cultural norms and beliefs about alcohol, and also the availability of alcohol (MacAndrew & Edgerton, 1969). For example, in some Muslim countries, consumption of alcohol is not permitted and thus frequency of alcohol abuse is low. Conversely, in wine-producing countries where there is a high per capita consumption of alcohol and regular alcohol consumption is considered normal, alcohol problems tend to be chronic, such as alcohol-induced disease and dependence. This contrasts with those countries in which binge drinking is a usual occurrence and associated problems with alcohol tend to be acute and social (eg. violence, injury, drink-driving, alcohol-poisoning).

Hawkins et al. (1992) describe several environmental risk factors that may be involved in the predisposition towards heavy drinking. These include severe poverty, low income and social status, low level of education and homelessness, societal disruption, heavy family drug use, presence of family conflicts and impoverished or inappropriate spouse or parent-child relationships. Other factors that may predispose to future alcohol abuse include early persistent antisocial behaviour, failure at school, poor relations with peers and association with drug-using peers. Additionally, positive attitudes to drug and alcohol use, and the use of alcohol at a relatively early age are more likely to lead to alcohol-related problems in later life.

Many psychological theories have been proposed to explain why some individuals become, and remain dependent on alcohol, and why others are able to deal with certain pressures and stressful situations that may otherwise result in a tendency towards alcohol abuse. For example, the way an individual employs coping strategies is thought to be a major determinant of whether excessive alcohol consumption will occur when placed under stress. Important factors include the kind of thinking employed by the individual (positive or negative), whether the individual demonstrates avoidance

behaviour (eg. not spending time with friends who drink), or involve themselves in distractive or substitutional behaviour, and whether or not the individual has access to, and relies on, social supports (eg. family, friends, groups etc.) (Litman et al., 1984).

1.4.2 Tolerance

In the natural sequence of alcoholism there must be the development of tolerance to, and dependence on alcohol. Tolerance is an adaptive response that results in a reduced effect of alcohol after repeated administration, and may contribute to increased consumption of alcohol in order to experience an effect (Cappell, 1981; Tabakoff & Hoffman, 1989; Harris & Buck, 1990). Thus, for a given amount of alcohol, an experienced drinker will be less affected than a novice drinker, given that all other factors are equal. Tolerance has also been shown to occur *in vitro*, where the same tissue concentration of alcohol elicits a reduced response after repeated administration (Buck & Harris, 1991). This adaptive response may be further classified as acute or chronic. Acute tolerance occurs after a single exposure to alcohol, whereas chronic tolerance is the result of long-term administration.

Tolerance occurs to the various effects of alcohol at different rates, and studies have shown that tolerance develops more rapidly to the depressant effects of alcohol than the stimulatory effects (Masur & Boerngen, 1980; Crabbe et al., 1982; Tabakoff & Kiianmaa, 1982). Thus, while an experienced and a novice drinker will both feel the stimulatory effects of alcohol, the novice drinker is more likely to be affected by the depressant effects of alcohol.

There are thought to be three major types of tolerance that occur in response to repeated administration of alcohol; metabolic, neuronal and behavioural. Metabolic tolerance occurs as a result of enzyme induction. Alcohol induces one of the minor enzymes involved in its own metabolism (P450IIE1), and levels of this enzyme are elevated in heavy drinkers. Thus, metabolism of alcohol in heavy drinkers will be more rapid, and result in a decreased effect of alcohol per amount consumed (Harris & Buck, 1990).

Neuronal, or cellular adaptation to the effects of alcohol plays a major role in the development of tolerance. The receptors and cell membranes thought to mediate the effects of alcohol may adapt to the frequent presence of alcohol (Cappell, 1981; Tabakoff & Hoffman, 1989; Harris & Buck, 1990; Buck & Harris, 1991; Little, 1991). The mechanisms by which this occurs include a down-regulation of

the receptors involved, in which receptors and certain systems become less sensitive than normal. Thus, consumption of alcohol will have less affect on these receptors, resulting in a decreased response to alcohol. Other mechanisms have been postulated to explain tolerance, which also appear to be related to the development of physical dependence and mediation of withdrawal symptomatology, as discussed in section *1.3, Neuropharmacological mechanisms underlying withdrawal.*

Learning, or behavioural tolerance also occurs following repeated exposure to alcohol. This has been shown to operate in two main ways. Firstly, repeated execution of a certain behaviour, or performance of a particular task when under the influence of alcohol will result in behavioural tolerance to the effects of alcohol when performing that task (Kalant et al., 1971; Harris & Buck, 1990). Secondly, the environment in which alcohol is consumed will also contribute to the development of behavioural tolerance. That is, a drinker will be more tolerant to the effects of alcohol in the environment in which he or she normally drinks, as compared with unfamiliar surroundings (Harris & Buck, 1990; Tabakoff & Melchior, 1981).

The fact that tolerance to the effects of alcohol does occur may contribute to an increased consumption of alcohol in order to experience an effect. Consequently higher blood alcohol levels can be maintained for longer periods of time which may result in serious organ damage. An obvious example of tolerance is found in those who are very heavy drinkers, who may appear to be sober with a blood alcohol concentration that would produce severe intoxication in a controlled or novice drinker.

1.4.3 Clinical and physical dependence

The DSM-IV provides diagnostic criteria for psychoactive substance dependence, and is relevant for alcohol (American Psychiatric Association, 1994). The criteria include cognitive, behavioural and physiological symptoms, in which at least three out of the total nine are necessary to make a diagnosis of dependence. Alcohol dependence, as defined by the DSM-IV (303.90), can provide an approximate assessment of severity of dependence, depending on how many of the criteria are fulfilled. A paraphrased version of the DSM-IV criteria for dependence, focussing on alcohol, is shown below.

A. At least three of the following:

1. Alcohol is consumed in larger amounts or for longer periods of time than the person originally intended. (For example, the person may decide to have only one drink of alcohol, but after the first drink continues to consume alcohol until heavily intoxicated).
2. A persistent desire or one or more unsuccessful attempts to reduce or control alcohol use (in other instances the person may desire to reduce their drinking, but has never actually made an effort to do so).
3. A great deal of time spent in activities necessary to obtain alcohol, consume alcohol, or recover from the effects of heavy drinking (in mild cases the person may spend a few hours recuperating from the effects of alcohol, but is able to spend the remainder of the day in their usual activities, - in severe cases, a significant proportion of the drinker's day is spent recovering from the effects of alcohol).
4. Frequently intoxicated or experiencing withdrawal symptoms when expected to fulfil major role obligations at work, school, or home (eg. does not go to work because of a hangover, goes to work or school intoxicated, or is in an intoxicated state when taking care of their children), or when alcohol abuse is physically hazardous (eg driving or using machinery when intoxicated).
5. Important social, occupational, or recreational activities are not continued or are markedly reduced, because of alcohol abuse (eg. the person may withdrawal from family activities and hobbies in order to spend more time consuming alcohol in private, or to be friends who also drink heavily).
6. Continued alcohol consumption despite the knowledge that their alcohol use is having persistent or recurrent social, psychological or physical problems that are caused or exacerbated by the use of the substance (eg. drinking despite a stomach ulcer worsened by alcohol, alcohol-induced aggression taken out on the person's family even though they may regret their aggression when sober).
7. The person experiences marked tolerance and the need for significantly increased amounts of alcohol. That is, at least a 50% increase in order to achieve intoxication or desired effect, or a significantly diminished effect with continued use of the same amount.

8. Characteristic withdrawal symptoms upon cessation of consumption (as specified by the DSM-IV for alcohol withdrawal).
9. Alcohol is often consumed in order to relieve or avoid withdrawal symptoms (this typically involves the consumption of alcohol early in the day, beginning soon after wakening).

B. Some of the above symptoms have persisted for at least one month, or have occurred repeatedly over a longer period of time.

It is worth noting that based on these criteria, the presence of withdrawal is not necessary to make an assessment of dependence. Physical dependence occurs when the frequency and intake of alcohol consumption progresses to a stage where a cessation or reduction in alcohol consumption will result in the manifestation of withdrawal (Harris & Buck, 1990). Withdrawal symptoms do not only occur following complete abstinence, but may manifest as blood alcohol concentrations decrease, for example following a short period of abstinence, such as following a period of sleep.

1.5 Physical and psychiatric complications of heavy drinking

Excessive alcohol consumption is associated with a wide range of biological complications including central and peripheral nervous system disorders, liver disease, gastrointestinal disorders, psychiatric and mood disturbances, pancreatic disease, cardiovascular disease, testicular function disorders, cancers, alterations in immune and haemostatic system function and teratogenicity (Turner et al., 1977a,b; Edwards, 1987; Holman et al., 1988; Lishman, 1990; Tonnesen, 1992; Thomsen et al., 1993). Alcohol related brain and nervous system injury, liver disease and psychiatric and mood disturbances occur as a result of the toxic effects of alcohol, and are often observed in the alcohol dependent population. These are discussed in more detail below.

1.5.1 Brain and nervous system injury

The Wernicke-Korsakoff syndrome is a well-characterised consequence of chronic excessive alcohol consumption (Victor & Adams, 1953; Turner et al., 1977b; Edwards, 1987; Price & Kerr, 1988; Lishman, 1990). Wernicke's encephalopathy and Korsakoff's psychosis are separate states, but are related consequences of the same pathology and may co-occur as the Wernicke-Korsakoff syndrome. The aetiology of these states is predominantly due to chronic malnutrition, particularly thiamine

depletion, which commonly occurs in heavy drinkers. The Wernicke component is acute and reversible, while the Korsakoff component is chronic and more resistant to treatment. Wernicke's encephalopathy is the usual forerunner for Korsakoff's psychosis, although Korsakoff's may develop without any obvious prior history of Wernicke's encephalopathy.

Wernicke's encephalopathy is characterised by acute confusion and general mental disorganisation, poor short term memory, ocular disturbances (such as nystagmus), ataxia and alcoholic polyneuropathy. Alcoholic polyneuropathy, which is characterised by peripheral nerve degeneration, may present either on its own or as a symptom of Wernicke's disease. Korsakoff's psychosis is predominantly characterised by cognitive disturbances, particularly memory impairment for recent events, confabulation, and an inability to learn new information, although long-term memories normally remain intact. Peripheral neuritis, hyperaesthesia, anaesthesia, paraesthesia, paralysis and muscular atrophy may also be present in the affected individual.

Several other neurologic syndromes have been observed in excessive drinkers including alcoholic dementia (Edwards, 1987). Alcoholic dementia appears to be more common and insidious than previously thought, and milder forms caused by lower doses of alcohol are characterised by subtle cognitive losses. These include some impairment to judgement, loss of concentration and minor memory disturbances (Turner et al., 1977b; Guthrie & Elliott, 1980; Brandt et al., 1983). At the other end of the spectrum is fully developed dementia. Other alcohol related brain and nerve injuries include pontine myelinolysis (Victor & Adams, 1953; Freund, 1985; Edwards, 1987), corpus callosum degeneration (Victor & Adams, 1953; Freund, 1985), neurobehavioural disorders (Wilkinson & Carlen, 1980; Tarter et al., 1989), memory loss and blackout (Turner et al., 1977b; Edwards, 1987).

1.5.2 Liver Disease

The liver is a primary target organ for the toxic effects of alcohol, and malnutrition may compound the damage. Alcohol-induced liver disease ranges from mild to severe, including fatty infiltration, fibrosis and inflammatory reactions, chronic hepatitis, cirrhosis and carcinoma of the liver (Turner et al., 1977a; Edwards, 1987). The extent of damage is largely dependent upon daily alcohol intake, duration of use and other co-morbid complications. While it is difficult to ascertain the relationship between the extent of damage and intake, risk levels have been estimated. Most persons

with liver disease have been consuming in the order of at least 150g daily for several years, although this may be a conservative estimate (Turner et al., 1977a). A smaller proportion of patients with liver disease have intake levels between 80 and 150g, however the proportion of drinkers who follow these schedules and do not develop liver disease is not known.

1.5.3 Psychiatric and Mood Disturbances

Psychiatric and mood disturbances are frequently associated with alcoholism (Reich et al., 1974; Keeler et al., 1979; Schofield, 1989; Chignon et al., 1991; Gasperini et al., 1991; Hartka et al., 1991; Hasin et al., 1991; Hesselbrook, 1991; Kiesler et al., 1991; Miller & Gold, 1991; Schonfeld & Dupree, 1991; McKenna & Paredes, 1992; Mueser et al., 1992); and include depression, anxiety, mania, hallucinatory states, schizophrenia, personality disorder and antisocial behaviour. Studies assessing the prevalence of co-occurring psychiatric disturbances and alcohol dependence have found that the frequency is high, up to 75% concordance in some cases, although this figure appears to depend on the population being studied, and the severity of psychiatric symptoms (Raphael, 1994).

The direction of causality between alcoholism and psychiatric and mood disturbance is not always clear, and it appears the direction can be either way (Hartka et al., 1991). That is, the presence of a psychiatric or mood disturbance may result in self-medication with alcohol which may progress to alcohol dependence (Edwards, 1987). In addition, the toxic effects of chronic excessive alcohol consumption may produce psychiatric and mood disturbances, such as depression and suicidal thoughts, anxiety, personality disorders or psychosis (Miller & Gold, 1991) which may diminish or disappear with abstinence (Kissin, 1979; De Soto et al., 1985; Schuckit, 1986; Kosten & Kleber, 1988).

Some psychiatric and mood disturbances, such as depression, anxiety, agitation, hallucinations, confusion and psychotic behaviour are also observed during the withdrawal syndrome (see section *1.2, Characteristics of the alcohol withdrawal syndrome*). Differentiation of psychiatric symptoms that occur as a result of withdrawal from alcohol, and symptoms that occur during abstinence as a carry over of the toxic effects of alcohol, is not always possible. There is strong anecdotal evidence based on reports from patients suggesting that symptoms of psychiatric and mood disturbance are far more severe during periods when drinking is reduced or has ceased, and that symptoms are relieved, at least initially, when drinking re-commences. This suggests that psychiatric and mood disturbances observed during abstinence reflect a true withdrawal component. However,

Gorelick & Wilkins (1986) report that symptoms such as depression, irritability and insomnia may also manifest during periods of alcohol intake.

In a review of protracted withdrawal symptomatology, Satel et al. (1993) propose that anxiety and CNS hyperexcitability reflect re-equilibrium processes that occur during withdrawal, but that other symptoms such as depression, impaired concentration and apathy may constitute the lingering toxic effects of alcohol. Overall, there is a lack of studies that clearly differentiate between withdrawal and recovery. As Satel et al. (1993) point out, there is an absence of longitudinal assessment of symptoms in studies (ie. those that assess the severity of symptoms both before *and* after drinking has ceased). There is also a paucity of studies that have re-administered alcohol during abstinence, in order to attempt reversal of symptoms which are thought to comprise withdrawal. A more detailed investigation of this area is found in Chapter 4.

1.6 Factors affecting the severity of withdrawal

There are several factors thought to affect the severity of withdrawal a patient may experience on cessation of drinking, and these are discussed in detail in Chapter 5. The first of these is the degree of prior exposure to alcohol. Accordingly, a 'rule-of-thumb' that may be utilised in a clinical detoxification setting is to assess the drinking history of the patient as a means of estimating the intensity of impending withdrawal. That is, the amount of alcohol consumed, and the period over which heavy drinking has occurred (both period of most recent intake and the number of years since heavy drinking commenced), are thought to be positive indicators of the degree of withdrawal severity.

There is some formal evidence based on studies in humans demonstrating that drinking history may be related to withdrawal severity (Hare, 1915; Isbell et al., 1955; Mendelson & La Dou, 1964; Hershon, 1977; Pristach et al., 1983; Gorelick & Wilkins, 1986; Schuckit et al., 1995; Schukit et al., 1998; Shaw et al., 1998). Some of the earlier studies referred to above used small sample sizes and narrow dose ranges, making it difficult to observe a dose-related effect. While these studies suggest a link between withdrawal severity and drinking history, a review of these studies by Turner et al. (1977) states that a direct relationship between intake and severity is not clearly evident. Later studies have used larger sample sizes and a broader range of drinking histories (concerning intake and duration), although many are limited by their use of subjective assessment of withdrawal severity. Thus, the strength of the relationship between drinking history and withdrawal severity is not completely clear. Moreover, there is some evidence to suggest that daily intake of alcohol may be

more relevant in predicting withdrawal severity than the duration of intake (Turner et al., 1977b; Pristach et al., 1983; Shaw et al., 1998).

The presence of concomitant complications is also thought to exacerbate alcohol withdrawal. A common complication is the presence of co-morbid illness, that may increase the severity of withdrawal symptoms (Victor & Adams, 1953; Tavel et al. 1961; Sellers & Kalant, 1976; Thompson, 1978; Baum & Iber, 1980; Gorelick & Wilkins, 1986; Romach & Sellers, 1991). Physiological factors that have been associated with an increased risk of severe withdrawal symptoms include malnutrition, liver disease, trauma, fever, and disturbances in fluid and electrolyte levels. These factors tend to particularly affect the symptoms of alcohol hallucinosis, seizures, cardiac arrhythmias and delirium tremens.

As mentioned above, psychiatric disturbances often accompany alcoholism. The presence of psychiatric co-morbid factors may result in more intense psychiatric withdrawal symptoms such as anxiety, depression, mania, delusions, hallucinations and schizophrenic tendencies (Brown et al., 1991; Johnston et al., 1991; Thevos et al., 1991; Schuckit et al., 1998). Many of the studies provide evidence for the presence of co-morbid anxiety increasing the severity of withdrawal-induced anxiety (Brown et al., 1991; Johnston et al., 1991; Thevos et al., 1991).

Finally, regarding complications that may be risk factors for severe withdrawal, there is some relatively recent evidence that polydrug use among alcohol-dependent persons may be involved (Schuckit et al., 1993; Schuckit et al., 1995). For example concomitant regular use or dependence on amphetamines, cannabis, cocaine, opiates or benzodiazepines may also be related to a more severe alcohol withdrawal, particularly the presence of convulsions and delirium tremens.

A third major factor thought to worsen withdrawal is kindling, in which withdrawal symptoms are intensified and occur more rapidly as a result of exposure to previous periods of withdrawal. Alcohol withdrawal related kindling has been demonstrated in animals (Walker & Zornetzer, 1974; Ballenger & Post, 1978; Poldrugo & Snead, 1984; Becker et al., 1997), and humans (Ballenger & Post, 1978; Brown et al., 1988; George et al., 1990; Schuckit et al., 1995; Shaw et al., 1998). Kindling may particularly affect the intensity of withdrawal seizures. The mechanism by which kindling is thought to occur is repeated stimulation of neurons during consecutive withdrawal attempts, resulting in a reduced discharge threshold. Subsequent stimulation at sub-threshold levels, that is at a lower degree

of stimulation than usual, may elicit a discharge, or firing of neurons. This may be observed clinically as an increase in the number and intensity of withdrawal seizures.

1.7 The protracted withdrawal syndrome

Clinical reports of withdrawal symptoms lasting longer than the acute detoxification period (approximately one week) have appeared in the literature for the last 50 years. These papers describe symptoms of alcohol withdrawal lasting for months, or even years, after the initial cessation of alcohol consumption (Wellman, 1954; Flaherty et al., 1955; Wellman, 1955; Kissin et al., 1959; Wagman & Allen, 1977; Kissin, 1979; Pettinati et al., 1982; Westermeyer & Neider, 1984; De Soto et al., 1985; De Soto et al., 1987). Protracted withdrawal symptomatology has clinical significance in that it reflects an impoverished 'quality of life' for those particular patients. Furthermore, it may be associated with anticipatory behaviour, or craving for alcohol, which may ultimately result in relapse drinking (Ludwig et al., 1977). A detailed review of the protracted withdrawal syndrome may be found in Chapter 4.

Protracted symptoms of mood and behavioural disturbances are the most frequently reported in studies of long-term withdrawal, including anxiety, depression, emotional lability, restlessness, fatigue, and sleep disturbances (Wellman, 1954; Wellman, 1955; Wagman & Allen, 1977; Pettinati et al., 1982; Westermeyer & Neider, 1984; De Soto et al., 1985; Bokstrom et al., 1989; Gillin et al., 1990; Le Bon et al., 1997). These symptoms are most severe within the first two weeks following cessation of drinking, and further decrease over the next six months. However, there have been reports of "waves" of symptoms occurring up to fifteen years later (Wellman, 1954). Based on the above investigations, the most commonly reported symptom appears to be depression, which may be manifested as guilty feelings, thoughts of death or dying, and early-morning waking.

Some studies have reported protracted physiological disturbances (Wellman, 1954; Kissin et al., 1959; Wagman & Allen, 1977), and include disturbances to the autonomic system, to the endocrine system and to muscle tension. These kinds of disturbances have been observed for up to two years following cessation of alcohol use.

Although there is clinical support for a protracted withdrawal syndrome, some difficulties exist with the concept (Satel et al., 1993). In the first instance, the definition of protracted withdrawal itself is ambiguous, having multiple terminology and meanings. In this thesis it is defined as withdrawal

symptoms that occur after one week following cessation of use. Secondly, some of the studies that have reported protracted withdrawal phenomena are cross-sectional rather than longitudinal. Further, many of the studies employ non-objective and non-standardised tools to assess withdrawal severity. This is mainly a problem for those studies investigating psychiatric and mood disturbances, although there is also very little objective data on physical symptoms of withdrawal that may persist into the protracted period.

The review of this literature on protracted withdrawal suggests there is a need to study the protracted phenomena longitudinally, using objective measures of physical symptoms, and standardised tests of psychiatric and mood disturbances.

1.8 Relapse drinking

It is unfortunate that a common outcome of treatment for alcohol dependence is relapse. As originally reported by Hunt et al. (1971) patients withdrawing from alcohol will 'exponentially' tend towards relapse. That is, within the first two weeks only 65% will have maintained abstinence, at three months only 40% and at one year only around 30% will have remained abstinent. Further studies have shown that even fewer remain after a period of two years (Armor et. al., 1978).

The Hunt study was carried out in the early 70's, and improved treatment services have increased the likelihood of maintaining abstinence (Volpicelli et al., 1992; O'Malley et al., 1992). However, relapse is still a likely event for many alcohol dependent persons attempting abstinence. Accordingly, much effort has been expended trying to understand the mechanisms and processes involved in relapse. A detailed investigation into the factors involved in relapse is shown in Chapter 7.

The factors contributing to relapse are not completely clear. Most of the research into factors that effect relapse are based on psychosocial investigations (Gerard et al., 1962; Rathod et al., 1966; Poulos, 1981; Litman et. al., 1984; Marlatt & Gordon, 1985; Macrae et al., 1987; Wilson, 1987; Allsop, 1990; Staiger & White, 1991; Watson, 1991; Gallant, 1992; Johnsen & Herringer, 1992; Prochaska et al., 1992). Several models of relapse have been proposed both to explain reasons for relapse, and to provide suggestions for treatment (Daley, 1988). There is some overlap between models. One popular model, based on cognitive-behavioural principles, suggests that the individual experiences a sense of perceived control, or self-efficacy, while maintaining abstinence (Marlatt & Gordon, 1985).

Self-efficacy is perpetuated or diminished depending on the individual's coping skills in response to pertinent challenges, or 'high-risk' situations. A 'high risk' situation is defined broadly as any situation that poses a threat to the individual's sense of control and increases the risk of potential relapse. (Litman et. al., 1984; Marlatt & Gordon, 1985; Glenn & Wagner, 1991). An inability to cope with any of these stressful, 'high risk' situations may result in reduced self-efficacy, and thus relapse.

Based on the model of relapse conceived by Marlatt & Gordon (1985) other related models have been proposed, including a psychoeducational model of prevention (Daley, 1985). The emphasis in this model is to educate patients concerning the relapse process, cognitive and behavioural coping strategies to deal with high-risk situations, and the development of personal relapse management plans.

There are several risk factors, or predictors of relapse. Most models of relapse try to incorporate coping strategies to deal with these risk factors. As mentioned above, 'high risk' situations that may be antecedents of relapse include negative emotional states such as anxiety, depression, boredom, anger and frustration (Marlatt & Gordon, 1985; Daley, 1988; Loosen et al., 1990; Brown et al., 1991; Schonfield & Dupree, 1991; Smith & Frawley 1993; Ellis & McClure, 1992; LaBounty et al., 1992; Brown et al., 1995). The presence of interpersonal conflicts in important relationships also may result in an increased risk of relapse (Daley, 1988; Maisto et al., 1988; Smith & Frawley, 1993; Jarvis et al., 1995) as may direct or indirect external social pressure on the patient to consume alcohol (Marlatt & Gordon, 1985; Daley, 1988; Maisto et al., 1988; Smith & Frawley, 1993; Jarvis et al., 1995). Another identified predictor of relapse is a lack of available social support for the patient (Schonfeld & Dupree, 1991; Ellis & McClure, 1992; Gallant, 1992; Johnsen & Herringer, 1993; Murphy & Hoffman, 1993; Jarvis et al., 1995). If social support is available, in the form of a partner or spouse, friends, family and social groups, then the chance of maintaining abstinence is increased. Other psychosocial predictors of relapse have been identified, and will be discussed in a later chapter.

However, the severity of the withdrawal syndrome experienced by the individual may also be a major determinant of relapse. Anecdotes noted by clinicians treating the patients, and patients themselves, suggest that withdrawal severity is a factor. While there is a large body of literature on psychosocial and behavioural determinants of relapse, only a few studies have examined the relationship between withdrawal symptomatology and relapse. These studies appear to support the

notion that withdrawal severity, particularly symptoms of tremor, anxiety, depression, craving and restlessness, may be involved in relapse drinking (Hershon, 1977; O'Connor et al., 1991; Bauer, 1994). Although the nature and magnitude of the relationship is largely unknown, it is clear that relapse is most likely in the first few weeks to months following cessation, when withdrawal is most severe (Hunt et al., 1971; Kissin, 1979; De Soto et. al., 1985).

That withdrawal severity may be a determinant of relapse was also noted by Edwards (1990). Edwards proposed that research should be directed toward understanding the potential of the total withdrawal syndrome to affect relapse, and subsequent determination of particular symptoms of importance within the syndrome.

1.9 Clinical assessment of alcohol withdrawal

A wide variety of scales and questionnaires have been developed to assess alcohol withdrawal severity, covering a range of physical and affective components. Two particular scales are widely used for assessment of alcohol withdrawal, as they are thought to be the most valid and reliable. These are the DSM-IV and the CIWA-Ar. The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition) developed by the American Psychiatric Association (1994) is a standard tool in the classification of a range of mental disorders, including substance (alcohol) dependence and the alcohol withdrawal syndrome. It continues to be revised and updated since its first appearance in 1952 as the DSM-I.

The DSM-IV classifies Uncomplicated Alcohol Withdrawal (291.80) as the presence of tremor of the hands, tongue or eyelids following a recent cessation or reduction in alcohol consumption by an individual who has been drinking heavy amounts of alcohol over a prolonged time period (ie. several days or longer). It also specifies that at least one of the following symptoms are present: nausea or vomiting, malaise or weakness, autonomic hyperactivity, anxiety, depressed mood or irritability, transient hallucinations or illusions, headache and insomnia. According to the DSM-IV, Uncomplicated Alcohol Withdrawal may be complicated by the presence of Alcohol Withdrawal Delirium (291.00) and Alcohol Hallucinosis (291.30).

Alcohol Withdrawal Delirium is less common than Uncomplicated Alcohol Withdrawal and is described by three primary criteria. Firstly, the presence of delirium developing following cessation of

heavy alcohol ingestion or a reduction in the amount of alcohol ingested (usually within one week); secondly, the presence of marked autonomic hyperactivity (eg. tachycardia, sweating), and finally that no other physical or mental disorder is present that may be causing the delirium.

Alcohol Hallucinosis is rare as a withdrawal complication, and is characterised by vivid and persistent auditory or visual hallucinations that develop within 48 hours after cessation or reduction in heavy alcohol consumption in a person who has fulfilled the criteria for Alcohol Dependence. Further, Alcohol Hallucinosis specifies no delirium should be present, as in Alcohol Withdrawal Delirium, and that hallucinosis is not due to any other physical or mental disorder.

The use of the DSM-IV in the assessment of alcohol withdrawal is limited in that the evaluation it makes is primarily quantal and not graded. That is, it does not give full indication of the intensity of the alcohol withdrawal syndrome. It appears to be most useful for identifying the *presence* of the alcohol withdrawal syndrome rather than the *severity*, and also in providing standards and diagnostic criteria for professional communication.

Gross and colleagues initiated research on the development of a scale to quantify the severity of withdrawal with the introduction of the Total Severity Assessment scale (TSA) (Gross et al., 1971). This was later shortened to the Selected Severity Assessment scale (SSA) (Gross et al., 1973). This research was needed because of the difficulties inherent in accurately assessing and appropriately treating patients in alcohol withdrawal.

The TSA consisted of 30 items, 11 of which formed the SSA. Items comprising the SSA included tremor, eating disturbances, paroxysmal sweats, sleep disturbances, clouding of sensorium, hallucinations, poor quality of contact, agitation, hyperthermia, tachycardia and convulsions. Symptoms of withdrawal not included in the SSA, but incorporated into the TSA included nausea and vomiting, pruritus, muscle pain, nightmares, tinnitus, visual disturbances, delusions, tactile hallucinations, insight, anxiety, depression, poor level of consciousness, snout reflex, paraesthesia, abnormal knee jerk reflex, abnormal biceps reflex, nystagmus, gait disturbances and schizophrenic behaviour. Most of the items in the scale were scored between 0 and 7, where a score of 0 indicated that the particular symptom is absent and a score of 7 indicated a high degree of severity. Gross found the SSA battery to be a reliable tool for assessing alcohol withdrawal. Thus, the items chosen from the TSA for the SSA were the symptoms most highly correlated with clinical judgement.

While various approaches have followed the work of Gross and colleagues in the development of alcohol withdrawal scales (Knott et al., 1981; Bokstrom & Balldin, 1992), the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) is the best validated clinical assessment for alcohol withdrawal as yet (Shaw et al., 1981; Romach & Sellers, 1991). Shaw and colleagues modified the SSA to a 15 item scale that could be applied every 30 minutes. It included some of the original SSA items of tremor, sweating, clouding of sensorium, hallucinations, quality of contact, agitation and seizures. Eating and sleep disturbances were not included in the CIWA-A, since these symptoms are not sensitive to changes over short time periods. However these items were replaced by nausea and vomiting and anxiety, which may vary from hour to hour. Sensory and thought disturbances, and headache and flushing were also included in the CIWA-A. Shaw showed the CIWA-A scores to be significantly correlated with both the clinician's estimate of global severity and also with an objective measure of tremor. Moreover the inter-rater reliability was also found to be high.

A revised version of the CIWA-A, the CIWA-Ar, was a briefer 10 item scale for the assessment of alcohol withdrawal severity, and also provided a structure for the training of nurses and physicians to assess patients (Sullivan et al., 1989). Each symptom was given a severity score ranging between 0 and 7. The relevant symptoms included nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache, and orientation and clouding of the sensorium. For example, for the symptom of tremor, no discernible tremor would receive a score of 0, while tremor that was not visible, but felt fingertip to fingertip would receive a score of 1. Similarly moderate tremor, as perceived by the examiner, would receive a score of 4. The highest score of 7 would be awarded to a patient perceived to have severe tremor, even with arms not extended.

The CIWA-Ar is used by the alcohol detoxification unit in Payneham, South Australia, to assess the severity of withdrawal. The score achieved by the patient determines whether they will receive pharmacological treatment in the form of benzodiazepines, and the dose and duration of benzodiazepine administration. The CIWA-Ar and closely related scales are also used in research situations to determine the degree of withdrawal severity in research subjects (eg. Johnston et al., 1991; Kanitz et al., 1994; Wetterling et al., 1998).

1.9.1 The CIWA-Ar: Implications of use

While the CIWA-Ar is a useful tool in clinical situations for the assessment of alcohol withdrawal severity, there may be problems involved with its use. The most obvious limitation is that assessment is based on the subjective appraisal of symptom severity. Further, variability may be exacerbated, as there are two different assessors with potentially different interpretation of symptom severity. That is, some symptoms are self-assessed by the patient (eg. nausea) while others are assessed by the clinician (eg. tremor). Moreover, since some symptoms are self-assessed, patients may under or over-report symptomatology in order to alter treatment (ie. to receive more medication, or to discharge before treatment completion). Finally, assessment with the CIWA-Ar is not always practical. Many patients experience severe withdrawal during the night, such as sweating and restlessness. Such symptoms are less likely to be noticed or treated by medical staff during the night, when assessment with the CIWA-Ar is difficult.

Despite the fact that Shaw and colleagues found the CIWA-A to be correlated with global withdrawal severity, and have a high inter-rater reliability (Shaw et al., 1981), the results were obtained following a concentrated training course for the medical staff, and were based on consistent results over a short period of time. While this was effective for Shaw and colleagues, the same scrutiny and self-monitoring may be difficult to maintain in a normal, hectic clinical environment.

A client presenting for alcohol withdrawal detoxification in South Australia will receive an intense course of vitamin therapy, particularly thiamine. The following drugs are also generally available upon request; diphenoxylate hydrochloride 2.5mg/atropine sulphate 25µg (®Lomotil) for diarrhoea, metoclopramide (®Maxolon) for gastrointestinal disturbances, paracetamol (®Panadol) for muscle pain, pruritis and headache, and temazepam (®Normison, ®Euhypnos) at night for insomnia. However, longer acting benzodiazepines such as diazepam (®Valium, ®Ducene), are usually only prescribed if withdrawal severity reaches a certain threshold, as assessed by the CIWA-Ar. Preferential treatment for patients achieving a score between 11 and 19 on the CIWA-Ar is 5 to 10mg of oral diazepam every few hours until their score drops below 10. Patients achieving a score of 20 or more will receive 20mg of diazepam every two hours until their score falls below 10, or the total daily dose reaches 120mg.

Those patients with a history of withdrawal seizures will be placed on a 'seizure prophylaxis regime'. This varies from patient to patient depending on their withdrawal severity, but it usually means administration of between 40 and 100mg of diazepam on the first day of detoxification, tapering to 10mg by the fourth day.

Accurate diagnosis of withdrawal severity is important in treatment, and there are clinical implications for incorrect assessment and subsequent under-treatment of patients. In the first instance, severe alcohol withdrawal may be fatal, particularly if it includes cardiac arrhythmias, seizures or delirium tremens. The likelihood of mortality is increased if the withdrawal syndrome is accompanied by other co-morbid factors. However, death as a result of alcohol withdrawal can be readily avoided if treated with benzodiazepines.

Secondly, withdrawal symptomatology is disturbing and unpleasant for patients and may result in premature self-discharge from the clinic. Accurate diagnosis and pharmacological treatment will not only result in the least painful withdrawal possible, but may also help to maintain abstinence in the long term.

Conversely there are implications for over-treatment with diazepam. Treatment for extended periods, and at higher doses than necessary may result in dependence on benzodiazepines.

Thus, accurate assessment of withdrawal severity has clinical, research and economic implications. Several studies have indicated that many patients can successfully withdraw from alcohol with supportive therapy only (Whitfield et al., 1978; Knott et al., 1981; Shaw et al., 1981); this includes reassurance, reality orientation, frequent symptom monitoring and general supportive care. The advantages of such a program are that professional medical staff need not always be present since some of the supportive care can be effectively issued by non-professionals. Moreover, the in-patient period may be shortened. This results in a more cost-effective means of detoxification. Furthermore, the effects of sedatives are not a concern and patients learn effective, non-chemical ways, of coping with stress (Whitfield et al., 1978).

Recently, Australian studies have suggested that many of those withdrawing from alcohol do not require in-patient care, but can successfully withdraw using out-patient services, with the exception of those in severe withdrawal and those with hazardous co-morbid factors (Stockwell et al., 1986; Stockwell et al., 1990; Stockwell et al., 1991; National Drug Strategy, 1993; Ali & Cormack, 1994).

The obvious advantage of treatment on an out-patient basis is a resultant reduction in government, community and medical costs, and also advantages to those persons who find it difficult to leave their home because of responsibilities (eg. those persons who have children in their care).

1.9.2 The ambulatory monitor

Accurate assessment of the severity of alcohol withdrawal has implications for both clinical and research situations. One of the major limitations of the CIWA-Ar scale for the measurement of withdrawal severity is that it is a subjective assessment tool. This study takes advantage of an unobtrusive portable monitor, developed at the University of Adelaide in the early 1990's (White et al., 1994). The monitor provides quantitative and objective measures of sweating, gross activity and skin temperature, all of which are disrupted during alcohol withdrawal and manifested as symptoms of the syndrome. Gross activity, as measured by the monitor indicates the degree of sleep restlessness that is experienced during the night, and reflects agitation and restlessness during the day. Previous studies have investigated sleep patterns in alcoholics using EEG recordings (Johnson et al., 1970; Allen et al., 1971; Kissin et al., 1973; Gross et al., 1973; Gross et al., 1974; Wagman & Allen, 1977; Gillin et al., 1990; Le Bon et al., 1997), which have the inconvenience of requiring subjects to sleep in laboratories, attached to an EEG machine. The monitor is far less cumbersome and is transportable. Overall, the monitor provides information about sweating, temperature and activity through the night, and also the diurnal rhythms of these symptoms, about which little is known.

The monitor consists of a sensor, which is attached to the anterior surface of the non-dominant forearm, and a compact microprocessor logger that is held in a pouch and attached around the subject's waist. The microprocessor can hold up to 72 hours of data, which is then down-loaded onto a computer in a form that is compatible with data analysis programs currently available.

Most studies to date have used subjective withdrawal measures. The monitor is a valuable tool that can be used to charter the alcohol withdrawal syndrome objectively, and to illuminate areas of alcohol research where understanding is limited. It is described in more detail in Chapter 2.

1.10 Experimental rationale and aims

The main aim of this thesis was to improve understanding of the alcohol withdrawal syndrome and its related features. As discussed in the literature review, there were several areas requiring further investigation. The first was characterisation and measurement of the intensity and duration of the separate elements that comprise withdrawal over an extended period of time. This aspect of the study incorporated both standardised and objective measurements of withdrawal symptoms, including physical symptoms, psychiatric and mood disturbances and health disturbances.

The second major area of this investigation aimed to identify features, or characteristics, that would predict the intensity of withdrawal. This incorporated a range of potential predictor variables. As discussed above in section *1.6*, '*Factors affecting the severity of withdrawal*', several factors are thought to influence the severity of alcohol withdrawal. Alcohol intake and duration of consumption were two major factors, along with concomitant complications and number of previous withdrawal attempts. These factors were investigated as potential predictor variables. In a separate investigation, biological markers of hazardous alcohol intake were also investigated as potential predictors of alcohol withdrawal severity. The markers that were incorporated into this phase of the study were gamma glutamyl transferase (GGT), erythrocyte mean corpuscular volume (MCV) and carbohydrate deficient transferrin (CDT). The rationale for investigating biological markers as predictors of withdrawal severity, is that they have the potential to provide an objective measure of drinking history, and may be related to withdrawal severity.

This second major phase of the study incorporated two output variables, or components, of withdrawal severity. The first was the severity of the total global syndrome that was a combined severity measure of all physical, psychiatric and health disturbances (as determined from the outcomes of the first major aim). The second component incorporated the severity of the physical global syndrome, which was a combined severity measure of physical disturbances only.

The third major area of investigation in this thesis was determination of predictors of relapse. Withdrawal severity was investigated as a predictor, as very few studies have considered this relationship. As with the previous aim, the intensity of withdrawal was reflected as the total global withdrawal syndrome, and also the physical components of withdrawal. Both acute withdrawal and protracted withdrawal severity were investigated for their potential to antedate relapse. Other potential

predictors of relapse were also considered including individual symptoms of withdrawal (as assessed in aim 1), as well as antecedents of withdrawal severity, and several psychosocial factors. The rationale of including these latter two variables was to obtain a comprehensive view of the relationship between psychosocial factors, withdrawal severity, and factors affecting withdrawal severity, regarding their potential to predict relapse. This section of the investigation was born out of a paucity of information concerning how various predictors of relapse may relate to each other.

Specifically the aims of the study were:

1. To characterise the intensity and duration of specific symptoms of alcohol withdrawal over a ten week period, including symptoms of physical, psychiatric, mood and health disturbances, by using objective and standardised assessment tools.

2. To investigate potential predictors of withdrawal severity incorporating objective and standardised measures of global withdrawal severity, and biological and non-biological potential predictor variables.

3. To investigate potential predictors of time to relapse during the first 70 days of abstinence, including objective and standardised measures of acute and protracted withdrawal severity, antecedents of withdrawal severity, and psychosocial variables.

These aims will be covered over several chapters. Aims 1 and 3 will be incorporated into one chapter each (Chapter 4 and Chapter 7 respectively), while Aim 2 will be presented as two separate chapters (Chapter 5 and Chapter 6). Although these were the specific research aims of the study, there was another peripheral, albeit important fourth aim. This was a methodological aim and concerned validation and calibration of the monitors, - the equipment used to objectively quantify physical withdrawal symptoms. This will be covered in Chapter 2 entitled, *'The Ambulatory Monitor'*. Thus, the fourth aim was:

4. To validate and calibrate the ambulatory monitors for the accurate and reliable recording of alcohol withdrawal symptomatology.

CHAPTER 2

2. THE AMBULATORY MONITOR

2.1 Introduction

The ambulatory monitor was developed by Dr. Jason White of the Department of Clinical and Experimental Pharmacology and Mr. Stan Flavel of the Department of Physiology, University of Adelaide. It was designed specifically to measure symptoms of alcohol withdrawal in humans. An important feature of the monitor is that it is able to be worn 'around the clock' for several days at a time, thus capturing fluctuations in withdrawal symptomatology that may occur over the course of a day, or over the course of several weeks.

The unit itself consists of two major connecting parts; a microprocessor controller (PSION Organiser II Model LZ64) and a custom-built interface unit by Digitron. The controller, or logger, is held in a leather pouch, which is attached to a belt that is worn around the subject's waist, or over the shoulder in a holster-like manner. The interface unit, or sensor, is attached to the anterior surface of the non-dominant forearm of the subject, with a length (about 20cm) of elastic bandage (FULFLEX Tubular Support Bandage, Size D, Orthopaedic Appliances Pty. Ltd.).

The logger is a programmable four channel device which receives signals, via a cable, from the interface unit. The interface unit contains four sensors: a temperature sensor, a humidity sensor, an accelerometer and a mercury tilt switch. These measure temperature, sweating, tremor and gross activity respectively. All output readings are in millivolts (mV) and readings do not exceed 2,500 mV. Validation and calibration of each channel is discussed in detail below.

The logger was programmed to take readings at five minute intervals, although this is a flexible function of the logger. Readings are stored in removable data-paks, analogous to a floppy disc, which are inserted into the monitor. Data-paks can hold up to four days, or 100 hours worth of data, and data is erasable using a PSION Organiser II Datapak Formatter.

Following data collection, readings are down-loaded from the monitor unit onto an IBM compatible personal computer via a cable. The data are presented in binary form as five minute readings from four channels using a Datalog Analysis Program (Version 2.02, Digitron Instrumentation Ltd.). Lotus-123 converts the data into a readily acceptable format for other spreadsheet programs.

Temperature measurement is made by a precision semiconductor sensor (LM35), mounted on the bottom of the sensor pack allowing close contact with the subject's skin. The logger activates the temperature sensor at five minute intervals, and stores the current skin temperature as a mV reading. The range over which temperature can be measured is between 5 - 200°C.

Sweating is recorded by a humidity sensor, employing a ceramic whose electrical resistance changes with relative humidity. The sensor comprises a DC measurement circuit that turns on when the logger is activated at five minute intervals, recording a mV reading which is proportional to the current humidity level. The range over which humidity may be measured is between 5 and 90%. The humidity sensor is also posteriorly located on the sensor pack, allowing close contact with the subject's skin.

The activity sensor is a miniature mercury tilt switch. When the sensor is held in the horizontal plane, a ball of mercury closes the switch. Lateral rotation in either direction beyond five degrees or more from the horizontal plane results in movement of the mercury ball and an opening of the switch. This generates pulses as the subject moves, which are counted and stored at the end of every five minute interval. These cumulative scores are presented as mV readings per five minutes, reflecting activity during that period. This activity sensor is mono-axial, detecting movement about one plane only.

The tremor channel of the monitor consists of an accelerometer, which produces small electrical signals proportional to the velocity and direction of sensor movement. The more violent the tremor, the larger the amplitude of the signals. The signals are band pass filtered to accept frequencies of range 6-10 Hz, which is the primary frequency in which tremor occurs (Carrie, 1965; Lefebvre-D'Armour et al., 1978; Brown et al., 1982; Elble, 1986; Martinelli, 1986; Neiman et al., 1990).

The accelerometer is a piezo-ceramic device that is most sensitive to "up and down" movement in the vertical plane, and insensitive to sideways movement in the horizontal plane. Accordingly the tremor value logged depends upon the orientation of the sensor. The small signals are first amplified in the sensor, and sent to the monitor where they are compared with a fixed voltage level or threshold level. The threshold level relates directly to sensitivity and is adjustable. When the tremor causes a signal that is higher than the threshold level, a pulse is generated which is recorded in a counting circuit and stored at the end of every five minute interval. The count value is passed to a converter circuit that produces a mV output proportional to the count value.

Before experimental work with the monitor proceeded, it was necessary to investigate three major issues:

(1) Validation - How do absolute values of temperature, sweating, activity and tremor relate to the mV output of the monitor? (eg. Temperature; what is the equivalent value of 200mV in degrees Celsius?)

(2) Calibration - How do the six monitors relate to each other in terms of sensitivity for each of the four channels? (eg. Does 200mV recorded for temperature on monitor 1 reflect the same temperature value as 200mV recorded on monitors 2, 3, 4, 5, and 6?)

(3) Consistency - How do the readings change over a range of low to high values, i.e. is there linearity?

These issues were investigated in the following studies. A major objective was to generate macro-equations for each monitor. These macros yield valid, calibrated results when applied to the raw data.

2.2 Temperature and Humidity

In order to meet the criteria for external validation of the temperature and humidity sensors, a chamber was developed that allowed manipulation of both temperature and humidity. Monitor sensors (1 - 6) were attached to the ceiling of the chamber, while the loggers remained outside the chamber. The chamber was warmed by an inside heating coil whose power source (50 Volt 5 Ampere Lab Power Supply) remained outside, under the control of the investigator. Both voltage (range 0 - 10 V) and current (range 1 - 5 A) could be manipulated, resulting in a power output range of 0 to 50 Watts (V x A = W) supplying adequate heating to the chamber.

Air humidity was affected by the presence of a shallow water container placed on the floor of the chamber, and was controlled via two separate mechanisms; temperature, and controlled release of air from the inside to the outside of the chamber. Relative humidity was increased by slowly

decreasing the temperature. As the temperature dropped, the water vapour in the air condensed, resulting in an increase in air moisture and subsequent humidity. Conversely, humidity was decreased by perforating the otherwise sealed chamber with small holes (these were re-covered for subsequent experiments), allowing moist air to escape. Both heat and air moisture was evenly distributed around the chamber by the use of a fan mounted on the wall of the chamber.

The chamber also contained a commercial thermometer/hygrometer (MICRONTA LCD Model 63-844) which presented temperature in degrees Celsius (°C) and humidity in % Relative Humidity (%RH). Readings were taken from this every five minutes in synchrony with monitor five minute readings.

Maximum heat (50W) was applied to the chamber until the temperature reached 37.5°C and remained steady. This took around three hours, in which time air was evenly distributed around the chamber. Following equilibration, readings were taken over 24 hours. During this time both temperature and humidity was manipulated until clinically relevant ranges of each were obtained (Table 2.1). Several readings were usually taken for each degree Celsius, and each point of humidity. This experiment was repeated twice on separate days. The end result was 276 readings of humidity and temperature by the commercial thermometer/hygrometer, and 276 readings in mV of temperature and humidity for each monitor. The range of these is shown in Table 2.1. The variation between ranges highlights the need for calibration between monitors.

Table 2.1

Ranges of Temperature and Humidity for monitors and thermometer/hygrometer

Variable	Range	Minimum	Maximum	Valid N	Description
Humid 0	44.0	34.0	78.0	276	Humidity in %RH -hygrometer
Humid 1	220.0	2.0	222.0	276	Humidity in mV - monitor 1
Humid 2	930.0	7.0	937.0	276	Humidity in mV - monitor 2
Humid 3	593.0	17.0	610.0	276	Humidity in mV - monitor 3
Humid 4	1075.0	17.0	1092.0	276	Humidity in mV - monitor 4
Humid 5	1205.0	15.0	1220.0	276	Humidity in mV - monitor 5
Humid 6	1182.0	10.0	1192.0	276	Humidity in mV - monitor 6
Temp 0	14.40	23.10	37.50	276	Temp in °C - thermometer
Temp 1	153.0	227.0	380.0	276	Temp in mV - monitor 1
Temp 2	160.0	250.0	410.0	276	Temp in mV - monitor 2
Temp 3	155.0	237.0	392.0	276	Temp in mV - monitor 3
Temp 4	153.0	227.0	380.0	276	Temp in mV - monitor 4
Temp 5	165.0	240.0	405.0	276	Temp in mV - monitor 5
Temp 6	157.0	235.0	392.0	276	Temp in mV - monitor 6

Data generated from this study were used to construct formulae by which millivolt values could be converted back to absolute values of either temperature or humidity. Correcting all monitors back to absolute values provided a correction factor between monitors to a "gold standard", thus rendering the monitors calibrated, and results equisensitive.

The transformation process for temperature and humidity is outlined below.

2.2.1 Temperature

Millivolt values of temperature were plotted against °C values of temperature for each monitor. As can be seen from Figs. 2.1 – 2.6, the relationship between these two variables is linear, and highly correlated for all monitors. Formulae for each were generated by finding the slope (m) and y-intercept (c) of each line, using monitor temperature in mV as the y-value to find the respective x value (temperature in °C is denoted as '*Temp*0').

For example for monitor 3;

$$y = mx + c \qquad (i)$$

where c is the y-intercept and m is the slope

$$x = \frac{y - c}{m} \qquad (ii)$$

$$Temp0 = \frac{Temp3 - c}{m} \qquad (iii)$$

where Temp0 is in °C, Temp3 is in mV, and c and m are constants

The graphs are shown below, and the corresponding formulae and correlation values in Table 2.2. These formulae were incorporated into a macro that was applied to the raw data generated from subjects wearing the monitor. Each monitor has its own macro which runs in SPSS and transforms the mV temperature values into absolute, equisensitive readings in °C (see appendices).

Table 2.2

Formulae and correlation values for temperature for all monitors

Monitor No.	Formula	Correlation (r)
Monitor 1	Temp 0 = (Temp 1 + 18.84) ÷ 10.65	0.999
Monitor 2	Temp 0 = (Temp 2 + 7.72) ÷ 11.13	0.999
Monitor 3	Temp 0 = (Temp 3 + 12.43) ÷ 10.83	0.999
Monitor 4	Temp 0 = (Temp 4 + 16.36) ÷ 10.60	0.999
Monitor 5	Temp 0 = (Temp 5 + 21.06) ÷ 11.36	0.999
Monitor 6	Temp 0 = (Temp 6 + 16.43) ÷ 10.90	0.999

Fig. 2.1 **MONITOR 1**

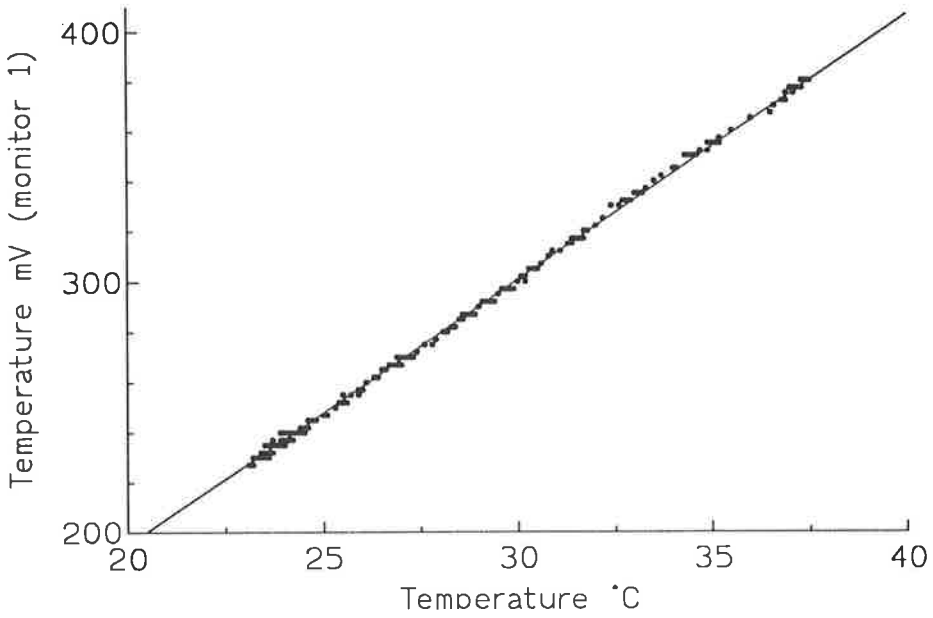


Fig. 2.1 Graph showing temperature in °C against temperature in mV for monitor 1

Fig. 2.2 **MONITOR 2**

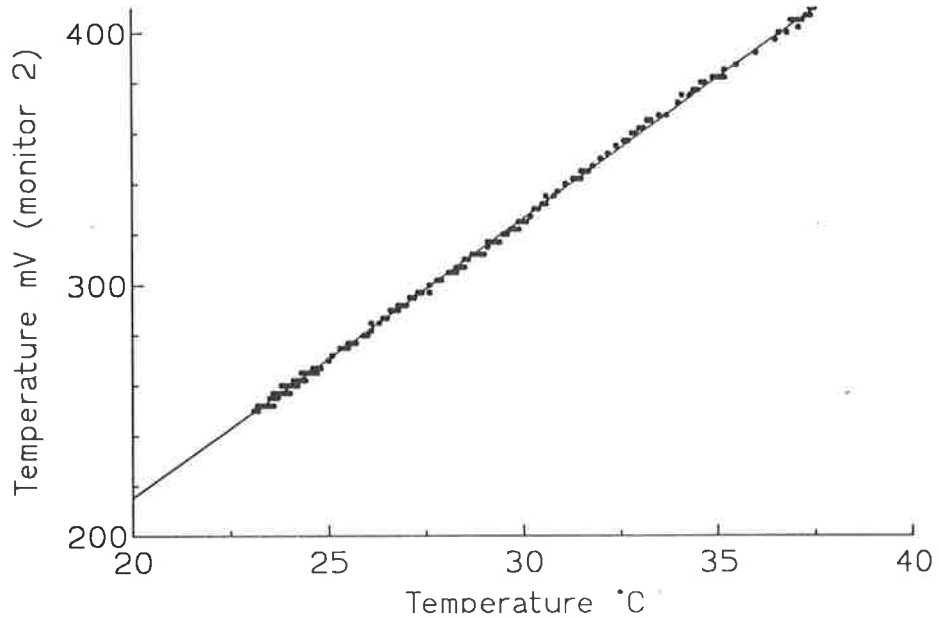


Fig. 2.2 Graph showing temperature in °C against temperature in mV for monitor 2

Fig. 2.3 **MONITOR 3**

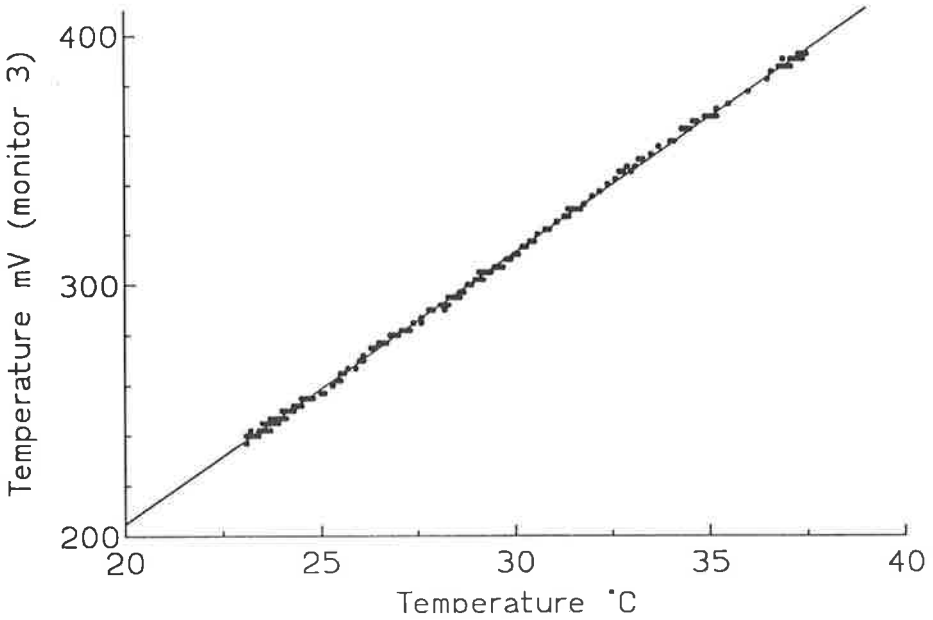


Fig. 2.3 Graph showing temperature in °C against temperature in mV for monitor 3

Fig. 2.4 **MONITOR 4**

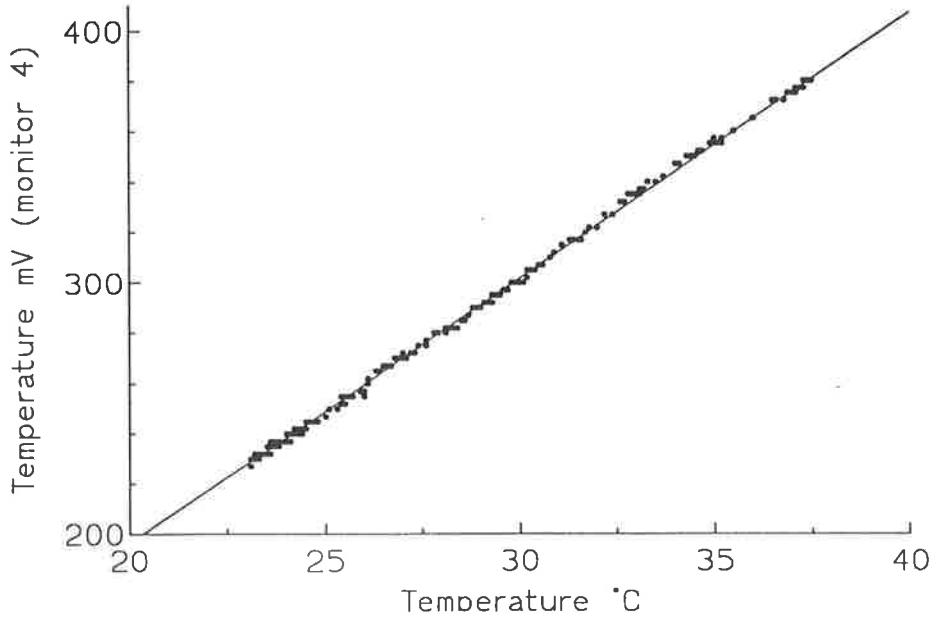


Fig. 2.4 Graph showing temperature in °C against temperature in mV for monitor 4

Fig. 2.5 **MONITOR 5**

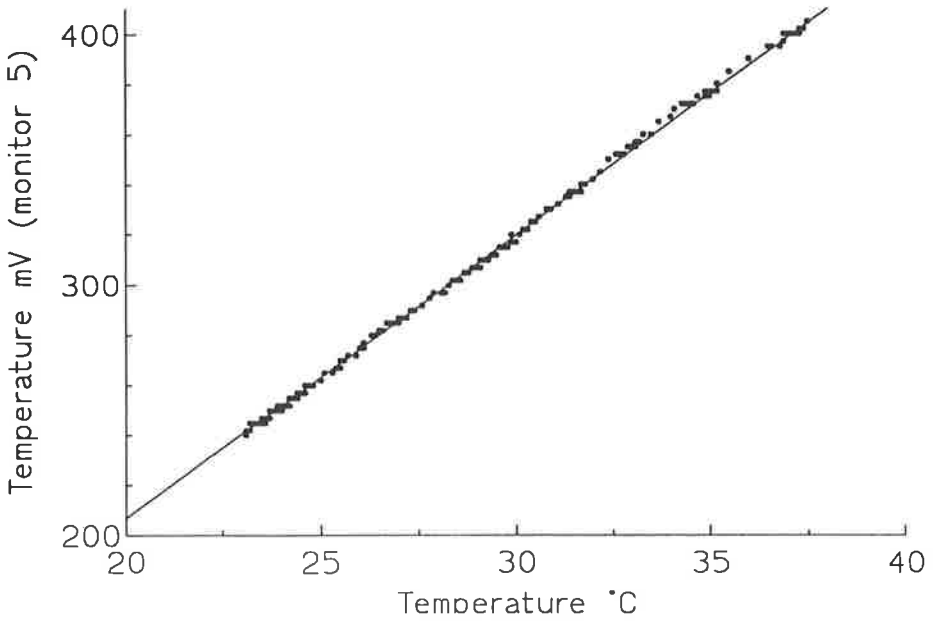


Fig. 2.5 Graph showing temperature in °C against temperature in mV for monitor 5

Fig. 2.6 **MONITOR 6**

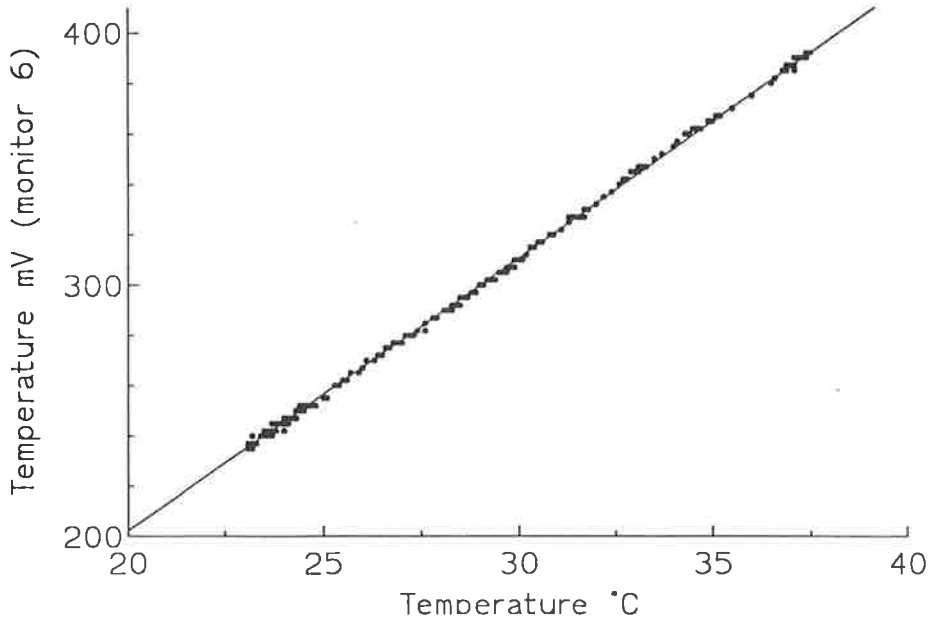


Fig. 2.6 Graph showing temperature in °C against temperature in mV for monitor 6

2.2.2 Humidity

The scatter of humidity in %RH against humidity in mV, was not linear as had been observed with temperature, indicating that movement between humidity extremes is not uniform. A correction factor (*CF*) was assigned, by which humidity in mV could be transformed into humidity in %RH. For example, monitor 3;

$$Humid0 = Humid3 \times CF \qquad (iv)$$

where humid0 is in %RH and Humid3 is in mV.

$$\therefore \quad CF = \frac{Humid0}{Humid3} \qquad (v)$$

Thus a correction factor was generated by dividing humidity in %RH by humidity in mV, the aim of which was to generate a meaningful mathematical relationship between humidity in mV and the correction factor. The result of finding such a relationship meant that for each value of humidity in mV, the respective humidity value in %RH could be obtained.

When humidity in mV was plotted against CF, a hyperbolic curve was generated for all monitors. Monitor 3 is shown as an example of the curve (Fig. 2.7).

Fig. 2.7 **MONITOR 3**

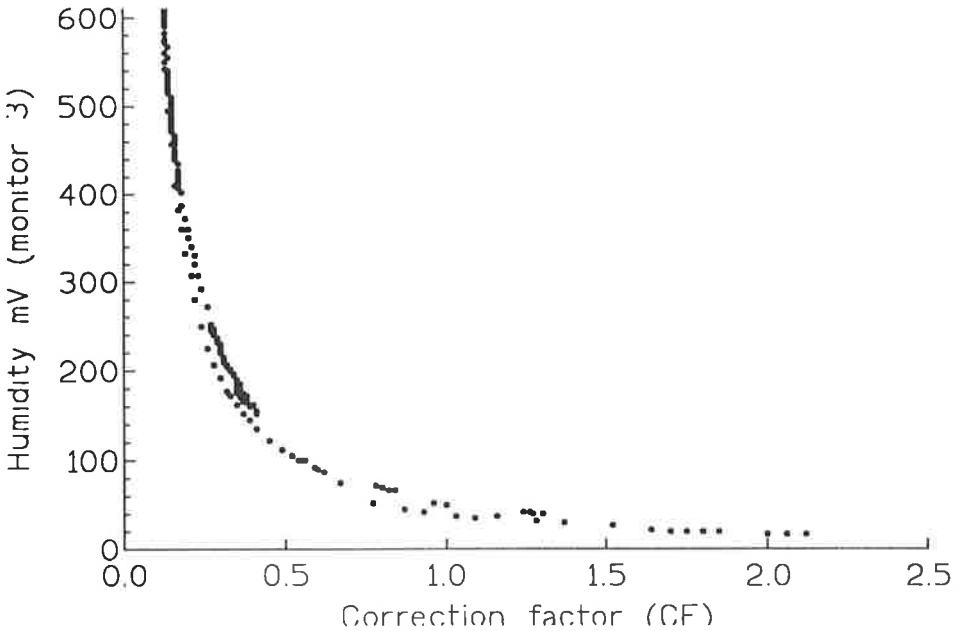


Fig. 2.7 Graph showing humidity in mV for monitor 3 against the correction factor (CF) for monitor 3

To generate the maximum amount of information from this data, the relationship required linearity. A characteristic of hyperbolic functions is that inversion of the X variable results in a linear relationship. Accordingly, inversion of the correction factor plotted against humidity in mV resulted in a highly correlated linear relationship for each monitor (Figs. 2.8 – 2.13 & Table 2.3). From this relationship, humidity in %RH could be obtained for each monitor, the working for which is shown below.

For example, for monitor 3;

from equations (i) and(ii),

$$x = \frac{Humid3 - c}{m} \qquad (vi)$$

where Humid3 is in mV, c is the y-intercept (constant), m is the slope (constant) and x is humidity in %RH (see Figs. 2.8-2.13).

however, from Fig. 2.7, $$x = \frac{1}{CF} \qquad (vii)$$

therefore, $$CF = \frac{m}{Humid3 - c} \qquad (viii)$$

however, from eqn. (v), $$CF = \frac{Humid0}{Humid3} \qquad (ix)$$

therefore, $$Humid0 = \left\{\frac{m}{(Humid3 - c)}\right\} \times Humid3 \qquad (x)$$

These formulae were incorporated into a macro for each monitor that was applied to the raw data in SPSS. This converted mV humidity values into absolute, equisensitive readings in %RH (see appendices).

Table 2.3

Formulae and correlation values for humidity for all monitors

Monitor No.	Formula	Correlation (r)
Monitor 1	Humid 0 = (Humid 1 + 11.53) ÷ 77.62	0.997
Monitor 2	Humid 0 = (Humid 2 + 54.85) ÷ 75.11	0.989
Monitor 3	Humid 0 = (Humid 3 + 37.40) ÷ 78.64	0.998
Monitor 4	Humid 0 = (Humid 4 + 95.43) ÷ 77.37	0.989
Monitor 5	Humid 0 = (Humid 5 + 94.96) ÷ 76.06	0.985
Monitor 6	Humid 0 = (Humid 6 + 86.49) ÷ 76.31	0.991

Fig. 2.8

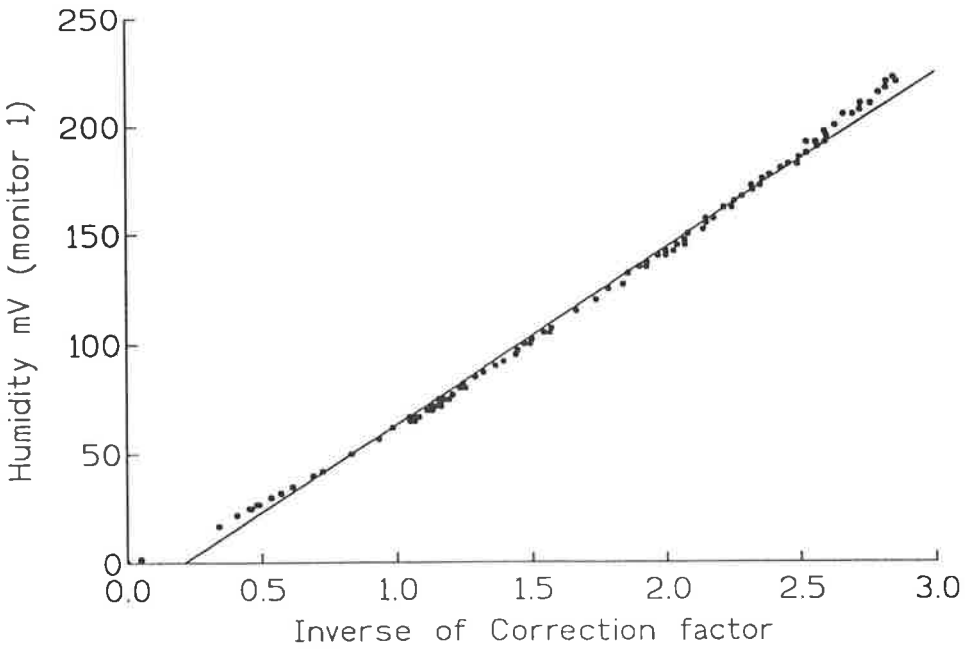


Fig. 2.8 Graph showing humidity in mV for monitor 1 against the inverse of the correction factor for monitor 1

Fig. 2.9

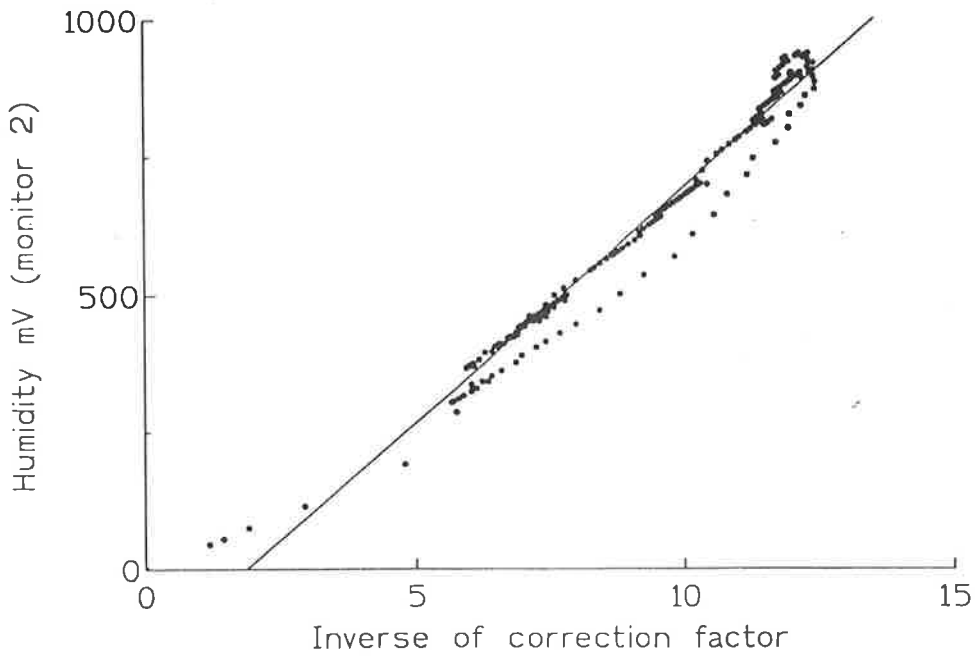


Fig. 2.9 Graph showing humidity in mV for monitor 2 against the inverse of the correction factor for monitor 2

Fig. 2.10

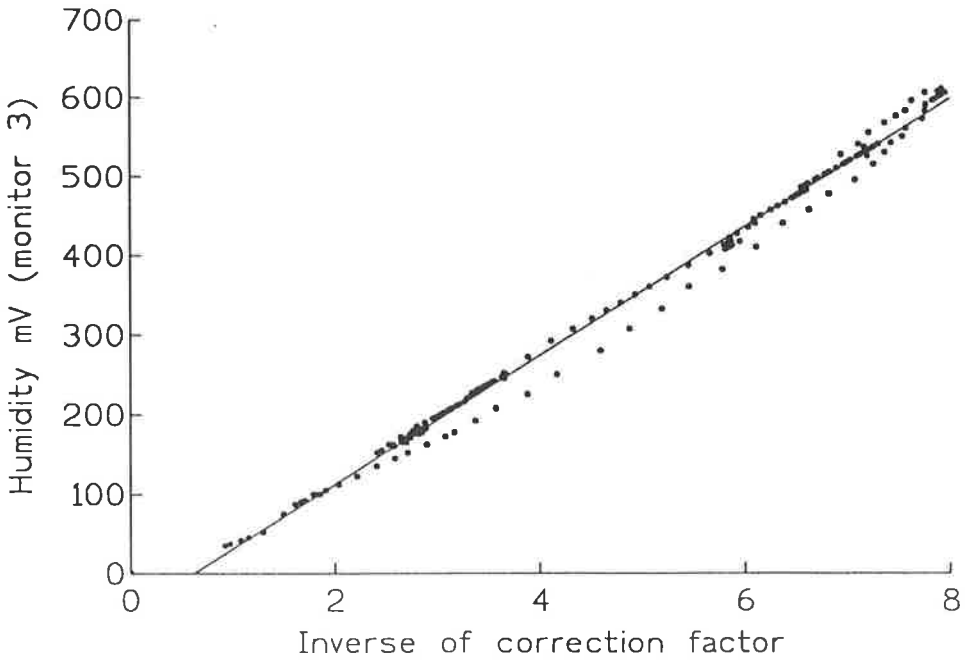


Fig. 2.10 Graph showing humidity in mV for monitor 3 against the inverse of the correction factor for monitor 3

Fig. 2.11

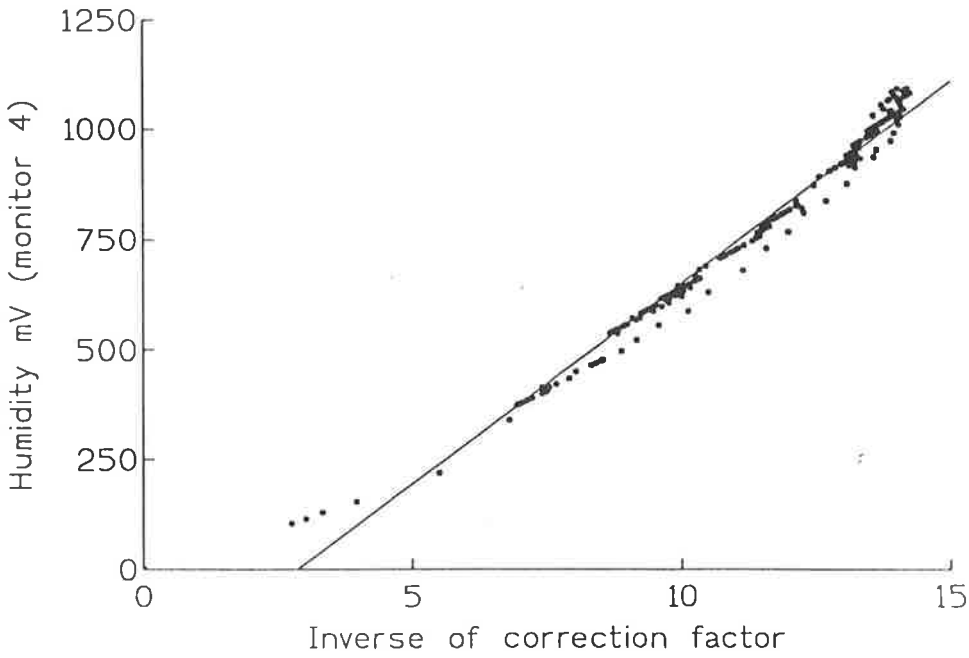


Fig. 2.11 Graph showing humidity in mV for monitor 4 against the inverse of the correction factor for monitor 4

Fig. 2.12

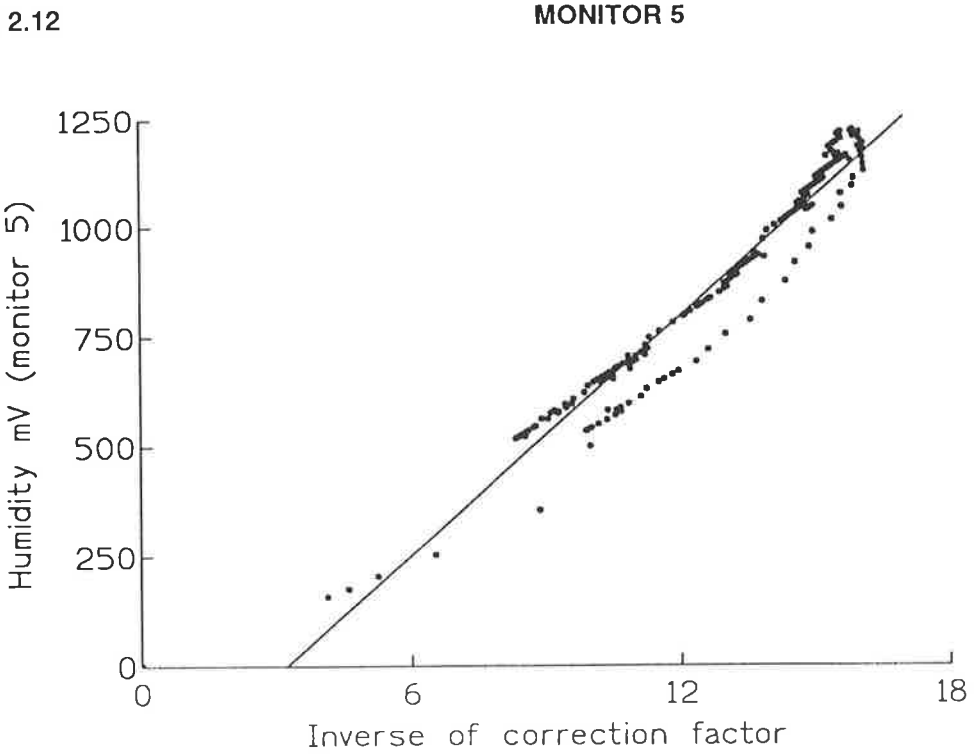


Fig. 2.12 Graph showing humidity in mV for monitor 5 against the inverse of the correction factor for monitor 5

Fig. 2.13

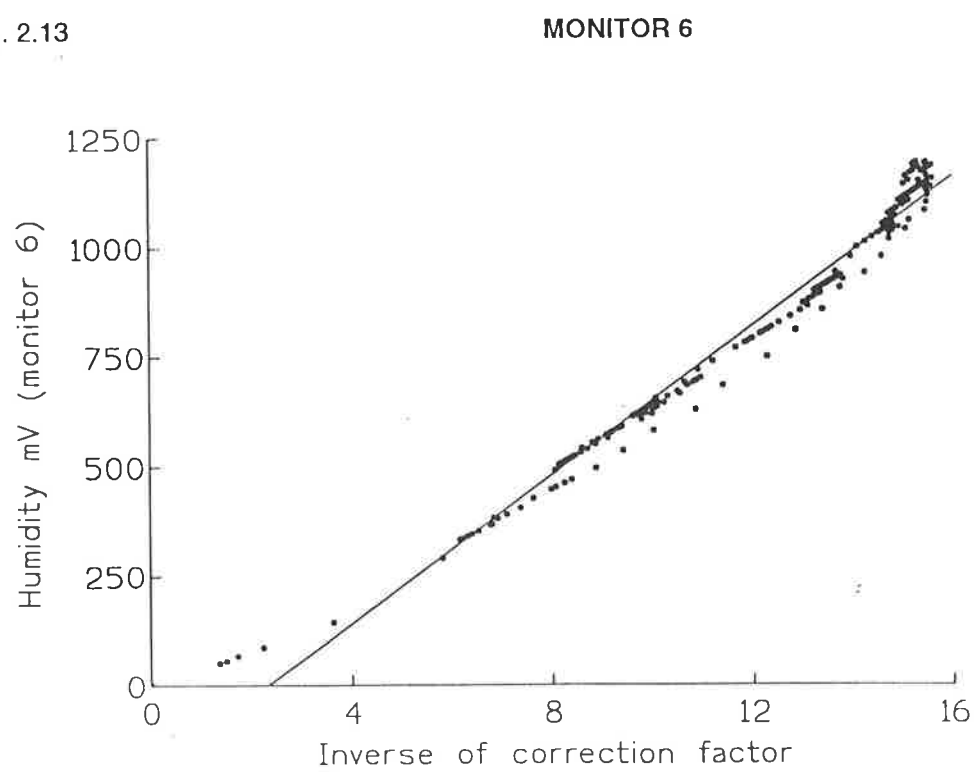


Fig. 2.13 Graph showing humidity in mV for monitor 6 against the inverse of the correction factor for monitor 6

2.3 Activity

Activity was included in the parameters measured as indicative of restlessness and agitation during the day, and sleep disturbance at night.

As mentioned in the introduction of this chapter, the tilt switch in the sensor measures activity when the sensor is moved laterally by five degrees or greater from the horizontal plane. Since activity is recorded in one plane only, the final count may be an underestimate of the amount of activity actually occurring. However, this method is acceptable for activity measurement (Tyron, 1991) as long as placement consistency is maintained.

Since a pulse is generated when the sensor is laterally moved greater than five degrees from the horizontal, the validation method consisted of this action. Sensors were rotated by hand from the horizontal, to the vertical at a rate of one turn per second. To calculate the ratio of turns to mV counts, the sensor was turned 25, 50, 75 & 100 times per discrete period. This was repeated four times for each monitor.

The results from this study showed that the number of turns was highly correlated with the mV output for each monitor. As an example, the data for monitor 3 are shown in Fig. 2.14. An equation was generated for each monitor allowing all results to be expressed in "turns greater than five degrees from the horizontal plane per five minutes" (*Turns*), thus effectively calibrating the monitors and rendering the results equisensitive (Table 2.4). Using monitor 3 as an example, the working is shown below;

from equations (i) and (ii)

$$Turns = \frac{Activity3 - c}{m} \qquad (xi)$$

where Turns = "turns greater than five degrees from the horizontal plane per five minutes", Activity 3 is in mV, c is the y-intercept (constant) and m is the slope (constant).

Fig. 2.14

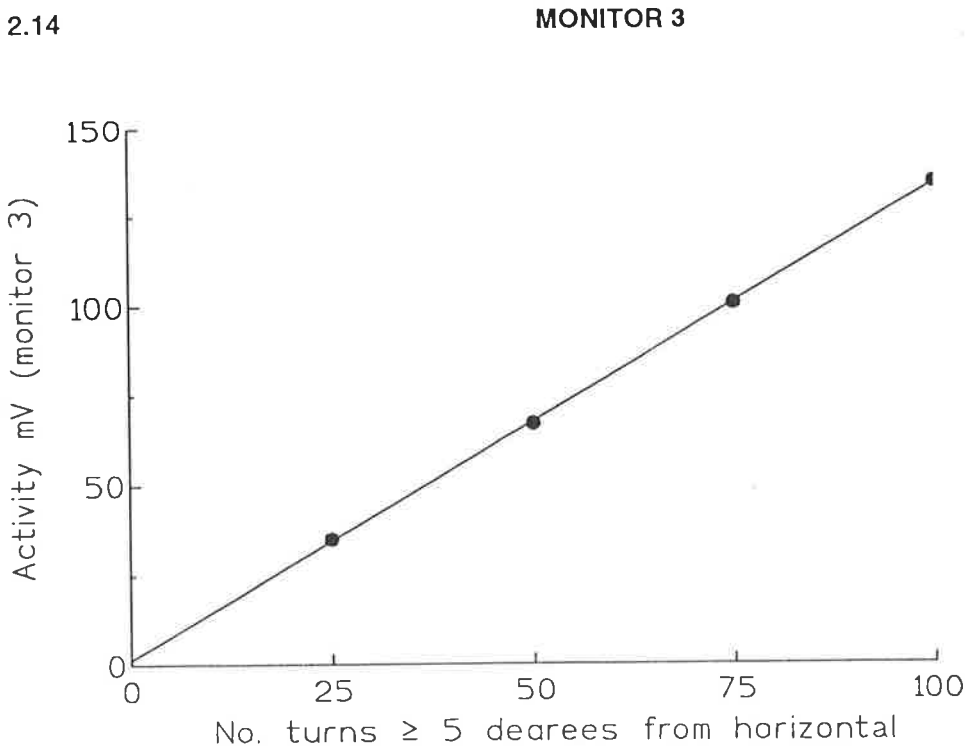


Fig. 2.14 Graph showing activity in mV against number of turns ≥ 5 degrees from the horizontal plane for monitor 3

Table 2.4

Formulae and correlation values for activity for all monitors, where activity for each monitor is expressed in mV

Monitor No.	Formula	Correlation (r)
Monitor 1	Turns per 5 mins = (Activity 1 - 0.50) + 1.43	0.999
Monitor 2	Turns per 5 mins = (Activity 2 - 4.25) + 2.63	0.999
Monitor 3	Turns per 5 mins = (Activity 3 - 1.37) + 1.33	0.999
Monitor 4	Turns per 5 mins = (Activity 4 - 1.00) + 1.26	1.000
Monitor 5	Turns per 5 mins = (Activity 5 - 1.75) + 1.25	0.999
Monitor 6	Turns per 5 mins = (Activity 6 + 0.50) + 1.27	1.000

These regression manipulations were incorporated into a macro and applied to the raw data generated by subjects wearing the monitor. This converted mV activity readings into absolute, equisensitive readings in Turns.

The results for this study were gathered all on one day. Interestingly, when the study was repeated a day later, the scores that each monitor generated were all consistently lower. That is, for any one monitor, all scores for each number of turns had decreased by the same factor (i.e. the slope of the line remained the same but the y-intercept had decreased). Based on this finding it was hypothesised that battery drainage may be affecting activity scores, although this had not been observed for either temperature or humidity.

A test was performed in which all monitors received new batteries and were then activity-tested over an eighty hour period; this being the maximum period a subject might wear the monitor. A discrete number of turns were made, as in the previous study, however this occurred 14 separate times during the 80 hour period. That is, readings were taken at 0, 3, 7, 10, 15.5, 20, 24, 29, 41, 46, 51, 56.5, 68.5 and 78.5 hours.

The results from this study showed that activity scores dropped for each monitor over this period (by up to as much as 20% of the first reading). Battery drainage was postulated to be the contributing factor. Fig. 2.15 shows the effects of battery drainage on activity where 100% on the Y-axis represents the initial battery charge at first reading.

Fig. 2.15

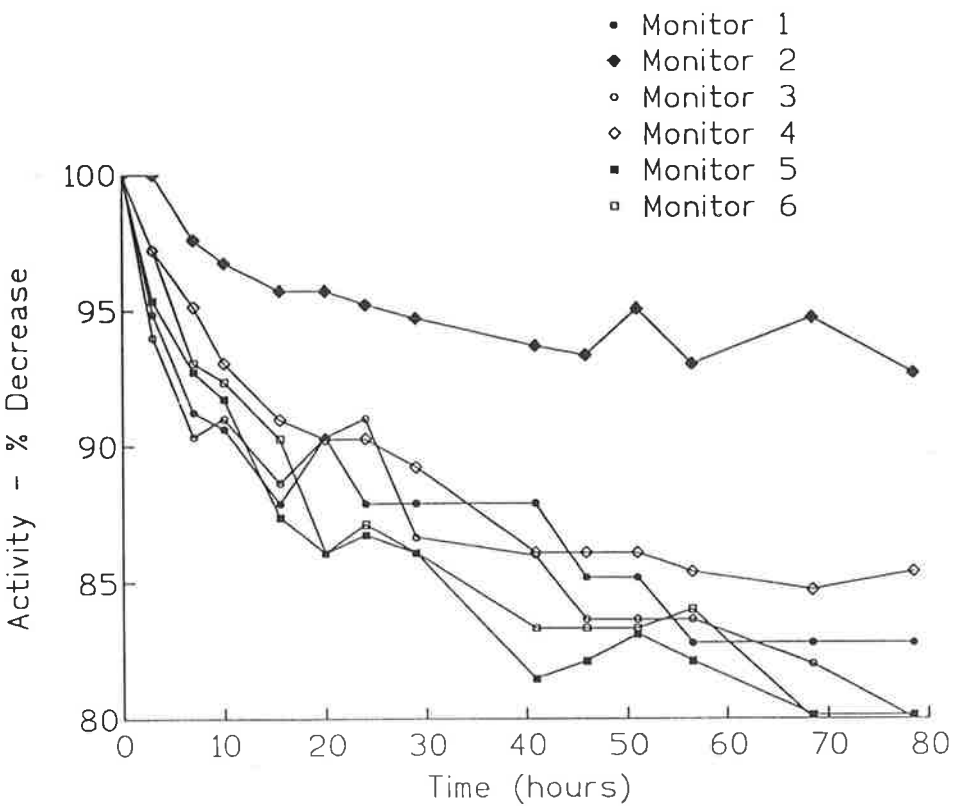


Fig. 2.15 Graph showing % decrease in activity from time zero, against time in hours for all monitors

The putative battery drainage problem could not be rectified by a physical adjustment of the monitors. Therefore, the drop in mV activity over time had to be incorporated into the macro-equation in order to calculate an accurate final activity score of turns per five minutes. The first step was to derive a mathematical function that would produce a linear relationship between activity in mV, and time. It was found that by plotting activity in mV against the log of time, a highly correlated linear relationship resulted (eg. monitor 6, Fig. 2.16). This was the case for all monitors with the exception of monitor 2, which showed greater correlation when mV activity was plotted against the inverse of time squared (i.e. $1+\{time^2\}$). These equations and correlations are shown in Table 2.5. However, the equations are based only on data from 3 to 78.5 hour readings (n=13), because the rate of change was most rapid in the first few hours following battery replacement. Correlations were higher if the first time point (0 hours) was excluded. Accordingly, data collection from subjects did not commence until monitors had been running for 2 or 3 hours.

Fig. 2.16

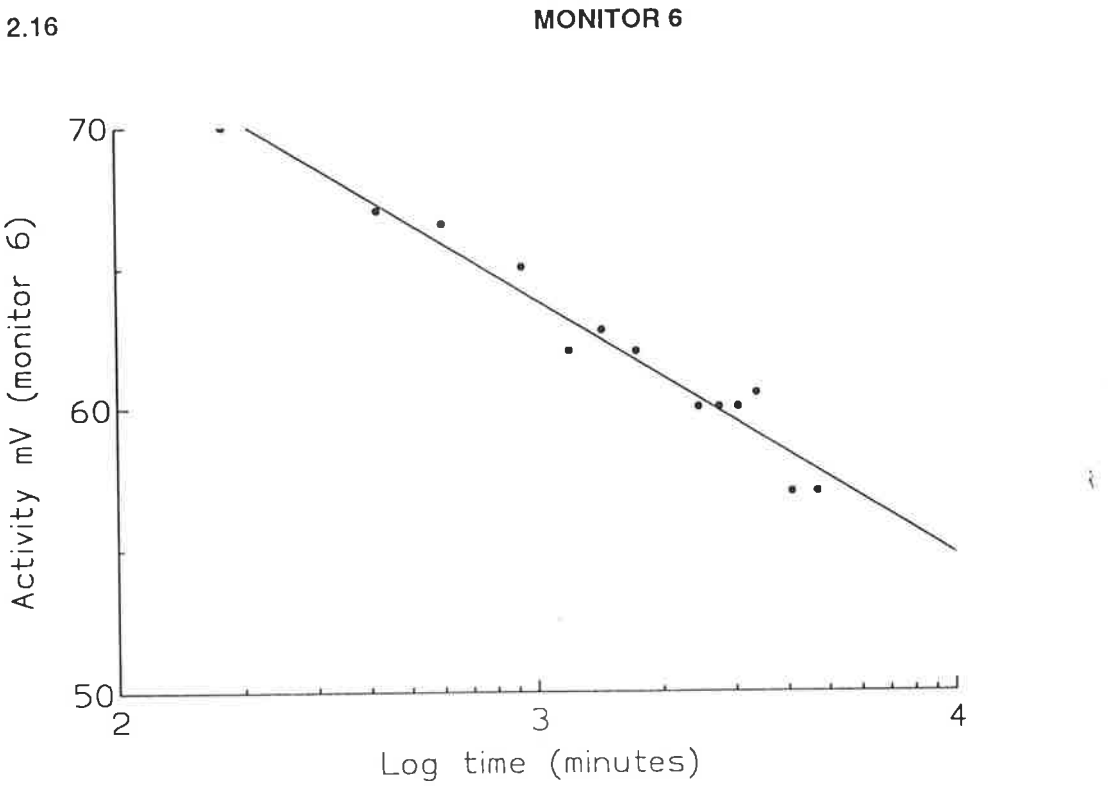


Fig. 2.16 Graph showing activity in mV against log time in minutes for monitor 6

Table 2.5

Formulae and correlation values for activity in mV (*y*-axis) against log time in minutes (*x*-axis) for all monitors

Monitor No.	Formula	Correlation (r)
Monitor 1	Log time = (Activity 1 - 94.31) + -6.92	-0.953
Monitor 2	Inv. time^2 = (Activity 2 - 137.79) + 259.52	+0.987
Monitor 3	Log time = (Activity 3 - 86.89) + -6.86	-0.943
Monitor 4	Log time = (Activity 4 - 85.94) + -6.84	-0.988
Monitor 5	Log time = (Activity 5 - 92.41) + -8.71	-0.981
Monitor 6	Log time = (Activity 6 - 90.74) + -8.96	-0.975

NB. *x*-axis for monitor 2 is the inverse of time squared (see text for explanation).

Following the generation of a mathematical relationship between time and activity in mV (Fig 2.16, Table 2.5) the number of turns per five minutes was calculated by incorporating this information with the now known relationship between turns and activity in mV. For example, monitor 6;

it is known from equation (xi) that,

$$Turns = \frac{Activity6 - c}{m} \qquad (xii)$$

and from Table 4, $$Turns = \frac{Activity6 - c_1}{1.27} \qquad (xiii)$$

where, c_1 is the y-intercept that changes over time, but is constant for any one point of time. based on equation (i), it is known from Fig. 2.16 and Table 2.5 that;

$$Activity6 = 8.96 \times \log_{time} + c_2 \qquad (xiv)$$

where c_2 is a y-intercept and a constant. However, Activity 6 in the above equation is essentially the changing y-intercept, i.e. equal to c_1.

thus, $$c_1 = -8.96 \times \log_{time} + c_2 \qquad (xv)$$

and inserting equation (xv) into equation (xiii),

$$Turns = \frac{Activity6 - \left(-8.96 \times \log_{time}\right) + c_2}{1.27} \qquad (xvi)$$

This equation has been incorporated into the macro for all monitors, generating activity scores in "Turns" corrected for battery drainage for any point in time (see appendices).

2.4 Tremor

Validation and calibration of the accelerometers for assessment of tremor proved to be difficult both in the clinical and laboratory setting.

Before laboratory testing occurred, the monitor was pilot tested in the clinic by placement on subjects who had a clinically obvious tremor. Results were compared with matched controls with no

obvious tremor, who also wore the monitor. The results from this pilot showed no difference in the tremor recorded between subjects and controls. Further inspection of these results revealed that the amount of activity generated by the wearer seemed to affect the tremor score recorded. That is, those who were more active had a higher tremor score, regardless of visually apparent tremor. The possible reasons for this are as follows;

- signal meshing,
- band pass filtering,
- 'heel-strike'

Since the monitor is an ambulatory device, tremor measurement occurs around a point that is not fixed; i.e. the wearer's wrist, which is also subject to movements brought about by any activity. This set-up is somewhat problematic, since some components of activity may have the same acceleration as tremor. Simply, waveforms of activity, and waveforms of tremor, present at closely occurring frequencies (1-5 Hz and 6-10 Hz respectively). The outcome of this may be signal-meshing, resulting in the swamping of one signal by another. Wave forms with lower frequencies have a longer wavelength, and have the potential to encompass co-occurring waveforms of higher frequencies with a shorter wavelength. Accordingly, activity waveforms, with their lower frequencies, may swamp tremor waveforms with their higher frequencies and shorter wavelengths.

Meshing is further complicated by band pass filtering. The nature of this type of filtering is that frequencies at the edge of the filter may be also be included, albeit to a lesser degree. For example, band pass filtering of tremor waveforms will include frequencies consisting predominantly of 6-10 Hz, but also frequencies occurring at 4 and 5 Hz, and 11 and 12 Hz. Thus, there is some overlap into the range of frequencies that include activity in band pass filtering of tremor waveforms.

An additional factor that compounds the problem of signal swamping is that of 'heel strike'. Each step, taken by the wearer of the monitor, generates enough activity to swamp the tremor signal (Michael Nordstrum, Department of Physiology, University of Adelaide, private communication, 1995).

The clinical observation that activity affects tremor measurement was confirmed in the laboratory. This was noted while validation studies for the activity channel were executed. A high activity score, generated by laterally rotating the sensor unit at a rate of one turn per second, also produced a high tremor score.

Attempts were made to rectify signal meshing by increasing the amplitude threshold of tremor acceptable for storage. This did not resolve the problem as increasing the threshold decreased the sensitivity of the tremor channel, resulting in only very violent tremor being recorded. In summary, there were problems in finding a threshold that was sensitive enough to record tremor, but insensitive to most general activity.

However, this is an inherent problem in this method of tremor measurement. As mentioned in the introduction of this chapter, input signals were band pass filtered at a frequency of 6-10 Hz, which is the frequency at which most tremor occurs. Those signals, or wave forms, that had an amplitude above a certain height were counted per consecutive five minute periods. Thus, the more counts per period, the more intense the tremor during that time. This method of tremor assessment gives no indication of the amplitude, or intensity, of signals, except to say they reach, or extend, a fixed threshold. A survey of the literature revealed that the most popular method of assessing tremor is by spectral wave analysis (Friedlander, 1956; Carrie, 1965; Growdon et al., 1975; Lefebvre-D'Armour et al., 1978; Zilm et al., 1979; Brown et al., 1982; Pimlott et al., 1983; Koller et al., 1985; Elble, 1986; Koller et al., 1986; Martinelli, 1986; Neiman et al., 1990). Spectral wave analysis provides an indication of the most common frequency of wave form, by estimating the energy in frequency bands occurring in a finite set of data samples. This process utilises Fourier transformation, and is a useful tool in pharmacological and physiological research (Akselrod, 1988; Gootman & Sica, 1994; Grant & McDonnell, 1993).

Spectral analysis provides the separation of different waveforms, and has the potential to distinguish between waveforms of different frequencies. However, spectral analysis is less workable on waveforms that occur with similar frequency, such as those of activity and tremor. Moreover, tremor and activity often occur simultaneously in a tremulous person, so there is no discrete time of the day where only one is present.

A popular method of managing this problem is to record tremor around a fixed point. That is, to secure the subject's wrist or finger so there is as little other movement as possible. This method has been used by many researchers (Friedlander, 1956; Carrie, 1965; Growdon et al., 1975; Lefebvre-D'Armour et al., 1978; Zilm et al., 1979; Brown et al., 1982; Neiman et al., 1983; Koller et al., 1985; Elble, 1986; Koller et al., 1986; Martinelli, 1986; Neiman et al., 1990) but is not practicable for tremor assessment in ambulatory subjects.

Interestingly, one research group has published a short communication on an ambulatory monitoring system for tremor using spectral wave analysis (Pimlott et al., 1983). The paper is based on a small study of patients with parkinsonian and essential tremor. However, a search of the literature for a follow-up to this study failed to yield any further information on this method.

In summary, there are two major problems with this method of tremor assessment, activity signals swamping tremor signals, and inability to employ spectral wave analysis to extract tremor waveforms. Accordingly, there was little justification to continue with this measure and it was not included in the assessment of alcohol withdrawal parameters.

2.5 Conclusion

In conclusion, validation and calibration was carried out successfully for three of the four channels of the monitor. These were temperature, sweating and activity. Macro-equations were generated based on these pre-clinical studies and were applied to the raw data generated from subjects wearing the monitor. This resulted in expression of parameters in absolute units as opposed to mV. In addition, results were equisensitive between monitors, and also over a range of values.

Tremor assessment was not included in the measure of withdrawal parameters. This was due to the difficulty of assessing tremor in the ambulatory subject. Further work is required on this area, but is beyond the scope of this thesis.

Despite forfeiting the tremor channel, the ambulatory monitor is an extremely useful tool in the study of alcohol withdrawal. Moreover, these validation/calibration studies show that the results generated can be accepted with confidence.

CHAPTER 3

3. GENERAL METHODOLOGY

3.1 Subjects

All subjects were volunteer patients from a medically based, public detoxification hospital in South Australia, who were admitted to detoxify from alcohol. The subjects remained as inpatients of the hospital for about six days, or until their detoxification was deemed complete by medical staff. During their stay, some subjects received one-to-one counselling and support therapy from nursing staff, as part of their inpatient treatment. All subjects had medical, social and drinking histories documented by staff, as part of their medical assessment.

Patients were administered a range of medications if withdrawal symptoms were too unpleasant or potentially fatal. Pharmacotherapy included daily multivitamins and thiamine. Paracetamol, anti-nauseants and anti-diarrhoeals were administered as requested by patients, and the minor tranquillisers, diazepam and temazepam, were given when CIWA-Ar scores exceeded a pre-set threshold. Sometimes temazepam was given at night, if patients reported poor sleep and requested further medication. In addition, patients continued taking any medications they had been prescribed before entering the detoxification hospital, or any further medication thought necessary by the unit's medical officer. Blood samples were taken routinely from patients by staff, and serology, liver function tests and hepatitis checks were performed by the Institute of Medical and Veterinary Science.

The inclusion criteria for the study were as follows:

- dependence on alcohol (as assessed by medical staff);
- intention to withdraw from alcohol only, and not any other medication (eg. benzodiazepines, opiates);
- aged between 18 and 65 years;
- no concomitant serious, life-threatening illness;
- not pregnant;
- scoring 5 or greater on the CIWA-Ar during their first day in detoxification;

- not having an inappropriate physical condition for wearing the monitor (eg. a broken arm or walking stick);
- living within a one hour drive from Adelaide, for potential follow-up (clients with no fixed address were also excluded if they had no plans for accommodation following detoxification).

3.2 Research Tools

3.2.1 The Ambulatory Monitor

Physical symptoms were assessed by the ambulatory monitor, which provided objective recordings of several physiological parameters affected by alcohol withdrawal. These were skin temperature, sweating and activity. Activity was indicative of daytime restlessness and agitation, and sleep disturbances during the night. The monitor was programmed to take readings of these parameters every 5 minutes, over a period of 24 hours.

3.2.2 Psychological Tests and Health Survey Instrument

Health status and psychological aspects of withdrawal were assessed using four standardised questionnaires: SF-36 (health); BDI (depression); STAI (anxiety); and POMS (general mood disturbance). A description of each questionnaire is given below.

3.2.2.1 Beck Depression Inventory (BDI) The Beck Depression Inventory (BDI) (Beck et al., 1979), is a widely accepted instrument in clinical psychology and psychiatry for assessing the severity of depression in adolescents, adults and psychiatric patients (Piotrowski et al., 1985; Steer et al., 1985).

The questionnaire consists of 21 items, each with 4 statements. The patients selected which statement, or statements, best described the way he or she had been feeling over the last 24 hours. This reflected the patient's current "state" depression, (as opposed to "trait" depression). BDI Item intensity is rated between 0 and 3, where 0 indicates normal functioning and 3 indicates severely disrupted functioning.

Overall test scores are calculated by summing the statement scores, the end result being a score between 0 and 63. An overall score between 0 and 9 is considered asymptomatic. A score of between 10 and 18 indicates mild to moderate depression, while a score of 19 to 29 indicates moderate to severe depression. Scores of 30 and above indicate extreme depression (Beck & Beamesderfer, 1974).

The symptoms and attitudes assessed by the BDI are: (1) Mood; (2) Pessimism; (3) Sense of failure; (4) Self-dissatisfaction; (5) Guilt; (6) Punishment; (7) Self-dislike; (8) Self-accusations; (9) Suicidal ideas; (10) Crying; (11) Irritability; (12) Social withdrawal; (13) Indecisiveness; (14) Body image change; (15) Work difficulty; (16) Insomnia; (17) Fatigability; (18) Loss of appetite; (19) Weight loss; (20) Somatic preoccupation; and (21) Loss of libido.

3.2.2.2 State Trait Anxiety Inventory (STAI) The State Trait Anxiety Inventory (STAI), developed by Spielberger and colleagues, is used widely in both research and clinical practice to assess the severity of both "state" and "trait" anxiety in adolescents, adults and psychiatric populations (Buros, 1978; Smith & Lay, 1974; Spielberger et al., 1970; Spielberger, 1989).

The questionnaire consists of two major parts, one that assesses "trait" anxiety, and the other, "state" anxiety. Only "state" anxiety was of interest in this study. The level of "state" anxiety was determined by recording the subject's response to 20 phrases that relate to anxious thoughts, feelings and behaviour. Subjects rate their response to each phrase by selecting one of four statements which best describe the way they have been feeling over the last 24 hours (ie. 'not at all', 'somewhat', 'moderately so', 'very much so'). These are given a rating of between 1 and 4, and summed at the end of the test to give a final score.

The maximum score for "state" anxiety is 80, and an asymptomatic score for normal adults is considered to be 35.

3.2.2.3 Profile Of Mood States (POMS) The Profile Of Mood States (POMS) provides an assessment of mood for both clinical and research purposes in normal and psychiatric populations (McNair et al., 1971; Buros, 1978).

The questionnaire comprises 65 adjectives that describe feelings that people may experience. Subjects rated how they felt over the last 24 hours for each adjective, by selecting the most appropriate of one of five statements (ie. 'not at all', 'a little', 'moderately', 'quite a bit', 'extremely'). The phrases were scored between 0 and 4, where "not at all" received the lowest score of 0, and "extremely" received the highest score of 4.

The POMS categorises mood into six identifiable affective states, where each adjective on the questionnaire falls into one of the six independent groups. The groups are: tension-anxiety; depression-dejection; anger-hostility; vigour-activity; fatigue-inertia; and confusion-bewilderment. Each mood factor is comprised of a group of between 7 and 15 adjectives, and scores are obtained for each mood factor by summing the responses for the adjectives defining the factor. Normal scores for each affective state are as follows: tension-anxiety = 12.1, depression-dejection = 12.5, anger-hostility = 8.1, vigour-activity = 11.4, fatigue-inertia = 6.4, confusion-bewilderment = 7.8.

3.2.2.4 Short Form 36 question health survey (SF-36)Health status was assessed by the Short Form Health Survey (SF-36) which is a relatively new measure of health assessment. It was developed as part of a medical outcomes study, and is a valid and reliable means of assessing health in patient populations (McHorney et al., 1993; Tarlov et al., 1989; Stewart & Ware, 1992; McCallum, 1995). Subjects in this study were asked about their health over the last two days.

The questionnaire comprises 36 items, each of which is associated with one of nine possible aspects of health. These are described below, along with their respective norms (Ware & Sherbourne, 1992):

- Physical Functioning - extent to which health limits physical activities such as self-care, walking, climbing stairs, bending, lifting, and moderate and vigorous activities (norm = 85.4);
- Physical Role Functioning - extent to which physical health interferes with work or other daily activities, including accomplishing less than wanted, experiencing limitations in the kinds of activities one was able to do, or having difficulty in completing tasks (80.2);

- Emotional Role Functioning - extent to which emotional problems interfere with work or other daily activities, including decreased time spent, accomplishing less than wanted, and not working as carefully as usual (norm = 87.5);
- Social Functioning - extent to which physical health or emotional problems interfere with normal social activities (norm = 88.2);
- Bodily Pain - intensity of pain and effect of pain on normal work, both inside and outside the home (norm = 77.2);
- Mental Health - general mental health, including depression, anxiety, behavioural-emotional control, general positive affect (norm =78.7);
- Vitality - feeling energetic and full of pep versus tired and worn out (norm =64.0);
- General Health Perceptions - personal evaluations of health, including current health, health outlook, resistance to illness (norm = 73.2);
- Change in health - evaluation of current health compared with one year ago.

SF-36 items and scales are scored so that a higher score indicates a healthier state. The item, 'Change in health' was not investigated in this study.

3.2.3 Biological markers

Serum carbohydrate deficient transferrin levels (CDT) were determined in all subjects by the investigator, at the laboratories of the Department of Clinical and Experimental Pharmacology at the University of Adelaide. CDT recently has been isolated as a specific and sensitive marker of hazardous alcohol intake (Stibler, 1991). Transferrin appears abnormal in the serum after regular intake of above 60g of ethanol per day, for at least one week, and normalises slowly during abstinence with a half life of approximately 15 days (Behrens et al., 1988). CDT as a marker has a sensitivity of 82% and a specificity of 97%, and levels vary depending on the degree of alcohol consumption. Assessment of CDT levels involves analysis of blood-serum using competitive enzyme radio-immunoassay.

Levels of gamma glutamyl transferase (GGT) and erythrocyte mean corpuscular volume (MCV) were determined by the Institute of Medical and Veterinary Science. These assays were

performed routinely for all inpatients of the detoxification hospital. GGT and MCV are markers of hazardous alcohol intake, while GGT is also a marker of liver disease.

3.2.4 Patient casenotes

Each inpatient at the detoxification unit had a case history taken by staff, with the information collated in casenotes. Each casenote followed a set format, and was administered in several parts by at least one medical officer, and two nursing staff. Casenotes contained information about the patient's current and past medical conditions, sociodemographic status, details about the client's inpatient stay including daily alcohol withdrawal severity (as assessed by the CIWA-Ar) and benzodiazepine administration during acute withdrawal. Casenotes also contained information about the drinking history of the client, which was collected by staff using the Quantity-Frequency (Q-F) approach, to establish how many standard drinks of alcohol were being consumed on a daily basis. The Q-F approach, developed by Cahalan and colleagues in 1967, is based on self-report of drinking by the client, in response to prompting by the staff member in an empathetic and non-threatening way. As mentioned above, more than one staff member took each client's drinking history, serving to corroborate the information that had been given by the client. Compared with other methods of collecting drinking history, for example, the Sobells' Timeline Followback method (Sobell & Sobell, 1992), the Quantity-Frequency method is a rapid and flexible means of assessing drinking history. While the Timeline Followback method has been demonstrated to have a high test-retest reliability, it can take at least 30 minutes to administer, which is not always feasible in a busy treatment setting (Dawe & Mattick, 1997).

The information that was extracted from casenotes for this study was as follows:

- Years - the total number of years the patient has been a heavy consumer of alcohol;
- Recent bout - the time period, in months, over which the client has been heavily consuming alcohol since their last period of abstinence (this is important because drinking histories are often punctuated with periods of abstinence);
- Intake - the average amount of alcohol (g/day) that the patient has consumed during their most recent bout. If the patient gave a daily range (eg. 2 - 4L of white wine/day), then the average was taken (ie. 3L white wine/day);

- Number of previous withdrawals - cumulative number of withdrawals at this detoxification unit or any other formal hospital/institution/prison. Also includes any home detoxification that the patient may have mentioned;
- History of seizures - whether the patient is prone to seizures upon cessation of drinking;
- Medical conditions - the number of concurrent medical conditions that the patient is experiencing during detoxification. This includes mental health conditions such as anxiety, depression, psychosis and also includes any previous condition that may weaken the patient's state (eg. cardiac arrest, kidney failure);
- Current prescribed drugs - the number of prescribed drugs that the patient is currently using in accordance with their physician's instructions;
- Current non-prescribed drugs - this includes tobacco and illicit drugs (eg. cannabis, heroin, street amphetamines), but not caffeine or alcohol. It also may include drugs that are usually prescribed, but are being abused by the patient, and not being used in accordance with their physician's instructions (eg. benzodiazepines, some opiates);
- Liver function enzymes and putative markers of hazardous alcohol intake, ie:
    - MCV - Mean Corpuscular Volume
    - GGT – Gamma Glutamyl Transferase
- Partner – whether the patient has a partner, including spouse, defacto or steady boyfriend/girlfriend;
- Employment – whether the patient has paid employment;
- Accommodation – patient's current residential status. The categories included 'no fixed address', 'boarding', 'renting', and 'lives in own home';

3.3 Procedure

3.3.1 The ambulatory monitor, questionnaires and casenotes

The measures described in the casenote section above were collected by staff from 47 inpatients experiencing alcohol withdrawal at the detoxification unit. Subjects fitting the selection criteria had the study explained to them, and agreement to participate in the study was confirmed by

signing a consent form in the presence of a witness. Subjects were paid $20 on completion of the inpatient study.

Subjects wore the monitor for 72 consecutive hours, commencing at 12 noon on their second day of abstinence, until 12 noon on their fifth day of abstinence. A patient's second day of abstinence usually corresponded with their second day at the detoxification unit (ie. their last drink was the day before they came in to detoxify). Subjects were administered the four questionnaires (BDI, STAI, POMS & SF-36) on their first day of wearing the monitor (day 1). All questionnaires, except the SF-36, asked subjects to reflect on how they had felt over the last 24 hours. The SF-36 inquired about their health over the previous 2 days. The BDI, STAI and POMS were also administered on patient's fifth day of abstinence (day 4 of wearing the monitor). The SF-36 was not administered on the fifth day of abstinence since it is thought that any changes to health would be negligible. Moreover, many subjects had difficulty with the length of the SF-36. Three of the 47 subjects chose not to participate in the monitor part of the study, but were administered the questionnaires. In addition, not all subjects completed all questionnaires, and some subjects did not complete any questionnaires at all, but only wore the monitor. This was because these inpatients were either too fatigued, experiencing withdrawal which was too severe to concentrate, or appeared to be too cognitively impaired to completely understand the questions.

The same 47 subjects were re-assessed at two weeks following their last drink. Assessment involved wearing the monitor for 36 consecutive hours, commencing at 9pm and ending at 9am, two nights and one day later. Subjects were also administered the same four questionnaires (BDI, STAI, POMS & SF-36). Subjects were re-assessed using the same measures at six and ten weeks after their last drink, and were paid $20 for every follow-up period they completed. If subjects relapsed during the ten week period, the time to relapse was noted in days, and follow-up ceased (see section *3.4.1* for a more detailed description of collection of relapse data).

3.3.2 Assessment of CDT levels

Levels of CDT were determined by the investigator of this study. Five millilitres of blood were taken from 38 of the 47 study patients on their third or fourth day at the detoxification unit. The blood

was left to clot at room temperature, and then centrifuged for 10 minutes at 1000-1300 g. The serum was transferred to a second container, and frozen at -80°C until all samples had been collected.

Levels of CDT were determined by radio-immunoassay (RIA) using a CDTect™ kit, commercially available from *Pharmacia* (CV ≤ 12%, measuring range 5-200 U/L, recovery between 98% - 103%, detection limit < 2.0 U/L). The kit included 50 microcolumns, duplicate standards (0, 5, 20, 50, 100 and 300 U/l of CDT), duplicate controls (≈13-23 U/l) and duplicate totals (1) in order to generate a standard curve and to ascertain test stability. Most serum sample values of CDT were determined in singlicate, however 8 were performed in duplicate. A summary of the methodology for this procedure, as provided by *Pharmacia*, is outlined below.

STEP 1. Equilibration of microcolumns. Microcolumns were provided by the kit to separate the serum samples into different isoforms. The columns were prepared by hydration with about 2ml of elution buffer for approximately two hours. Following this step, the microcolumns were ready for use.

STEP 2. Iron saturation of samples. Fifty microlitres of serum sample was placed in a test tube with 200µl of Ferric citrate solution and 1.0 ml of elution buffer, and thoroughly mixed.

STEP 3. Sample separation. Five hundred microlitres of the above sample was pipetted directly onto the equilibrated microcolumns, and collected at the bottom of the microcolumn using another container.

STEP 4. RIA Procedure. The unknown samples, 500µl of control solution, and 500µl of standard, were each mixed with 25µl of radio-labelled transferrin (^{125}I), 50µl of antibody and 2ml of well-shaken decanting suspension. Totals were simply 50µl of the radio-labelled transferrin. All samples were incubated for one hour at room temperature, and then centrifuged for 10 minutes at 1500xg. Tubes were then decanted, leaving radioactive precipitate in the bottom of the tube, and placed on paper to absorb any remaining moisture. Levels of radioactivity in cpm were determined by placing samples in a gamma counter for a one minute period.

STEP 5. Calculation of results. Test stability was determined by expressing mean counts of the zero standard against mean counts of the total activity as a percentage. According to CDTect™ criteria, greater than 45% suggested that the reagents in the test procedure were performing correctly.

Values for standards, controls and unknowns were expressed as a percentage of mean counts of the zero standard (% activity bound). A standard curve was generated by plotting standard CDT

values (0, 5, 20, 50, 100, 300 U/l) against concurrent percent activity bound values, and unknown levels of CDT were determined from the standard curve.

3.4 Statistical analysis

A biomedical statistician was consulted while the experiments were being planned, to ensure experiments had been suitably designed for optimal data collection and statistical analysis. This included the determination of appropriate sample sizes before the data was actually collected, to guarantee adequate power (60%-80%) and to minimise the possibility of making Type II errors associated with too little power. Following data collection, the statistician and the statistician's resources were utilised to analyse the data. The investigator played an integral role in determining the both the design of the experiments and the nature of the comparisons. However, because the data set was so large, the data was analysed using the statistician's computer, software and resources, which were specially designed to manage large data sets and the type of analysis required.

3.4.1 Aim 1 – Chapter 4

In order to investigate the first major aim of this thesis, that is, characterisation of withdrawal severity and duration, monitor data from 30 of the 47 subjects were compared with monitor data from 30 sedentary controls that were not dependent on alcohol, or experiencing alcohol withdrawal. The 30 subjects who were chosen for this phase of the study included all those who remained abstinent until at least day 14 (ie. n = 25), in order to maximise sample numbers on days 14, 42 and 70. The remaining 5 were randomly selected from the remaining 22 subjects. The results from this phase of the study are shown in Chapter 4, '*Characterisation of intensity and duration of alcohol withdrawal symptomatology*'.

Controls wore the monitor for one session only lasting 36 hours (2 nights and 1 day), and were paid $20 as compensation. Criteria for the selection of controls included being matched to subjects with respect to age, sex and approximate body size. Each withdrawal subject had one matched control only, who remained their comparative match for the entirety of the study. Similarly, no control subject was matched to more than one withdrawal subject. Controls also wore the monitor in the same season as their matched withdrawal subject, in order to reduce any influence of climate. In addition, controls were asked to abstain from alcohol consumption while wearing the monitor.

There is some evidence that when sleep is measured (in any subjects), the recordings on the first night reveal heightened sleep restlessness, compared with sleep restlessness on subsequent nights (Drew Dawson, The Queen Elizabeth Hospital, South Australia, private communication, 1994). Accordingly, during the inpatient period, the withdrawal subjects' first night of wearing the monitor was compared with the control subjects' first night of wearing the monitor. The control subjects' second night was used as a comparison for the withdrawal subjects' second and third night. The control subjects only wore the monitor for long enough to collect one set of 'daytime' readings, which were used as a comparison for all 'daytime' readings of withdrawal subjects.

During the follow-up period, the withdrawal subjects were asked to wear the monitor for two nights and one day, but only data from the second night was used for this study, since first night readings were more variable. These data were compared with the control subjects' second night of wearing the monitor. While data collected on the first night was not used for comparison during the outpatient period, it was utilised during the inpatient period. This is because withdrawal subjects were experiencing major physiological changes in the first few days of abstinence, which were deemed important for this investigation. It is recognised that in this study, sleep disturbances of withdrawal subjects may have been exacerbated on the first night of wearing the monitor, although data were compared with those of control subjects who were also wearing the monitor for the first night.

In ideal study conditions, control subjects would have worn the monitor for exactly the same period as the withdrawal subjects. However, control subjects did not appear to be as compliant as the withdrawal subjects. That is, none of the control subjects wished to wear the monitor for longer than the minimum period of 36 hours, thus the same control monitor data was used at each time point of the study, even though the withdrawal data varied between time points. It is worth noting that in Chapter 4, control subjects were sometimes referred to as 'inpatient' controls or 'outpatient' controls. This does not mean that the controls were inpatients or outpatients, but that they were specifically matched with withdrawal subjects who were inpatients and outpatients. Accordingly, average control values did not remain the same for each day, since some withdrawal subjects relapsed. Thus, those control subjects who were matched with the subjects who relapsed at some point over the seventy days, were no longer included in the graphical representation or analysis of the data.

While monitor recordings were collected from control subjects to compare the physical response of withdrawal subjects, control values of psychological and health status were ascertained from the literature associated with each test (ie. BDI, STAI, POMS and SF-36).

There were 288 readings per day for each monitor variable (skin temperature, sweating, activity). These were compressed into hourly readings (twenty four per day) resulting in a formalised representation of the diurnal rhythms of the above parameters for both withdrawal and control subjects. Hourly data from withdrawal subjects were compared with hourly data from control subjects for all days (ie 24 readings per day on days 1, 2, 3, 14, 42 and 70). These were analysed using a mixed model analysis of variance, which is a statistical procedure similar to an analysis of variance for repeated measures, and provides an overall assessment of statistical difference between the two diurnal rhythms (control and experimental). However, a mixed model analysis of variance is able to cope with changes in sample size, as would have been the case due to relapse (an attrition in sample size over time), and also occasional missing data points, for example a subject taking the monitor off for half an hour or so to take a shower. While the mixed model analysis of variance provided an overall difference between diurnal rhythms, specific hourly times of significance difference between the diurnal rhythms of control subjects and withdrawal subjects was further analysed using least squared means procedure, followed by a post-hoc test (Newman-Keuls).

The 288 readings were also compressed into one mean value per twenty four hour period, for all days (day 1, 2, 3, 14, 42 and 70). Comparisons were also made between the average value over a twenty four hour period between controls and experimental subjects, on all days. As with the diurnal data, 24 hour average data was analysed using a mixed model analysis of variance.

The data that was collected from psychological and health status tests from withdrawal subjects was collated into a daily score (Days 1, 4, 14, 42 and 70 for the BDI, STAI and POMS, and Days 1, 14, 42 and 70 for the SF-36). These daily scores were compared with the norms provided for each test, and the same norm was used on all days of comparison. The POMS and the SF-36 were compared with norm values for each of their components (ie six POMS components and eight SF-36 components). As with the monitor data, statistical analysis was performed using a mixed model analysis of variance to assess overall difference between scores over seventy days and the norm score. Accordingly, a least squared means procedure and Newman-Keuls post-hoc test was used to

determine significant differences between experimental subjects' scores and norm values on specific days.

3.4.2 Aim 2 – Chapter 5 & Chapter 6

The second major aim of this thesis concerned determination of predictors of withdrawal severity. The second phase of this study utilised data from all 47 subjects, however was separated into two components (Chapters 5 and 6). The first part (Chapter 5), entailed using subject characteristics as predictors of withdrawal severity including, subjects' drinking history (years, recent bout, intake), predisposition towards kindling (number of previous withdrawal episodes, history of seizures), and concomitant complications during withdrawal, (number of concurrent medical conditions, number of prescribed medications currently used, and number of non-prescribed drugs currently used). The second part (Chapter 6) investigated biological predictors of withdrawal severity. Biological parameters included mean corpuscular volume (MCV), the liver function enzyme gamma-glutamyl transferase (GGT), as well as the newer marker of hazardous alcohol intake, carbohydrate deficient transferrin (CDT).

Principal component analysis (PCA) was used to combine twenty one measures of withdrawal severity, into one Total Global Principal Component. This consisted of 16 measures of psychiatric and health disturbances, and 5 measures of physical parameters of withdrawal severity. The Total Global score, or end product derived from PCA was used as an outcome measure to determine both biological and other predictors of acute withdrawal severity (that is, in the first five days of abstinence).

The psychiatric and health disturbances incorporated into the global withdrawal score were: average BDI score during the first two administrations (days 1 and 4), average STAI score during the first two administrations (days 1 and 4), average POMS score for each dimension (D, T, C, F, A, V) during the first two administrations (days 1 and 4), and SF-36 scores during the first administration for all eight dimensions (PF, SF, PRF, ERF, BP, MH, GH, V).

The physiological, or physical withdrawal disturbances were selected on the basis of when they were most intense during the inpatient period (as illustrated in Chapter 4). Accordingly, the following five measures were included: average sleep activity over the first three nights, average skin temperature over the first three days between 2pm and 4pm, average maximum sweating achieved

over first three days, average sweating over first three days between 2am and 9am, and average activity over the first three days at 1pm.

Principal component analysis is a multivariate technique used to examine the relationship among the above quantitative variables. From the data set with 21 numeric values (for example, In the case of the Total Global Principal Component, 16 psychiatric and health parameters and 5 physical parameters), 21 principal components are computed. Each principal component is a linear combination of the 21 variables incorporated, with coefficients equal to the eigenvectors of the correlation. Eigenvectors are simply the coefficients or numerical values within a matrix, that have a direction (either positive or negative, hence termed a vector). The principal components are sorted by descending order of the eigenvalues, which are equal to the variances of the components, but are all jointly uncorrelated with each other. PCA was used in this instance to summarise the data available on different aspects of withdrawal, and to detect the most linear relationship amongst the variables. In this case the linear combination was termed the Total Global Principal Component.

For this phase of the study (Chapter 5 & Chapter 6), two Global Principal Components were determined. The first, as mentioned above, incorporated both physical and psychiatric/health measures of acute withdrawal (termed Total Global Principal Component). This study was also concerned with the physical component of withdrawal, since physical withdrawal is often the target of acute treatment. For this reason, an acute Physical Global Principal Component was also determined which incorporated only the physical aspects of withdrawal.

In Chapter 5, univariate analysis was used to determine which subject characteristics significantly predicted total global withdrawal severity and physical global withdrawal severity. In addition, variables that had a probability value of $p \leq 0.15$, were incorporated into a multivariate analysis to determine the effect of each variable in the presence of other potentially significant variables. Similarly, univariate and multivariate analysis was employed in Chapter 6 to determine the predictive value of GGT, MCV and CDT to affect total global withdrawal severity and physical global withdrawal severity. However, the multivariate analysis in Chapter 6 also incorporated variables from Chapter 5 that were $p \leq 0.15$, in order to increase the number of variables included in the multivariate analysis, and determine the relationship between all potential predictors of withdrawal severity. The incorporation of potential predictor variables (determined through univariate analysis) that have a

probability value of greater than 0.05 (eg. $p \leq 0.15$) is an acceptable and standard procedure in multivariate analysis (Armitage and Berry, 1994). This is because factors that *approach* significance, but are not quite $p < 0.05$ in a univariate analysis, may become statistically significant in a multivariate analysis, in which the effects of other factors are taken into account. For example, a variable that is $p = 0.10$ in a univariate analysis but not strictly statistically significant, may actually be $p \leq 0.05$ in a multivariate analysis and account for a significant proportion of the variance.

3.4.1 Aim 3 – Chapter 7

The third major aim of this thesis concerned determination of predictors of relapse using univariate and multivariate survival analysis. Survival analysis is used when the variable of direct interest is the length of time (survival) that elapses before a certain event (relapse) occurs. Survival analysis allows investigation of how survival, or time to the event, is related to certain variables during a set time period (70 days) (Armitage & Berry, 1994). Time to relapse was recorded in days for all 47 subjects, and was censored at 70 days. This score was utilised as the outcome measure.

Relapse in this study was defined as 30 standard drinks or more over 3 days or less, for male subjects. This definition is similar to the relapse criteria employed by Allsop et al. (1997) in their investigation of relapse. The definition of relapse for female drinkers was set at 15 standard drinks or more over 3 days or less (Steve Allsop, National Centre for Education and Training on the Addictions, South Australia, private communication 1995). This definition of relapse appeared to differentiate between a lapse (a brief period of drinking followed by abstinence) and relapse (return to continuous heavy drinking).

Subjects were assessed for relapse at each point of follow up according to the above criteria (days 14, 42 and 70). Subjects had their addresses and phone numbers taken at the beginning of the study, and also gave the phone numbers of any relevant friends or family. Subjects were encouraged at the commencement of the study to inform the investigator if they had recommenced drinking, and it appeared that most subjects were quite honest. There were a few occasions in which family or friends were utilised to confirm whether relapse had occurred. If subjects had relapsed, then the actual day of relapse was determined through discussion with the subject, or their family or friends. Some of the subjects in the study who had relapsed did not wait until the next follow up appointment, but initiated

contacted with the investigator to inform that they had recommenced drinking. The results from this study are shown in Chapter 7.

Using a method similar to the one employed in Chapters 5 & 6, univariate analysis (survival analysis) was used to determine the predictive effect of withdrawal severity on time to relapse. Withdrawal severity in this phase of the study included the global measures of acute withdrawal (total global and physical global) as determined by principal components analysis in Chapter 5. Univariate survival analysis also was used to investigate the predictive nature of individual symptoms of withdrawal on relapse. That is:

- Depression. BDI - mean score over days 1 and 4
- Anxiety. STAI - mean score over days 1 and 4
- Tension/Anxiety - POMS mean score over days 1 and 4
- Depression/Dejection - POMS mean score over days 1 and 4
- Anger/Hostility - POMS mean score over days 1 and 4
- Vigour/Activity - POMS mean score over days 1 and 4
- Fatigue/Inertia – POMS mean score over days 1 and 4
- Confusion/Bewilderment – POMS mean score over days 1 and 4
- Physical functioning – SF-36 score on day 1
- Role function physical – SF-36 score on day 1
- Role function emotional – SF-36 score on day 1
- Social functioning – SF-36 score on day 1
- Bodily pain – SF-36 score on day 1
- Mental health – SF-36 score on day 1
- Vitality – SF-36 score on day 1
- General health – SF-36 score on day 1
- Sleep activity – mean activity during sleep over nights 1, 2 & 3
- Skin temperature between 1400 and 1600 – mean over days 1 to 4
- Maximum sweating over 24 hour period – mean over days 1 to 4
- Early morning sweating between 0200 and 0900 – mean over days 1 to 4
- Restlessness – mean activity at 1300 over days 1 to 4

A second analysis section involved investigation of the potential of protracted withdrawal on day 14 to predict relapse. Principal components were determined for total global withdrawal severity and physical global withdrawal severity on day 14 of withdrawal. Univariate survival analysis was used to determine the potential of protracted withdrawal to predict relapse. Measures of protracted withdrawal included total global withdrawal severity and physical global withdrawal severity (day 14), and also individual symptoms of withdrawal severity. That is:

- Depression. BDI - score on day 14
- Anxiety. STAI - score on day 14
- Tension/Anxiety - POMS score on day 14
- Depression/Dejection - POMS score on day 14
- Anger/Hostility - POMS score on day 14
- Vigour/Activity - POMS score on day 14
- Fatigue/Inertia – POMS score on day 14
- Confusion/Bewilderment – POMS score on day 14
- Physical functioning – SF-36 score on day 14
- Role function physical – SF-36 score on day 14
- Role function emotional – SF-36 score on day 14
- Social functioning – SF-36 score on day 14
- Bodily pain – SF-36 score on day 14
- Mental health – SF-36 score on day 14
- Vitality – SF-36 score on day 14
- General health – SF-36 score on day 14
- Sleep activity – mean activity during sleep on night 14
- Skin temperature between 1400 and 1600 – mean during day 14
- Maximum sweating over 24 hour period – maximum on day 14
- Early morning sweating between 0200 and 0900 – mean during day 14
- Restlessness – mean activity at 1300 during day 14

It was not possible to investigate the potential of protracted withdrawal measures taken on days 42 and 70 to predict relapse, since sample sizes were too small on these days for the analysis procedures employed.

A third analysis section involved investigation of factors affecting withdrawal severity, as potential predictors of relapse. Factors affecting withdrawal severity were described in Chapter 5. Accordingly, input measures for the univariate survival analysis were as follows:

- Drinking history
  - Number of years of heavy drinking
  - Number of months spent in most recent drinking bout
  - Intake (g/day) during recent drinking bout
- Kindling
  - Number of previous withdrawal episodes
  - History of seizures
- Complications
  - Number of current medical conditions
  - Number of prescribed drugs currently used
  - Number of non-prescribed drugs currently used

    (including tobacco, but not alcohol)

A fourth analysis section involved univariate survival analysis of lifestyle factors thought to affect relapse drinking. Lifestyle parameters were determined from subjects' casenotes and included whether or not the subject had a stable partner -which was evidence of social support, whether or not the subject was employed, and the type of residence the subject was living in -which was evidence of residential stability. The residential categories included; 'no fixed address', 'boarding' 'renting' and 'lives in own home'. The outcome measure was days to relapse.

The fifth and final section was a multivariate survival analysis that incorporated all variables from the previous three sections that were $p \leq 0.10$. The criterion for entering the multivariate analysis was strict due to the small sample size for an analysis of this kind ($p \leq 0.10$ compared with $p \leq 0.15$ in Chapters 5 & 6). Once again, the outcome measure was time to relapse.

CHAPTER 4

4. CHARACTERISATION OF INTENSITY AND DURATION OF ALCOHOL WITHDRAWAL SYMPTOMATOLOGY

4.1 Introduction

Investigations of withdrawal from heavy alcohol consumption over the last fifty years have established that there is a 'syndrome' which occurs with abstinence from alcohol, and that it is characterised by specific signs and symptoms. Research efforts into alcohol withdrawal symptomatology have consisted of both clinical and experimental observations, various experimental designs and methods of data collection, and have tended to focus on one of three major dimensions of withdrawal: psychiatric signs and symptoms, physiological or physical signs and symptoms, and biochemical changes. There has also been a trend for withdrawal studies to concentrate on either one of two major 'phases' of sobriety. That is, either the period within the first week of abstinence (acute withdrawal), or at any time after the first week of abstinence (late or protracted withdrawal). While there have been great advances in the knowledge and treatment of alcohol withdrawal, the total syndrome is not completely understood. Very few comprehensive studies exist that investigate more than one or two major symptoms of withdrawal, or assess withdrawal during both acute and protracted phases. The limitations that seem to recur in the available literature include:

- subjective assessment of withdrawal severity
- use of unstandardised scales to assess withdrawal severity
- cross-sectional rather than longitudinal study designs
- narrow symptom focus
- confusing withdrawal symptomatology with symptoms of recovery from the toxic effects of alcohol

These limitations have been further discussed below.

4.1.1 Limitations of studies of alcohol withdrawal

A common feature of studies of acute withdrawal, and of protracted withdrawal, is the reliance on data obtained from formal and informal interviews. Many are also based on results from unique scales developed specifically for that research (Victor & Adams, 1953; Wellman 1954; Flaherty et al., 1955; Isbell et al., 1955; Wellman, 1955; Mendelson & La Dou, 1964; Gross et al., 1971; Gross & Lewis, 1973; Gross et al., 1973; Feuerlein, 1974; Edwards & Gross, 1976; Sellers & Kalant, 1976; Hershon, 1977; Romach & Sellers, 1991). These methods of data collection have obvious limitations, since they employ subjective and non-standardised measures of withdrawal severity, although have contributed markedly towards our understanding of the syndrome, and the development of current tools of clinical withdrawal assessment.

There are also limitations in some long term investigations of withdrawal. Some employ longitudinal methods, in which withdrawal is measured in the same subjects at several different time points following cessation of drinking. This method of time-series assessment is not always used, since it requires a substantial degree of effort and time, however more accurate results are achieved. In contrast, a cross-sectional approach which utilises subjects who have been abstinent for different periods of time, requires less effort, but introduces greater variability into the results. Although many researchers have employed cross-sectional data collection, they have been amongst the first few to identify that there is indeed, a protracted withdrawal syndrome (Wellman, 1954; Flaherty et al., 1955; Wellman 1955; Kissin, 1959; De Soto et al., 1985; De Soto et al., 1987)

While not strictly a limitation, investigations of only one aspect of withdrawal are common - for example, an item of psychiatric symptomatology such as depression (e.g. Pettinati et al., 1982; Brown et al., 1995), or physiological symptomatology such as sleep (e.g. Gillin et al., 1990; Le Bon et al., 1997). While these can be insightful and informative, they do not provide any indication of how the intensity of one symptom relates to another. A comprehensive approach to withdrawal - that is, assessment of a range of physical and psychiatric symptoms, is less common. Of those that exist, there is a tendency to employ unique scales of assessment, which are not standardised, but developed specifically for the study (e.g. Gross & Lewis, 1973; Gross et al., 1973; Hershon, 1977).

Finally, a major problem for many investigators is the differentiation between withdrawal, and other symptoms. That is, there are a number of signs and symptoms that will occur following

abstinence from heavy alcohol consumption, which improve with abstinence. A large subset of these are withdrawal symptoms, however there will also be symptoms of recovery from the direct, toxic effects of alcohol. Another subset of signs and symptoms that will show improvement over time are those which have developed as a result of chronic, albeit reversible, damage from excessive alcohol consumption.

4.1.2 Review of studies of alcohol withdrawal symptomatology

The research efforts on alcohol withdrawal symptomatology, both their contributions and limitations, are reviewed below. However, this overview pertains to studies that have employed either standardised or objective methods of assessment. The findings of other studies that have used subjective and/or unstandardised and/or unique scales of assessment are summarised in Chapter 1 (*Characteristics of the alcohol withdrawal syndrome*). Despite their limitations, the studies summarised in Chapter 1 do have the advantage of being somewhat more comprehensive than those which have been reviewed below (Victor & Adams, 1953; Wellman, 1954; Isbell et al., 1955; Wellman, 1955; Mendelson & La Dou, 1964; Gross & Lewis, 1973; Gross et al., 1973; Feuerlein, 1974; Edwards & Gross, 1976; Sellers & Kalant, 1976; Hershon, 1977; Murphy & Hoffman, 1993).

4.1.2.1 Mood and psychiatric disturbances De Soto et al. (1985 & 1989) used the Symptom Check List 90 (National Institute of Mental Health-Diagnostic Interview Schedule) to generate a Global Severity Index in a cross-sample population of alcoholics, abstinent from less than 6 months to greater than 15 years. Symptoms were found to be most severe during the early stages of abstinence, but decreased with time, and normalised after about 10 years of sobriety. The most intense symptoms were found to be depression, interpersonal sensitivity, obsessive-compulsive thoughts and guilt.

Several studies have examined mood disturbances in withdrawal. Bokstrom et al. (1989) delivered the Mood Adjective Check List (MACL) to three groups of subjects at three stages of alcohol withdrawal. These were inpatients in early withdrawal, inpatients in late withdrawal, and outpatients who had been abstinent for a median of five years (range 1 to 18 years). The MACL covers 6 mood dimensions and was administered over a period of several days or weeks to the subjects. They found that subjects in early withdrawal (first week) scored significantly lower than the normal scores for

pleasantness/unpleasantness, calmness/tension, activation/deactivation and control/lack of control on the first evening of their withdrawal. All six dimensions (including positive/negative social orientation and extroversion/introversion) significantly improved by day 7 of assessment, although it is unknown how these values compared with normal scores. The subjects in late withdrawal who were assessed every week from weeks 1 to 7, showed further significant improvement in test scores over time except for the dimensions extroversion/introversion and positive/negative social orientation which remained relatively stable over time. Once again, there was no indication how these compared with normal scores, although it appears from the data given, that most dimensions were not significantly different from normal values during this time. The out-patients who had been abstinent for a median of five years showed no differences in mood dimensions over the week they were studied, and they were all within the normal range. These results were similar to a second study executed by the same investigators in 1991 (Bokstrom et al., 1991).

McMahon & Davidson (1986) examined mood using the Profile Of Mood States (POMS) of in-patients on their first and forty fifth day of withdrawal. Subjects showed significant improvement in all six mood dimensions, when scores on day 1 were compared with scores on day 45. The greatest changes were observed in dimensions of tension/anxiety, depression/dejection and confusion/bewilderment. Anger/hostility, vigour/activity and fatigue/inertia also were improved, although these showed less difference between days 1 and 45. Scores on day 45 of withdrawal subjects were comparable with POMS scores from psychiatric outpatients, however this study did not compare them with normal population scores.

It appears that only a few studies have investigated anxiety as a separate psychiatric item of alcohol withdrawal (Bowen et al., 1984; Ludenia et al., 1984; Roelofs & Dikkenberg, 1987; Schuckit et al., 1990; Brown et al., 1991). Ludenia et al. (1984) administered the State Trait Anxiety Inventory (STAI) to inpatients on days 4 and 30 of withdrawal from alcohol. The results show that state anxiety scores improved significantly over this time. No comparison was made with normal scores, although it appeared that on day 30 scores were within the normal range, albeit slightly higher. Brown et al. (1991) administered the STAI to inpatients at weeks 1, 2, 3 and 4 following admission to treatment, and then at 3 months as outpatients. They found that state anxiety decreased during the entire 3 month period. Improvement was most marked during the inpatient period and returned to within the normal

range by 2 to 3 weeks of abstinence. Roelofs & Dikkenberg (1987) also found improvement in STAI scores over time. State anxiety decreased between the inpatient period and the first outpatient period, a median of 17 months later. A further decrease was observed in the second outpatient period about one year following, however the differences in scores between sessions were quite small, as was the sample size.

Depression as a discrete psychiatric symptom in alcohol withdrawal has received a little more attention than assessment of anxiety (Pettinati et al., 1982; Westermeyer & Neider, 1984; Clark et al., 1985; Dorus et al., 1987; Brown & Schuckit, 1988; Haviland et al., 1988; Pary et al., 1988; Clark et al., 1993; Schuckit et al., 1994; Brown et al., 1995) although there is still a paucity of studies in this area. The two most frequently-used tools to assess depression in these studies were the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAM-D), although some, not reviewed here, have used the Zung scale for depression (Westermeyer & Neider, 1984) and the Minnesota Multiphasic Personality Inventory (Pettinati et al., 1982).

Clark et al. (1985 & 1993) administered the BDI to two groups of inpatients which had been abstinent an average of five days, and two and a half weeks respectively. The studies found that both groups of inpatients scored higher than normal scores. Haviland et al. (1988) administered the BDI to inpatients who had been abstinent for seven days or less, and then three weeks later. The patients' BDI scores were high at the first administration, and significantly improved by the second to within the normal range. The second assessment corresponded with three to four weeks of abstinence. Similarly Dorus et al. (1987) administered the BDI to inpatients on days 1, 4 and 24 following their last drink, and found subjects were significantly depressed on day 1, partially recovered by day 4, and within the normal range by day 24.

In two different studies, Brown & Schuckit (1988) and Brown et al. (1995) administered the HAM-D to inpatients at weeks 1, 2, 3, 4 and weeks 2, 3, 4, 5 after their last drink respectively. Both studies report that depressive symptomatology had returned to a normal level after two to three weeks. Brown & Schuckit (1988) also assessed scores on the basis of the four HAM-D clusters: dysphoric mood, vegetative symptoms, dysfunctional cognitions and anxiety/agitation. They found that dysphoric mood dominated in early abstinence (week 1), but then rapidly decreased and stabilised, while vegetative symptoms and anxiety/agitation persisted over the entire four week period.

4.1.2.2 Physiological disturbances Gross and colleagues (1975) recorded core body temperature (rectal) of 10 inpatients on days 1, 2 and 3 (early withdrawal), and days 4, 5 and 6 (late withdrawal). Temperature was taken at three time points; 10pm, 6am and 1pm, and were compared with the core body temperature of 'control' subjects who were alcoholics (outpatients) who had been sober for an average of three and a half weeks. The core temperature of the inpatients was increased at 10pm in early, but not late withdrawal. Further, core temperature at 6am was comparable with the 'control' group during early withdrawal, and markedly decreased during late withdrawal. Finally, temperature at 1pm was comparable with the 'control' group in both early and late withdrawal. These results suggest that alcohol withdrawal may disrupt diurnal temperature rhythms, although it is not clear from this study whether the 'control' subjects after three and a half weeks abstinence had fully completed withdrawal.

Roelofs & Dikkenberg (1986) measured respiratory excitability by monitoring CO_2 levels at two time points. The first measurement was taken on fifteen inpatients who had been abstinent for an average of 12 weeks (range 3 - 32 weeks). The second measurement was taken approximately 29 months later, on five subjects from the original group. The results showed that subjects had significantly increased respiratory excitability at the first time point, but not the second.

Kissin and colleagues conducted a study in 1959 which has received some attention over subsequent years. They examined several physiological and biochemical functions in recently sober subjects (about 5 days), and in a second group of subjects that had been abstinent from alcohol for approximately two years or greater. Sympathetic nervous system irregularity was found in both groups based on a significant decrease in diastolic cold-pressor response. In addition, muscle tension as measured by the graphodyne (light writing) test, was increased in both groups of subjects. Respiratory irregularity as assessed by CO_2 levels was also observed at both time points.

A large proportion of the studies which employ objective assessment tools of physiological withdrawal symptoms have been concerned with sleep disturbances, employing EEG, and sometimes EMG, to record the brain's electrical activity and muscle tension respectively. Overall, most of the studies show similar results. That is, alcohol withdrawal is characterised by a decrease in stages III and IV of sleep (slow wave sleep), an increase in stage I sleep, an increase in REM sleep and/or density, an increase in the number of stage shifts, delayed sleep onset latency, reduced total sleep

time punctuated with frequent wakenings, and increased muscle twitching and movement during the night (Johnson et al., 1970; Allen et al., 1971; Lester et al., 1973; Gross and Hastey, 1977; Wagman and Allen, 1977; Gillin et al., 1990; Hemmeter et al., 1993; Le Bon et al., 1997). Sleep apnoeas have also been observed more frequently in alcohol withdrawal subjects (Aldrich et al., 1993; Le Bon et al., 1997).

Some of the above studies investigated sleep in the protracted period, but this has been only up to about one month later. Similar findings to those of the acute studies were found, reporting overall sleep fragmentation and deterioration (Johnson et al., 1970; Allen et al., 1971; Gillin et al., 1990; Hemmeter et al., 1993; Le Bon et al., 1997).

The advantage of measuring sleep disturbances in withdrawal is that EEGs provide objective recordings of withdrawal symptoms. The disadvantage is that usually these investigations are more labour intensive and intrusive, and require subjects to sleep in a laboratory environment and wear EEG apparatus.

4.1.2.3 Biochemical Changes The number of studies investigating biochemical changes during alcohol withdrawal exceeds the number investigating objective recordings of physiological features - except those on sleep. Biochemical disturbances that occur during acute withdrawal have received more attention than changes during protracted withdrawal. The following review of the literature focuses on studies that have investigated changes in biochemical parameters over time.

Kissin and colleagues (1959) reported parasympathetic disturbances in two groups of subjects in alcohol withdrawal. The first group had been abstinent an average of five days, and the second abstinent for at least two years. Both groups showed an increased rate of decline in % glucose tolerance in the first 30 minutes of testing. This is evidence of disturbances to the parasympathetic nervous system, since a rapid rate of decline is associated with increased parasympathetic activity, and vagotonia. Disruptions to adrenal cortex activity (endocrine function) were also observed for both groups as demonstrated by increased salivary potassium levels, decreased urinary sodium/potassium ratio, and attenuated urinary 17-hydroxycorticoids and 17-ketosteroids.

Another group reported protracted neuroendocrine functional disturbances. Balldin et al. (1993) found reduced D2 dopamine receptor function in nine subjects who had been abstinent for an average of 7 ± 6 years.

Khan et al. (1984) administered the dexamethasone suppression test (DST) to withdrawal subjects at approximately 3, 10, 19 and 33 days after drinking cessation. They found that DST scores, which reflect endogenous depression, were abnormal in early abstinence, but returned to within the normal range after about two weeks.

There are other studies, not reviewed here, which also have reported biochemical disturbances during alcohol withdrawal (Alling et al., 1982; Balldin et al., 1992; Sudha et al., 1995). These studies show there are significant changes following heavy drinking, although it is unclear in some studies whether the biochemical indicators reflect actual withdrawal symptomatology, or are a direct result of chronic alcohol consumption.

4.1.3 Experimental rationale and aims

There are several important reasons for characterising the events that occur after heavy drinking ceases. Besides the academic contribution to the field of alcohol research, mapping the abstinence syndrome has significant clinical and treatment implications, including determination of the adequacy of current clinical practice and protocols. Moreover, treatment services would benefit from knowing better which symptoms are the most intense, and thereby require special attention, and the period over which certain symptoms should be treated. Furthermore, an objective baseline of symptom severity could be used in the future for evaluation purposes, such as investigating the effects of novel pharmacotherapies or psychotherapies.

Obtaining a baseline of withdrawal severity and duration also provides an opportunity to investigate other important aspects of the syndrome. These include identification of predictors of withdrawal severity, which would allow clinicians to determine which patients are going to experience a severe withdrawal. Furthermore, some investigators have suggested that a particularly intense or protracted withdrawal may contribute to relapse drinking (Himmelsbach, 1942; Kissin et al., 1959; Kissin, 1979; Meyer, 1989; Satel et al., 1993), but as yet this has not been fully investigated. Access to objective, standardised baseline data would allow these, and other investigations to proceed.

Specifically, the aims of this study were to characterise the intensity and duration of the withdrawal syndrome over a ten week period, by assessing a range of withdrawal signs and symptoms, and utilising both standardised and objective tools of assessment. Characterisation included measuring changes in intensity of signs and symptoms over time, and deviation of signs and symptoms from the normal range, as provided by control subjects who were not experiencing alcohol withdrawal. As indicated above in section *4.1.1 'Limitations of studies of alcohol withdrawal'*, there is some difficulty associated in differentiating between 'true' symptoms of withdrawal, and those associated with other processes of recovery from the toxic effects of alcohol. This study did not aim to differentiate between the symptoms of withdrawal and recovery, but recognised that some of the symptoms that were assessed in this study may have constituted both withdrawal and recovery. This was more likely to be the case for some of the mood and psychiatric disturbances and changes in overall health, than the physical symptoms. This is because the physical symptoms measured in this study reflect autonomic hyperactivity, which is known to underlie many of the symptoms of withdrawal (Gross et al., 1973; Gross et al., 1974; Hershon, 1977; Clark & Friedman, 1985; King et al., 1991; Romach & Sellers, 1991).

4.2 Methodology

4.2.1 Procedure

The methodology for this study was as previously discussed in Chapter 3, *General Methodology*. In brief, the subjects were 30 inpatients experiencing alcohol withdrawal, who commenced wearing the monitor on days 1, 2 & 3, and some of whom wore the monitor on days 14, 42 and 70. The BDI, STAI and POMS questionnaires were administered on days 1, 4, 14, 42 and 70. The SF-36 was administered on the same days, with the exception of day 4. If subjects relapsed before the end of 70 days, they were excluded from further assessment (and therefore did not wear the monitor or complete questionnaires). Accordingly, the sample size decreased over time due to relapse. The sample sizes for those withdrawal subjects wearing the monitor on days 1, 2, 3, 14, 42 and 70 were n = 30, 30, 30, 25, 15, & 12 respectively. Accordingly, sample sizes for the control subjects were the same, since controls were matched to withdrawal subjects. The sample sizes for those subjects completing the BDI, STAI and the POMS on days 1, 4, 14, 42 & 70 were n = 30, 30, 26, 16 & 14 respectively. The sample sizes for subjects completing the SF-36 on days 1, 14, 42 & 70 were n = 30, 24, 15 & 13 respectively.

The results obtained from the monitor recordings were expressed in two major ways. The first was as an average for all subjects over a twenty four hour period, resulting in a mean and SEM for each twenty four hour period (ie. Days 1, 2, 3, 14, 42, 70). Skin temperature, sweating and activity results were all expressed in this way. Activity was further separated into average 'day' activity, ie. between the hours of 8am and 11pm, and average 'sleep' activity. The period which comprised 'sleep' was ascertained by sleep diaries which were kept by all subjects (withdrawals and controls). Specifically, it was the activity during the period in which subjects said they were sleeping, or attempting sleep.

The second major way that monitor data was expressed was as diurnal rhythms, resulting in hourly means of subjects' data (SEMs were not included on the graphs to avoid confusion between data sets, however all SEMs appear in the appendices). Skin temperature, sweating and activity recordings were all expressed in this way. Both skin temperature and sweating were expressed over twenty four hour periods for all the days they were recorded (Days 1, 2, 3, 14, 42, 70). Activity was

separated into average hourly 'day' activity between the hours of 8am and 11pm, and average hourly 'night' activity between midnight and 7am, and results were expressed for all days (ie. 1, 2, 3, 14, 42, 70). The rationale for classifying activity as day and night was because of the difference in the scales required to best express changes in activity. That is, degree of activity during the night was much less than activity during the day. Accordingly, any differences between control and withdrawal subjects in night time activity would not have been obvious on a graph whose scale was large enough to encompass changes in day activity. It should also be noted that night activity was not exactly the same as 'sleep' activity, although there were similarities between the two. Night activity was expressed as activity commencing and ending at set, pre-determined hours, and thus could be expressed diurnally. Activity during the 'sleep' period was not expressed diurnally, because subjects commenced and terminated sleep at various times.

The effects of benzodiazepines (usually diazepam) on withdrawal-induced changes to diurnal skin temperature and sweating during the inpatient period was investigated, by separating withdrawal subjects into two groups, according to whether or not diazepam had been administered during the inpatient period. The diurnal patterns of skin temperature and sweating for withdrawal subjects administered diazepam was compared with diurnal rhythms for subjects that did not receive diazepam. These results were expressed for days 2 and 3 of withdrawal, but not day 1, since almost all inpatients were administered benzodiazepines on day 1, and thus could not be compared with a group that had not received diazepam. Results were expressed in this way in order to observe the effects of benzodiazepines on some of the features of withdrawal. The sample size of subjects who had not been administered diazepam on days 2 and 3 was n = 7. Accordingly, these data were compared with results from 23 subjects on days 2 and 3 who had been administered diazepam.

The results obtained from the questionnaires were all expressed longitudinally as mean scores and SEMs on each day that the questionnaire was administered (days 1, 4, 14, 42, 70, with the exception of the SF-36 which was not administered on day 4). BDI scores were displayed as total scores of depression, and were compared with the norm, or 'control' value for that questionnaire. STAI scores for anxiety were expressed in the same way. In addition, item scores for both the BDI and STAI were shown longitudinally, both in a graphical and table format. STAI item scores were compared with normal item scores. Normal item scores were unavailable for the BDI, so item scores were compared

with the 'average item normal score', which was determined by dividing the total normal score (9) by the number of items on the questionnaire (21).

The results obtained from the POMS questionnaire were divided into each of its six dimensions, and compared with each 'normal' dimension score. Similarly, the SF-36 was displayed as each of its eight dimensions, and compared with each 'normal' dimension score.

4.2.2 Subject characteristics

Subjects were 23 males and 7 females, with a mean age of 44.2 ± 2.0 years (range, 27 to 65). Subjects had been drinking heavily for an average of 15.3 ± 1.9 years (range, 0.2 to 40), and had consumed an average of 315.6 ± 25.5 grams of alcohol per day (range 105 to 700) over their most recent drinking bout which was an average of 9.2 ± 3.2 months long (range, 0.25 to 72).

Subjects were administered an average of 26.3 ± 5.5 *mg* of diazepam on their first day of abstinence (range 0 to 120), 12.4 ± 2.4 *mg* on their second (range, 0 to 55), 9.6 ± 2.1 *mg* on their third (range, 0 to 45), 4.2 ± 1.5 *mg* on their fourth (range, 0 to 35) and 2.2 ± 1.6 *mg* of diazepam on their fifth day of abstinence (range, 0 to 35). Subjects remained an average of 6.1 ± 0.3 days in the detoxification unit (range, 3 – 9).

4.3 Results

4.3.1 Skin temperature - average over twenty four hours

Fig. 4.1 shows that there were no significant differences in mean twenty four hour skin temperature between control subjects and alcohol withdrawal subjects during the inpatient period (days 1, 2 and 3). During the outpatient period, the average skin temperature of the subjects in withdrawal was elevated above those of the controls on all days (14, 42 and 70). Skin temperature was highest on day 14, but had reduced in intensity by day 42, and was further attenuated by day 70. Only day 14 was significantly different compared with the control value (*$p<0.05$). The means and SEMs are shown in the appendices.

Fig. 4.1

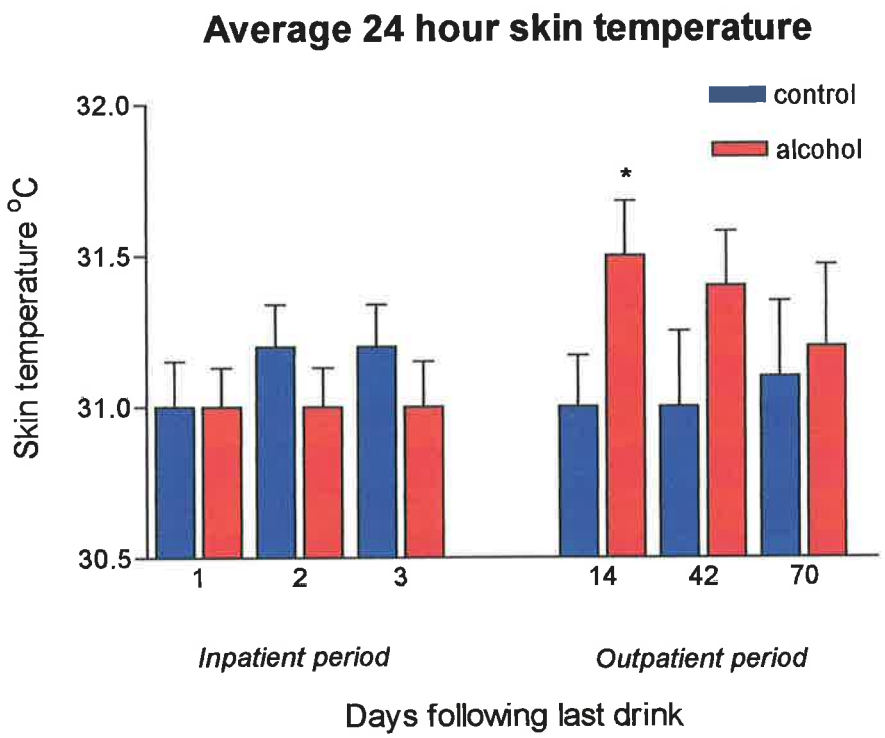


*Fig. 4.1 Comparison of average 24 hour skin temperature between withdrawal and matched control subjects for days 1, 2, 3, 14, 42 & 70 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 1, n=30; day 2, n=30; day 3, n=30; day 14, n=25; day 42, n=15; day 70, n=12.*

4.3.2 Skin temperature - Twenty four hour diurnal recordings

Alcohol withdrawal subjects showed a variation in their diurnal skin temperature rhythm compared with the diurnal rhythm of control subjects (Figs. 4.2, 4.3, 4.4, 4.5, 4.6, 4.7). On all days (1, 2, 3, 14, 42, 70) the control subjects showed a relatively consistent diurnal skin temperature rhythm, which seemed to comprise two major components; 'day' and 'night'. In general, skin temperature during the night (around 2400 to 0700) was higher than during the day (0800 - 2300). In more detail, the diurnal skin temperature of control subjects was characterised by a small trough at around 1500 (a decrease compared with skin temperature at noon). Following this nadir, skin temperature gradually increased and stabilised at around 2000, although there were some fluctuations. At around 2400 (midnight) skin temperature increased rapidly remaining well elevated until around 0700, with the exception of a brief fall at around 0400. At approximately 0700, skin temperature decreased rapidly, and reached its lowest point in the twenty four hour cycle between about 0900 and 1000. Following this, skin temperature ascended gradually towards 'daytime' skin temperature levels. The diurnal skin temperatures of control subjects are shown in Figs. 4.2, 4.3, 4.4, 4.5, 4.6 and 4.7. Figs. 4.6 and 4.7 display a greater degree of fluctuation in skin temperature, albeit small, compared with Figs. 4.2, 4.3, 4.4 and 4.5. This is most likely the result of a reduced sample size for days 42 and 70.

In comparison with the diurnal temperature rhythm of control subjects, withdrawal subjects experienced some relatively consistent variations in their temperature rhythm on days 1, 2 and 3. Day 1 was characterised by a small increase in skin temperature during the early afternoon, rising above the skin temperature of the control subjects, and reaching statistical significance at 1500 ($*p<0.05$). From this time, skin temperature decreased slowly, eventually to below the level of the control subjects. At 2400 withdrawal subjects, like control subjects, experienced a rapid increase in skin temperature. However withdrawal subjects did not show a decline in skin temperature at 0400 as the controls had, but appeared to experience their highest skin temperature at this time. Similar to the control subjects, the withdrawal subjects experienced a rapid decline in skin temperature at around 0700, and reached the lowest point at 1000. Following this nadir, the skin temperature of withdrawal subjects increased, as had the skin temperature of the control subjects (Fig. 4.2, means and SEMs shown in appendices).

Fig. 4.2

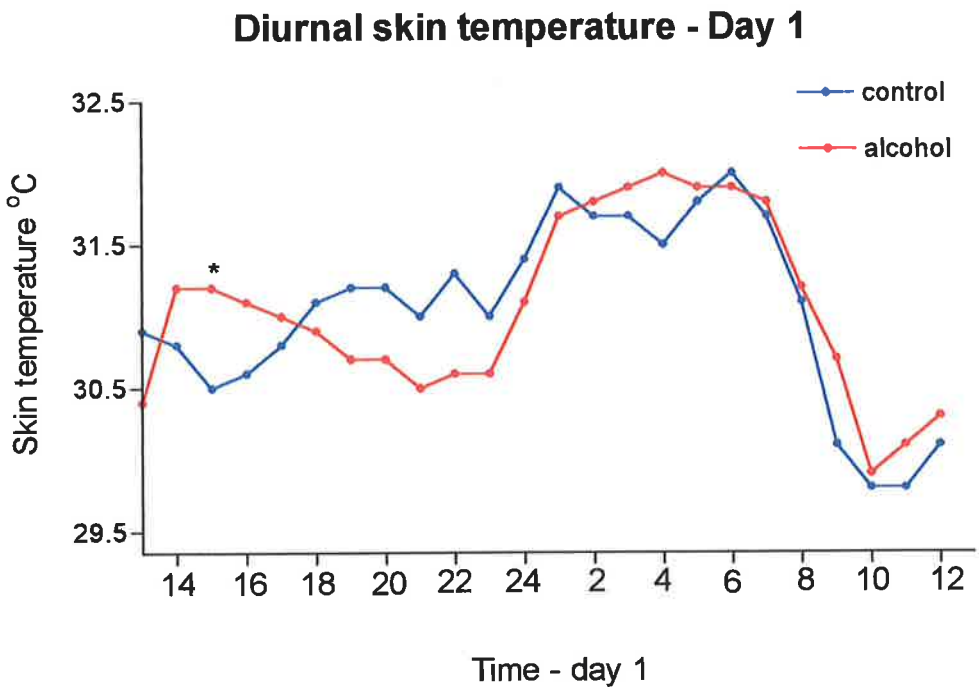


*Fig 4.2 Diurnal skin temperature expressed hourly, comparing control subjects with withdrawal subjects on day 1 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 1, n=30 at each time point.*

Day 2 for the withdrawal subjects was comparable with the first day, although the fluctuations in the withdrawal subjects' skin temperature appeared to have increased. Consequently, withdrawal subjects experienced statistically significant increases in skin temperature compared with controls at 1500 (*p<0.05), but also at 0400 (*p<0.05). Moreover, skin temperature was significantly attenuated compared with the skin temperature of control subjects at both 1000 and 1100 (Fig. 4.3, means and SEMs shown in appendices). This decrease was not observed on day 1 of withdrawal.

Fig. 4.3

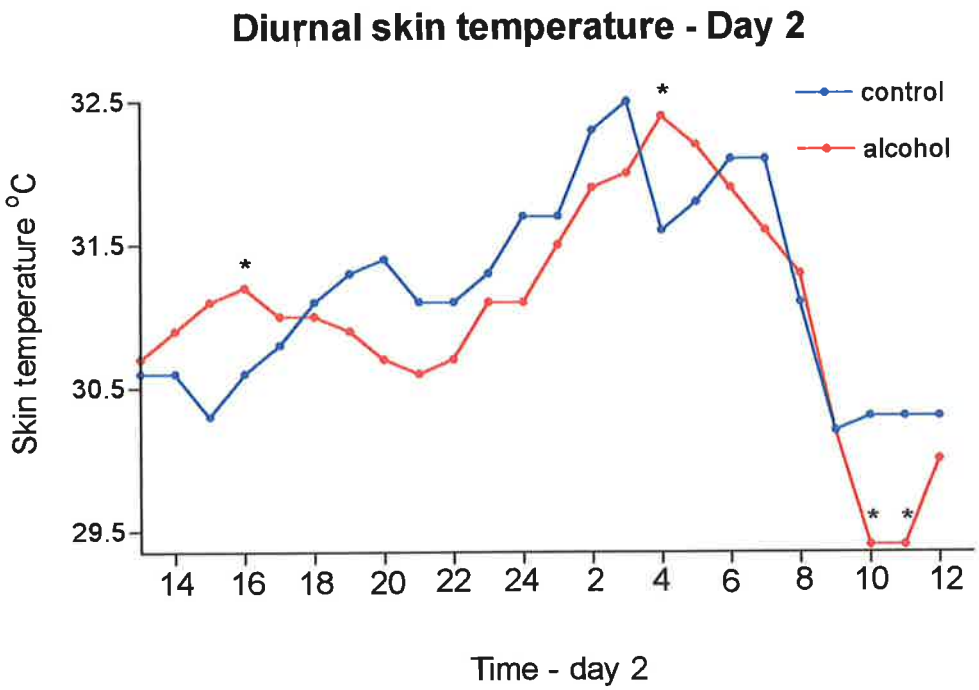


*Fig 4.3 Diurnal skin temperature expressed hourly, comparing control subjects with withdrawal subjects on day 2 following last drink, * p≤0.05. Size of each group (control and experimental): day 2, n=30 at each time point.*

Day 3 of withdrawal showed a temperature rhythm very similar to that observed on day 2, although fluctuations were not as obvious, and did not reach statistical significance at any time (Fig. 4.4, means and SEMs shown in appendices).

Fig. 4.4

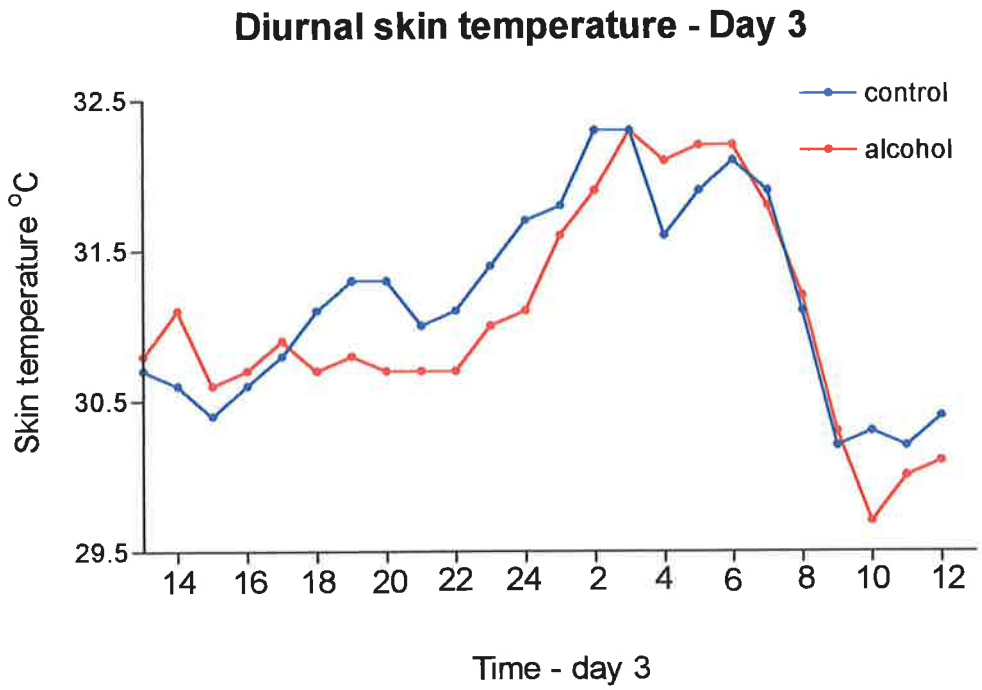


*Fig 4.4 Diurnal skin temperature expressed hourly, comparing control subjects with withdrawal subjects on day 3 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 3, n=30 at each time point.*

The disruption to diurnal skin temperature rhythm appeared to persist in the withdrawal subjects into the outpatient period (day 14, Fig. 4.5). However, it appeared that the temperature rhythm they experienced during the outpatient period was somewhat different compared with the diurnal rhythm they experienced during the inpatient period (days 1, 2 and 3). That is, the skin temperature of the withdrawal subjects remained elevated above the skin temperature of the control subjects for the majority of the twenty four hours. In more detail, withdrawal subjects experienced an increased skin temperature during the afternoon from midday until about 1900, and this was statistically significant at 1500 (**$p<0.01$) and 1600 (*$p<0.01$). Although skin temperature decreased from 1600 to midnight, it was not to the same extent as during the inpatient period, and was not dissimilar to the control subjects' skin temperature. Once again, withdrawal subjects experienced a rapid increase in skin temperature at around 2400, which culminated in two significant peaks at 0400 (*$p<0.05$) and 0500 (*$p<0.05$), above those of the control subjects. This was followed by a rapid descent from around 0700, reaching a minimum at 1000, and then re-ascending. However, skin temperature of the withdrawal subjects remained elevated above the control subjects' skin temperature during the morning, with statistically significant differences observed at 0900 (*$p<0.05$), 1100 (**$p<0.01$) and 1200 (*$p<0.05$). (Fig 4.5, means and SEMs in appendices).

Fig. 4.5

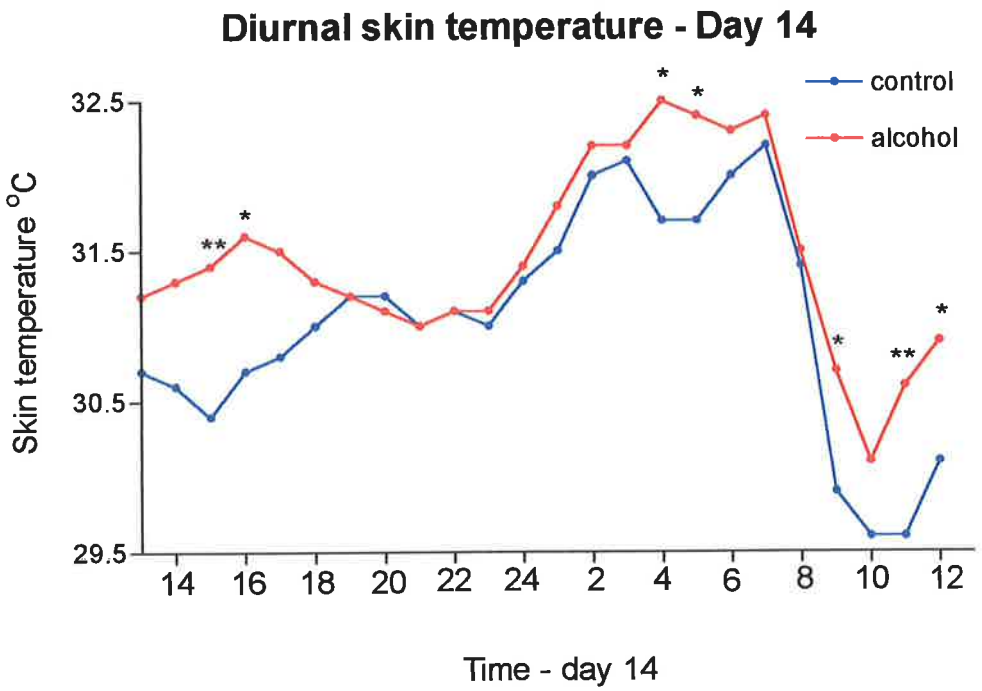


*Fig 4.5 Diurnal skin temperature expressed hourly, comparing control subjects with withdrawal subjects on day 14 following last drink, * p≤0.05, ** p≤0.01. Size of each group (control and experimental): day 14, n=25 at each time point.*

Day 42 of withdrawal yielded a similar diurnal rhythm as day 14. Overall the skin temperature of the withdrawal subjects remained almost entirely above that of the controls, except for a period of almost two hours during the night. Withdrawal subjects experienced an increase in skin temperature over the early afternoon, which became statistically significant at 1500 (*$p<0.05$). Temperature dropped slowly from around 1800, reaching its minimum at 2300, and then rapidly ascending until 0100. At 0300 the withdrawal subjects' skin temperature fell briefly below that of the controls, until approximately 0400 when temperature increased above the skin temperature of the control subjects. Once again, withdrawal subjects experienced a rapid decrease in skin temperature at 0700 reaching a nadir at 1000, and then re-ascending. Similar to day 14, the skin temperature of the withdrawal subjects was greater than that of the controls from 0900 to 1200, but was not quite statistically significant (Fig. 4.6 means and SEMs in appendices).

Fig. 4.6

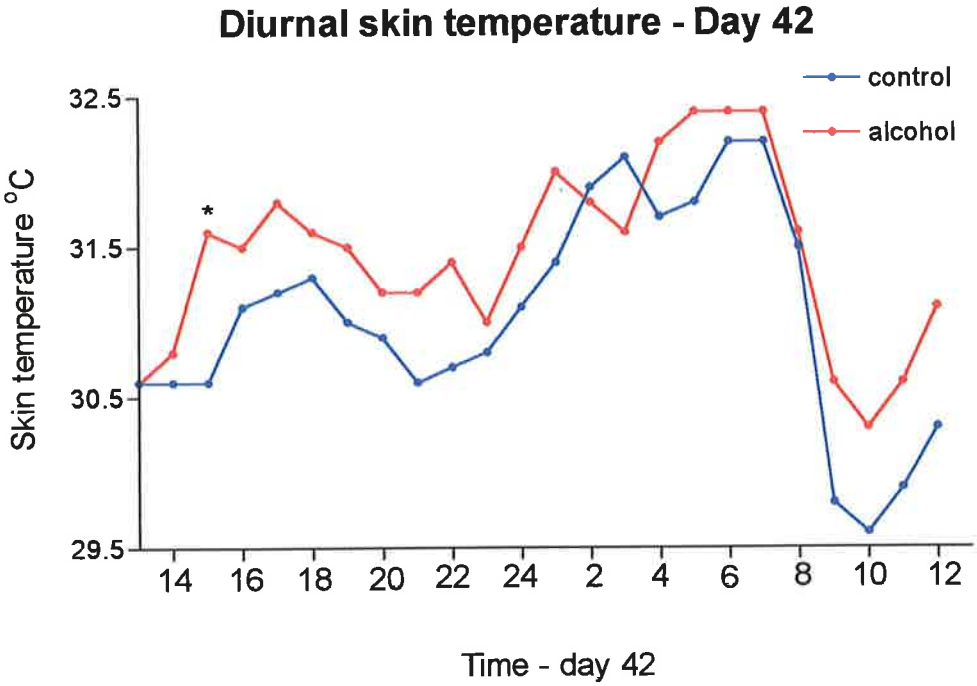


*Fig 4.6 Diurnal skin temperature expressed hourly, comparing control subjects with withdrawal subjects on day 42 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 42, n=15 at each time point.*

Day 70 of the outpatient period showed that the diurnal temperature rhythm of the withdrawal subjects showed greater similarity to the diurnal skin temperature of the controls than on previous days, although some irregularities persisted (Fig 4.7). These included a sharp decrease in temperature at 1800, and an increased temperature at 2300, both of which were close to being significant. Skin temperature dropped rapidly at around 0700 for both controls and withdrawal subjects, although the decline occurred at a faster rate for the withdrawal subjects, resulting in a significant decrease at 0800 (*$p<0.05$). Overall, it appeared that the diurnal temperature rhythm of the outpatient withdrawal subjects was approaching a 'normal' range, as demonstrated by the control subjects.

Fig. 4.7

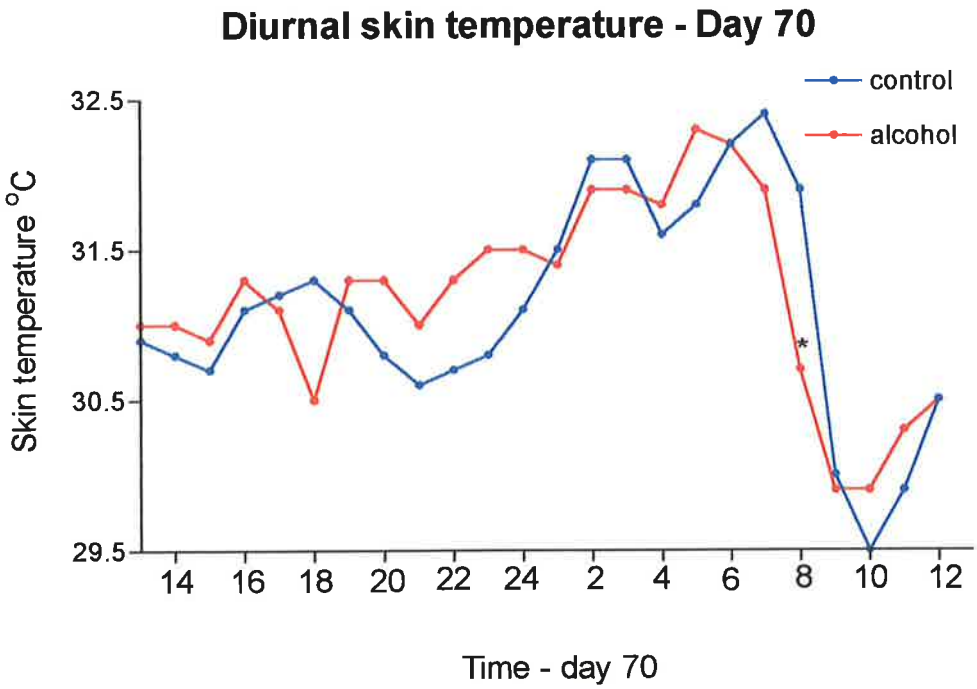


*Fig 4.7 Diurnal skin temperature expressed hourly, comparing control subjects with withdrawal subjects on day 70 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 70, n=12 at each time point.*

4.3.3 Sweating - average over twenty four hours

There were no significant differences between control and withdrawal subjects in sweating as % Relative Humidity (%RH) either during the inpatient period (days 1, 2 and 3) or the outpatient period (days 14, 42 and 70). However, there was a trend for the withdrawal subjects to have higher levels of sweating than the controls, particularly during the inpatient period. Means and SEMs shown in appendices (Fig. 4.8).

Fig. 4.8

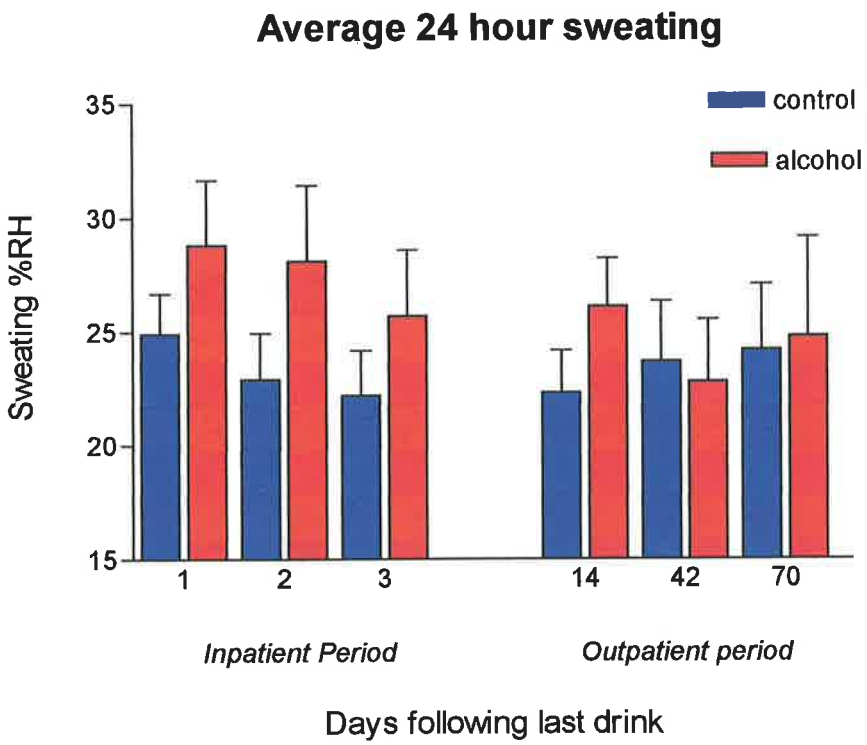


*Fig. 4.8 Comparison of average 24 hour sweating between withdrawal and matched control subjects for days 1, 2, 3, 14, 42 & 70 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 1, n=30; day 2, n=30; day 3, n=30; day 14, n=25; day 42, n=15; day 70, n=12.*

4.3.4 Sweating - twenty four hour diurnal recordings

The withdrawal subjects showed markedly varied diurnal sweating patterns during the inpatient period compared with the control subjects (Figs. 4.9, 4.10, 4.11). On all days, control subjects experienced two major phases of sweating; 'day' and 'night'. 'Day' sweating was characterised by an average of around 20 %RH from 1300 until about 2300. At 2300 ('night') sweating increased fairly rapidly by about 5 - 10 %RH by about 0200. Following this culmination, sweating slowly decreased, with some small fluctuations, reaching the day's previous level around 1000 to 1200.

On day 1, between the hours of 1300 and 2300, withdrawal subjects experienced similar levels of sweating compared with those of the controls (about 20 %RH). Sweating of withdrawal subjects increased rapidly at around 2300, but continued beyond the level of control subjects for most of the night by about 5 - 10 %RH, and culminated at 0700 with a relative humidity of around 35 %. Withdrawal subjects experienced significantly increased sweating at 0600, 0700 and 0800 ($^*p<0.05$ for all) compared with control subjects. Sweating gradually decreased to the day's previous level by about midday (Fig. 4.9, means and SEMs in appendices).

Fig. 4.9

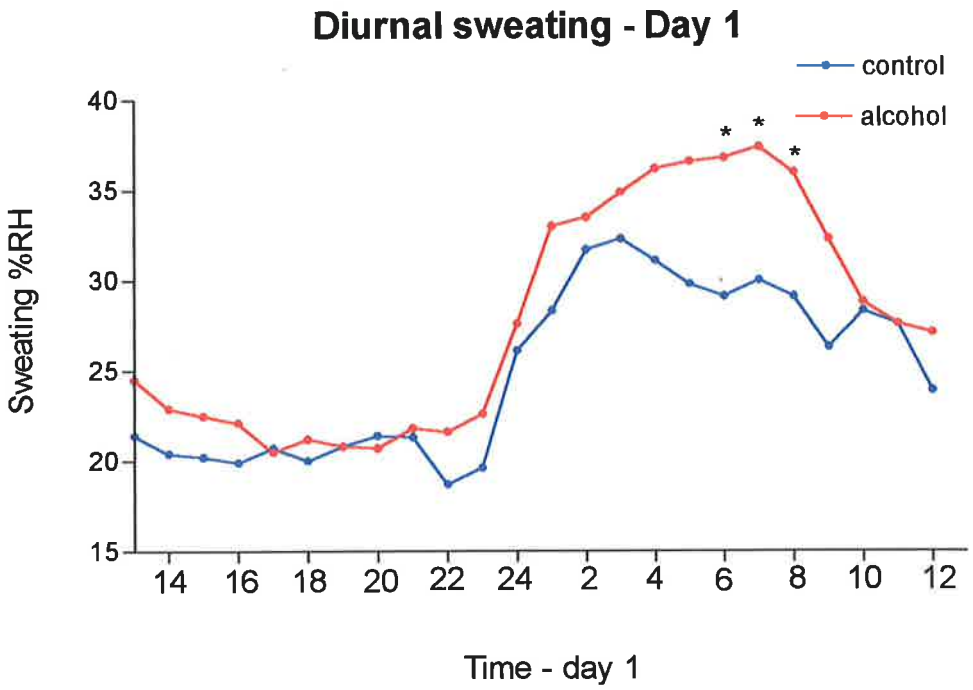


*Fig 4.9 Diurnal sweating expressed hourly, comparing control subjects with withdrawal subjects on day 1 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 1, n=30 at each time point.*

On day 2, the withdrawal subjects displayed a similar diurnal sweating pattern as they had on day 1. However, night sweating was more intense, as shown by a significant increase over a period of eight hours from 0300 (*p<0.05), 0400 and 0500 (***p<0.001 for both), 0600 and 0700 (**p<0.01 for both), 0800 (***p<0.001) through to 0900 and 1000 (*p<0.05 for both). Night sweating culminated at around 0400, with a relative humidity of almost 40 % (Fig. 4.10, means and SEMs in appendices).

Fig. 4.10

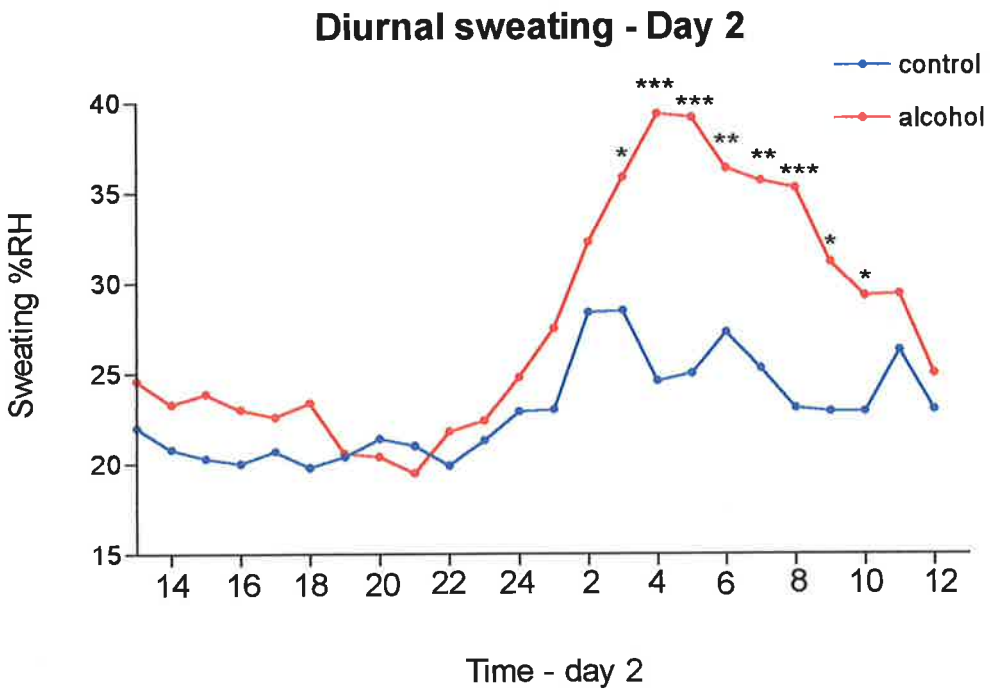


*Fig 4.10 Diurnal sweating expressed hourly, comparing control subjects with withdrawal subjects on day 2 following last drink, * p≤0.05, ** p≤0.01, *** p≤0.001. Size of each group (control and experimental): day 2, n=30 at each time point.*

Day 3 yielded similar results to day 2, showing significantly higher levels of sweating for withdrawal subjects from the hours of 0300 (**p<0.01), 0400 and 0500 (***p<0.001 for both), 0600 (**p<0.01), 0700 (***p<0.001), 0800 (**p<0.01) to 0900 (*p<0.05), culminating at around 0300 with a relative humidity of around 40 % (Fig. 4.11, means and SEMs in appendices).

Fig. 4.11

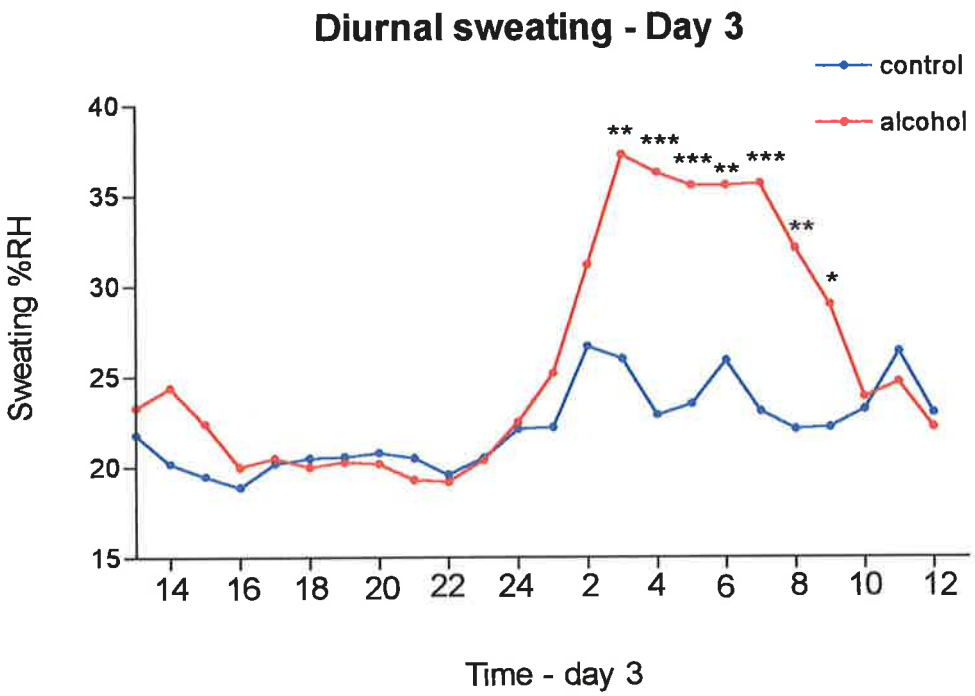


*Fig 4.11 Diurnal sweating expressed hourly, comparing control subjects with withdrawal subjects on day 3 following last drink, * p≤0.05, ** p≤0.01, *** p≤0.001. Size of each group (control and experimental) day 3, n=30 at each time point.*

By day 14, withdrawal subjects displayed a sweating pattern that more closely resembled the pattern of the control subjects (Fig. 4.12). Night sweating was not as severe as had been observed during the inpatient period, but day sweating appeared to have increased in severity, particularly between 1300 and 1900. However, these differences were not statistically significant (means and SEMs in appendices).

Fig. 4.12

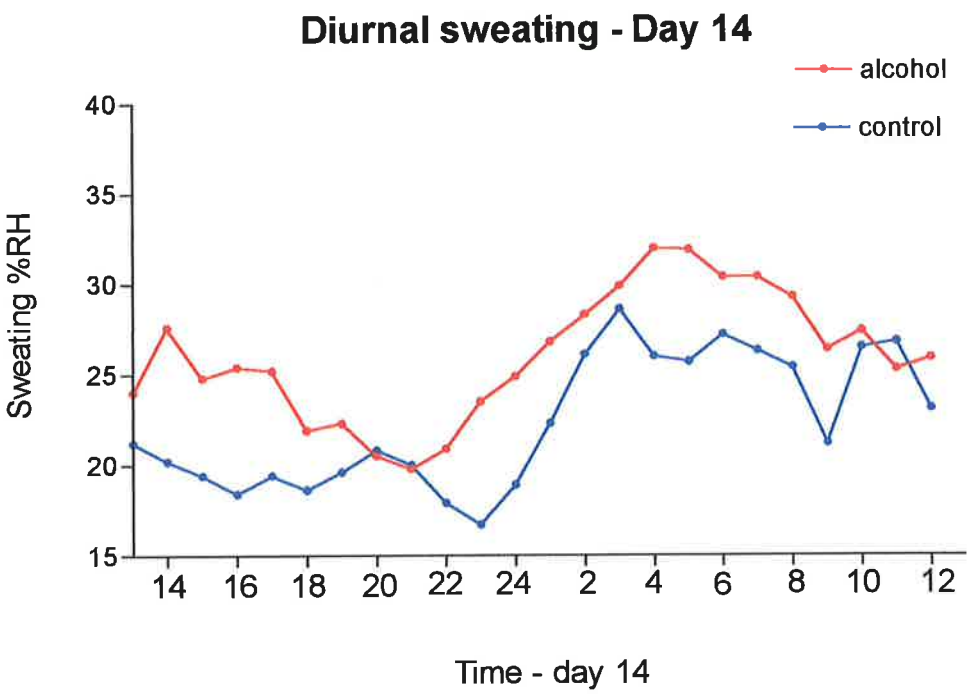


*Fig 4.12 Diurnal sweating expressed hourly, comparing control subjects with withdrawal subjects on day 14 following last drink, * $p \leq 0.05$. Size of each group (control and experimental) day 14, n=25 at each time point.*

Days 42 (Fig. 4.13) and 70 (Fig. 4.14) showed similar diurnal sweating patterns, and also more closely resembled the control subjects' sweating pattern in structure and intensity. The main differences, albeit small, were that withdrawal subjects had slightly less intense sweating than the control subjects during the night, and slightly more severe sweating than the controls during the afternoon, although none of these differences were statistically significant (Fig. 4.13 & Fig. 4.14, means and SEMs in appendices).

Fig. 4.13

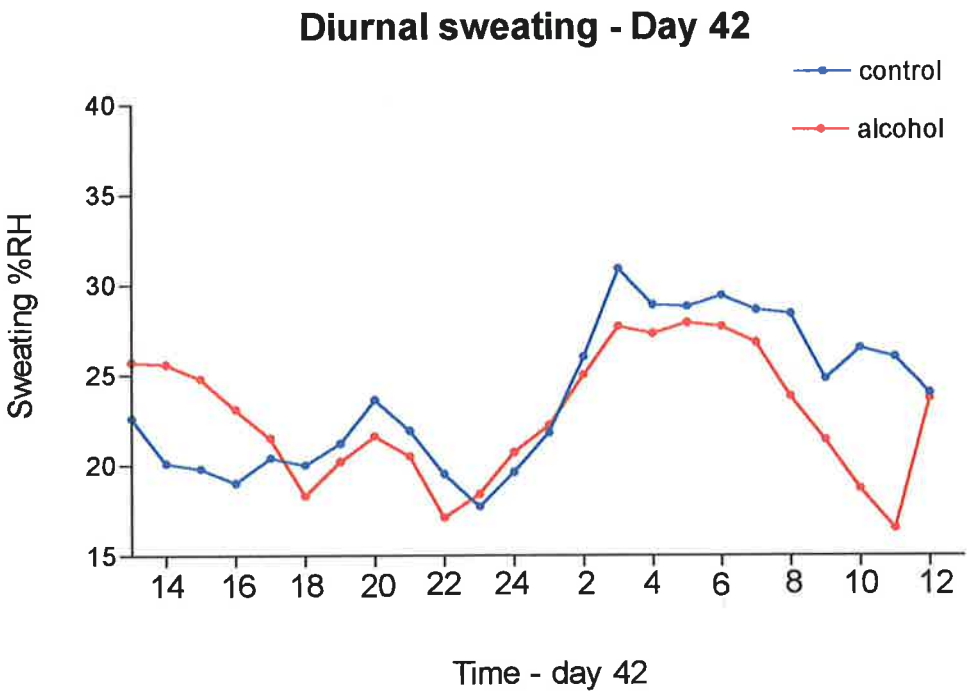


*Fig 4.13 Diurnal sweating expressed hourly, comparing control subjects with withdrawal subjects on day 42 following last drink, * $p \leq 0.05$. Size of each group (control and experimental) day 42, n=15 at each time point.*

Fig. 4.14

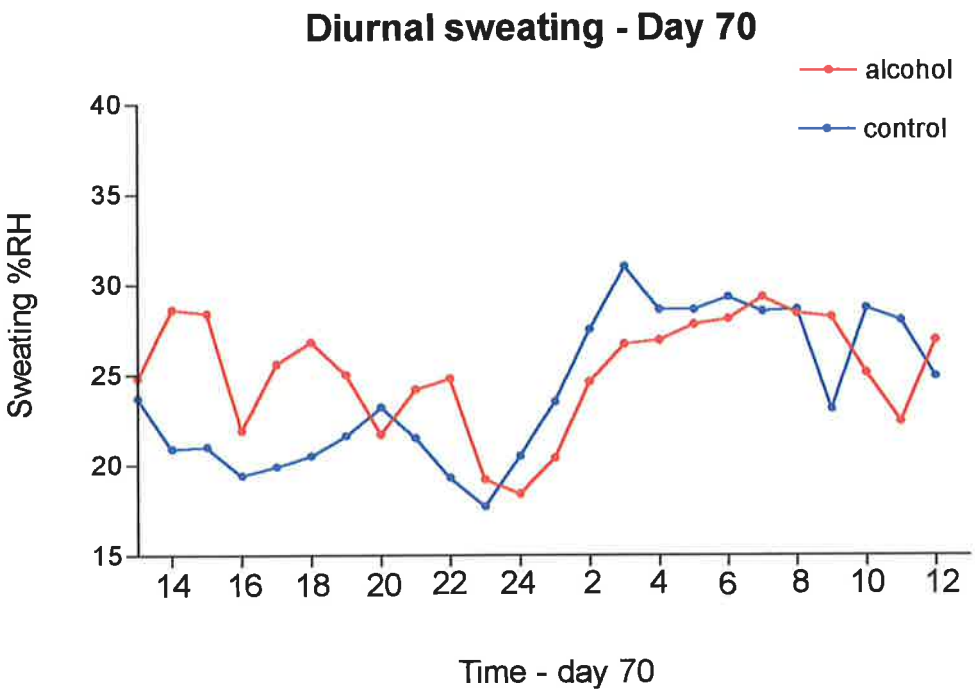


*Fig 4.14 Diurnal sweating expressed hourly, comparing control subjects with withdrawal subjects on day 70 following last drink, * p≤0.05. Size of each group (control and experimental): day 70, n=12 at each time point.*

4.3.5 Effect of benzodiazepines on sweating and skin temperature

Sweating Figs. 4.15 and 4.16 show the effects of benzodiazepine (BZD) administration (predominantly diazepam) on intensity of diurnal sweating on days 2 and 3. The control groups used were the same as the previous diurnal sweating graphs (Figs. 4.10 and 4.11), however, the alcohol withdrawal group was separated into those that received benzodiazepines on that day, and those that did not (n=23 and n=7 for both days respectively). There were only 3 subjects who did not receive benzodiazepines on day 1 which was not a large enough sample to perform statistical analysis.

The analysis from day 2 (Fig. 4.15) showed that subjects who were not administered benzodiazepines had higher levels of sweating throughout the 24 hour period than the subjects that did receive benzodiazepines. Significant differences were observed at 2100, 2300 and 0100 (all *p<0.05) and at 2400 (***p<0.001). Day 3 (Fig. 4.16) was similar, showing increased sweating in those withdrawal subjects who did not receive benzodiazepines, with significant differences between the two withdrawal groups at 1800, 2100, 2200, 2300 and 0100 (*p<0.05 for all).

Fig. 4.15

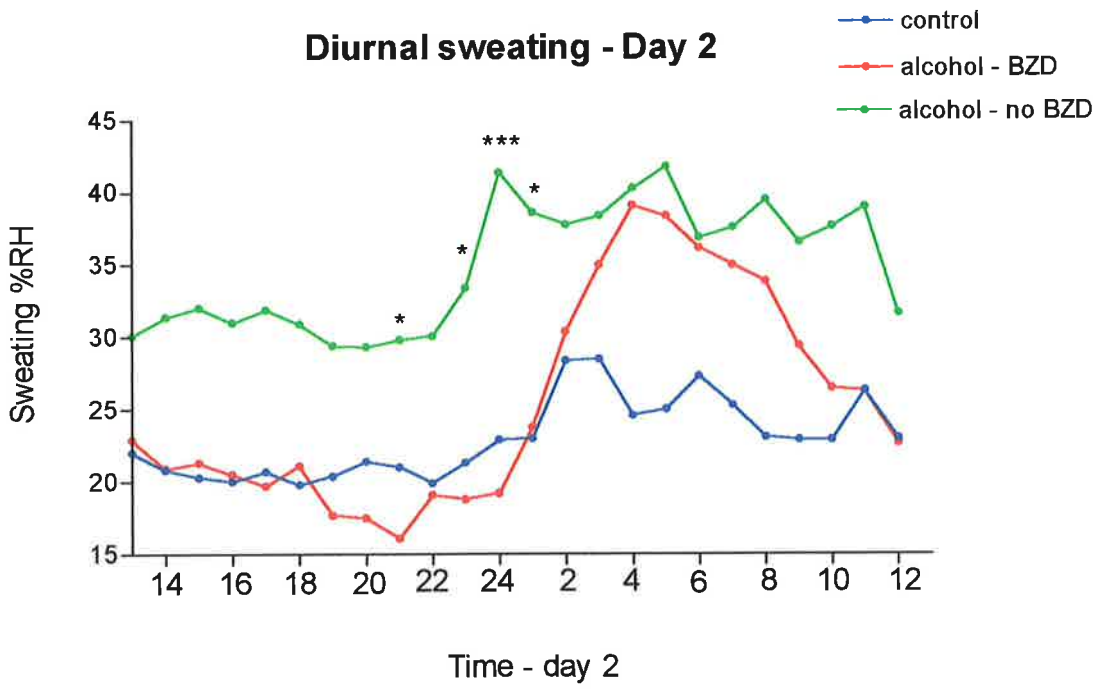


*Fig 4.15 Diurnal sweating expressed hourly, showing control subjects, and comparing withdrawal subjects who received BZDs with withdrawal subjects who did not receive BZDs, on day 2 following last drink, * p≤0.05, *** p≤0.001. Size of control group day 2, n=30; size of alcohol withdrawal alone day 2, n=7; size of alcohol withdrawal and BZD day 2, n=23.*

Fig. 4.16

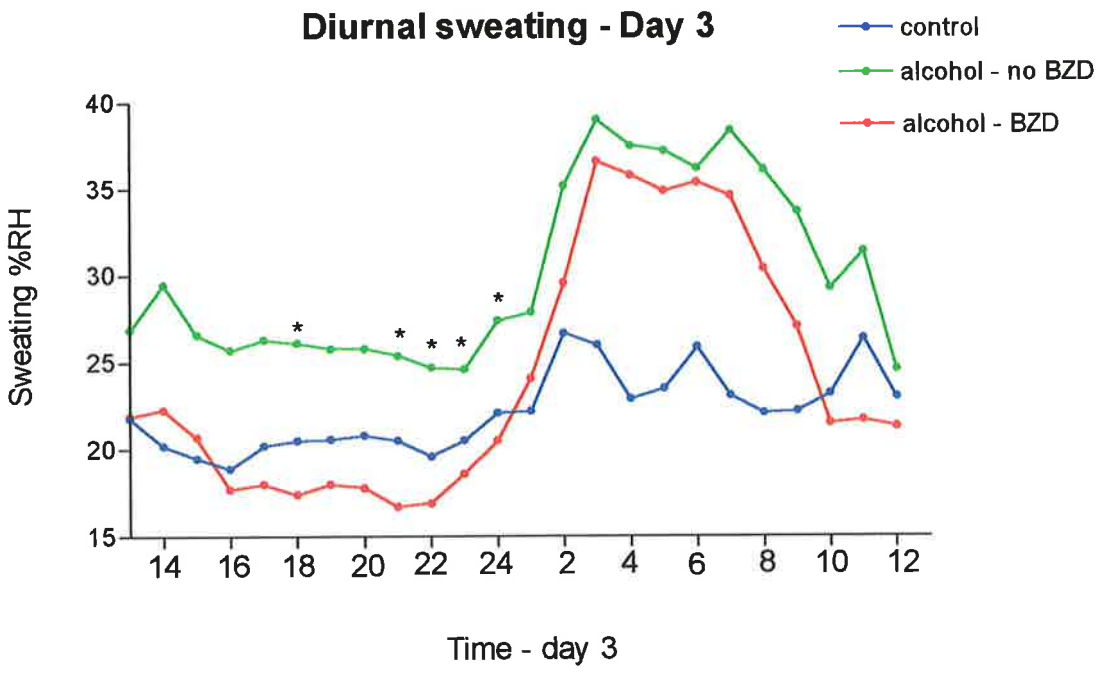


*Fig 4.16 Diurnal sweating expressed hourly, showing control subjects, and comparing withdrawal subjects who received BZDs with withdrawal subjects who did not receive BZDs, on day 3 following last drink, * $p \leq 0.05$. Size of control group day 3, n=30; size of alcohol withdrawal alone day 3, n=7; size of alcohol withdrawal and BZD day 3, n=23.*

Skin Temperature Figs 4.17 and 4.18 show the effect of benzodiazepine administration on days 2 and 3 of diurnal skin temperature. The control group was the same as for the previous diurnal skin temperature graphs (Figs. 4.3 and 4.4). Accordingly, the withdrawal groups were classified by whether or not the subject received benzodiazepines on that day.

Day 2 shows that the two withdrawal groups had similar diurnal patterns, characterised by an increase in skin temperature in the afternoon, a decrease in the late afternoon to evening, a peak at around 0400 and a decrease in morning skin temperature. However, the group that were not administered benzodiazepines appeared to show enhanced skin temperature fluctuations, both in size and rate. This was particularly obvious for the increase in skin temperature at the beginning of the night, as evidenced by a more rapid increase (2400, $*p<0.05$), and decline (0600, $*p<0.05$) in the withdrawal subjects who did not receive benzodiazepines.

On day 3 (Fig. 4.18) the group not receiving benzodiazepines displayed a similar pattern as on day 2, although with an enhanced elevation in afternoon skin temperature compared with the benzodiazepine group (1300, $*p<0.05$). Skin temperature for the night period was similar for all three groups, although both withdrawal groups demonstrated a peak, contrasting with the trough at 0400 of the control group. Overall the benzodiazepine group displayed a skin temperature rhythm that was closer to the control group than the group that did not receive benzodiazepines.

Fig. 4.17

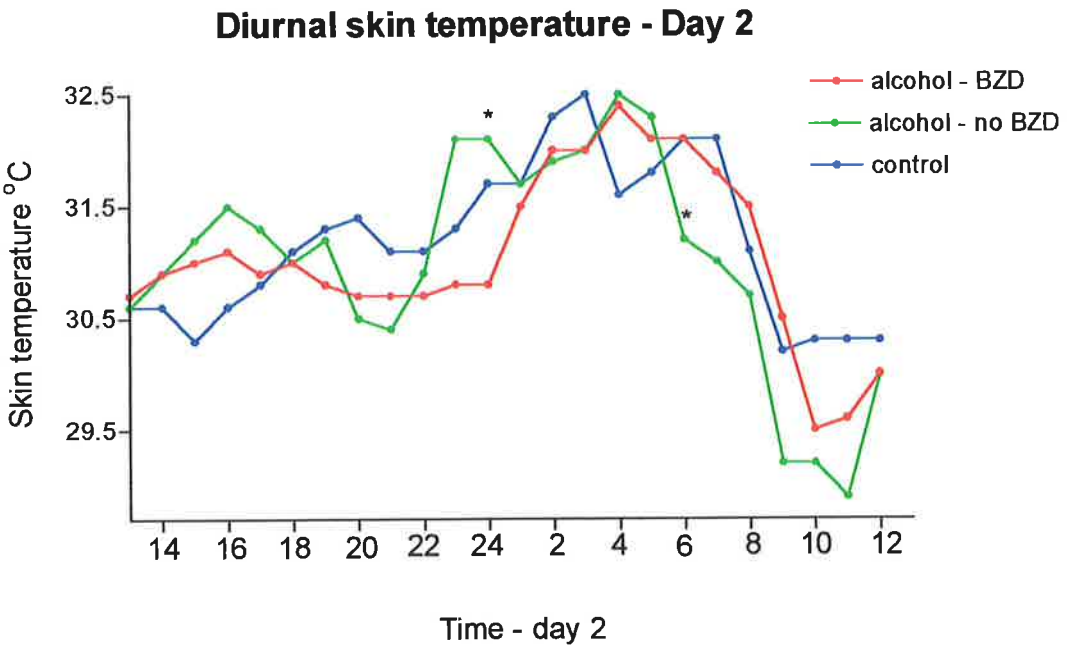


*Fig 4.17 Diurnal temperature expressed hourly, showing control subjects (n=30), and comparing withdrawal subjects who received BZDs (n=23) with withdrawal subjects who did not receive BZDs, on day 2 following last drink (n=7), * p≤0.05.*

Fig. 4.18

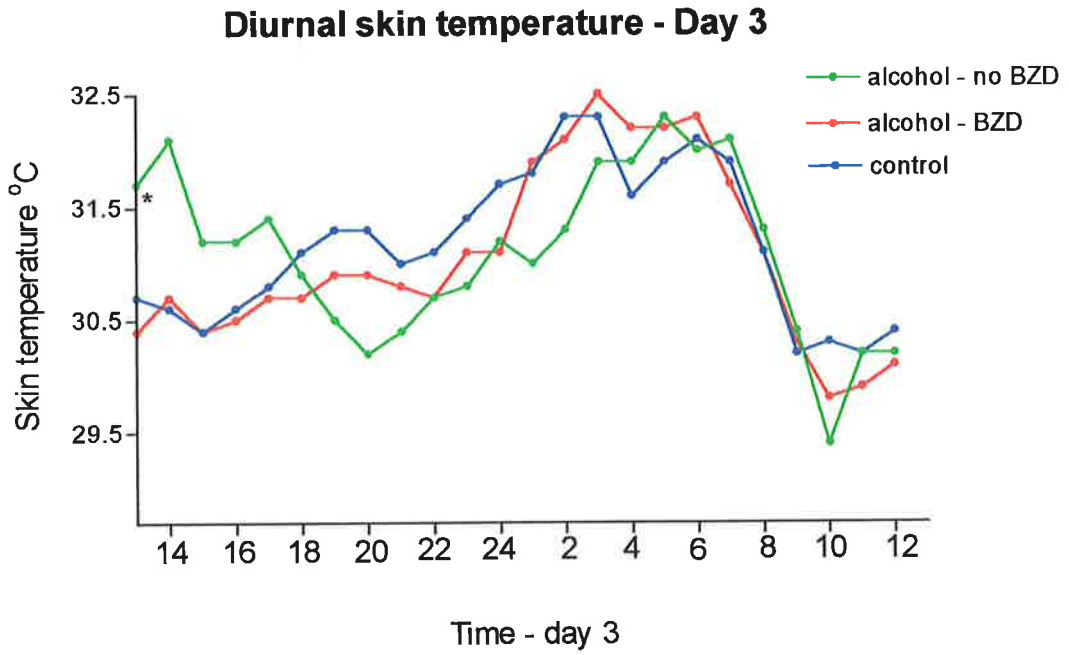


*Fig 4.18 Diurnal temperature expressed hourly, showing control subjects (n=30), and comparing withdrawal subjects who received BZDs (n=23) with withdrawal subjects who did not receive BZDs, on day 3 following last drink (n=7), * p≤0.05.*

4.3.6 Activity - average over twenty-four hours

There were no significant differences in average, twenty four hour activity between control subjects and withdrawal subjects (Fig. 4.19). This was the case for both inpatient and outpatient periods. However, it appeared that both control and withdrawal subjects expressed greater levels of activity during the outpatient period. Mean and SEMs are shown in appendices.

Fig. 4.19

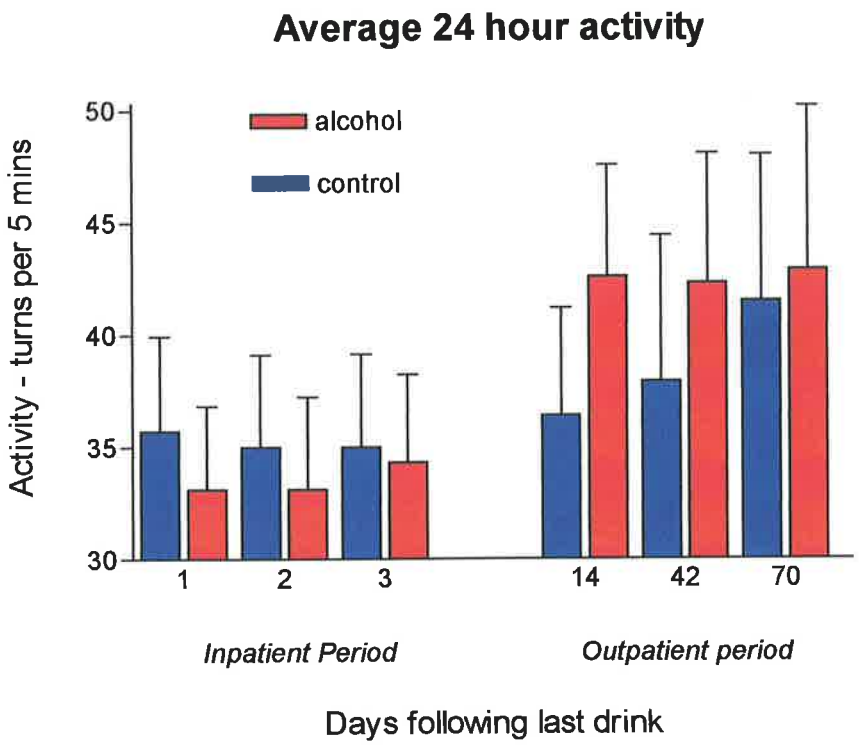


*Fig. 4.19 Comparison of average 24 hour activity between withdrawal and matched control subjects for days 1, 2, 3, 14, 42 & 70 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 1, n=30; day 2, n=30; day 3, n=30; day 14, n=25; day 42, n=15; day 70, n=12.*

4.3.7 'Day time' activity - average between 8am - 11pm

When total activity over twenty four hours was divided into two major phases - activity during sleep, and activity during the day (hours 8pm to 11pm) - no significant difference between control subject and withdrawal subjects in day activity was observed (Fig. 4.20). This was the case for both inpatient and outpatient periods. However, there was a trend for withdrawal subjects to be less active than control subjects during the inpatient period, and more or equally as active than their matched controls during the outpatient period. While not investigated statistically, the control subjects who were matched with withdrawal subjects that had not relapsed and whose data was presented during the outpatient period, appeared to be more active persons. The means and SEMs are shown in the appendices.

Fig. 4.20

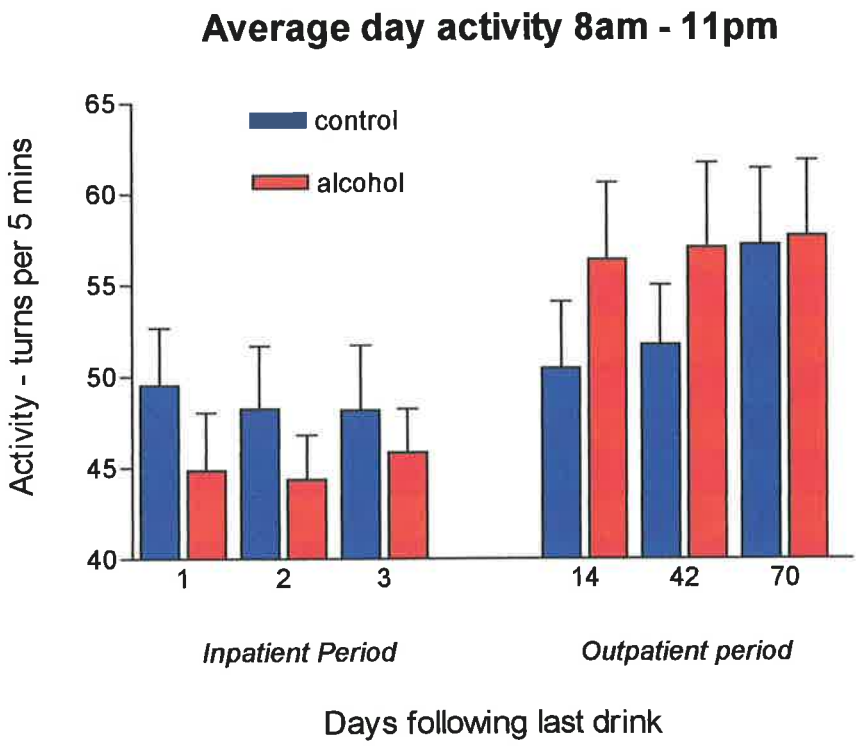


*Fig. 4.20 Comparison of average day activity (8am – 11pm) between withdrawal and matched control subjects for days 1, 2, 3, 14, 42 & 70 following last drink, * $p \leq 0.05$. Size of each group (control and experimental): day 1, n=30; day 2, n=30; day 3, n=30; day 14, n=25; day 42, n=15; day 70, n=12.*

4.3.8 Mean activity during sleep

When activity was assessed during the period when subjects were sleeping, those experiencing withdrawal from alcohol had significantly greater levels of activity compared with control subjects, for all days during the inpatient period (Days 1 & 2, **p<0.01; Day 3 *p<0.05) (Fig. 4.21). During the outpatient period, withdrawal subjects had significantly increased levels of activity during sleep on the nights of day 14 (***p<0.001) and day 42 (*p<0.05), and tended to have increased sleep restlessness on day 70, although this was not significant (p = 0.16). The means and SEMs are shown in the appendices.

Fig. 4.21

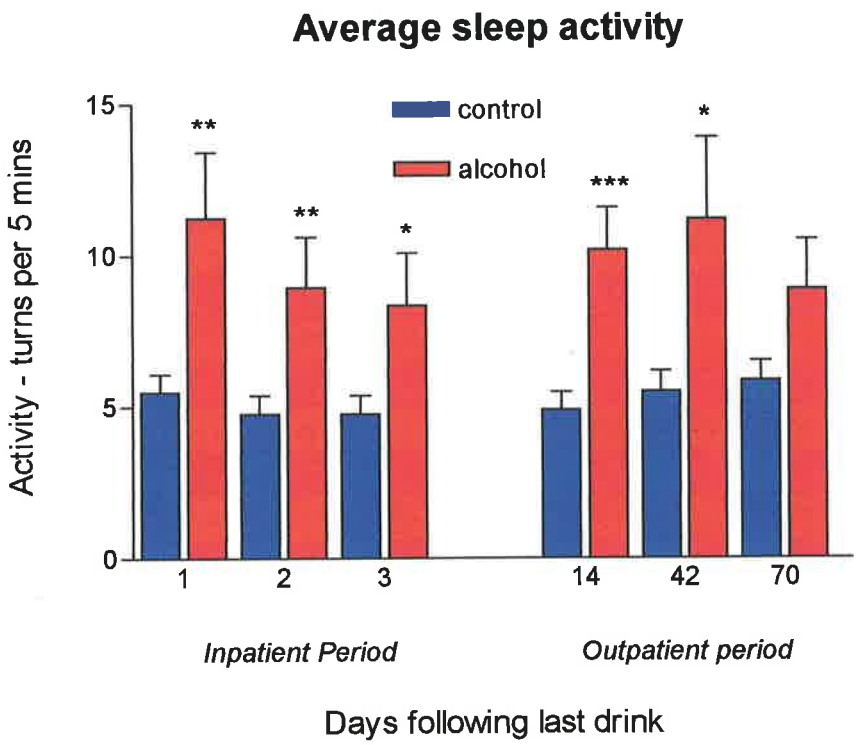


*Fig. 4.21 Comparison of average sleep activity between withdrawal and matched control subjects for days 1, 2, 3, 14, 42 & 70 following last drink, * p≤0.05, ** p≤0.01, *** p≤0.001. Size of each group (control and experimental): day 1, n=30; day 2, n=30; day 3, n=30; day 14, n=25; day 42, n=15; day 70, n=12.*

4.3.9 'Day time' activity - diurnal recordings between 0800 and 2300

The control subjects displayed a consistent activity pattern between 0800 and 2300 (Figs. 4.22 - 4.27). This was characterised by a rapid increase in activity from 0800, culminating in a peak of activity at 1000. This was the most active time of day for the control subjects. Activity gradually decreased over the remainder of the morning, and descended to a minimum by 1300. During the course of the afternoon, activity slowly increased until around 1800, where it rapidly dropped to a level comparable with that seen at 1300. There was another small rise in activity from 1900, culminating at around 2100, and then gradually decreasing for the night.

The withdrawal subjects displayed contrasting day activity rhythms compared with those of the control subjects. During the inpatient period, the activity pattern for withdrawal subjects was similar on all days (Days 1, 2 and 3 correspond with Figs. 4.22, 4.23 and 4.24 respectively). This was characterised by a lower level of activity than control subjects from 0800 to 1200, which was significant on day 1 (1000 and 1100, ***$p<0.001$), and tended to be lower on days 2 and 3, although did not reach significance (day 2: 1100 $p=0.06$, 1200 $p=0.10$; day 3: 1000 $p=0.16$, 1100 $p=0.12$). At 1200 activity increased, culminating at a peak at 1300 which was significant on days 1 (***$p<0.001$), 2 and 3 (*$p<0.05$ for both). The peak at 1300 was the highest level of activity displayed between 0800 and 2300, particularly on day 1.

Following the maxima at 1300, activity rapidly decreased, returning to a level comparable with control data by between 1400 and 1500. Similar to the control subjects, there was an increase in activity at around 1800. This tended to occur more rapidly for withdrawal subjects than for control subjects, particularly on days 1 and 2. In contrast to control subjects, there was no other period of increased activity, but rather a gradual decrease in activity until 2300 (means and SEMs shown in appendices).

Diurnal daily activity 8am - 11pm

Fig. 4.22

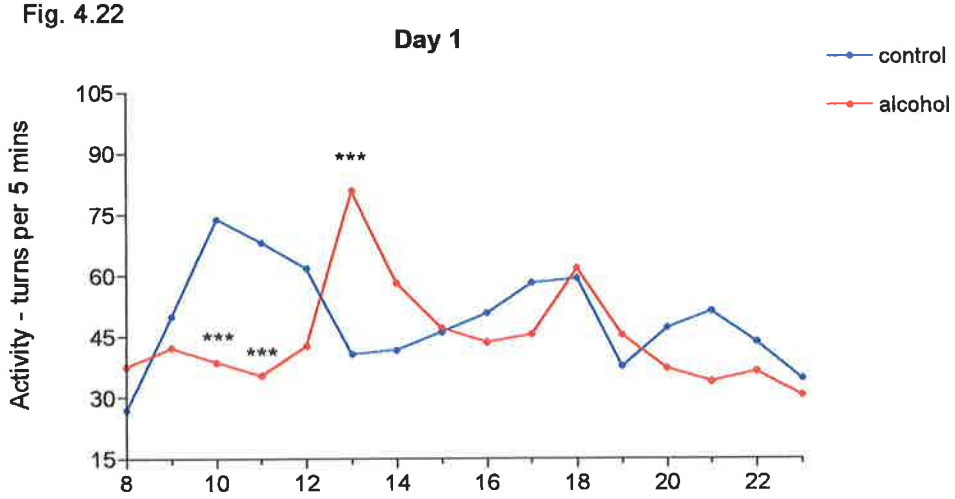


Fig. 4.23

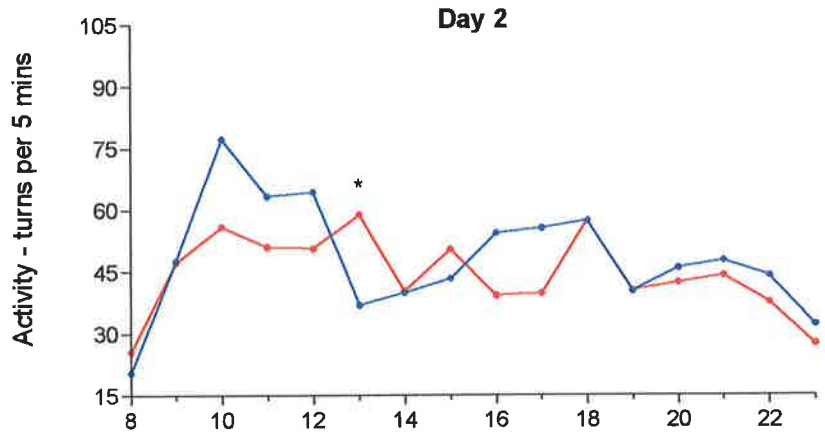
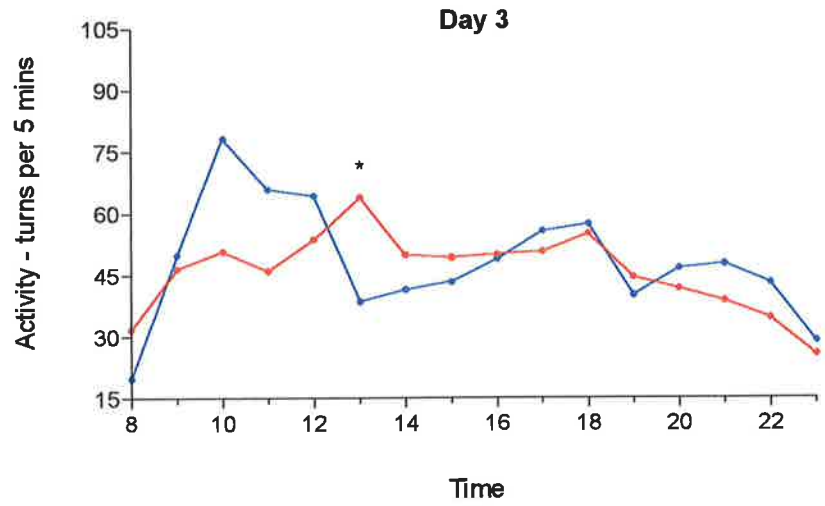


Fig. 4.24



*Figs. 4.22, 4.23 & 4.24 Diurnal daily activity (8am-11pm) expressed hourly, comparing control subjects with withdrawal subjects on days 1 (n=30), 2 (n=30) & 3 (n=30) respectively, following last drink, *p≤0.05, ***p≤0.001.*

During the outpatient period the withdrawal subjects experienced an overall increase in activity levels, although maintained a structurally similar pattern to the activity expressed during inpatient period (Days 14, 42 and 70 correspond with Figs. 4.25, 4.26 and 4.27). The peak observed at 1300 during the inpatient period was significantly enhanced, and tended to last for longer during the outpatient period - day 14 (***1300 $p<0.001$, 1400 **$p<0.01$, 1500 *$p<0.05$, 1600 $p = 0.08$), day 42 (1300 ***$p<0.001$, 1400 *$p<0.05$, 1500 $p = 0.12$) and day 70 (1300 ***$p<0.001$).

Morning activity (0800 to 1200) during the outpatient period was comparable with control levels of activity during that time, particularly on days 14 and 42. However, day 70 also showed a rapid and significant increase in activity from 0800 (*$p<0.05$) to 0900 (**$p<0.01$), which dropped back to control levels by 1000, where it remained until 1200.

Following the peak in activity at 1300, activity decreased, gradually on day 14 until 2300, and by 1500 on days 42 and 70. The remainder of days 42 and 70 involved a few small increases in activity during the afternoon, and then a fairly rapid drop in activity at 2100, resulting in a nadir at 2200 on days 42 (**$p<0.01$) and 70 (*$p<0.05$). However, the control subjects also expressed a higher level of activity at this time compared with previous days (means and SEMs shown in appendices).

Diurnal daily activity 8am - 11pm

Fig. 4.25

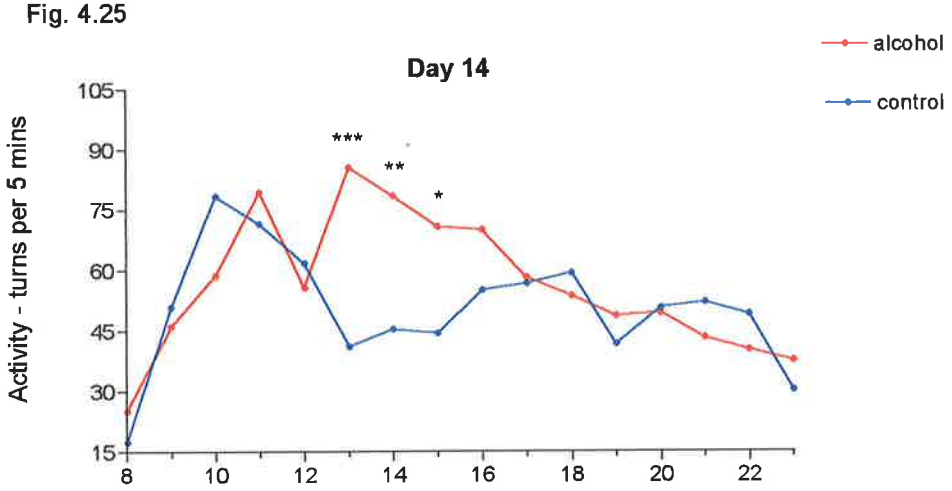


Fig. 4.26

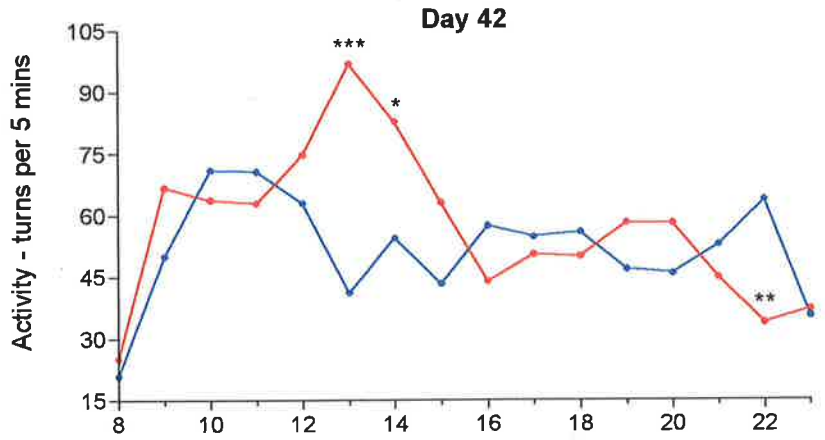
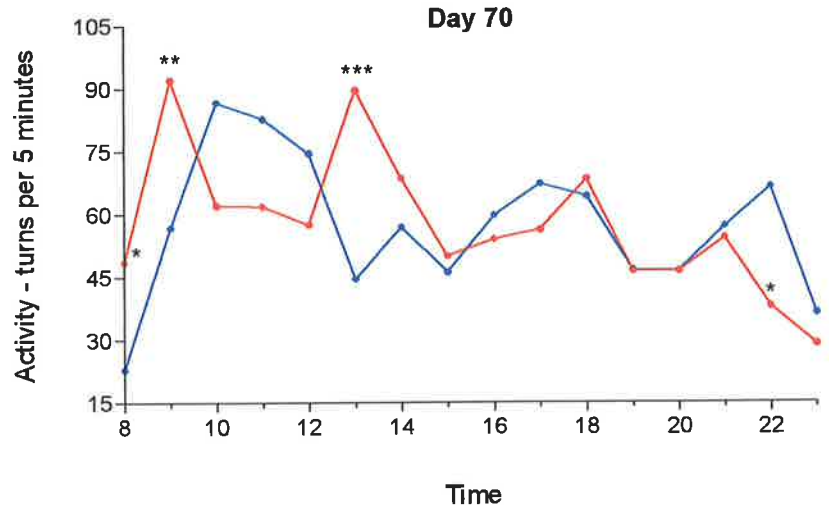


Fig. 4.27



*Figs. 4.25, 4.26 & 4.27 Diurnal daily activity (8am-11pm) expressed hourly, comparing control subjects with withdrawal subjects on days 14 (n=25), 42 (n=15) & 70 (n=12) respectively, following last drink, *p≤0.05, **p≤0.05, ***p≤0.001.*

4.3.10 Activity - night diurnal recordings between 2400 and 0700

Night activity for the control subjects was characterised by a gradual decline in activity at the beginning of the night, which stabilised by around 0300, and commenced rising, albeit slowly, at around 0500 (Figs. 4.28 - 4.33. Means and SEMs in appendices).

Night activity for the withdrawal subjects was fairly consistent on most of the nights. Overall, withdrawal subjects had higher levels of activity than control subjects at most time points, although there was no statistical significance for any one time point. Days 1, 2, 3, 14 ,42 and 70 correspond with Figs. 4.28, 4.29, 4.30, 4.31, 4.32 and 4.33 respectively. The prominent feature of withdrawal night activity was enhanced activity at the beginning and/or the end of the night compared with control activity, the only exception being night 42. The other characteristic feature of night activity were peaks of activity that occurred during the night. This was observed for withdrawal subjects on nights1 at 0400, night 14 at 0500, night 42 at 0400 and night 70 at 0100. However, control subjects also experienced a peak on night 1 at 0500.

Diurnal night activity 12am - 7am

Fig. 4.28

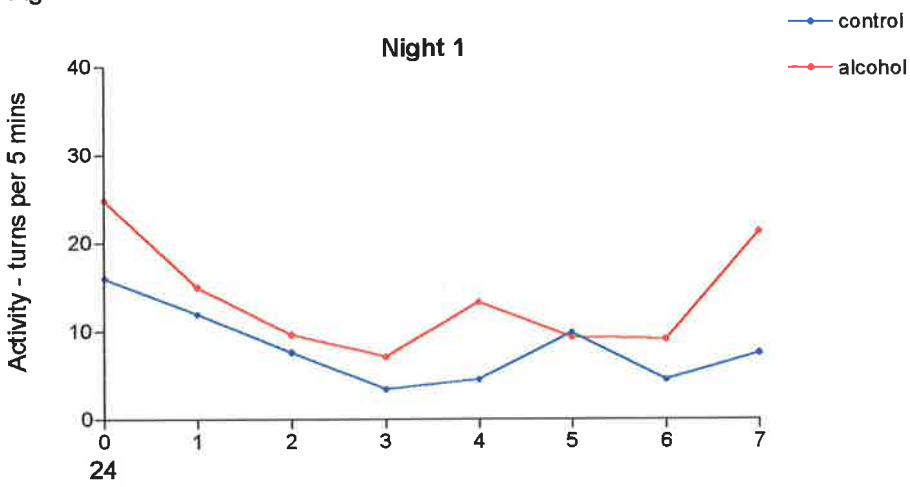


Fig. 4.29

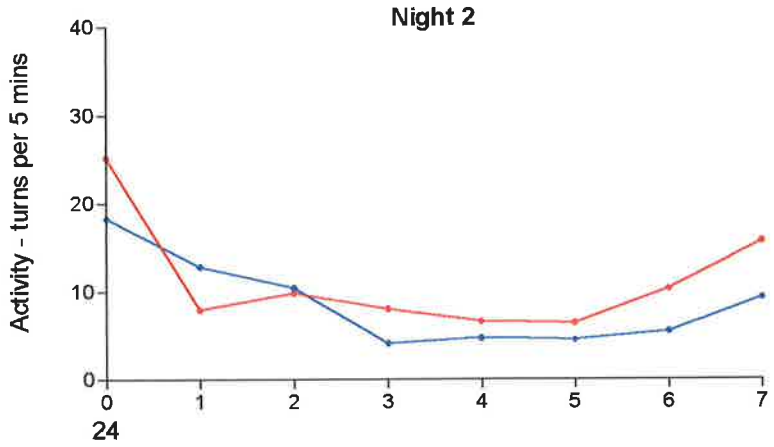
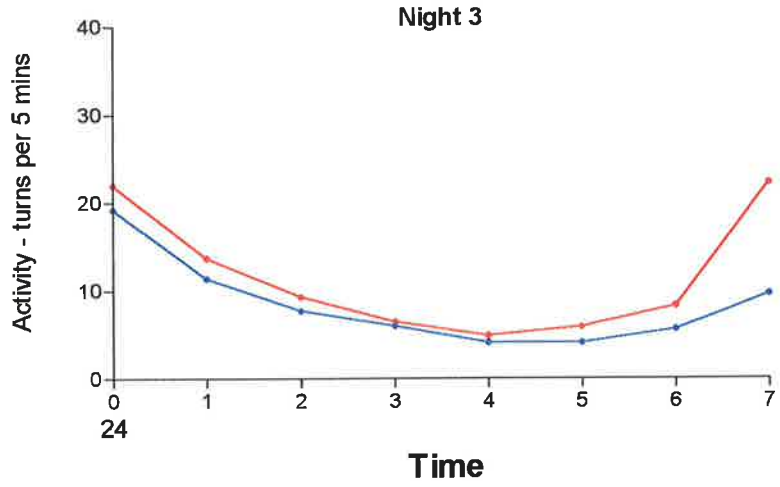


Fig. 4.30



*Figs. 4.28, 4.29 & 4.30 Diurnal night activity (12am-7am) expressed hourly, comparing control subjects with withdrawal subjects on days 1 (n=30), 2 (n=30) & 3 (n=30) respectively, following last drink, *p≤0.05.*

Fig. 4.31

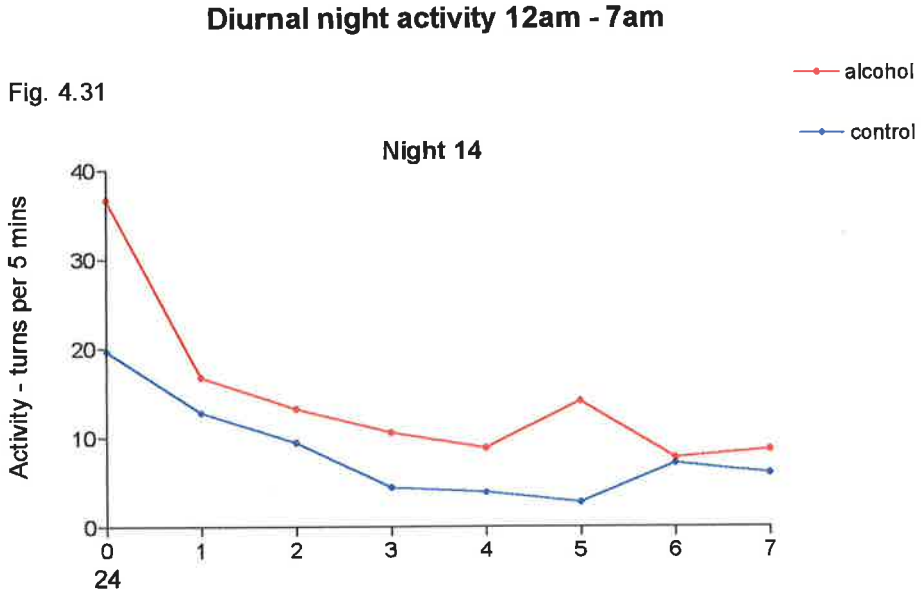


Fig. 4.32

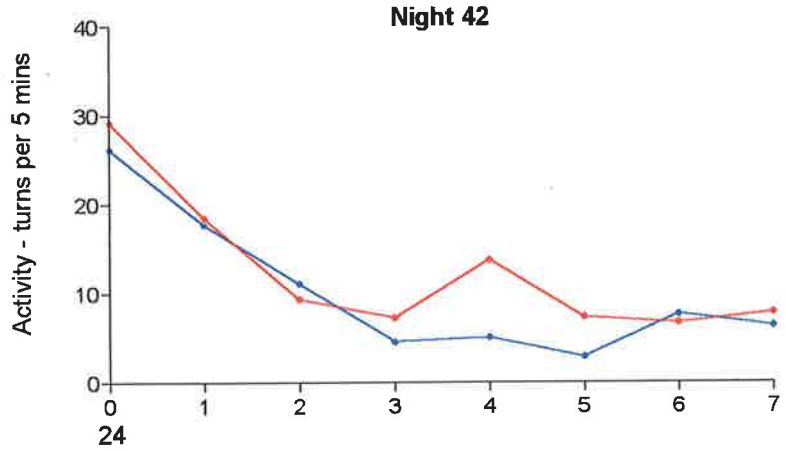
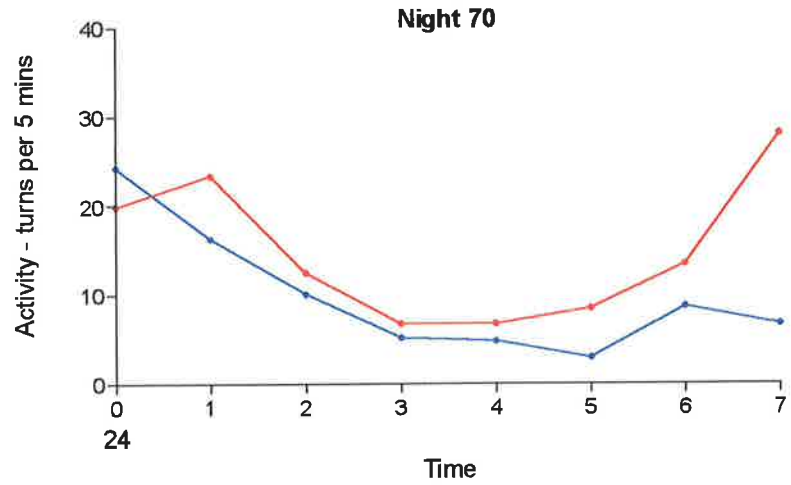


Fig. 4.33



*Figs. 4.31, 4.32 & 4.33 Diurnal night activity (12am-7am) expressed hourly, comparing control subjects with withdrawal subjects on days 14 (n=25), 42 (n=15) & 70 (n=12) respectively, following last drink, *p≤0.05.*

4.3.11 Beck Depression Inventory - total scores

Withdrawal subjects had significantly higher BDI scores on days 1, 4 and 14 when compared with the questionnaire norm (***p<0.001 for all days, norm = 9, Fig. 4.34). However, BDI scores improved over time and were within the asymptomatic range on days 42 and 70. Means and SEMs of BDI scores are shown in the appendices.

Fig. 4.34

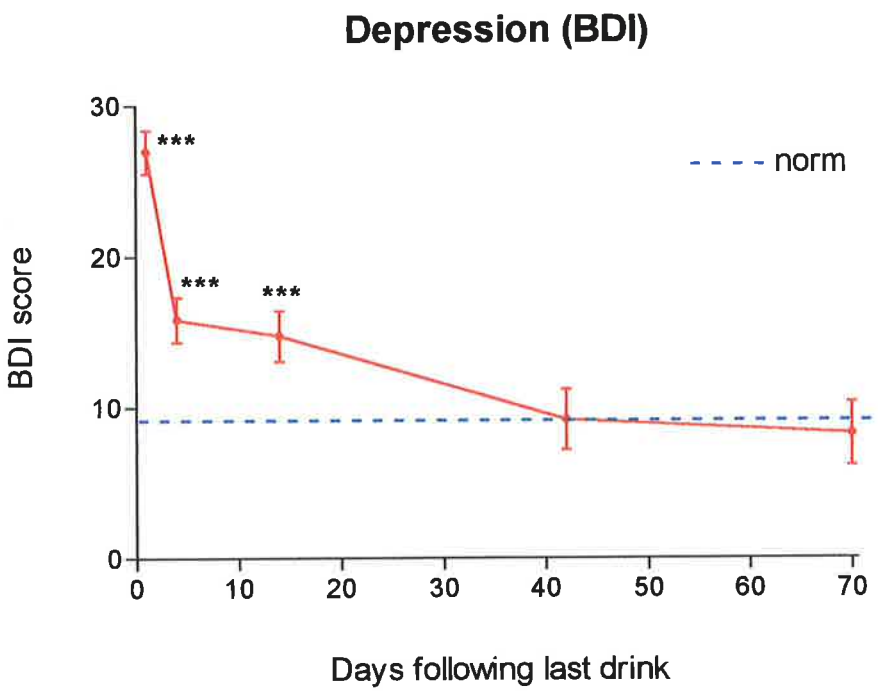


*Fig. 4.34 Mean BDI depression scores of withdrawal subjects compared with BDI asymptomatic norm on days 1, 4, 14, 42 & 70 following last drink, ***p≤0.001. Sample sizes were: day 1, n=30; day 4, n=30; day 14, n=26; day 42, n=16; day 70, n=14.*

4.3.12 State Trait Anxiety Inventory - total scores

Fig 4.35 shows that STAI scores for withdrawal subjects improved over the 70 day period, although were significantly higher than the questionnaire norm (norm = 36).on days 1, 4, 14 (***p<0.001), day 42 (**p<0.01) and while not significant on day 70, remained elevated (p=0.10). Means and SEMs of STAI scores are shown in the appendices.

Fig. 4.35

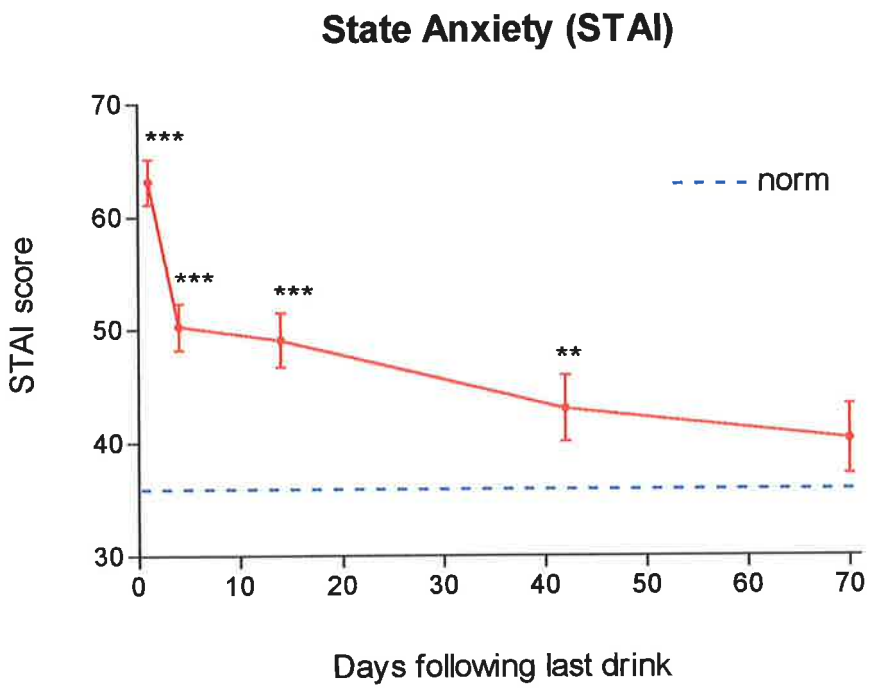


*Fig. 4.35 Mean STAI state anxiety scores of withdrawal subjects compared with STAI asymptomatic norm on days 1, 4, 14, 42 & 70 following last drink, **p≤0.01, ***p≤0.001. Sample sizes were: day 1, n=30; day 4, n=30; day 14, n=26; day 42, n=16; day 70, n=14.*

4.3.13 Beck Depression Inventory - item scores

In general, item scores improved over time, however some were particularly intractable. Moreover, there was a tendency for these symptoms to be associated with the highest scores on day 1. Table 4.1 shows mean item scores and the significance associated with the comparison of item scores with the normal score. The normal item score was obtained by dividing the normal total score (9) by the number of questions (21), yielding a normal item score of 0.428. The rationale for this method of comparison will be considered in the discussion.

The items, in order of low to high intensity and duration, are indicated below. All 21 items were significantly increased above the item norm on day 1. The items that were significantly elevated on day 1 only were; Q2 hopelessness, Q9 suicidal thoughts, Q12 social withdrawal, Q18 loss of appetite and Q19 weight loss. Items that remained significantly elevated above the item norm until day 4 only were; Q1 feeling sad, Q5 guilt, Q10 crying, Q11 irritability, Q14 body image and Q20 somatic preoccupations. Items that remained significantly raised until day 14 were; Q3 sense of failure, Q4 self-dissatisfaction, Q6 punishment, Q7 self-dislike, Q13 indecisiveness, Q17 fatigability and Q21 loss of libido, however Q21 was not significantly elevated on day 4. Items that remained significant until day 42 were; Q8 self accusations, Q15 work difficulty and Q16 insomnia. There were no significantly elevated items on day 70. The SEMs for item scores are in the appendices.

Table 4.1

Norm and mean values for Beck Depression Inventory (BDI) items on days 1, 4, 14, 42 & 70

Question number	Corresponding symptoms	Norm	Day 1	Day 4	Day 14	Day 42	Day 70
1	mood/feeling sad	0.428	**1.488**	**0.745**	0.508	0.212	0.374
2	Pessimism /hopelessness	0.428	**1.116**	0.525	0.615	0.313	0.525
3	sense of failure	0.428	**1.395**	**1.040**	**0.904**	0.646	0.552
4	self-dissatisfaction	0.428	**1.441**	**0.974**	**0.801**	0.536	0.345
5	guilt	0.428	**1.395**	**0.830**	0.620	0.364	0.151
6	punishment	0.428	**1.488**	**0.798**	**1.126**	0.515	0.740
7	self-dislike	0.428	**1.558**	**0.910**	**0.889**	0.524	0.472
8	self-accusations	0.428	**1.581**	**1.141**	**0.936**	**0.951**	0.655
9	suicidal ideas	0.428	**0.697**	0.377	0.280	0.047	0.106
10	crying	0.428	**1.325**	**0.836**	0.614	0.285	0.345
11	irritability	0.428	**0.976**	**0.800**	0.692	0.812	0.428
12	social withdrawal	0.428	**0.790**	0.388	0.510	0.264	0.316
13	indecisiveness	0.428	**1.488**	**0.806**	**0.711**	0.531	0.334
14	body image	0.428	**1.023**	**0.736**	0.636	0.472	0.461
15	work difficulty	0.428	**1.488**	**0.943**	**0.924**	**0.773**	0.400
16	insomnia	0.428	**1.720**	**1.041**	**1.051**	**0.870**	0.552
17	fatigability	0.428	**1.372**	**0.965**	**0.997**	0.450	0.551
18	loss of appetite	0.428	**1.418**	0.514	0.321	0.074	0.088
19	weight loss	0.428	**1.000**	0.383	0.307	0.241	0.216
20	somatic preoccupations	0.428	**1.441**	**0.766**	0.675	0.320	0.323
21	loss of libido	0.428	**0.744**	0.494	**0.795**	0.213	0.394

Item scores in **bold** denote significantly greater than average BDI item norm $p<0.05$.

4.3.14 State Trait Anxiety Inventory - item scores for state anxiety

Overall, item scores improved over time, however some items were raised above the item norm for longer than others. In contrast to the BDI, normal item scores were available for the STAI, and are shown in Table 4.2. Items that were most intractable also seemed to be the most severe on day 1. Table 4.2 shows the means and probability values for the withdrawal subjects' item scores compared with normal item scores.

The items, in order of low to high intensity and duration, are indicated below. All items were significantly increased from their item norms on day 1. The items that were significant on day 1 only were; Q7 worry about possible misfortune, Q9 feeling frightened, Q19 not feeling steady and Q20 feeling unpleasant. One item, Q8 dissatisfaction, remained significantly elevated above its norm until at least day 4. Items that remained elevated above their norms until at least day 14 were; Q1 not feeling calm, Q3 tension, Q4 strain, Q6 feeling upset, Q10 discomfort, Q12 nervousness, Q15 not feeling relaxed and Q17 worry. Items that were significantly greater than their norm at least until day 42 were; Q2 insecurity, Q5 dis ease and Q13 feeling jittery. The items that remained significantly elevated at least until day 70 were Q11 not feeling confident, Q12 nervousness, Q14 indecisiveness and Q18 confusion.

Table 4.2

Norms and mean values for State Trait Anxiety Inventory (STAI) items (state) on days 1, 4, 14, 42 & 70

Question number	Corresponding symptoms	Norm	Day 1	Day 4	Day 14	Day 42	Day 70
1	not feeling calm	1.74	**3.48**	**2.71**	**2.37**	2.06	2.02
2	insecurity	1.79	**3.27**	**2.53**	**2.62**	**2.27**	2.21
3	tension	1.54	**3.16**	**2.61**	**2.55**	1.89	1.97
4	strain	1.42	**3.04**	**2.66**	**2.30**	1.85	1.68
5	dis-ease	1.79	**3.34**	**2.79**	**2.54**	**2.78**	1.85
6	upset	1.35	**2.79**	**1.93**	**1.86**	1.54	1.33
7	worry about possible misfortune	2.12	**3.06**	2.42	2.27	2.04	2.04
8	dissatisfaction	2.46	**3.13**	**2.78**	2.71	2.66	2.52
9	frightened	2.01	**2.58**	2.19	1.80	1.76	1.40
10	discomfort	2.01	**3.39**	**2.59**	**2.51**	2.30	2.19
11	unconfident	1.58	**3.23**	**2.78**	**2.60**	**2.37**	**2.21**
12	nervousness	1.42	**3.11**	**2.47**	**2.17**	1.64	**1.90**
13	jittery	1.35	**3.20**	**2.26**	**2.11**	**1.71**	1.51
14	indecisive	1.43	**2.81**	**2.39**	**2.44**	**2.05**	**1.78**
15	not feeling relaxed	1.95	**3.44**	**2.61**	**2.72**	2.27	2.24
16	not feeling confident	2.37	**3.41**	**2.63**	**2.99**	2.55	2.70
17	worry	1.89	**3.18**	**2.63**	**2.58**	2.03	2.17
18	confusion	1.21	**2.83**	**2.29**	**2.32**	**1.85**	**1.85**
19	unsteady	2.98	**3.34**	2.53	2.58	2.63	2.34
20	unpleasant	2.28	**3.23**	2.33	2.45	2.26	2.06

Item scores in **bold** denote significantly greater than average STAI item norm $p<0.05$.

4.3.15 Profile Of Mood States

Depression-dejection Fig. 4.36 shows that these scores improved over time, and were within the normal range on days 42 and 70. Day 1 had the highest score, and was significantly higher than the questionnaire norm for depression-dejection (***p<0.001). Days 4 and 14 were also significantly elevated (**p<0.01 and *p<0.05). The means and SEMs of scores on days 42 and 70 were within the normal range (norm = 12.5). The means and SEMs are shown in the appendices.

Confusion-bewilderment Fig. 4.37 shows that there was an improvement in these scores over time. Day 1 had the highest score, which was significantly increased compared with the questionnaire norm (***p<0.001). Days 4 and 14 were also significantly elevated (*p<0.05 and **p<0.01 respectively). Days 42 and 70 were within the normal range for confusion-bewilderment (norm = 7.8). The means and SEMs are shown in the appendices.

Fatigue-inertia Fig 4.38 shows that fatigue-inertia improved over time. Day 1 scores were the highest, and was significantly greater than the questionnaire norm (***p<0.001). Days 4 and 14 were also significantly elevated above the norm (***p<0.001 for both). Days 42 and 70 were within the normal range (norm = 6.4). The means and SEMs are shown in the appendices.

Tension-anxiety Fig. 4.39 shows that tension-anxiety scores decreased over time. Day 1 had the highest score, which was significantly greater than the questionnaire norm for this parameter (***p<0.001) as was day 4 (**p<0.01). Days 14, 42 and 70 were within the normal range (norm = 12.1). The means and SEMs are shown in the appendices.

Anger-hostility Day 1 showed a significantly higher score than the questionnaire norm for anger-hostility (***p<0.001, Fig. 4.40). Anger-hostility had decreased by day 4 and was within the normal range. Day 14 showed an increased average score, although this was not significant. Days 42 and 70 showed reduced anger-hostility compared with day 14, and were within the normal range (norm = 8.1). The means and SEMs are shown in the appendices.

Vigour-activity Fig. 4.41 shows that vigour-activity improved over time, where higher scores indicate greater vigour-activity. The withdrawal subjects had the lowest score on day 1, followed by days 4 and 14, none of which were significantly less than the questionnaire norm (norm = 11.4). On days 42 and 70, subjects had significantly high vigour-activity scores compared with the norm (**p<0.01). The means and SEMs are shown in the appendices.

Fig. 4.36

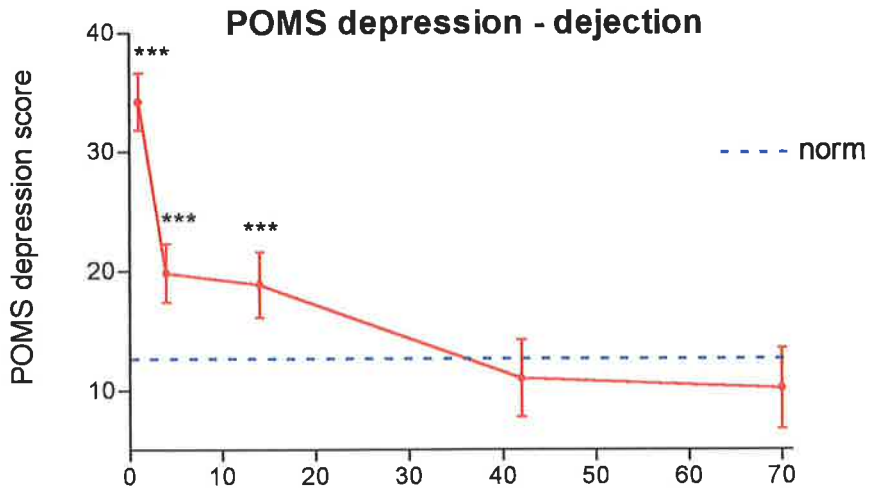


Fig. 4.37

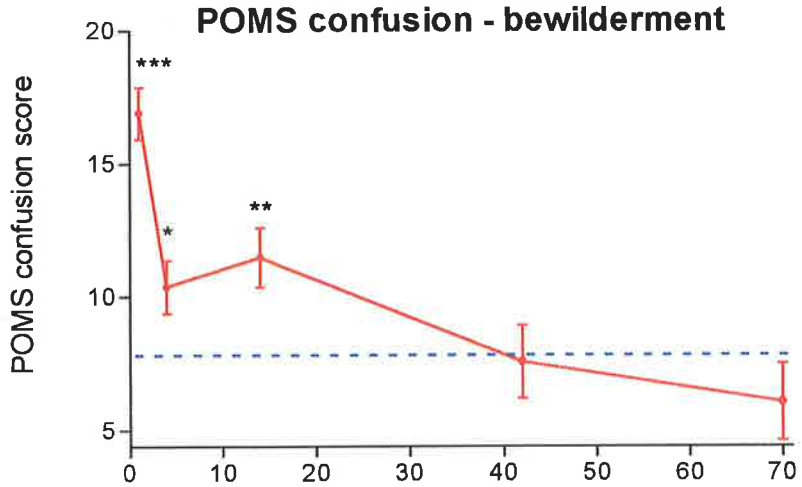
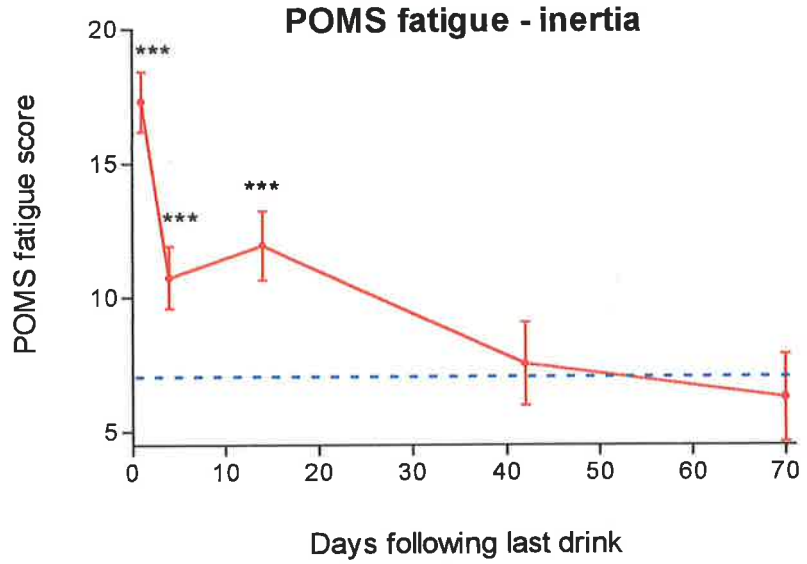


Fig. 4.38



*Figs. 4.36, 4.37 & 4.38. Mean POMS scores (depression-dejection, confusion-bewilderment, fatigue-inertia) of withdrawal subjects compared with asymptomatic norms on days 1, 4, 14, 42 & 70 following last drink, *p≤0.05, **p≤0.01, ***p≤0.001. Sample sizes were: day 1, n=30; day 4, n=30; day 14, n=26; day 42, n=16; day 70, n=14*

Fig. 4.39

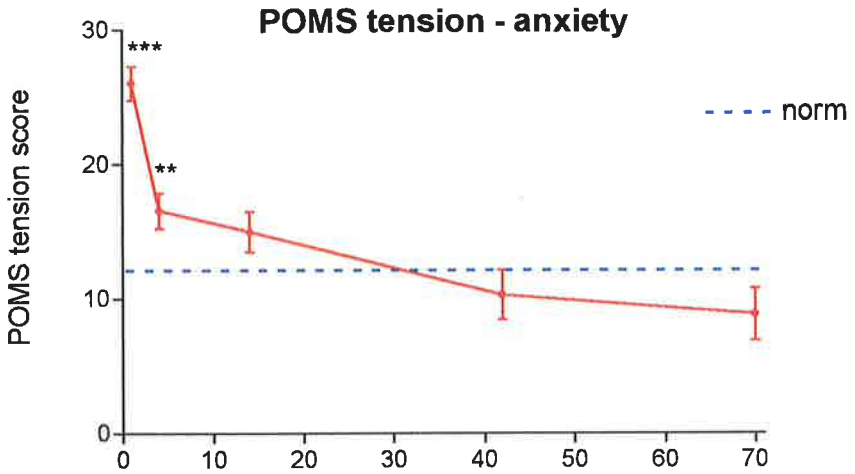


Fig. 4.40

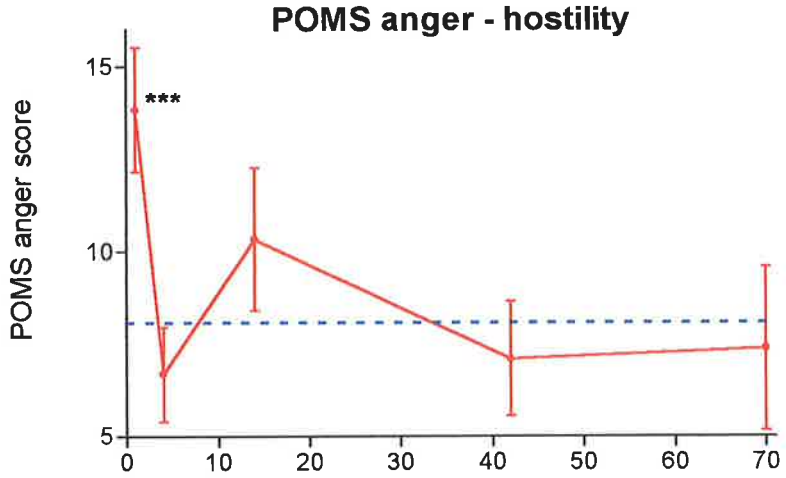
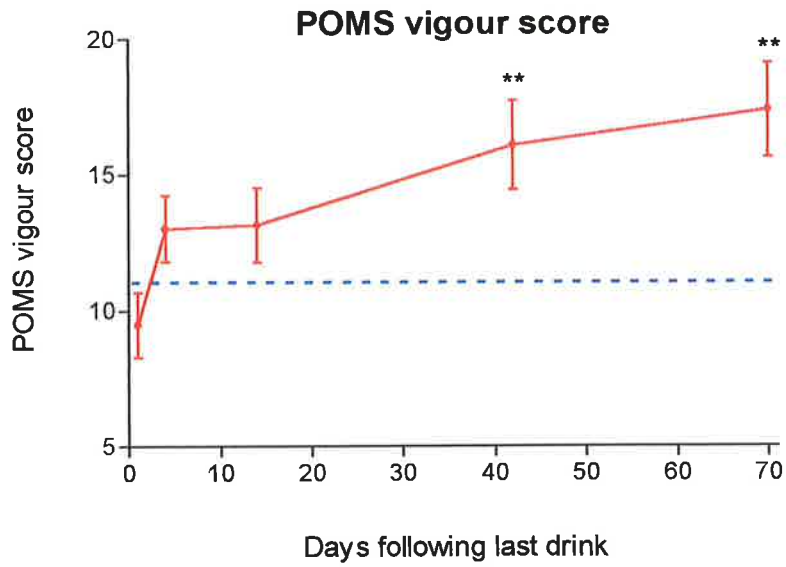


Fig. 4.41



Days following last drink

*Figs. 4.39, 4.40 & 4.41. Mean POMS scores (tension-anxiety, anger-hostility, vigour) of withdrawal subjects compared with asymptomatic norms on days 1, 4, 14, 42 & 70 following last drink, *p≤0.05, **p≤0.01, ***p≤0.001. Sample sizes were: day 1, n=30; day 4, n=30; day 14, n=26; day 42, n=16; day 70, n=14.*

4.3.16 Short Form 36 health survey

Role-function physical Fig 4.42 shows that physical role-function improved over time, where higher scores reflect greater physical role-functionality (this directional rule applies to all items in the SF-36). Day 1 had the lowest score (***p<0.001), followed by day 14 (***p<0.001) in comparison with the norm (norm = 80.2). Days 42 and 70 were within the normal range. The means and SEMs are shown in the appendices.

Physical functioning Fig 4.43 reveals that physical functioning was poor for withdrawal subjects on day 1 (***p<0.001), day 14 (**p<0.01) and day 42 (p=0.08), but well within the normal range by day 70 (norm = 85.4). The means and SEMs are shown in the appendices.

Role-function emotional Fig. 4.44 shows that emotional role-function was significantly decreased compared with the normal value on all days (norm = 87.5). That is, scores were significantly decreased on day 1 (***p<0.001), day 14 (***p<0.001), day 42 (*p<0.05) and day 70 (**p<0.01). The means and SEMs are shown in the appendices.

Social functioning Fig. 4.45 indicates that social functioning improved over time, however scores were significantly lower than the norm on days 1 and 14 (***p< 0.001 for both). Days 42 and 70 had scores within the normal range (norm = 88.2). The means and SEMs are shown in the appendices.

Fig. 4.42

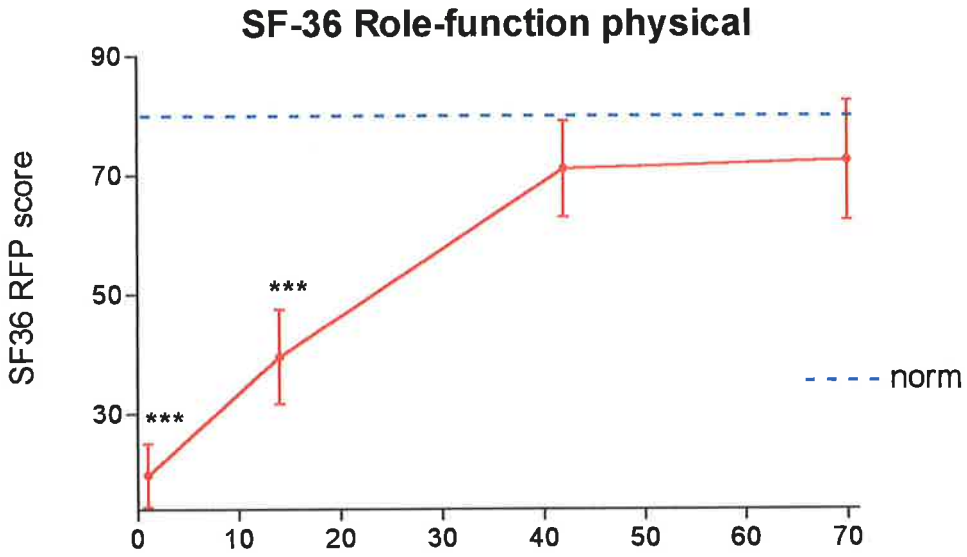
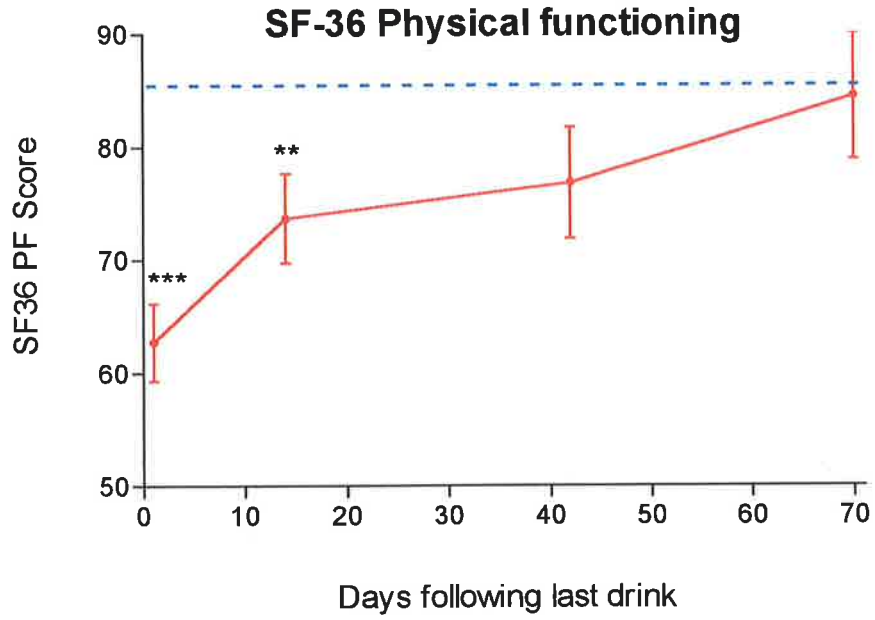


Fig. 4.43



*Figs. 4.42 & 4.43. Mean SF-36 scores (role-function physical, physical functioning) of withdrawal subjects compared with asymptomatic norms on days 1, 14, 42 & 70 following last drink, **p≤0.01, ***p≤0.001. Sample sizes were: day 1, n=30; day 14, n=24; day 42, n=15; day 70, n=13.*

Fig. 4.44

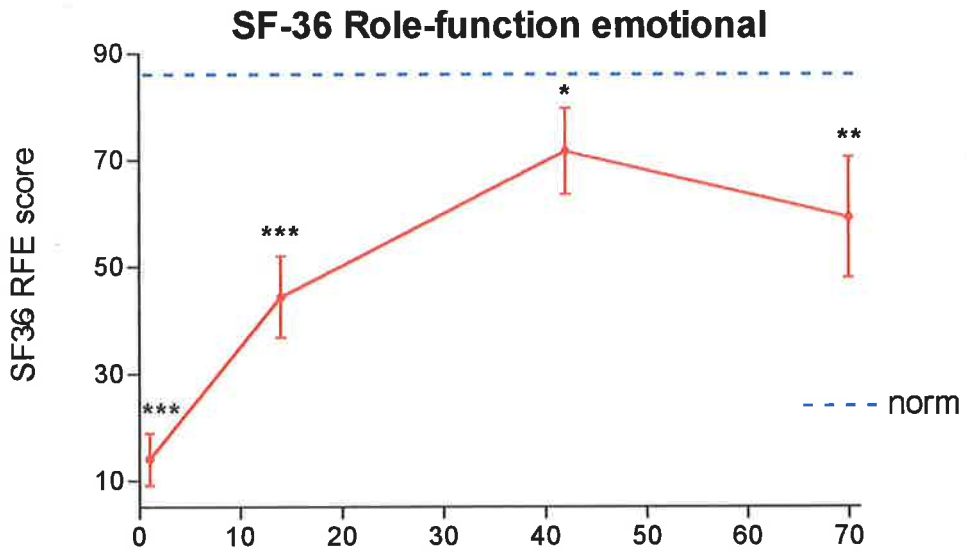
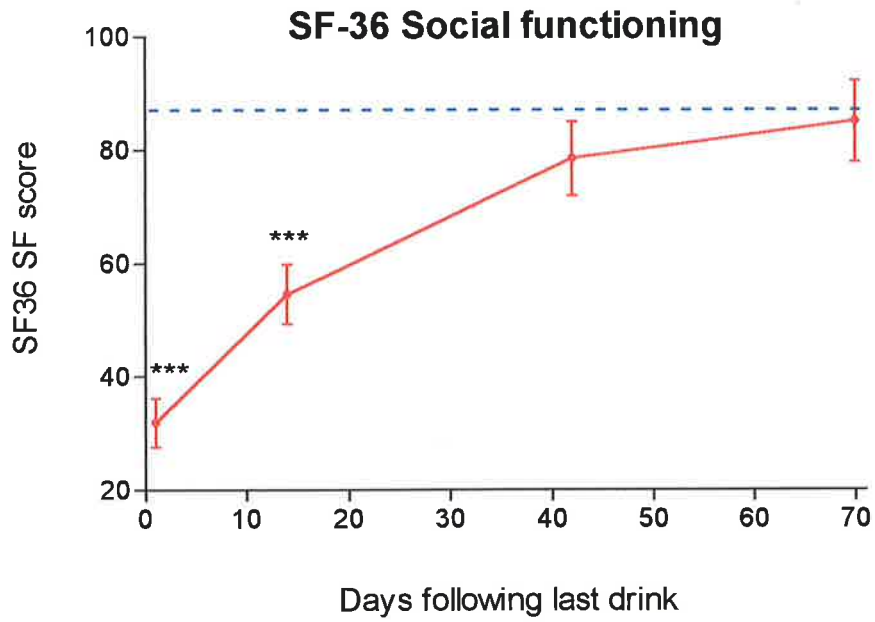


Fig. 4.45



*Figs. 4.44 & 4.45. Mean SF-36 scores (role-function emotional, social functioning) of withdrawal subjects compared with asymptomatic norms on days 1, 14, 42 & 70 following last drink, *p≤0.05, **p≤0.01, ***p≤0.001. Sample sizes were: day 1, n=30; day 14, n=24; day 42, n=15; day 70, n=13.*

Bodily pain Fig 4.46 shows the results of bodily pain scores, which were significantly worse on day 1 (***p<0.001), and day 14 (*p<0.05) but were within the normal range on days 42 and 70 (norm = 77.2). The means and SEMs are shown in the appendices.

Mental health Fig 4.47 shows that mental health scores were significantly decreased on days 1 and 14 (***p<0.001 for both), and showed a trend of attenuation on days 42 (p=0.12) and 70 (p=0.09) (norm = 78.7). The means and SEMs are shown in the appendices.

General health Fig. 4.48 shows that the withdrawal subjects' perception of their general health improved over time, albeit slowly. Days 1, 14 and 42 had significantly attenuated scores compared with the questionnaire norm (***p<0.001, ***p<0.001, **p<0.01). Day 70 approached the norm (norm = 73.2). The means and SEMs are shown in the appendices.

Vitality Similar to mental health, vitality improved over time, and was within normal levels by day 42 (Fig. 4.49). Probability values were ***p<0.001 for days 1 and 14 compared with the norm (norm = 64). The means and SEMs are shown in the appendices.

Fig. 4.46

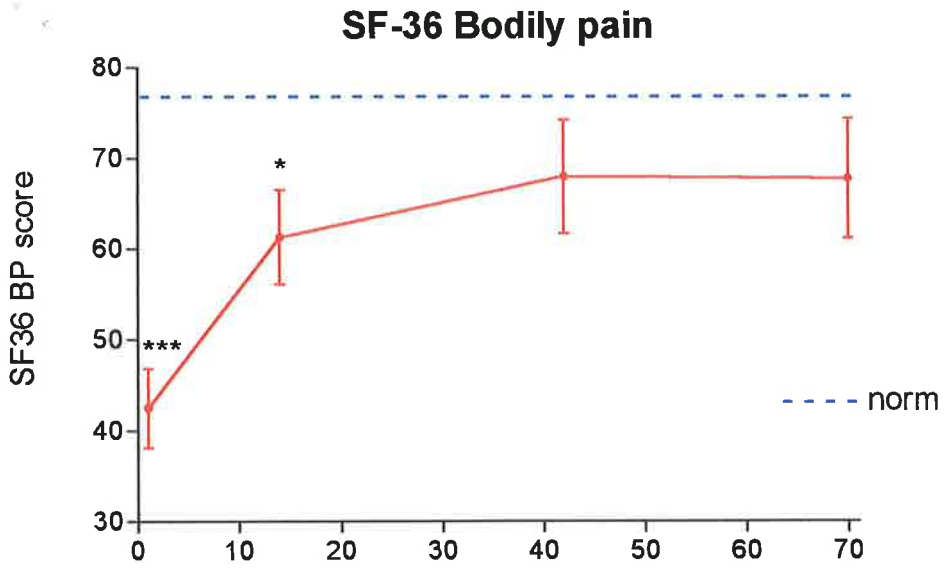
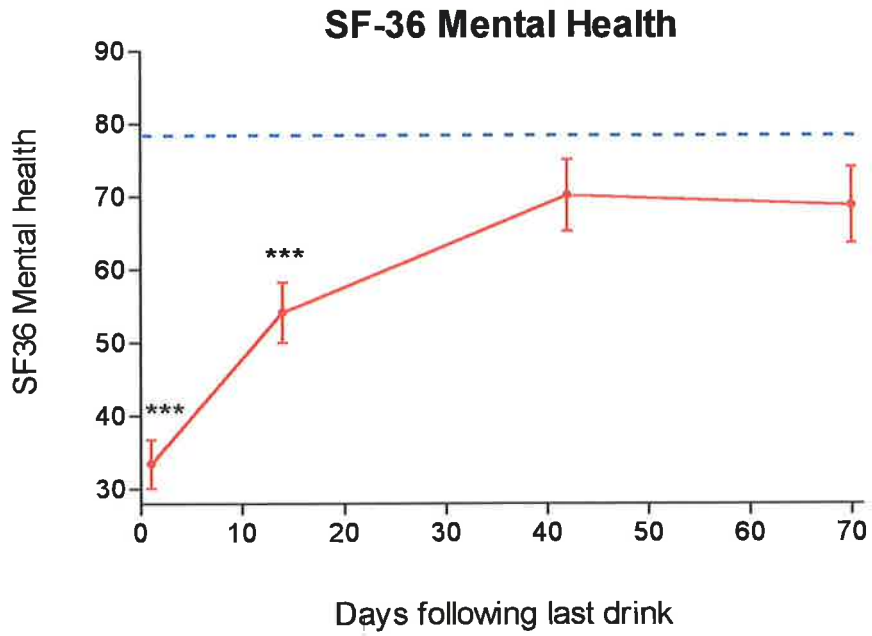


Fig. 4.47



*Figs. 4.46 & 4.47. Mean SF-36 scores (bodily pain, mental health) of withdrawal subjects compared with asymptomatic norms on days 1, 14, 42 & 70 following last drink, *p≤0.05, ***p≤0.001. Sample sizes were: day 1, n=30; day 14, n=24; day 42, n=15; day 70, n=13.*

Fig. 4.48

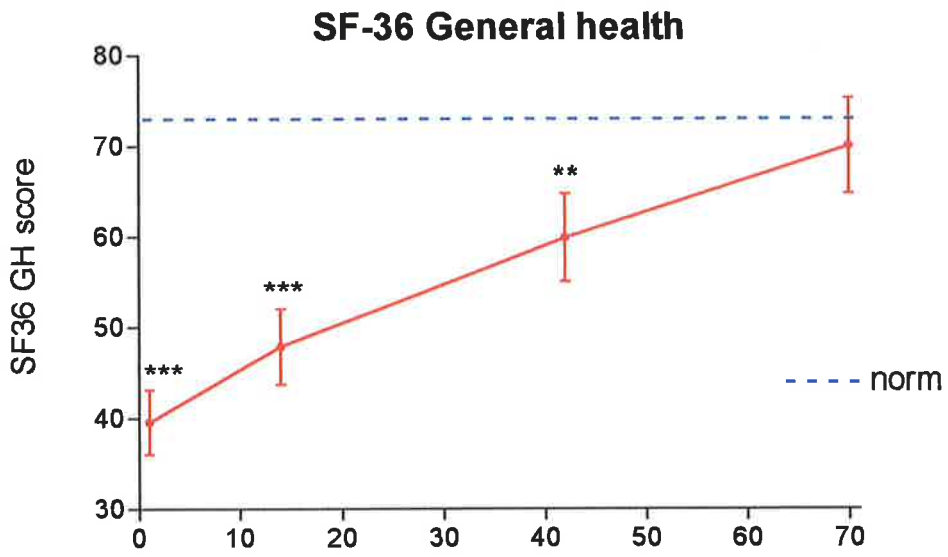
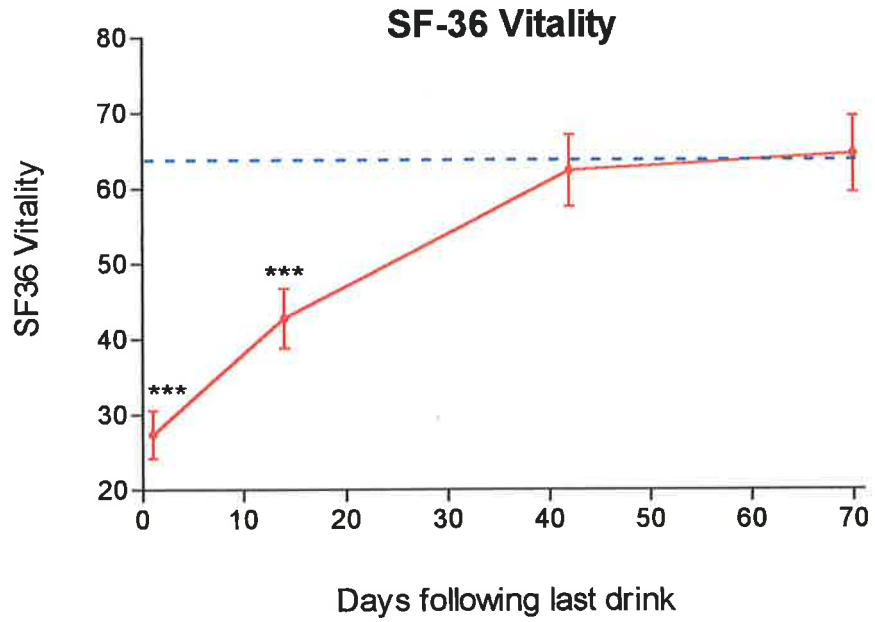


Fig. 4.49



*Figs. 4.48 & 4.49. Mean SF-36 scores (general health, vitality) of withdrawal subjects compared with asymptomatic norms on days 1, 14, 42 & 70 following last drink, **p≤0.01, ***p≤0.001. Sample sizes were: day 1, n=30; day 14, n=24; day 42, n=15; day 70, n=13.*

4.4 Discussion

4.4.1 Physical symptoms of withdrawal

Withdrawal from alcohol appeared to have two main effects on skin temperature: disruption to the diurnal rhythm, and overall hyperthermia. Disruption to the diurnal skin temperature rhythm was most obvious from observations of skin temperature hour by hour, rather than average twenty four hour skin temperature. While differences and fluctuations in temperature may always be observed between individuals, the disrupted temperature rhythms of withdrawal subjects followed a relatively consistent pattern over the inpatient period. However, average twenty four hour skin temperature clearly demonstrates the hyperthermia produced by alcohol withdrawal, although in the outpatient period only. Similarly, the hyperthermic effects of withdrawal were more obvious in the outpatient recordings of diurnal skin temperature. This may indicate a delayed effect of alcohol withdrawal on skin temperature, in which hyperthermia does not show until at least after the fourth day of withdrawal. However, a more plausible explanation is that the administration of benzodiazepines during the inpatient period suppressed the hyperthermia experienced by the withdrawal subjects. This is confirmed by other studies which have observed hyperthermia during acute withdrawal (Gross et al., 1973; Gross et al., 1974; Hershon, 1977; Clark & Friedman, 1985; King et al., 1991; Romach & Sellers, 1991).

Disruption to the diurnal skin temperature rhythm appeared to last well into the outpatient period, although it seems that the diurnal rhythm of withdrawal subjects was similar to the diurnal rhythm of the control subjects by day 70. Hyperthermia appeared to persist for about two to six weeks following cessation of drinking. While not strictly statistically significant on day 42, there was a trend for average twenty four hour skin temperature to be increased at this time, and significance may have been achieved had the sample sizes not been reduced due to loss of subjects through relapse.

The effects of alcohol withdrawal on skin temperature may be extrapolated to changes in core body temperature, since core and skin temperatures are related to each other in a relatively fixed manner. Over any twenty four hour period, the diurnal rhythm of core body temperature has an architecture which approximately reflects the mirror image of skin temperature (Houdas & Ring, 1982). That is, in normal or control subjects, core body temperature has two major components: a drop in

core temperature over the course of the night, and a rise in core temperature during the day. In contrast, skin temperature is increased during the night, and tends to be reduced during the day. This appears to be as a result of the body's homeostatic mechanisms to keep core temperature constant, and following a set diurnal pattern (Houdas & Ring, 1982). Since the relationship between core body temperature and skin temperature is relatively fixed, if core body temperature markedly increases beyond it's usual safe range, for example with fever, skin temperature also increases. The relationship between the diurnal pattern of skin temperature and core body temperature is still the same, however both are phase-shifted upwards. This appears to be the body's attempt to 'cool' the body down by letting off excess heat through the skin (Houdas & Ring, 1982). Accordingly, significant increases in skin temperature during alcohol withdrawal appear to reflect an increase in core body temperature.

Average twenty four hour sweating was also increased, although not significantly, during withdrawal from alcohol. The increase in sweating in withdrawal subjects was more pronounced during the inpatient period, than the outpatient period. However, the lack of statistical significance appeared to be a result of the wide variation in sweating over a twenty four hour period, as was demonstrated by the diurnal hour by hour recordings of sweating. The diurnal sweating recordings indicate that sweating in withdrawal subjects was markedly increased at night, commencing around midnight, and was most severe in the early hours of the morning. Sweating then slowly returned to 'day time' levels by noon the following day.

These results confirm patients' reports of more severe sweating during the night than during the day. Excessive sweating at night appeared to have returned to near normal levels by day 14. Interestingly, while 'day time' levels of sweating in withdrawal subjects seemed quite comparable with control subjects during the inpatient period, they appeared to be more elevated during the outpatient period. This may be due to increased variation because of the smaller sample size in the outpatient period. Alternatively, it may be that benzodiazepines, which were administered to inpatients predominantly during the day, as opposed to at night, suppressed 'day time' sweating. Since benzodiazepines were not received by subjects during the outpatient period, the 'unsuppressed' symptoms of sweating during the day were observed. (NB. Patients received benzodiazepines based on their CIWA-Ar scores of withdrawal severity, which were assessed several times daily. This study

population consisted of a random selection of subjects, some of whom received benzodiazepines during their inpatient stay, and some of whom did not).

Suppression of 'day time' sweating appears to be confirmed by the results showing the effects of benzodiazepines on sweating and skin temperature. Subjects who did not receive benzodiazepines demonstrated significantly more intense sweating during the day. While sweating was also increased at night in these subjects, it was not to the same degree as during the day, possibly because benzodiazepines were not administered at night to any of the inpatients, with the exception of 10 - 20 *mg* of temazepam. Temazepam has a short duration of action (t 1/2 = 6 - 20 hours) and 10 - 20 *mg* would also have a reduced effect in these subjects due to their increased tolerance to sedatives. Therefore it is unlikely that temazepam would have had any major effect on suppression of withdrawal symptoms.

As would be expected, benzodiazepines (predominantly diazepam) partially suppressed increased sweating caused by withdrawal from alcohol. This was also true for skin temperature disruption. The subjects who did not receive benzodiazepines had diurnal rhythms further 'removed' from the control subjects than the withdrawal subjects who did receive benzodiazepines. In conclusion, benzodiazepines suppressed withdrawal symptom severity (namely sweating and temperature rhythm disruptions), although not completely in these subjects. However, this data serves as an approximate guide to the effects of benzodiazepines on withdrawal. Some of the subjects who did not receive benzodiazepines may have been influenced, albeit to a small degree, by active metabolites of a drug taken the previous day. That is, diazepam has a half life of 20 hours or greater, and its active metabolite nordiazepam, while having a reduced efficacy, has a half life of greater than forty hours. However, effects of any benzodiazepine on these subjects would be greatly reduced, due to cross-tolerance between alcohol and this drug class.

Restlessness and agitation have been reported as symptoms of acute withdrawal (Gross et al., 1973; Edwards & Gross, 1976; Hershon, 1977). However, average twenty four hour activity was not increased in these inpatient subjects. Moreover, observations of average day activity between 8am and 11pm showed that the withdrawal subjects were less likely to be active than the control subjects during the inpatient period, and more active during the outpatient period, particularly on days 14 and 42. These differences were not significant, and the SEMs were quite large, suggesting a wide range of

variation in activity scores over a twenty four hour period. Interestingly, the average activity of the control subjects also appeared to be greater during the 'outpatient' than 'inpatient period' (NB. 'outpatient' control subjects refers to those control subjects who were matched to withdrawal subjects who were assessed during the outpatient period). The reason for this apparent heightened activity is unclear.

While average restlessness and agitation during the day were not marked, restlessness during sleep was, and withdrawal subjects were significantly more active during their sleep phase compared with controls. Moreover, hyperactivity during the sleep phase seemed to persist for at least six weeks, and possibly up to ten weeks. These data confirm patients' reports of difficulty in getting to sleep, early morning waking, punctuated periods of waking during the course of the night, and an overall disturbed sleep. While reports of disturbed sleep are not uncommon in the literature (Johnson et al., 1970; Allen et al., 1971; Lester et al., 1973; Gross and Hastey, 1977; Wagman and Allen, 1977; Gillin et al., 1990; Hemmeter et al., 1993; Le Bon et al., 1997), this appears to be the first study which has investigated sleep disturbance for a period of longer than four weeks, and found that disturbance of sleep is an intractable symptom lasting between six and ten weeks. Moreover, it has been investigated using methods which are readily transportable, and more comfortable for the subject.

Diurnal recordings of activity yielded novel information about activity patterns of withdrawal subjects. Most interesting were the differences in 'day time' (8am to 11pm) diurnal activity patterns, between control and withdrawal subjects. Control subjects experienced a lull in activity following lunch, preceding a morning of increased activity. However, withdrawal subjects consistently demonstrated a significant increase in activity following lunch, culminating in a peak of activity at around 1pm. This was a persistent feature of withdrawal, and appeared to last for at least ten weeks.

While withdrawal subjects appeared to experience a dampening of activity between 8am and noon during the inpatient period, they became almost equally as active as the control subjects at this time during the outpatient period. The culmination of activity at 1pm was also more intense during the outpatient period.

As mentioned above, agitation and restlessness are not uncommon in withdrawal, however it is interesting that withdrawal subjects appeared to be more restless at certain times of the day. Moreover, this feature of withdrawal persisted for at least ten weeks after drinking had stopped. It may

be that there was some degree of activity suppression by benzodiazepines during the inpatient period, only to be expressed with full intensity during the outpatient period, when benzodiazepines were not received by subjects. Once again, this was a novel finding, and suggests that hyperactivity is more intractable than previously realised, and is more likely to occur at specific times of the day.

Diurnal night activity recordings, between 12am and 7am demonstrated that withdrawal subjects showed a trend of higher levels of activity compared with controls at almost every time point, and that these differences were greatest at the beginning and end of the night. This persisted for the entire study period, and may support patient's reports of difficulty in getting to sleep, and early morning waking.

4.4.2 Mood and psychiatric changes

Withdrawal subjects were severely depressed on day 1 of withdrawal, and scored significantly higher than the normal score for the BDI. Moreover, their scores were comparable with diagnosis of a major depressive order (Steer et al., 1986; Steer et al., 1987). However, by the second and third administration (days 4 and 14), BDI scores had markedly improved, although still remained significantly elevated above an asymptomatic, normal score. Depression had significantly improved by days 42 and 70, and scores were within the normal range. The rate of improvement from day 14 to day 42 was not investigated in this study, although other researchers have found that depression of sober alcoholics had returned to within the normal range by three or four weeks of abstinence (Dorus et al., 1987; Brown & Schuckit, 1988; Haviland et al., 1988; Brown et al., 1995).

Depression also appeared to be symptom, or item specific, with some items of depression showing more evidence of impairment than others. All items were significantly increased on the first day, compared with the average item norm. Since normal item scores were not available for the BDI, the average item norm was calculated from the scores available. That is, division of the normal score (9) by the number of questions (21) yielding an average item norm of 0.428, with which all item scores were compared. While it is recognised that this is not the most accurate way of dealing with item scores, it was designed to be an approximate guide for comparison.

The items of depression for which scores were the most severe on the first day of assessment also tended to be the most intractable. The items that persisted until at least day 14 were sense of

failure, self-dissatisfaction, punishment, self-dislike, self-accusations, indecisiveness, work difficulty, insomnia, fatigability and loss of libido. Moreover, work difficulty, insomnia and self-accusations lasted until day 42.

It appears that both cognitive/affective and vegetative/somatic symptoms of depression were present in subjects experiencing alcohol withdrawal, which has also been observed in other alcoholic outpatient populations (Steer et al., 1983). Although overall depression was elevated, some items of depression may have been elevated due to other symptoms of alcohol withdrawal, particularly somatic/vegetative items. For example, insomnia is a well established withdrawal symptom, and is also a feature of depression. Furthermore, some items of the BDI may have been measuring the direct, toxic effects of alcohol, such as loss of appetite, weight loss and loss of libido.

State anxiety, as determined by total score received on the STAI, was more severe and persistent than depression, and subjects were severely anxious at the first administration of the STAI. While scores had markedly improved by the second and third administration, they were comparable with levels of anxiety among neuropsychiatric patients (Spielberger et al., 1970). Anxiety remained significantly elevated until day 42 of administration, and scores were comparable with levels of anxiety among general medical and surgical inpatients (Spielberger et al., 1970). By day 70, anxiety scores were elevated above the norm, although did not quite reach significance. These data indicate that anxiety is a severe and persistent symptom of withdrawal. This contrasts somewhat with other investigations, which have found that anxiety in withdrawing alcoholics had returned to normal levels by between fourteen and thirty days of abstinence (Ludenia et al., 1984; Brown et al., 1991).

Anxiety also appeared to be symptom, or item specific, with some items of anxiety appearing to be more intense than others. However, anxiety as measured by the STAI tended to be more homogeneous than depression, since STAI items focus on cognitive/affective events, rather than somatic symptoms of anxiety (eg. increased heart rate, sweating, increased respiration, paraesthesia, chest pains etc.). All items were significantly increased on the first day, compared with the item norm provided by the STAI manual. All items remained significantly elevated on days 4 and 14 with the exception of 'worry about possible misfortune', 'feeling frightened', 'not feeling steady', 'dissatisfaction' and 'feeling unpleasant' which appeared to improve more rapidly than the other items. Items remaining elevated by day 42 were 'insecurity', 'dis-ease', 'jittery', 'unconfident', 'indecisive' and

'confusion'. These last three items were also significantly elevated on day 70, along with 'nervousness'.

This appears to be one of the first investigations of specific symptoms of anxiety over a ten week period. The specific symptoms of anxiety most likely to persist seem to be those which reflected a lack of self-esteem and control over one's life.

Results from the POMS indicated a similar pattern of recovery from depression-dejection, as had the BDI. Similarly, tension-anxiety showed improvement over time, although this was expressed as a less intractable symptom compared with the results from the STAI. This is probably because the STAI is more sensitive to changes in anxiety than the POMS.

Interestingly, fatigue-inertia persisted for at least two weeks after drinking had stopped, and this was confirmed by anecdotes from clients reporting persistent feelings of tiredness and fatigue. Levels of fatigue in the first two weeks were comparable with those experienced by psychiatric inpatients (McNair et al., 1971). Certainly fatigue may be a result of experiencing a myriad of other withdrawal symptoms, but it may also reflect recovery from the toxic effects of alcohol.

In conjunction with a reduction in fatigue-inertia, vigour improved over time, and was even significantly elevated above normal on days 42 and 70. This may reflect expression of suppressed hyperactivity, as suggested in the discussion on physical activity and benzodiazepines above. Alternatively, it may have a psychological rather than pharmacological basis. That is, an increase in vigour due to feelings of 'having a new lease in life' as was suggested by some subjects, or working harder than usual to complete tasks that had been postponed due to prior heavy alcohol consumption.

Anger-hostility as recorded by the POMS shows that this mood dimension was significantly elevated on the first day, but was within the normal range at every assessment thereafter. This suggests that anger-hostility may not be a withdrawal symptom *per se*, but may have been exacerbated on day 1, possible due to increased levels of agitation and pain at the time of admission.

Finally, confusion-bewilderment was also significantly elevated for at least two weeks after cessation of drinking. It was most severe on the first day of the POMS administration, and comparable with confusion-bewilderment levels in psychiatric inpatient populations (McNair et al., 1971). Confusion-bewilderment had markedly improved by days 4 and 14, but was still consistent with levels observed in psychiatric outpatients (McNair et al., 1971).

Confusion has been reported by other investigators as a withdrawal symptom, sometimes presenting as part of disorientation and clouding of the sensorium (Victor & Adams, 1953; Gross et al., 1973). However, it is not clear whether confusion-bewilderment is a withdrawal symptom *per se*, or occurs as a result of the presence of other withdrawal symptoms, such as lack of sleep, headache, anxiety and depression.

Alcohol is a powerful neurotoxin, and chronic alcoholism is associated with cognitive impairments of memory function, ability to maintain attention, visuospatial capacity, abstracting ability, problem solving and learning capacity (Page & Hansens-Schaub, 1977; Turner et al., 1977b; Guthrie & Elliot, 1980; Brandt et al., 1983; Tarter et al., 1989). These cognitive disturbances improve with abstinence, and while not confusion-bewilderment *per se*, may certainly contribute to its presence.

4.4.3 SF-36 Health changes

The SF-36 provided novel information about health changes in the first ten weeks of abstinence. Some of the dimensions of health recorded by the SF-36 reflected recovery processes as well as withdrawal symptomatology, although differentiation between the two was not determined in this study. Physical role-function, vitality, and physical and social functioning were significantly attenuated on the first two administrations of the SF-36 (Days 1 and 14), but approached the normal range by days 42 and 70. Scores on all these dimensions on days 1 and 14 were comparable to, or more severe than, scores achieved by patients with serious medical conditions, including Type II diabetes, congestive heart failure, hypertension, recent myocardial infarction, stroke and cancer (excluding skin) (McHorney et al., 1993; McCallum, 1995). In the first two weeks of withdrawal, all the above dimensions, excluding physical functioning, were also comparable with patients who had a mixed psychiatric and serious medical condition (McHorney et al., 1993). Although scores on days 42 and 70 were not significantly different from normal scores, on day 42 they were comparable with patients diagnosed with a psychiatric condition, and on day 70 they were comparable with scores of patients who had a minor medical condition (McHorney et al., 1993; McCallum, 1995).

These data suggest that withdrawal subjects experienced significant difficulties with their usual daily activities due to compromised physical health, lack of vitality and moreover, that their health affected their usual physical and social activities. Although these dimensions improved with time,

subjects were still experiencing health problems, albeit minor, after ten weeks of abstinence. The rate of recovery of these symptoms was similar to other symptoms assessed by this study, such as depression, confusion, fatigue, lack of vigour and night sweating.

Bodily pain as assessed by the SF-36, was also significant on days 1 and 14 and then tended towards the normal range, although there was not a marked improvement in bodily pain between the second, sixth and tenth week. The reduced sample size at the last two administrations may be responsible for the lack of significance. On day 1, bodily pain was comparable with patients having both a psychiatric condition and serious medical condition (McHorney et al., 1993), while days 14, 42 and 70 were comparable with patients having a serious medical condition (McHorney et al., 1993; McCallum, 1995).

Increased bodily pain may have incorporated other withdrawal symptoms (eg. muscle aches and pains, headache, gastro-intestinal irritation) or may have occurred as a direct toxic effect of alcohol, for example, liver pain, pancreatitis or polyneuropathy.

The remaining health parameters investigated by the SF-36 proved to be the most intense and intractable of all SF-36 items. Mental health was significantly compromised at the first two administrations of the SF-36, and was comparable with patients diagnosed with both a psychiatric and serious medical condition (McHorney et al., 1993). It tended toward normal levels following the second assessment, but did not appear to improve between the sixth and tenth week. Mental health at this time was comparable with patients having either a serious medical condition or a psychiatric condition (McHorney et al., 1993; McCallum, 1995). The small sample sizes at these times may be responsible for the observed lack of significance. Moreover, the apparent persistence of compromised mental health may reflect both protracted withdrawal symptoms, and pre-existing mental health problems, frequently observed in this population.

Subjects' perception of their general health remained significantly compromised for at least six weeks, and was within the normal range by day 70. That is, even though many aspects of their health had appeared to improve, subjects perceived themselves to be in poor health. It seems they only began to feel well after ten weeks of abstinence. On day 1, general health of the withdrawal subjects was comparable with patients having a mixed psychiatric and serious medical condition. On days 14 and 42 general health was comparable with patients diagnosed with either psychiatric or serious

medical condition, and on day 70 was comparable with having a minor medical condition (McHorney et al., 1993; McCallum, 1995). Improvement in general health may reflect a combination of easing of withdrawal phenomena, recovery from the toxic effects of alcohol, and reversal of some of the effects of alcohol related injury.

The most intense and persistent dimension of health status was poor emotional role-function. This dimension remained significantly compromised for the entirety of the study, and did not appear to show signs of improvement, even at the final administration of the SF-36. This suggests that subjects felt that their emotional health significantly affected their work and daily activities for at least ten weeks after drinking had ceased. In the first two weeks, emotional role-function was comparable with patients having a mixed psychiatric and serious medical condition. For the remainder of the time (ie. at least ten weeks) emotional role-function was comparable with patients diagnosed with either a psychiatric condition, or a serious medical condition (McHorney et al., 1993; McCallum, 1995). Impairment of emotional role-function during the ten week period most likely reflected persistent symptoms of withdrawal (such as anxiety), symptoms related to the direct toxic effects of alcohol, and pre-existing psychiatric disturbances.

In summary, the results from this study provide a comprehensive 'map' of the abstinence syndrome, relying on both objective and standardised tools to determine the severity and duration of withdrawal symptomatology, up to ten weeks after cessation of drinking. This is relatively new information considering the limitations of the current literature, and our current knowledge of the abstinence syndrome as a whole.

4.4.4 Conclusions and recovery from alcohol dependence

The current picture of withdrawal, based on previous research efforts and clinical observations, includes the presence of hyperthermia, sweating, insomnia, restlessness and agitation, fatigue, confusion and disorientation, anxiety and depression, and other psychiatric and mood disturbances, during the first week of abstinence. During this time, withdrawal symptomatology has been shown to be the most severe, but is markedly improved over the first five to seven days. However, there are very few details as to what happens immediately after the first week of withdrawal. Most efforts to collect data on protracted symptoms concentrate on long-term abstinence, that is, after six months to

fifteen years of sobriety, and there is some evidence, albeit scant, that withdrawal may still be occurring at these times. Less is known about the withdrawal syndrome in the first few months of abstinence, with the exception of the first five to seven days. As mentioned in the introduction of this chapter, there is some evidence, based on standardised assessments, that insomnia, anxiety, depression and other mood disturbances still appear to be improving within the first two to six weeks of withdrawal, compared with first week severity (Johnson et al., 1970; Allen et al., 1971; Ludenia et al. 1984; Clark et al., 1985; McMahon & Davidson, 1986; Dorus et al., 1987; Roelofs & Dikkenberg, 1987; Brown & Schuckit, 1988; Haviland et al., 1988; Pary et al., 1988; Bokstrom et al. 1989; Gillin et al., 1990; Clark et al., 1993; Hemmeter et al., 1993; Schuckit et al., 1994; Brown et al., 1995; Le Bon et al., 1997). This suggests that withdrawal symptomatology may persist beyond the first week of sobriety, although little is known about when the return to 'normal levels' occurs.

The results from this study inform the current opinion of withdrawal in the first ten weeks of abstinence. It bolsters the findings that withdrawal symptomatology is most severe in the first week of sobriety. However, our understanding of first week withdrawal is further enhanced by new evidence that alcohol withdrawal affects diurnal rhythms of temperature, sweating and activity. Concerning temperature, alcohol withdrawal disrupts the diurnal temperature rhythm, while exerting an overall hyperthermic affect. Most investigators, with the exception of Gross et al. (1975), have reported hyperthermia only, but it appears that there are certain times of the day in which this is not the case, or in which hyperthermia is less pronounced. Temperature rhythm disruption and hyperthermia appear to persist for two to six weeks, and in this sample hyperthermia was most obvious in the protracted phase of withdrawal, presumably because subjects were not medicated with benzodiazepines at this time.

Diurnal sweating is also affected by withdrawal, and while withdrawal causes elevated sweating throughout the day, sweating is significantly more severe during the night. This coincides with patient's reports, although has not been demonstrated empirically until now. This may be particularly uncomfortable for patients since benzodiazepines, which would otherwise diminish enhanced sweating, may be less readily available during the night.

Interestingly, diurnal activity patterns are also affected by alcohol withdrawal, both within the first week, and thereafter. The first, and most obvious diurnal effect on activity is the difference between day and the night. As expected, subjects are less active at night than during the day,

although night restlessness is certainly enhanced in subjects compared with controls. However, alcohol withdrawal appears to affect activity patterns during the day, as demonstrated by the persistent contrast in activity patterns of subjects compared with controls. This suggests that there are particular times of the day in which patients in withdrawal may feel restless and agitated, evidenced by an increase in general activity.

Thus, the first week of sobriety is an unpleasant time for most alcohol dependent persons, as they experience a gamut of physical symptoms including increases in temperature, fluctuations in temperature, intense sweating – particularly at night, agitation and restlessness followed by malaise and tiredness, difficulty sleeping, although feeling continually fatigued. This is compounded by severe anxiety, depression and confusion, the severity of which is comparable with major psychiatric disorders. A degree of pain may also be present, accompanied by poor physical and emotional health which interferes with one's ability to perform usual daily activities, including social activities and interactions with others.

The current picture of the withdrawal syndrome suggests that the above-mentioned symptoms are predominantly resolved after one week of sobriety. However, this study shows that while improvement does occur, all symptoms are still present in varying degrees, for at least two weeks after drinking has ceased. Over the following four weeks of abstinence, increased sweating will resolve, along with feelings of confusion and fatigue. There will be some return to normal functioning including an improvement in physical health, and an increased ability to execute daily tasks. Social interaction will increase, and bodily pain will lessen. While physically more capable of usual activities, compromised mental health will still interfere with all aspects of life, and may be accompanied by a frustrating awareness of one's own continual poor health. Feelings of depression will begin to resolve, although anxiety will persist. Disruption to diurnal activity rhythms will still be present, although less severe. However, at the end of six weeks feelings of vitality and vigour will begin to emerge, and hyperthermia and temperature fluctuations will have disappeared.

Over the next four weeks of sobriety, insomnia and anxiety will lessen, and tend towards resolution. However, disrupted activity patterns will still be present until at least ten weeks of abstinence, and patients may still feel particularly restless and agitated at certain times of the day. Emotional problems will still interfere with usual daily activities, compounded by compromised mental

health. While the ability to interact socially will improve, along with ability to function physically, and lessening of bodily pain, at the end of ten weeks patients' overall health status will still be comparable with patients that have a minor medical condition.

In conclusion, this study provides a detailed map of symptom severity occurring in the first ten weeks of abstinence from alcohol, and markedly enhances the current available picture of the withdrawal syndrome. However, as mentioned previously, some of the symptoms assessed in this study may reflect recovery from the toxic effects of alcohol, as well as actual symptoms of withdrawal. There are few studies which differentiate between withdrawal and recovery symptoms, because realistically it almost impossible in a human population, including the sample used in this investigation. As Satel et al. (1993) point out, there are two possible methods in humans which could provide some differentiation. However, neither are ethically feasible since both these approaches require the administration of high doses of alcohol to subjects under study conditions. The first approach involves assessment of symptoms both before *and* after drinking has ceased. This would allow researchers to observe whether the withdrawal symptoms in question were present during intoxication, and whether they worsened with a reduction in alcohol consumption. The second method entails administering alcohol to patients already in withdrawal, to attempt reversal of symptoms which are thought to comprise withdrawal.

Two such studies were performed in humans, in the fifties and sixties when ethical experimentation was less of a concern (Isbell et al., 1955; Mendelson & La Dou, 1964). In both, subjects who had a history of drug and or alcohol dependence were observed both during a period of intoxication, followed by a period of abstinence. Symptoms of tremor, disorientation, memory deficit, hallucinations, gastrointestinal disturbances, insomnia, sweating, hyperreflexia, agitation, delirium and increased depression were significantly more likely in the withdrawal phase than the intoxication phase. This suggests these are "true" withdrawal symptoms, rather than symptoms occurring as a direct result of alcohol toxicity.

However, the best approach currently available is to rely on reports from patients and their treating clinicians, and also on data from non-human animal studies. While these both have their limitations, they do provide a guide of which symptoms reflect withdrawal, and conversely which may reflect recovery. Animal studies generally involve the administration of continual, high doses of alcohol

over a short time period (days or weeks). The animals are not exposed to alcohol for long periods, which markedly lessens the risk of direct toxic alcohol effects, however administration of alcohol in this way is enough to induce acute physical dependence. Accordingly, cessation of alcohol administration in dependent animals results in withdrawal, and this has been demonstrated in a range of animals including rodents, dogs, cats and non-human primates. The range of withdrawal symptoms that have been observed across these species include: tremor, muscle fasciculation, spastic rigidity, teeth chattering, leg sprawling, wet dog shakes, tail arch, hyperactivity, hypoactivity, anxiety, irritability, aggression, fright and apprehension, stereotypy, increases and decreases to startle reactivity, scratching, insomnia, spontaneous vocalisations, hallucinatory behaviour, gastrointestinal disturbances, mydriasis, photophobia, tachycardia, increased and decreased respiration, hyperthermia, hypothermia, sweating, increased salivation, piloerection and convulsions (Freund, 1969; Goldstein & Pal, 1971; Goldstein, 1972; Goldstein, 1978; Friedman, 1980; Aaronson et al., 1982; File et al., 1989; Rassnick et al., 1992; Humeniuk et al., 1994).

These data provide evidence on what symptoms comprise withdrawal, but not necessarily on what symptoms do not comprise withdrawal. For example, depression *per se* has not been observed in animal studies, although it is not possible to tell if it is because it is absent as a withdrawal symptom, or if it is just because it is a very difficult parameter to assess in animals.

Anecdotal evidence from clinical observations suggests that the signs and symptoms assessed in this study do comprise withdrawal. While the results from some of the questionnaires, particularly the SF-36, may not be pure measures of withdrawal symptoms, they certainly reflect parameters which would be, at least in part, affected by the presence of withdrawal symptoms.

Aside from the problem of differentiating between recovery and withdrawal phenomena, it is possible that some of the withdrawal symptoms measured, may be a reflection of problems that existed before drinking began, that were masked by the consumption of alcohol. This is particularly the case for psychiatric and mood disturbances which are frequently associated with alcoholism (Schofield, 1989; Chignon et al., 1991; Mueser et al., 1992), although it is difficult to determine the direction of causality (Hartka et al., 1991). Differentiation between the magnitude of pre-existing conditions, including psychiatric and mood disturbances, and the severity of symptoms that occur during withdrawal is not always possible, and as Satel et al. (1993) point out, there is an absence of

longitudinal assessment of symptoms in studies (ie. those that assess the severity of symptoms both before and after drinking has ceased). However, there is evidence that pre-existing psychiatric and mood disturbances may result in more intense psychiatric withdrawal symptoms when drinking has ceased (Brown et al., 1991; Johnston et al., 1991; Thevos et al., 1991; Schuckit et al., 1998). Thus, while it is not possible to know to what degree pre-existing conditions may contribute to overall withdrawal severity, it appears that part of the withdrawal syndrome may include the exacerbation of pre-existing conditions in some individuals.

It is also worth noting other possible limitations of this study in this conclusions section. In particular, the influence of declining subject numbers over the weeks, as a result of relapse. Since numbers significantly decreased, especially towards the end of the outpatient period, it is difficult to know how representative their withdrawal experience was, compared with other abstinent alcoholics at this time. Indeed, it is possible that patients who remained abstinent were at the higher or lower end of the severity spectrum, which may have altered the final conclusions drawn from this study. However, people who remained abstinent did not appear to have any different withdrawal severity to the withdrawal severity of the larger sample assessed during the first two weeks. That is, there did not appear to be a biasing effect.

While results from this study are applicable to many persons experiencing withdrawal from alcohol, results from subjects in this study best represent the withdrawal severity of persons who detoxified from alcohol at the medically based, public detoxification hospital in South Australia, during the period over which this study was executed.

4.4.5 Clinical and research implications

There are several clinical implications of this study. The first involves consideration of the effects that withdrawal has on diurnal rhythms, and also the intensity of night symptoms - an area that has not received much attention in the past. Current treatment regimes of acute withdrawal appear almost to 'ignore' what happens during the night to patients, when in actual fact symptoms may worsen. The most obvious example is that of increased sweating. Longer acting benzodiazepines, such as diazepam, suppress sweating during the day, but are rarely administered at night. This means the patient experiences an increase in sweating compared to day time levels, both due to diurnal

influence, but also because of the comparative absence of benzodiazepines. Secondly, sleep appears also to be exceptionally poor during acute withdrawal. Once again, longer acting benzodiazepines are not usually delivered during the night. Short acting benzodiazepines, such as temazepam may sometimes be given, but these results show this is not particularly successful in promoting sleep in this population. Since sleep is an integral part of life, and is also associated with the promotion of good health, it may require more attention in withdrawing patients, either through pharmacological and/or other means.

Finally, hyperthermia during the night also appears be under-estimated in current treatment regimes of acute withdrawal. This is partly because, as with sweating and insomnia, withdrawal intensity is rarely assessed during the night. In addition, temperature does not remain constant during the day. This has implications for treatment, considering that temperature may fluctuate dramatically between assessments, and hyperthermia may go untreated.

The other striking aspect of acute withdrawal that appears to go unnoticed in current treatment regimes is the severity of depression, anxiety and other mood disturbances experienced in acute withdrawal. Certainly, these do improve with time, although they can be extremely unpleasant for patients, and may even contribute to incomplete detoxification and early relapse. Medical detoxification treatment regimes do not particularly embrace supportive therapy during withdrawal, and tend to focus on the provision of 'medical care' only. Support therapy may be a useful adjunct, particularly if focussed on issues of anxiety and depression. The end result may be an easing of these 'physically harmless', yet debilitating symptoms.

Further clinical implications of this study concern the contrast between the length of treatment period and the duration of withdrawal symptoms. That is, current treatment practices usually last between three to six days. However, the results from this study indicate that most symptoms persist for at least two weeks suggesting that treatment could be extended beyond the first six days, possibly for two weeks.

The results from this study show that some withdrawal symptoms are particularly persistent, lasting beyond two weeks. Following the first fortnight, this study assessed withdrawal on a monthly basis, and changes were noted between time points. Accordingly, outpatient follow-up at fortnightly intervals may be beneficial for patients, for the first ten weeks, since some change may be discernable

from fortnight to fortnight. Specifically, some symptoms will require more attention than others. In physical terms, restlessness and agitation are long-lasting, both during the day, and at night as sleep disturbance. While most clinicians would be cautious to administer benzodiazepines for a extended periods, patients may benefit from education about sleep hygiene and associated factors. Hyperthermia and temperature rhythm disturbances also may be relevant for some patients in the first six weeks, and perhaps could be solved simply by administration of a non-steroidal anti inflammatory drug. Moreover, since these results suggest that withdrawal disturbs normal rhythms, encouragement to maintain a daily, and nightly, routine may help ameliorate some of these symptoms. Melatonin therapy may also be beneficial to facilitate return to normal diurnal rhythms. Physical health disturbances are also relevant, particularly in the first six weeks of abstinence, and patients may benefit from a support person, or to be in an environment which does not place as many demands on them as usual. In general, patients' health overall is affected by withdrawal for at least ten weeks, which may include bodily pain, lack of vitality and compromised general health. While external support for patients may not always be available, at least recognition of these disturbances, and reassurance that health will improve, should be given as part of outpatient treatment.

Psychiatric and mental health disturbances appear to be even more persistent than most physical symptoms, and may act as triggers for relapse back to heavy drinking. Anxiety and depression are particularly relevant, and it appears that they also may have a debilitating effect on performing normal daily activities and social functioning. Treating clinicians should be aware that depression, and particularly anxiety are likely to be experienced by many patients for several weeks after abstinence, and support or other cognitive therapy may be beneficial. While depression is not significantly elevated at the six week point, and anxiety not significantly increased at the ten week marker, it should be recognised that patients are still scoring at the highest end of the normal range for at least ten weeks. While not statistically significant, it is congruent with anecdotal reports by patients at that time of, 'feeling below par emotionally'. Indeed it could be said that any 'normal' person who had achieved those kinds of scores on the BDI or STAI would probably feel they were 'having a bad day'.

The results from this study have implications for further research, some of which are investigated in other chapters of this thesis. Because these results provide a baseline of withdrawal

severity, novel pharmacotherapies or psychological interventions could be examined for their effects on the intensity and duration of withdrawal. Moreover, the results could be used to determine predictors of withdrawal severity using methods that do not appear to have been employed previously: the use of standardised and objective measures of withdrawal severity. Finally, there is anecdotal evidence that more intense withdrawal results in an increased likelihood of relapse. This has received little formal empirical examination, and these results could be incorporated into a novel study of withdrawal severity, provided by objective and standardised recordings, and relapse.

CHAPTER 5

5. PREDICTORS OF ALCOHOL WITHDRAWAL SEVERITY: INVESTIGATION OF DRINKING HISTORY AND OTHER SUBJECT CHARACTERISTICS

5.1 Introduction

Since its first formal scientific recognition at the beginning of this century, there have been radical improvements in both the assessment and treatment of the alcohol withdrawal syndrome. This has resulted in a significant reduction in death and serious morbidity due to alcohol withdrawal, and a dramatic improvement in patients' comfort and quality of life when undergoing a period of withdrawal. Part of this improved treatment process is a consequence of repeated clinical and research observations resulting in better early recognition of withdrawal, better tools with which to assess withdrawal severity, improved pharmacological treatment of withdrawal, and more options for long term rehabilitation.

While understanding of the syndrome has improved, there are still gaps in our knowledge. One of these absences concerns the factors that may affect the severity of withdrawal a patient will experience when he or she ceases heavy alcohol consumption. There are several reasons for wanting to gain insight in this area, the main one concerning the treatment of patients in withdrawal. The ability to predict the degree of withdrawal severity a patient will experience would markedly improving the matching of patients to treatments. That is, it would allow clinicians to pre-determine what degree of medical care, if any, was required. This would reduce the risk of death, serious morbidity or severe patient discomfort due to lack of medical care. Conversely, it would also decrease the cost of providing expensive twenty four hour medical care to those with a less severe withdrawal, who could be adequately treated with supportive therapy only.

There are several factors thought to affect the severity of withdrawal a patient may experience on cessation of drinking. The first is the drinking history of the patient. That is, the amount of alcohol consumed, and the period over which heavy drinking has occurred, are thought to be positive indicators of the degree of withdrawal severity. A second factor that is thought to be important in determining withdrawal severity is the number of previous withdrawal episodes a patient has previously

experienced. That is, a history of repeated withdrawal episodes is thought to result in a subsequently more severe withdrawal. The mechanism underlying this is thought to be one of kindling, and will be discussed in more detail below. Finally, the degree of withdrawal severity a patient will experience is also thought to be related to the number of concomitant complications a patient may have. For example, the presence of co-morbid illness is thought to be a factor, and patients with underlying physical or psychiatric distress may experience a more severe withdrawal from alcohol. There is also some evidence that polydrug use may also be a complicating factor in withdrawal.

Much of the evidence supporting the above-mentioned parameters as elements affecting withdrawal severity has resulted from clinical anecdotes. However, there have been some, albeit scant, formal research efforts that have investigated possible predictors, or correlates, of withdrawal severity. Some factors have been better researched than others, and all are discussed in more detail below.

5.1.1 Drinking history

Investigations into the effects of drinking history on withdrawal severity may be classified into two categories: studies using animals, and studies using humans. Indeed, there are several animal studies indicating that at least some aspects of drinking history have an effect on the subsequent withdrawal severity (Goldstein & Pal, 1971; Goldstein, 1972; Goldstein & Arnold, 1976; Majchrowicz & Hunt, 1976; Ritzmann and Tabakoff, 1976; Pieper & Skeen 1977; Goldstein, 1978; Friedman 1980; Le Bourhis & Aufrere, 1983). For example, Ritzmann and Tabakoff (1976) varied the number of days duration of alcohol liquid diet administration to mice and found that the duration of alcohol consumption was positively correlated with the intensity and time course of the resulting convulsive withdrawal symptoms. Goldstein (1972) exposed mice to several different combinations of alcohol intake and duration, and found that the intensity of resulting withdrawal seizures was related to both the dose of alcohol, and the recent duration over which it had been administered. However, the author was unable to ascertain the relative effects of intake and duration of drinking on withdrawal intensity.

Goldstein and Arnold (1976) demonstrated that withdrawal intensity in mice was related to the number of consecutive recent days of exposure to alcohol, and that there was a certain threshold dose that had to be exceeded in order to produce withdrawal. Majchrowicz and Hunt (1976) showed that

rats exposed to alcohol for between one and four days produced a withdrawal response that varied in intensity according to the duration of exposure. However, they found that five or seven days duration of alcohol administration produced no more severe withdrawal than had four days alcohol administration.

The results from animal studies implicate the amount of alcohol consumed as a significant factor in the resulting withdrawal intensity. The duration over which alcohol was recently consumed also appears to be important, and in the case of animal studies this was usually days or weeks. Since the animals were intoxicated for relatively short periods of time, no information can be ascertained about the effects of long term drinking (ie. years) on withdrawal intensity. However, some of the above-mentioned animal studies do seem to suggest that there is a threshold number of days of drinking required before withdrawal occurs, and also a threshold number of days after which any further drinking will not result in any additional effect on withdrawal severity.

Some of the earliest human studies involved in establishing that an alcohol withdrawal syndrome exists also observed that drinking history may play a role in the degree of withdrawal severity that results upon abstinence (Hare, 1915; Isbell et al., 1955; Mendelson & LaDou, 1964). For example, Isbell et al. (1955) observed the responses of 10 ex-morphine addicts exposed to a regime of two weeks control period, in which no alcohol was consumed, followed by a period of alcohol intoxication, and then a period of alcohol withdrawal. The subjects consumed a mean dose of between 210 and 386 *gm* of alcohol per day, over a period of 6 to 87 days. The severity of resulting withdrawal symptoms, including tremor, nausea, insomnia, hallucinatory behaviour and disorientation were graded from mild withdrawal up to most severe withdrawal. The investigators noted that the greatest withdrawal severity was observed in the subjects who drank the most alcohol each day, over the longest period of time. In a similar study Mendelson and La Dou (1964) observed 10 sober alcoholics who were intoxicated for twenty four days following a control period of sobriety. The amount of alcohol consumed ranged between 200 and greater than 300 *gm* per day of alcohol. The presence of certain withdrawal features was recorded, and the authors noted that the volume of alcohol consumed may have been a significant factor in the initiation of withdrawal symptoms.

While these studies suggest a link between amount consumed and recent intake, a review of these studies by Turner et al. (1977) states that a direct relationship between intake and severity is not

clearly evident. Criticisms of these studies include the small sample sizes employed, and the narrow range of alcohol intakes incorporated into the studies. Further information could be ascertained by incorporating a range of intakes, from low to very high, rather than a cluster around the middle of the drinking range as these studies have. Another limitation is in the way withdrawal was measured – using very simple, unstandardised and subjective scales, which increases the likelihood of further variability and error in the results.

More recent efforts to determine the relationship between drinking history and withdrawal severity have resolved some of the limitations of the earlier studies, such as increasing the sample size, and thereby incorporating a greater range of alcohol 'doses' into the study. However, there appear to be comparatively few investigations in this area (Hershon, 1977; Pristach et al., 1983; Gorelick & Wilkins, 1986; Schuckit et al., 1995; Schuckit et al., 1998; Shaw et al., 1998).

Schuckit et al. (1995) examined 1648 alcohol dependent subjects and classified 191 of them as experiencing severe withdrawal by the presence of delirium tremens and/or convulsions. Compared with the remainder of the alcohol dependent sample, the subjects that had experienced delirium tremens and/or convulsions reported a longer drinking history (years), more days recent drinking and a greater number of drinks over any twenty four hour period. Similarly, Shaw et al. (1998) assessed withdrawal severity in 160 alcohol dependent subjects using a modified version of the SSA (Gross et al., 1973). Multiple regression using total withdrawal scores demonstrated that withdrawal was more severe in subjects consuming alcohol in excess of 24 standard drinks or more per day. Other researchers have also found that the amount of alcohol consumed is predictive of withdrawal severity (Hershon, 1977; Pristach et al., 1983; Schuckit et al., 1998), as is the number of days spent drinking in the most recent bout (Hershon, 1977). However, the evidence that the number of years spent in heavy drinking affects withdrawal severity is less compelling (Pristach et al., 1983; Shaw et al., 1998).

While assessment of withdrawal severity is improved in some of the newer studies, they are limited by their reliance on either subjective assessments of withdrawal severity, or the presence or absence of certain withdrawal symptoms as indicative of a certain level of withdrawal severity. Nonetheless, the evidence available suggests that at least some aspects of drinking history may affect withdrawal severity, although as yet definite predictors of withdrawal severity have not been isolated, due to the variation between studies, and the relatively small number of investigations in this area.

5.1.2 Kindling

Kindling is demonstrated in animals by stimulation of the brain, particularly the limbic system, at stimulus intensities that on their own are too low to produce any behavioural or EEG changes. However, periodic repetition of the stimulus eventually results in EEG changes, motor effects and convulsions (Goddard et al., 1969; Racine 1972; Ballenger & Post, 1978). A kindling mechanism has also been proposed to explain increases in alcohol withdrawal severity. Repeated electrical stimulation of the brain potentiates the effects of subsequent alcohol withdrawal, and increases the susceptibility to seizures in animals (Pinel & Van Oot, 1975; Pinel, 1980). Similarly, each alcohol withdrawal episode experienced is thought to be comparable with a repeated low grade stimulus, resulting in progressive increases in withdrawal severity. This phenomenon has been repeatedly demonstrated in animals, in which withdrawal severity and duration (usually assessed by the number and intensity of seizures) is significantly correlated with the number of previous withdrawal experiences (Walker & Zornetzer, 1974; Ballenger & Post, 1978; Poldrugo & Snead, 1984; Becker et al., 1997).

There is some evidence that kindling may be responsible for increases in withdrawal intensity following repeated withdrawal episodes in humans (Brown et al., 1988; George et al., 1990; Schuckit et al., 1995; Shaw et al., 1998). For example, Brown et al. (1988) found that male alcoholics who had a history of seizures had experienced significantly more withdrawal episodes compared with those alcoholics who did not have a history of seizures. Interestingly, a relationship between history of alcohol use and seizures was not found. In a larger study, Schuckit et al. (1995) found that 211 alcohol dependent subjects who had experienced at least one episode of delirium tremens and or convulsions had significantly more prior withdrawal attempts compared with 1437 alcoholic subjects with no history of convulsions or DTs. Finally, Shaw et al. (1998) assessed withdrawal severity in 160 alcohol dependent subjects using a withdrawal scale which was a modified version of the SSA (Gross et al., 1973). Regression analysis revealed that the severity of the withdrawal syndrome, and the incidence of significant complications of withdrawal were higher in those with a previous history of four or more episodes of detoxification.

These results suggest that the number of previous withdrawal attempts may have some role in the resulting withdrawal severity, although at this stage there are not many studies in humans to prove

this is the case. Further, some of the above studies investigate the presence of only one aspect of withdrawal, such as seizures, convulsions and DTs. These tend to be among the more severe features of withdrawal, and provide no information about the remainder of the withdrawal syndrome. Indeed Shaw et al. (1998) demonstrated that composite withdrawal scores were affected, although they were limited by the use of a subjective assessment of withdrawal severity.

5.1.3 Complications

There is a body of clinical evidence to suggest that, in general, the presence of serious co-morbid illness enhances the pending withdrawal severity (Sellers & Kalant, 1976; Baum & Iber, 1980; Gorelick & Wilkins, 1986; Romach & Sellers, 1991). As an example, a case study by Kessel et al. (1984) observed that alcoholics referred to detoxification units by emergency rooms and doctors offices tended to experience more severe withdrawal than those who had been referred by the police or courts.

The presence of concurrent liver disease, pancreatitis or pneumonia is associated with an increase in the duration and severity of DTs (Tavel et al. 1961; Thompson, 1978). Increases in withdrawal severity, particularly delirium tremens, have also been associated with dehydration (Johnson, 1961), fever (Gross et al., 1971) and electrolyte abnormalities (Johnson, 1961; Tonneson, 1982; Sheehan, 1983).

There are also a few recent studies that investigated more formally the effects of physical comorbid illness on withdrawal. A large study by Schuckit and colleagues (1998) classified 3,395 alcohol dependent subjects into two major groups. The classification was based on whether or not alcohol withdrawal was present or absent, as defined by DSM-III-R criteria. Those who had been classified as experiencing alcohol withdrawal had more physiological complications compared with the group not experiencing alcohol withdrawal, including head trauma, concussion, seizures and liver disease. This suggests that the expression of withdrawal is related to the presence of physiological complications, although some of these complications may have occurred as a result of the toxic effects of consuming more alcohol, since the withdrawal group were obviously physically dependent on alcohol compared with the non-withdrawal group.

An earlier study by Schuckit et al. (1995) found that alcohol dependent subjects who had experienced at least one episode of delirium tremens and/or convulsions, had a greater number of medical problems compared with alcohol dependent subjects who had not. However, Mander et al. (1989) observed that there was no correlation between fluid balance disturbance and the severity of withdrawal symptoms in patients experiencing alcohol withdrawal.

Overall, there is some suggestion that physical complications may affect withdrawal, although it appears that this is predominantly expressed in the most severe cases of withdrawal, such as with the occurrence of delirium tremens.

While there is a large body of literature on the relationship between alcoholism and psychiatric disorders, there appear to be very few formal investigations on the effects of co-morbid psychopathology on pending withdrawal severity. However anecdotal evidence suggests that such an influence does exist.

Of the systematic studies, many tend to focus on anxiety (Brown et al., 1991; Johnston et al., 1991; Thevos et al., 1991). For example, Brown et al. (1991) found that withdrawal symptoms of anxiety were more common in primary alcoholics with a history of panic or generalised anxiety disorders. Johnston et al. (1991) measured symptoms of alcohol withdrawal using the CIWA-Ar in two groups of alcoholics: those with a co-existing anxiety disorder, and those without. The dual-diagnosed group exhibited more severe withdrawal symptomatology than the alcohol only group, as evidenced by increased total CIWA-Ar scores. Additionally, the elevated scores persisted for the first three weeks of abstinence.

A large study by Schuckit et al. (1998) investigated general emotional/psychiatric symptoms (particularly depression and anxiety) in alcohol dependent subjects. Subjects who met the DSM-III-R criteria for alcohol withdrawal were more likely to report psychopathology than subjects who did not meet the criteria for presence of alcohol withdrawal. However, increased psychopathology may have occurred as a result of the toxic affects of consuming more alcohol, since the withdrawal group was obviously physically dependent on alcohol.

In general, there is some suggestion that psychiatric complications may affect pending withdrawal severity, particularly withdrawal items such as anxiety and depression. However, since there are few studies in this area, it is not possible to ascertain the strength of this relationship.

Finally, regarding complications that may be risk factors for severe withdrawal, there is some relatively recent evidence that polydrug use among alcohol-dependent persons may play a role (Schuckit et al., 1993; Schuckit et al., 1995). Schuckit et al. (1995) observed that convulsions and/or DTs were significantly more likely in alcohol-dependent patients who had used amphetamines, opiates, benzodiazepines, or any drug intravenously, ten times or more in their lifetime. Furthermore, substance dependence on either amphetamines, cannabis, cocaine, opiates or benzodiazepines was also related to a more severe alcohol withdrawal, as evidenced by convulsions and or delirium tremens.

In conclusion, evidence extracted from clinical anecdotes, and the few studies available, suggests that at least some complications may be responsible for mediating a more severe withdrawal in some cases. It appears also that physical complications have a greater deleterious effect on withdrawal than psychiatric complications, although this may just be a reflection of the amount of work that has been done in the respective areas. In general, there are limitations in the above mentioned investigations in their assessment of withdrawal severity. Similar to research efforts into the effects of drinking history and kindling, withdrawal severity has often measured using subjective, and sometimes non-standardised, scales of assessment. While the results are informative, there is an increased likelihood of error. Indeed, other studies have chosen to reflect withdrawal severity as either being present or absent, using the presence of seizures, convulsions and/or delirium tremens as markers. While this is a little more objective, it does not take into account that withdrawal follows a continuum of severity, and may appear on a spectrum of anywhere from mild to moderate, to severe. Thus, little information is provided concerning the effects of complications on mild or moderate withdrawal.

5.1.4 Experimental rationale and aims

The general aim of this study was to assess the predictive value of drinking history, kindling effects and complications, using both standardised and objective assessments of withdrawal severity. This was executed in two parts. The first involved assessing the predictive value of the various parameters against a total global withdrawal score that incorporated physical, psychiatric/emotional and health aspects of withdrawal during the first five days of the syndrome. The methods of assessment were standardised in the case of psychiatric/emotional and health aspects, and objective

in the case of physical aspects. Total global withdrawal severity included sweating, hyperthermia, restlessness, sleep disturbance, depression, anxiety, confusion, fatigue and compromises to health.

The second involved assessing the predictive value of the various parameters against a physical global withdrawal score, incorporating objective assessments of sweating, hyperthermia, restlessness and sleep disturbance. This was because physical features of withdrawal are more likely to necessitate intensive, twenty four hour medical care.

Drinking history was classified into three separate components for assessment, the number of years the subject had consumed alcohol heavily, the length of the most recent drinking bout in months, and alcohol intake in grams per day over the most recent bout. A range of different drinking histories was incorporated to achieve a full "dose-response" effect. That is, a variety of different subjects were included in the study, ranging from those with relatively short drinking histories and low intakes to others who had been consuming alcohol at a much higher rate for longer periods of time. To assess whether kindling was responsible for increases in withdrawal severity, the number of prior withdrawal episodes was recorded, along with any history of seizures. Finally, complications were classified as the number of current medical conditions, including general medical, mental health disturbances, chronic pain, alcohol-related injury (eg. polyneuropathy, pancreatitis), complications of past trauma (eg. head injury), and whether or not the subject had recently had serious surgery. The number of licit, or prescribed drugs, that were currently being taken by the patient was also recorded, to serve as another indicator of medical complications. Polydrug complications were determined by recording the number of non-prescribed drugs that the subject used on a regular basis, without necessarily being dependent. This included tobacco, opioids, cannabis, stimulants, benzodiazepines, hallucinogenics and inhalants. However, the subjects in this study were not withdrawing from any drug except alcohol.

5.2 Methodology

The methodology for this chapter is outlined in more detail in Chapter 3 entitled, 'General Methodology'. In brief, data from all 47 subjects (37 males, 10 females, mean age = 44.6 ± 1.5 years) were utilised to determine possible predictors of withdrawal severity. Principal Component Analysis was used to derive a score of Total Global withdrawal severity, which included the salient features of withdrawal in the first five days of abstinence, as assessed by the monitor and questionnaires. The same technique was also used to determine a score of Physical Global withdrawal severity based on monitor data only. Thus, a second principal component was also determined which excluded any psychological/psychiatric component of withdrawal.

Parameters that reflected the possible predictor variables of drinking history, kindling, complications and age were extracted from the subjects' casenotes. Casenote data were collected by clinical staff of the detoxification unit. The parameters recorded were incorporated into univariate analyses to investigate if these variables could predict total global withdrawal severity and/or physical global withdrawal severity. Multivariate analysis was not performed in this particular study, since there was only a small number of variables, few of which met the criteria for inclusion (ie. being $p<0.15$).

5.3 Results

5.3.1 Outcome of Principal Components Analysis

Table 5.1 shows the eigenvalues of the PCA correlation matrix, resulting in the final componential relationship for Total Global withdrawal severity (21 psychological/psychiatric and physical variables) and Physical Global withdrawal severity (5 physical variables).

Table 5.1

Eigenvalues of the PCA correlation matrix. Column 2 denotes eigenvalues for Total Global withdrawal severity, Column 3 denotes eigenvalues for Physical Global withdrawal severity.

Withdrawal parameters	**Eigenvalue Total Global**	**Eigenvalue Phys. Global**
Depression. BDI - mean score over days 1 and 4	6.94	NA
Tension/Anxiety - POMS mean score over days 1 and 4	2.12	NA
Depression/Dejection - POMS mean score over days 1 and 4	2.02	NA
Anger/Hostility - POMS mean score over days 1 and 4	1.57	NA
Vigour/Activity - POMS mean score over days 1 and 4	1.29	NA
Fatigue/Inertia – POMS mean score over days 1 and 4	1.21	NA
Confusion/Bewilderment – POMS mean score over days 1 and 4	1.02	NA
Anxiety. STAI - mean score over days 1 and 4	0.86	NA
Physical functioning – SF-36 score on day 1	0.81	NA
Role function physical – SF-36 score on day 1	0.67	NA
Role function emotional – SF-36 score on day 1	0.49	NA
Social functioning – SF-36 score on day 1	0.41	NA
Bodily pain – SF-36 score on day 1	0.37	NA
Mental health – SF-36 score on day 1	0.29	NA
Vitality – SF-36 score on day 1	0.22	NA
General health – SF-36 score on day 1	0.17	NA
Sleep activity – mean activity during sleep nights 1, 2 & 3	0.13	1.94
Skin temperature between 1400 and 1600 – mean days 1 to 4	0.09	1.65
Maximum sweating over 24 hour period – mean days 1 to 4	0.06	0.86
Early morning sweating between 0200 & 0900 – mean days 1 to 4	0.05	0.42
Restlessness – mean activity at 1300 over days 1 to 4	0.02	0.11

5.3.2 Demographic profile of predictor variables.

Table 5.2 shows the demographic profile of some of the predictor variables used for the analysis. Subjects had diverse drinking patterns ranging from low amounts of alcohol and brief periods of intoxication, to long periods of intoxication and very high doses of alcohol. Similarly, subjects' experiences of previous withdrawal episodes also varied in number.

The majority of subjects interviewed had only one concurrent medical condition (38.3%), while 23.4% had two, and 24.3% reported having none. The remainder (14.9%) reported either 3, 4 or 6 concurrent medical conditions. Similarly, around one third (36.2%) reported taking only one prescribed medication, although 40.4% stated they did not use any medications. The remainder (23.5%) took between 2 and 5 prescribed medications.

Concerning polydrug use, the majority (76.7%) claimed to be using only one non-prescribed drug, and this was usually tobacco. Seventeen percent reported no other drug use besides alcohol, and 6.4% said they used two other non-prescribed drugs besides alcohol.

Finally, 21.3% of subjects reported a history of seizures, while 78.7% had no such history. It is worth noting that none of the subjects experienced a seizure during the particular withdrawal episode investigated in this study.

Table 5.2

Profile of predictor variables of alcohol withdrawal subjects

Predictor Variable	Mean ± SEM (or %)	Range (min.-max.)
Drinking history		
Number of years of heavy drinking	14.8 ± 1.3 yrs	0.2 – 40.0
Number of months spent in most recent drinking bout	9.2 ± 2.7 mo.	0.25 – 84.0
Intake (g/day) during recent drinking bout	317.2 ± 21.4 gm	100 - 700
Kindling		
Number of previous withdrawal episodes	5.25 ± 1.2	0 - 30
Percentage of subjects with history of seizures	23.1%	NA
Complications		
Number of current medical conditions	1.4 ± 0.18	0 - 6
Number of prescribed drugs currently used	1.2 ± 0.2	0 - 5
Number of non-prescribed drugs currently used (including tobacco, but not alcohol)	0.89 ± 0.07	0 - 2

5.3.3 Predictors of total global withdrawal severity (Table 5.3)

The results from the univariate analysis demonstrated that some elements of drinking history appeared to be predictive of total global withdrawal severity. The number of months spent in the most recent drinking bout was significantly predictive of total global withdrawal severity ($p \leq 0.05$). The mean amount of alcohol consumed per day over the recent drinking bout tended towards significance (p=0.08), however, the number of years spent in heavy drinking did not appear to have a significant predictive effect.

Kindling, as reflected by the number of previous withdrawal episodes, and whether or not the patient had a history of seizures, was not significantly predictive of total global withdrawal severity. Similarly, the variable 'complications' as reflected by the subjects' number of current medical conditions, the number of prescribed drugs currently used, and polydrug use, was not significantly predictive of total global withdrawal severity.

Table 5.3

Predictors of total global withdrawal severity - Univariate Analysis

Predictor Variable	Significance
Drinking history	
Number of years of heavy drinking	0.57
Number of months spent in most recent drinking bout	**0.05**
Recent Intake (g/day) during recent drinking bout	0.08
Kindling	
Number of previous withdrawal episodes	0.28
History of seizures	0.91
Complications	
Number of current medical conditions	0.57
Number of prescribed drugs currently used	0.32
Number of non-prescribed drugs currently used (including tobacco, but not alcohol)	0.11

NB. **p** values in bold denote statistical significance, **$p \leq 0.05$**.

5.3.4 Predictors of physical global withdrawal severity (Table 5.4)

The results from the univariate analysis indicated that none of the elements of drinking history assessed in this study were predictive of physical global withdrawal severity. Similarly, kindling effects were not significantly predictive of physical global withdrawal severity.

The only parameters that appeared to be predictive of physical global withdrawal severity in this model were some of the complicating elements of withdrawal. The number of current medical conditions that the subject had while withdrawing appeared to be significantly predictive of physical global withdrawal severity ($p \leq 0.05$), while the number of prescribed drugs currently used closely approached significance (p=0.06). The number of non-prescribed drugs currently used did not appear to be predictive of physical global withdrawal severity.

Table 5.4

Predictors of physical global withdrawal severity - Univariate Analysis

Predictor Variable	Significance
Drinking history	
Number of years of heavy drinking	0.66
Number of months spent in most recent drinking bout	0.73
Recent Intake (g/day) during recent drinking bout	0.89
Kindling	
Number of previous withdrawal attempts	0.41
History of seizures	0.91
Complications	
Number of current medical conditions	**0.04**
Number of prescribed drugs currently used	0.06
Number of non-prescribed drugs currently used (including tobacco, but not alcohol)	0.83

NB. **p** values in bold denotes statistical significance, **$p \leq 0.05$**.

5.4 Discussion

This study has investigated predictors of withdrawal severity in a novel way, and has dealt with some of the limitations of previous studies. An extensive search of the literature indicates that this may be one of the first efforts to determine predictors of withdrawal severity using objective measures of withdrawal. Additionally, few other studies have used standardised scales in their assessment of the psychiatric component of withdrawal, nor have they considered a spectrum of withdrawal severity, but tend to concentrate on the presence or absence of withdrawal, or the most severe items of withdrawal, such as delirium tremens or convulsions. This study has considered a continuous spectrum of withdrawal intensity, ranging from mild to severe.

The findings of this study indicate that drinking history is a less important predictor of severity of physical withdrawal, but a better predictor of the total global withdrawal syndrome, with both its physical and psychiatric components. This suggests that drinking history may be a better indicator of the intensity of the syndrome as a whole, and also which patients may experience more severe psychiatric disturbances in withdrawal, such as depression and anxiety. This contrasts with the findings of Schuckit et al. (1995) that demonstrated that drinking history did affect physical withdrawal severity. However, physical withdrawal severity in their study was concerned with the presence of delirium tremens and or convulsions, which are among the most severe withdrawal symptoms. Thus, it may be that these particular severe physical withdrawal items are influenced by drinking history, while less severe symptoms are not. Since this study did not assess the presence of delirium tremens and convulsions, the effects of drinking history may not have been as obvious.

However, the results from this study are similar to the findings of other investigations that have provided evidence for the positive effects of drinking history on the general withdrawal syndrome, incorporating both physical and psychiatric components (Hershon, 1977; Pristach et al., 1983; Schuckit et al., 1998; Shaw et al., 1998). Specifically, this study found that the length of the most recent bout (usually in months), was a significant predictor of total global withdrawal severity, and that daily intake of alcohol over that period, while not strictly statistically significant (p=0.08), also appeared to be an important factor. The number of years spent in heavy drinking was not a predictor of withdrawal severity, which is congruent with the findings of Pristach et al. (1983) and Shaw et al. (1998). Schuckit

et al. (1995) found that the number of years of heavy drinking was correlated with the presence of delirium tremens and or convulsions in withdrawal. However, in keeping with the other aspects of drinking history, it may be that the length of lifetime heavy drinking affects only the most severe symptoms of withdrawal, such as delirium tremens and convulsions.

The fact that none of the parameters of drinking history were predictive of physical withdrawal severity, and were only somewhat predictive of total global withdrawal severity, also may be a result of variation in the collection of drinking history data. That is, the accuracy of data collection could have been compromised in several ways. Firstly, it is reasonable to assume that some patients will forget the details of their drinking history, and compounded by the deleterious cognitive effects of alcohol, provide only an estimate of how much they have been drinking, and the period over which it has occurred. In addition, patients may sometimes overestimate their drinking to clinical staff, usually to affect the course of their treatment, for example, to get immediate admission to detoxification, or to ensure benzodiazepine administration. However, some patients may underestimate drinking out of embarrassment or guilt, or to try and avoid admission to detoxification because it is not their choice to be admitted (of course there may be other reasons, not listed here, to explain over or underestimation of drinking history). Moreover, variation of drinking history data may be further compounded by misinterpretation of information, and differences in interviewing style and data collection by clinical staff. Certainly in this study, inconsistencies sometimes were noted in the details of drinking history, provided by different staff for the same subject. In these cases the average was taken, but it is recognised that the drinking history data may have been an approximation in some instances.

Regarding the effects of kindling, the results from this study show that the number of previous detoxifications a subject had experienced was not predictive of pending physical or total global withdrawal severity. This suggests that kindling was not responsible for the variation in withdrawal severity observed in these subjects. While there has been little examination of kindling and alcohol withdrawal in humans, the results from this investigation appear to contrast with the findings of the studies available (Brown et al., 1988; George et al., 1990; Schuckit et al., 1995; Shaw et al., 1998). That is, that the number of previous withdrawal events does affect pending withdrawal severity. However, it may be that kindling affects the occurrence and severity of specific symptoms, such as seizures and delirium tremens. For example, Brown et al. (1988) suggested kindling was responsible

for an increase in the frequency of seizures. Schuckit et al. (1995) observed that severe withdrawal symptoms, namely DTs and convulsions may have occurred as a result of kindling. Moreover, there may be a threshold at which the effects of kindling become more obvious. For example Shaw et al. (1998) indicated that subjects experienced an increase in withdrawal severity after at least four detoxification events, while Brown et al. (1988) observed a threshold effect occurring after least five previous detoxifications.

This study did not incorporate seizures or delirium tremens in its assessment of withdrawal severity, nor did it focus specifically on the most severe withdrawal symptoms, which may explain the lack of effect concerning kindling. Moreover, if there is a threshold affect, some of the subject sample may have not experienced a sufficient number of detoxifications to achieve an effect. It is also worth noting that kindling may not occur if withdrawal is adequately medicated, that is, if the patient only experiences minimal symptoms.

Alternatively, it is possible that there were errors in the calculation of the number of previous detoxifications a subject had experienced. The number was ascertained by hand-searching through patients' casenotes of all their admissions to the particular detoxification unit utilised for this study. Detoxifications at other units were also recorded as withdrawal events, as were the number of home detoxifications a patient had experienced. However, it is possible that this information, particularly of home detoxification, was omitted from some patients' casenotes, because it is not always appraised as important by clinical staff. It is also feasible that some subjects could forget the number of detoxification attempts, particularly those with a long drinking history.

Concerning the effects of complications on withdrawal severity, the findings of the study indicate that complications are a more important predictor of severity of physical withdrawal than of the total global withdrawal syndrome, with both its physical and psychiatric components. Specifically, the number of medical conditions was a significant predictor of physical withdrawal severity, which was also reflected in the near-significance of the number of prescribed medications subjects were currently using (p=0.06). This suggests that comorbidity and its associated effects (medication usage), are more likely to affect the physical features of withdrawal, than the syndrome as a whole, and psychiatric features such as anxiety and depression. This is somewhat congruent with the literature for which there is more evidence available that comorbidity affects the physical symptoms, rather than the

psychiatric symptoms of withdrawal. Interestingly, this study improves the information available on the effect of comorbidity on physical withdrawal features. That is, most investigations have demonstrated the effects of comorbidity on severe withdrawal symptomatology (usually delirium tremens), whereas this study reports that comorbidity may affect other physical withdrawal phenomena, of varying intensities (Johnson, 1961; Tavel et al. 1961; Gross et al., 1971; Thompson, 1978; Tonneson, 1982; Sheehan, 1983; Schuckit et al., 1995). It is possible that this has not been previously identified, due to the paucity of objective measurements of physical withdrawal.

Another complication that was considered in this study was the use of non-prescribed drugs. Polydrug use did not appear to be predictive of either physical or total global withdrawal severity. This contrasts with the findings of Schuckit and colleagues (1995), who found that polydrug use increased the frequency of delirium tremens and convulsions. However, it may be that polydrug use affects only severe withdrawal phenomena, as has been suggested for the other putative predictors of withdrawal severity. Alternatively, an effect may not have been observed in the present study due to the conservative repertoire of drug use behaviour in these subjects. That is, all subjects used only zero, one or two other drugs besides alcohol, with the majority using only one other non-prescribed drug (generally tobacco). It may be that polydrug use of tobacco with alcohol does not affect pending withdrawal severity, compared with other drugs of dependence that may affect withdrawal severity but were not able to be investigated in this sample.

The findings of this study inform and challenge the current understanding of predictors of withdrawal severity, and consequently have several clinical implications. Firstly, it appears that drinking history does not affect exclusively physical withdrawal severity, but rather the syndrome as a whole. Accordingly, it may be that psychiatric withdrawal symptoms are more affected by drinking history than physical features, and suggests these features of withdrawal should be more closely monitored and treated in patients with more severe drinking histories. These patients may respond well to support, and other types of cognitive therapy. It also appears that the number of years of heavy drinking has little to do with the severity of withdrawal, but that the length of the most recent drinking bout, and intake over that period are more important in this context. Accordingly, patients with high intakes, who have not had a period of abstinence for some time may have particularly intense withdrawals, and should be monitored closely.

Secondly, it appears that the number of previous withdrawal attempts has little effect on withdrawal as a whole, and therefore should not be considered as a risk factor for the occurrence of a severe withdrawal syndrome. However, it is worth noting that previous research efforts (eg. Brown et al., 1988; George et al., 1990; Schuckit et al., 1995; Shaw et al., 1998) have demonstrated that the number of previous withdrawal attempts may play a role in seizure facilitation, and in the most severe situations of withdrawal in which delirium tremens or convulsions are present.

Finally, the number of comorbid complications and concomitant medication use appears to be related to physical withdrawal severity, and less likely to affect psychiatric features of withdrawal. Current knowledge suggests that comorbidity affects only severe withdrawal phenomena, such as convulsions and delirium tremens, however, this study indicates that several features of physical withdrawal are affected (ie. insomnia, restlessness and agitation, hyperthermia, disruption to diurnal temperature rhythms, sweating). In clinical terms, this implies that patients with comorbid complications may have a worse physical withdrawal, and should receive treatment accordingly.

CHAPTER 6

6. PREDICTORS OF ALCOHOL WITHDRAWAL SEVERITY: INVESTIGATION OF BIOLOGICAL MARKERS

6.1 Introduction

The previous chapter investigated the potential of drinking history, kindling and concomitant complications to predict the severity of pending alcohol withdrawal. As has already been mentioned, determination of predictors is important for treatment services in order to develop patient-specific and cost-effective treatments. The results from chapter 5 found that some aspects of drinking history may determine the intensity of withdrawal a patient will experience once drinking has ceased. However, it was also recognised that there may have been some error in the collection of drinking history data, both in this thesis, and in other research efforts that have investigated the effects of drinking history on withdrawal. In brief, the assessment of drinking history is a subjective exercise, in that patients may distort the truth, forget, or be misunderstood by clinical staff collecting the information. Thus, it is not clear how accurate predictors really are, that rely on information collected in this way. For this reason, the aim of this study was to investigate the potential of objective biological markers of alcoholism to predict the intensity of withdrawal a patient may experience.

Biological markers of alcoholism are generally classified into two main categories: diagnostic tests (state markers) which help in assessment of the current state of the patient, and trait markers, which provide information about the likelihood, or risk, of developing future conditions (Whitfield, 1991; Whitfield, 1994). This study concentrated on state markers, since there was interest in determining the current state of subjects in withdrawal. Furthermore, no reliable trait markers for alcoholism have yet been determined.

State markers for alcoholism are divided into one of three main categories: those which reflect physical disease as a consequence of alcohol abuse, those which reflect dependence on alcohol, and those that reflect hazardous intake of alcohol (Whitfield, 1991; Whitfield, 1994). Markers have not been identified for all categories, particularly dependence, however it is thought that there is a strong relationship between the three groups of state markers. For example, in some situations a marker of

hazardous intake of alcohol may also indicate dependence, or may reflect physical disease due to alcohol consumption.

Currently the most reliable markers are those which identify the presence of physical disease due to alcoholism, and markers which reflect the hazardous intake of alcohol. At present, reliable markers of dependence have not been identified. Since this study was interested in drinking history as a predictor of withdrawal severity, the group of markers that were of most interest were those reflecting hazardous intake of alcohol. This group includes gamma-glutamyl transpeptidase\transferase (GGT) (Rollason et al., 1972; Whitfield et al., 1978; Chick et al., 1981; Whitfield et al., 1981a; Whitfield, 1991; Conigrave et al., 1993; Conigrave et al., 1995), erythrocyte mean corpuscle volume (MCV) (Whitfield et al., 1978; Chick et al., 1981; Whitfield, 1991), adducts of protein acetaldehyde (APA) (Lin et al., 1990) and the more recently determined marker, carbohydrate deficient transferrin (CDT) (Behrens et al., 1988; Gjerde et al., 1988; Kapur et al., 1989; Stibler, 1991; Whitfield, 1991; Bell et al., 1992; Voltaire-Carlsson et al., 1993).

This study has chosen to concentrate on the two most commonly utilised markers of hazardous intake, GGT and MCV, and also the newer marker CDT, as potential objective predictors of withdrawal severity. These are discussed in more detail below. There would be advantages in having objective biological predictors of withdrawal severity, as opposed to predictors that have been determined through clinical assessment, such as drinking history. In the first instance, biological markers are not affected by the usual limitations of subjective clinical assessment of patients (ie. distortion of information through incorrect recall etc.). Furthermore, if biological predictors of withdrawal severity were obtained, levels of the marker could be assessed prior to admission to detoxification, allowing clinicians to more accurately determine the severity of withdrawal a patient will experience, and hence determine the appropriate course of treatment. This also has implications for admission to general hospitals, particularly patients presenting for surgery where a history of alcoholism is suspected.

6.1.1 Gamma-glutamyl transferase (GGT)

GGT is an inducible biliary canalicular membrane bound enzyme, which may be abnormally elevated following consumption of alcohol at greater than 80 grams per day, for at least one week. If

drinking is controlled (four or fewer drinks per day), then serum GGT levels return to normal over a period of 6 to 12 weeks (Conigrave et al., 1995); that is, within the range of 0 to 60 U/L. The mechanism by which alcohol affects GGT is not completely understood, and thus the significance of a raised GGT is uncertain. There is some evidence that a raised GGT is indicative of damage, and results from the large Malmo study which investigated some 8000 middle-aged males showed that an elevated GGT was the most significant risk factor for death, even more so than elevated cholesterol (Trell et al., 1985; Whitfield, 1991). Alternatively, GGT may reflect a protective mechanism, by acting to maintain a supply of glutathione precursors to cells, thus buffering against oxidative stress (Speisky & Israel, 1990).

GGT is one of the most frequently investigated markers in heavy drinkers, or suspected heavy drinkers, as a potential indicator of liver damage and hazardous alcohol consumption. However, GGT is not a highly sensitive marker, because it is not raised in all individuals who drink excessively (Chick et al., 1981; Whitfield et al., 1981b). Moreover, there is a poor correlation between serum GGT and alcohol consumption in individuals under 30 years of age, particularly adolescents (Conigrave et al., 1995). GGT is also a less sensitive marker for females than males (Whitfield et al., 1978). The sensitivity of GGT has been shown to vary from study to study, however is generally between 60% and 70% in alcoholic populations, and around 40% in community settings (Stauber et al., 1994; Stibler, 1991; Van Pelt, 1997).

GGT is not a highly specific marker (Schiele et al., 1977; Whitfield et al., 1978; Conigrave, 1995; Trell et al., 1985), and may be elevated in people with other non alcohol-related disease states, (Whitfield, 1991) particularly other liver conditions (Wu et al., 1976; Kryszewski et al., 1977; Whitfield et al., 1981a; Trell et al., 1985; Bell et al., 1992; Conigrave et al., 1995). GGT is also used clinically as an indicator of liver diseases, including those that have not been caused by alcohol. The specificity of GGT as a marker for hazardous intake of alcohol has also been shown to be quite variable, although is generally found to be around 50%.

6.1.2 Erythrocyte mean corpuscle volume (MCV)

MCV may also be a marker for hazardous intake of alcohol, when drinking exceeds 60 grams of alcohol per day. Since red blood cells can survive for around 120 days after their release into the

circulation, MCV remains elevated for around three months after drinking has ceased, before returning to normal levels (80 – 96 fl). The mechanism by which alcohol affects MCV is not clear (Conigrave et al., 1995).

In a similar manner to GGT, MCV can also be insensitive for hazardous alcohol intake (Unger & Johnson, 1974; Eschwege et al., 1978; Whitfield et al., 1978; Chick et al., 1981; Whitfield, 1991; Conigrave et al., 1995; Stauber et al., 1994; Van Pelt, 1997). Sensitivity has been shown to vary, and is usually between 20% and 30% in a community setting, and slightly higher (~50%) in an alcoholic inpatient population. Despite its poor sensitivity, elevated MCV is quite specific for hazardous alcohol intake, with values usually around 90% (Conigrave et al., 1995; Stauber et al., 1994; Van Pelt, 1997), although it has also been shown to be increased by folate deficiency, recent blood loss and abnormal thyroid metabolism (Conigrave et al., 1995).

6.1.3 Carbohydrate deficient transferrin (CDT)

A recently isolated marker for the hazardous intake of alcohol is carbohydrate deficient transferrin (CDT) (Behrens et al., 1988; Gjerde et al., 1988; Kapur et al., 1989; Stibler, 1991; Whitfield, 1991; Bell et al., 1992; Voltaire-Carlsson et al., 1993). Transferrin is a naturally occurring protein that transports iron molecules in the blood. The transferrin molecule is comprised of two complex carbohydrate chains, each consisting of four different carbohydrates, the exact content of which may also vary. One of these carbohydrates is sialic acid, which is unique in that it is the only charged carbohydrate present on the transferrin molecule. The transferrin molecule carries a charge due to sialic acid residues, which are measured by isoelectric focussing in pI units (isoelectric points). The transferrin molecule normally carries a pI charge of around 5.4. The effect of heavy alcohol consumption on transferrin is such that the pI of the molecule is significantly increased (Stibler, 1991). The mechanism by which this occurs is uncertain, but it is thought that acetaldehyde may mediate an inhibition of the formation of the carbohydrate portion of transferrin, in particular sialic acid.

Abnormal transferrin appears in the serum after regular intake of around 60g and above of ethanol per day (about six standard drinks) for at least one week, and normalises slowly during abstinence with a half life of approximately 15 days (Stibler et al., 1986; Behrens et al., 1988; Gjerde et al., 1988; Stibler, 1991; Voltaire-Carlsson et al., 1993). A review paper by Stibler (1991) which

summarised a number of studies involving a total of ~2500 alcoholic and non-alcoholic (community setting) subjects, demonstrated that CDT presents with a sensitivity of around 82%, and a specificity of 97%. Interestingly, CDT does not seem to be sensitive to concomitant liver disease, however false-positive CDT values may arise due to primary biliary cirrhosis, chronic active hepatitis, drug hepatopathy, genetic D-variants of transferrin and individuals with carbohydrate-deficiency glycoprotein (CDG) syndrome, which is a rare inborn error of glycoprotein metabolism resulting in extremely high CDT levels. Furthermore, it appears that females have slightly higher CDT levels than males, as demonstrated by Bell et al. (1993b) who found a mean CDT value of 13.5 U/L for healthy males, and 17.1 U/L for healthy females.

Determination of CDT has now been used in a number of situations. These include detection of alcohol abuse in patients with chronic liver disease (Bell et al., 1992; Bell et al., 1993a; Rubio et al., 1994), licence reinstatement for drivers with drink-driving charges (Iffland, 1996; Morgan & Major, 1996) and confirmation that relapse drinking has occurred (Rosman et al., 1994; Anton et al., 1996). Investigations and assessments such as those outlined above tend to employ cut-off scores of 20 U/L for males and 25 U/L for females. While these scores are greater than mean CDT levels for healthy individuals, high cut-off scores minimise the risk of false positive conclusions.

6.1.4 Experimental rationale and aims

The aim of this study was to investigate the biological markers GGT, MCV and CDT as potential objective predictors of the degree of withdrawal severity. The rationale behind this was as follows: since these markers reflect hazardous intake over a period of at least one week, they may also reflect some aspects of drinking history such as intake and duration of the most recent drinking bout. Thus, they may also indicate physical dependence on alcohol, and hence withdrawal phenomena upon cessation of drinking. Anecdotal evidence from clinical situations suggests that this may be the case. That is, persistent hazardous intake results in withdrawal phenomena when drinking ceases. The advantage of this study is that hazardous intake is assessed using objective means, and withdrawal severity is assessed using objective and standardised measures.

6.2 Methodology

The methodology for this study has been discussed fully in Chapter 3, *General Methodology*. In brief, serum samples were extracted from the blood of subjects who also wore the monitor and completed questionnaires. Blood was collected on the third or fourth day of abstinence. Levels of CDT were determined by the investigator of this study from serum samples using a double antibody radioimmunoassay. The levels of GGT and MCV were established by a pathology laboratory for each patient admitted to the detoxification unit, and recorded in their casenotes. This was a part of each patient's routine clinical assessment by the detoxification unit. Blood samples were generally taken on the second or third day of admission. All subjects (n=47) had their MCV and GGT levels determined. Of these, 38 subjects (30 males, 8 females) had their blood assayed for CDT levels. The remaining 9 subjects did not have blood taken, either because their veins were too poor to extract blood, or because they did not wish to participate in this section of the study.

The statistical procedure by which the predictive value of the biological parameters was determined was the same as for Chapter 5, *Predictors of alcohol withdrawal severity: Investigation of drinking history and other subject characteristics*. In brief, two principal components were isolated, namely total global withdrawal severity, and physical global withdrawal severity. Univariate analysis was performed on both of these components to assess the predictive value of GGT, MCV and CDT. Multivariate analysis was also employed, using the biological predictor variables determined from the univariate analyses in this study which had p values of less than 0.15, and also included the predictor variables determined via univariate analysis in Chapter 5 that were $p<0.15$. That is, multivariate analysis of total global withdrawal severity in this study also incorporated the following variables determined in Chapter 5: the number of months spent in heavy drinking ($p=0.05$), recent intake of alcohol in g/day ($p=0.08$) and number of non-prescribed drugs currently used ($p=0.11$). The variables incorporated for physical global withdrawal severity multivariate analysis from Chapter 5 were number of current medical conditions ($p=0.04$) and number of prescribed drugs currently used ($p=0.06$).

6.3 Results

6.3.1 Biological profile of predictor variables (Table 6.1)

Table 6.1 shows the biological profile of GGT, MCV and CDT in the subjects used for this analysis. There were a diverse spread of GGT values, ranging up to 1734 U/L, although fifty percent of subjects had GGT values of 85 U/L or less, while 38.6% of subjects had values that were considered to be within the normal range for GGT (0 – 60 U/L). MCV scores were less diverse and less skewed. Fifty percent of subjects had a MCV value of 97 fl or less, which was quite close to the mean value of 98.3 fl. The levels which are thought to indicate non-hazardous drinking are between 80 and 96 fl, and 44.2% of subjects were within this range. No subject had a MCV of less than 80 fl.

There was a moderate spread of CDT values, although fifty percent of subjects had levels of 16.4 U/L or less. The geometric mean for normal non-alcoholic males is around 13.5 U/L, and 17.1 U/L for females (Bell et al., 1993b). Taking the mean value of a sample of both males and females (15.3 U/L), 50% of subjects had CDT levels above the mean. A scatter plot of the distribution of CDT values for all subjects, and separately for male and female subjects, with respective cut-off scores is shown in Fig 6.1. However, in clinical and legal situations cut-off values are often set at 20 U/L for males and 25 U/L for females, to minimise the risk of false positives. Taking a mean value of 22.5 U/L of a sample of both males and females, 31.6% of subjects were above this cut off score.

The demographic profile of the sub-group of 38 subjects who had their CDT levels tested were similar to the total group (n=47) who had their GGT and MCV values determined (shown in chapter 5). Subjects whose serum was assayed for CDT were a mean age of 44 years, and had been drinking heavily for 15.2 years (range 0.3 – 40). Their most recent drinking bout was 10.6 months (range 0.25 – 84) and they had been consuming an average amount of 313.5 *gm* of alcohol per day.

Table 6.1

Profile of biological markers in this sample of subjects in alcohol withdrawal

	GGT U/L	MCV fl	CDT U/L
N	47	47	38
Mean ± SEM	206.4 ± 51.3	98.3 ± 0.9	22.5 ± 3.2
Median	85.0	97.0	16.4
Minimum	11	84.2	6
Maximum	1734	111.0	94

Fig. 6.1

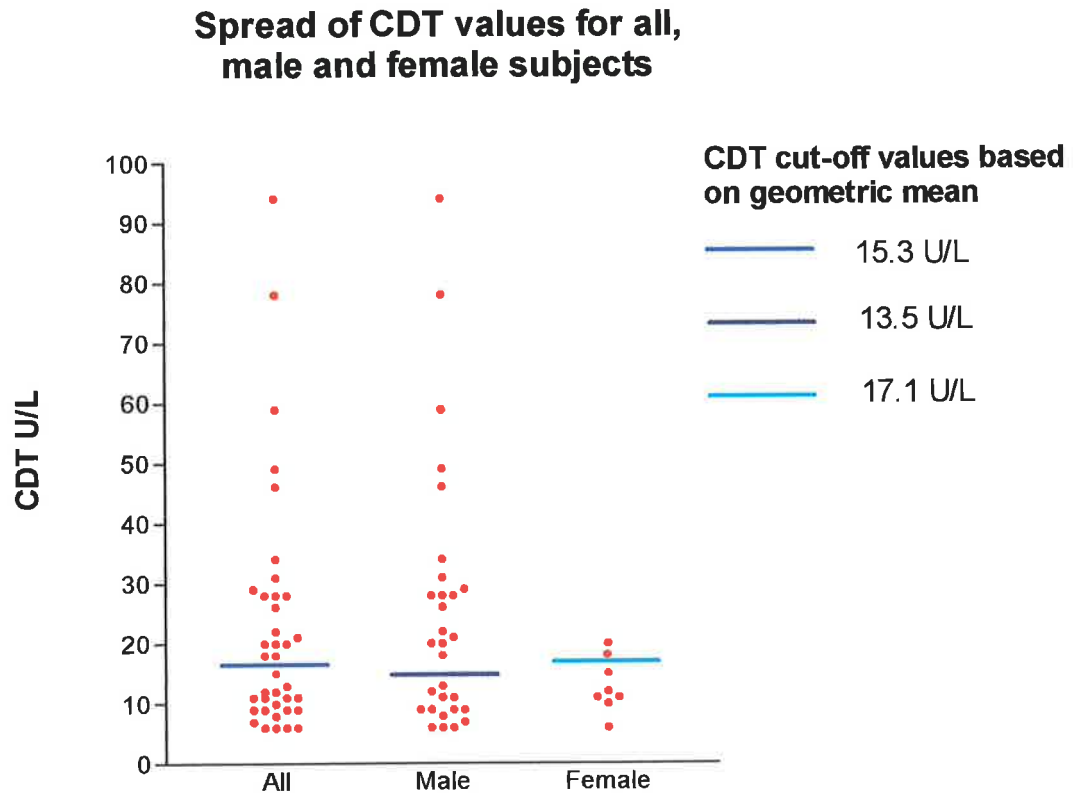


Fig. 6.1 Spread of CDT values in this sample of subjects in alcohol withdrawal for all, male and female subjects, and showing their comparative placement to the geometric mean of CDT for healthy persons.

6.3.2 Predictors of total global withdrawal severity (Table 6.2)

The results of the univariate analysis showed that neither GGT, MCV or CDT was predictive of total global withdrawal severity (Table 6.2). MCV approached significance with a *p* value of 0.08, however this was in a negative direction suggesting that higher MCV scores reflected an attenuated total global withdrawal severity. When MCV was incorporated into a multivariate analysis with other potential predictors determined in Chapter 5, (ie. number of months spent in heavy drinking, recent intake g/day, and number of non-prescribed drugs currently used), the results showed that none of the variables, including MCV, were statistically significant. This suggests that total global withdrawal severity is not significantly affected by any of the variables incorporated into the multivariate analysis.

Table 6.2

Biological predictors of total global withdrawal severity - Univariate and multivariate analysis

Predictor Variable	**Significance Univariate analysis**	**Significance Multivariate analysis**
GGT	0.25	NA
MCV	0.08 (-ve direction)	0.65
CDT	0.81	NA

NB. p values in *italics* were used for multivariate analysis (ie $p \leq 0.15$). Sample size for each variable ranges from 28 to 33. NA means 'not applicable'.

6.3.2 Predictors of physical global withdrawal severity (Table 6.3)

Table 6.3 shows the results of univariate and multivariate analysis using physical global withdrawal severity as an outcome measure. GGT and MCV were not predictive of physical global withdrawal severity. However, CDT was significantly predictive of physical global withdrawal severity at p=0.01. When incorporated into a multivariate analysis with other potential predictors from chapter 5 (ie. number of current medical conditions and number of prescribed drugs currently used), CDT remained significantly predictive of physical global withdrawal severity (p=0.05) and accounted for 29% of the variance. The other variables incorporated into the multivariate analysis were not predictive of physical global withdrawal severity.

Table 6.3

Biological predictors of physical global withdrawal severity - Univariate and multivariate analysis

Predictor Variable	**Significance Univariate analysis**	**Significance Multivariate analysis**
GGT	0.20	NA
MCV	0.54	NA
CDT	***0.01***	**0.05**

NB. p values in *italics* were used for multivariate analysis (ie $p \leq 0.15$), p values in **bold** denotes statistical significance ($\mathbf{p \leq 0.05}$). Sample size for each variable ranges from 36 to 44. NA means 'not applicable'.

6.4 Discussion

Neither GGT nor MCV were predictive of total global or physical global withdrawal severity. CDT was not predictive of total global withdrawal severity, although appeared to be a significant predictor of physical global withdrawal severity. This indicates that CDT may be a better predictor of the physical symptoms of withdrawal, rather than of the total syndrome which also comprises psychiatric aspects of withdrawal such as depression and anxiety. CDT remained significantly predictive of physical withdrawal severity, even in the presence of other potential predictors (concomitant medical conditions and prescription drug use), suggesting that CDT accounts for a significant proportion of the variance observed in physical withdrawal severity.

This is a novel and interesting finding. A search of the literature reveals that very few studies have investigated the potential of biological markers of hazardous alcohol intake to predict pending withdrawal severity. Of the few studies available, their findings are inconsistent. In one study, Kanitz et al. (1994), divided 209 alcohol dependent patients into two groups, withdrawing and non-withdrawing, as determined by the CIWA-A. Each group was further divided into one of two other categories according to whether they were above or below a certain CDT level (20 U/L for males and 26 U/L for females). The authors found that the presence of withdrawal did not correlate with CDT levels. However, this lack of effect may be a result of restricting the data set, since the authors expressed the data as four discrete groups rather than as two continuous variables (ie. CDT level and CIWA-A score).

In a second study by Wetterling et al. (1998), withdrawal severity was determined in 161 alcohol dependent subjects using a modified version of the CIWA-A (the AWS scale). Subjects were classified into four discrete groups identified by 'no apparent withdrawal symptomatology', 'mild withdrawal', 'moderate withdrawal' and 'severe withdrawal'. CDT levels correlated with the duration of the withdrawal period, but not with maximum AWS scores achieved. Moreover, CDT was found to correlate with the 'mental component' of the alcohol withdrawal scale, but not the 'somatic component'. The study also determined GGT and MCV levels, but did not correlate them with withdrawal severity. They found that GGT and MCV were positive predictors for the 'severe withdrawal' subjects occurring

at around 59% for GGT and 71% for MCV. However, both GGT and MCV had low negative predictive values (GGT 25%, MCV 44%), suggesting they may not be reliable predictors of withdrawal severity.

The results from the latter study suggest that CDT levels may be related to withdrawal severity. However, the results should be interpreted cautiously as there were some limitations in the study. The current study is improved in that it was not subject to these limitations. That is, withdrawal severity was expressed as a continuous variable, rather than four discrete variables. Moreover, withdrawal in the current investigation was assessed using objective and standardised measures, whereas the Wetterling et al. (1998) study employed a subjective scale of assessment of withdrawal severity. For these reasons the results from the current study can be accepted with more confidence. That is, CDT appears to be a predictor of some aspects of withdrawal severity, specifically physical withdrawal symptomatology, while GGT and MCV do not seem to be predictors of withdrawal severity.

It is not completely clear why CDT and withdrawal severity may be related. The most obvious conclusion is that CDT correlates with the degree of alcohol consumption, which in turn reflects pending withdrawal severity. Moreover, since CDT is a more specific and sensitive marker of intake than GGT and MCV, it follows that CDT may be a better predictor of withdrawal severity than GGT and MCV, as was found in this study.

Several studies have demonstrated a positive relationship between CDT and the degree of intake. Stibler et al. (1991) divided a mixed group (males and females) of 251 subjects into alcohol abusers and non-abusers, according to their daily alcohol consumption. They found a significant correlation of 0.38 between subjects' CDT levels, and total daily alcohol consumption. Similarly Bell et al. (1993b) classified a mixed male and female sample of 502 subjects into six different groups of daily alcohol consumption. They found a significant correlation of 0.52 between CDT levels and daily alcohol consumption. Sillanaukee et al. (1993) investigated CDT levels in a sample of 122 male subjects, separated into three groups of alcohol consumption. The results showed that CDT significantly correlated with weekly alcohol consumption at r=0.53. Similarly, Saini et al. (1997) found a significant correlation of 0.56 between CDT levels and alcohol consumption in a sample of 22 males, but did not find a significant correlation in a sample of 16 females.

In contrast, some investigations have found the relationship between CDT and alcohol intake to be poor. For example, Casini et al. (1994) examined a mixed male and female sample of 42

subjects and found that CDT did not correlate with daily alcohol consumption. Aithal et al. (1998) divided a mixed male, female sample of 81 subjects into three groups according to alcohol consumption. They did not find a significant relationship between CDT and alcohol consumption. Finally, Lesch et al. (1996) separated a sample of 92 male subjects into five groups according to alcohol consumption, and found no correlation between CDT levels and daily alcohol intake.

It is not clear why there appears to be a relationship between CDT and alcohol consumption in some investigations and not others. There are several possible explanations for the variation, including errors in the collection of drinking history data and statistical limitations in which data sets are restricted by forcing subjects into discrete groups rather than maintaining the data as a continuous variable. Furthermore, there are factors that may alter the level of CDT found, which may have varied from study to study. That is, CDT may differ according to the method of detection employed, whether absolute or relative CDT values are used, gender balance in the sample employed, and variation between subjects in transferrin deficiency (Stibler et al., 1986; Kwoh-Gain et al., 1990; Stibler, 1991; Whitfield, 1994).

Overall, it appears that there is some evidence to support the notion that CDT affects physical withdrawal severity, because of its positive relationship with intake. Chapter 5 found that there was a close relationship between daily intake, length of most recent drinking bout and total global withdrawal severity, but not physical withdrawal severity. It is not clear why daily intake and length of most recent drinking bout seem to affect only total global withdrawal severity, while CDT levels affect only physical withdrawal severity, particularly as CDT is thought to reflect hazardous intake of alcohol over a given time period (one week or more). However, while it has been shown in some studies that there is a relationship between CDT and daily intake, it is not known how CDT relates to the length of time of the most recent drinking bout, nor total number of years of heavy drinking. These unknown variables may contribute to the differences observed in the findings of Chapter 5 and Chapter 6.

Overall it seems there is a relationship between intake, length of drinking bout, CDT and specific aspects of the withdrawal syndrome, but further research is required to determine the nature of the relationship between them.

A curious finding of this study was that while a relationship between CDT levels and physical withdrawal severity was established, half of the subjects had CDT levels below those of the geometric

mean of a non-alcoholic population. Further, around sixty eight percent of subjects' CDT levels fell below what would be considered a cut-off score in clinical and legal situations. That is, going by CDT scores alone, sixty eight percent of the subjects would be considered non-hazardous consumers of alcohol. As mentioned previously, these cut-off scores are set high (usually accordingly to the 98th percentile of CDT levels in a healthy, non-alcoholic population) to eliminate the risk of false positive conclusions. However, this study was not interested in cut-off scores, or placement of subjects in particular categories as determined by CDT level (eg. relapsed versus abstinent). This study recognised that CDT levels and withdrawal severity were both continuous variables, and treated them accordingly.

The time of sampling may be a possible explanation as to why some CDT levels appeared to be lower than expected. That is, blood samples were taken from subjects on their third or fourth day of abstinence, during which time CDT levels may have declined from the level they were prior to detoxification. Behrens et al. (1988) demonstrated that CDT levels decline at a rate such that they reach fifty percent of their original value within a mean of 16 days. Decrey et al. (1994) noted that in withdrawing alcoholics, CDT levels had fallen by a mean of around thirty three percent following seven days of abstinence. Similarly, Lesch et al. (1996) found mean rates of decline in withdrawing alcoholics to be around fifteen percent after two days of abstinence, and around forty eight percent following seven days of abstinence. The results from these studies suggest that CDT levels after three or four days abstinence may have been somewhat lower than levels prior to detoxification in the current study.

In conclusion, it appears that CDT is predictive of physical withdrawal severity, as measured by the withdrawal symptoms of hyperthermia, sweating, sleep disturbance and restless as in this study. The results from this study may also be interpreted, albeit cautiously, as evidence that CDT is a biological marker for physical dependence on alcohol. However, this is a relatively new area and further research is warranted, particularly since this study may be limited to some degree, by its modest sample size. The results from this study also have clinical implications. Since CDT appears to be predictive of physical withdrawal severity, determination of CDT prior to detoxification could be used in conjunction with other information to ascertain the intensity of withdrawal the patient will experience.

Because CDT is an objective marker, assessing clinicians could have more confidence in the accuracy of prediction of pending withdrawal severity, and also in the choice of patient-specific treatment.

CHAPTER 7

7. PREDICTORS OF RELAPSE: INVESTIGATION OF ALCOHOL WITHDRAWAL SEVERITY AND ITS RELATIONSHIP TO OTHER ANTECEDENTS OF RELAPSE

7.1 Introduction

Various models of relapse have been discussed in Chapter 1, section *1.8, 'Relapse drinking'*. While different models imply variations in treatment regimes, they tend to rely on similar underlying factors that may affect relapse. These factors have largely been determined through psychosocial research aimed at isolating antecedents, or predictors of relapse, that is, investigation of the factors that are involved in causing a patient to resume drinking again, after they have had a period of abstinence. If these factors are known, then they can be incorporated into treatment models. Moreover, they serve as early warning markers to treating clinicians that a patient may have an increased risk of relapse. Identified factors, or predictors of relapse, are described in more detail below. While discrete factors exist, there is certainly overlap between variables thought to be responsible for resumption of drinking.

A range of 'high risk situations' have been identified as being possible antecedents of relapse. Firstly, when negative emotional states are experienced by the patient, they may be at greater risk of having a drink (Litman et al., 1983; Marlatt & Gordon, 1985; Daley, 1988; Smith & Frawley 1993). This includes situations in which the patient experiences negative or unpleasant emotions and feelings associated with intrapersonal events and/or reactions to nonpersonal environmental occurrences. Accordingly, psychosocial stressors such as frustration, boredom, anger, anxiety and depression may serve as a stimulus to have a drink. Anxiety and depression are particularly well documented as antecedents to lapse and relapse (Loosen et al., 1990; Brown et al., 1991; Schonfield & Dupree, 1991; Ellis & McClure, 1992; LaBounty et al., 1992; Brown et al., 1995). It is worth noting that there are individual differences in what constitutes a 'high risk situation'. For example, positive mood states, such as euphoria, or those associated with celebrations or special events, may be high risk for some individuals.

A second 'high risk situation' that may result in resumption of drinking is the experience of interpersonal conflicts by patients. Marlatt & Gordon (1985) define interpersonal conflict as "situations

involving an ongoing or relatively recent conflict associated with any interpersonal relationship, such as marriage, friendship, family members, or employer-employee relations. Arguments and interpersonal confrontations frequently occur in this category." That interpersonal conflicts result in an increased risk of relapse also has been noted by other investigators and clinicians (Daley, 1988; Maisto et al., 1988; Smith & Frawley, 1993; Jarvis et al., 1995).

A third 'high risk situation' is thought to be one of social pressure on the patient to influence their decision to have a drink. Social pressure may come from an individual, or a group of people, sometimes friends with whom the patient used to drink. Social pressures may be experienced as a result of direct interpersonal contact and verbal persuasion, or by indirect exposure, merely by being in the presence of other people who are drinking. Exposure to these kinds of social pressures are thought to be predictors of relapse drinking (Marlatt & Gordon, 1985; Daley, 1988; Maisto et al., 1988; Smith & Frawley, 1993; Jarvis et al., 1995).

Classical or Pavlovian conditioning is a factor that has often been described in the resumption of drinking. While Pavlovian conditioning has been proposed as a model for predicting and treating relapse, it may also be involved in mediating 'high risk' situations like those that have been described above. In this model, relapse is explained in terms of drug-related cues. Accordingly, an individual's consumption of alcohol (unconditioned stimulus) results in the experience of the pharmacological and social effects of alcohol, such as euphoria, relaxation, loss of inhibitions, social interaction etc. (unconditioned response). However, situational or temporal cues (conditioned stimuli) which are present when alcohol is consumed will elicit a conditioned response of anticipation and positive expectancy, and an increased desire or craving for the effects of the alcohol, even when alcohol has not been consumed. Conditioned stimuli or situational cues commonly include the sight, smell or taste of alcohol, or the sights, sounds and smells of the environment in which alcohol is normally consumed. Potentially, mood states and other less well defined stimuli may also be conditioned stimuli for some individuals. The outcome of exposure to conditioned stimuli may result in a consummatory response, that is consumption of alcohol (Wilker, 1973; Strickler et al., 1979; Poulos et al, 1981; Marlatt & Gordon, 1985; Macrae et al., 1987; Staiger & White, 1991). Thus, the presence of certain cues could be thought to result in a high risk situation for some individuals and subsequent relapse.

Craving, or desire for alcohol, may also be a precursor to relapse. That is, an urge to drink or craving for alcohol, may result in the consumption of alcohol (Ludwig & Stark, 1974; Ludwig & Wilker,

1974; Ludwig et al., 1977; Poulos et al., 1981; O'Connor et al., 1991; Miller et al., 1996). The same can be said for other drugs of abuse such as opiates or tobacco, and a craving for the drug may result in use of the drug. Ludwig and colleagues demonstrated that craving was associated with emotional dysphoria, such as feelings of depression, anxiety, stress and failure (Ludwig & Stark, 1974; Ludwig & Wilker, 1974; Ludwig et al., 1977). Craving was also associated with positive feelings such as happiness, success and relaxation, although to a much lesser degree than with negative feelings. Accordingly, these investigators proposed that abstinent patients were at a greater risk of relapse during states of emotional dysphoria, since these states are conducive to craving for alcohol.

However, there are difficulties in defining craving, and in associating craving with alcohol use (or drug use) and relapse (Tiffany, 1990; Tiffany & Carter, 1998). Tiffany (1990) reviewed a body of literature that associated craving with consumption measures (of alcohol or drugs) and found a correlation of 0.4. Thus, it appears craving for alcohol may not necessarily always result in alcohol consumption, although may to contribute to the likelihood of relapse drinking, along with other factors (Miller et al., 1996).

Clinicians treating abstinent patients and investigators of relapse have observed that a patient's motivation to change their behaviour is an important determinant in whether or not drinking (or other drug use) will re-occur (Marlatt & Gordon, 1985; Daley, 1988; Prochaska et al., 1992; Ryan et al., 1995). Patients who are less motivated to maintain abstinence are at a greater risk of relapse. For example, Hall & Havassy (1986) investigated the survival of alcohol and other drug users (opiates and tobacco), and found that subjects with the most determined resolution for change were the most successful. That is, the subjects who indicated that they intended to be abstinent and never use again, were slower to return to drug and/or alcohol use than their less well resolved counterparts.

Several lifestyle factors are also thought to influence the likelihood of relapse. Lifestyle factors incorporate the social, physical and financial environment in which the patient lives. An important variable that has been shown to affect the likelihood of relapse is whether or not social support is available for the patient (Schonfeld & Dupree, 1991; Ellis & McClure, 1992; Gallant, 1992; Johnsen & Herringer, 1993; Murphy & Hoffman, 1993; Jarvis et al., 1995). If social support is available, then the chance of maintaining abstinence is increased. In fact, this has been shown to be the case for patients with other health problems, for example cardiovascular disease or cancers. The presence of social support increases the likelihood of a positive prognosis (Taylor, 1986). The degree of social

support available is generally classified as the number of friends and relatives, including partners, spouses and organised social groups, with whom the patient has contact. As the number of supports and frequency of contact increases, so does the likelihood of abstinence. Thus, patients who have impoverished social support are at a greater risk of resuming hazardous drinking. Of course the quality of the social support is also important. Contact with social groups and friends who are drinkers themselves, may result in increased social pressure to drink. Further, a poor and argumentative relationship with a partner or spouse may also result in relapse drinking. Besides lack of social support, other lifestyle factors that may increase the likelihood of relapse are unemployment (Ellis & McClure, 1992; Murphy & Hoffman, 1993), low socioeconomic status (Ellis & McClure, 1992; Yates et al., 1993), high levels of stress (Morrisey & Schuckit, 1978; Marlatt & Gordon, 1985; Daley, 1988), residential instability (Schonfeld & Dupree, 1991), and a generally impoverished lifestyle including poor diet, little exercise and few recreational activities (Gary & Guthrie, 1972; Marlatt & Gordon, 1985; Daley, 1988; Jarvis et al., 1995).

The availability of coping skills to deal with 'high risk' situations and addictive behaviour styles appears to facilitate the maintenance of abstinence and the prevention of relapse (Litman et al., 1984; Marlatt & Gordon, 1985; Daley, 1988; Klingemann, 1992; Murphy & Hoffman, 1993; Myers et al., 1993; Brown et al., 1995; Jarvis et al., 1995; Marlatt, 1996; Miller & Gold, 1998). Patients participating in coping methods such as learning to recognise high-risk situations (Marlatt & Gordon, 1985; Daley, 1988; Murphy & Hoffman, 1993; Jarvis et al., 1995), problem solving (Jarvis et al., 1995), cognitive restructuring (Marlatt & Gordon, 1985; Jarvis et al., 1995), learning communication skills (Jarvis et al., 1995), positive thinking (Litman et al., 1984), meditation and relaxation (Marlatt & Gordon, 1985; Jarvis et al., 1995), avoidance, distancing, diversion and distraction (Litman et al., 1984; Klingemann, 1992; Murphy & Hoffman, 1993), self monitoring (Marlatt & Gordon, 1985; Daley, 1988; Klingemann, 1992), and regular exercise (Gary & Guthrie, 1972; Murphy et al., 1984), reduce the likelihood of resuming drinking. Therefore, a lack of coping skills in an individual could be interpreted as a potential predictor of relapse.

Overall, investigation of factors affecting relapse has tended to be predominantly psychosocial in nature. It is worth noting also at this point that a moderate proportion of the research involved in identifying predictors of relapse has been based on a retrospective, as opposed to a prospective study design. This is especially the case for some of the earlier work in the area that identified particular

'high risk' situations. For example, the seminal work by Marlatt and colleagues, and others in the field (eg. Litman et al., 1983; Marlatt & Gordon, 1985; Maisto et al., 1988). One of the problems with retrospective self-reporting on reasons for relapse is that incorrect or biased recall may effect the reasons proposed for the resumption of drinking. Prospective investigations identify potential precipitating factors prior to the event and are thereby more objective, although they are more difficult to implement.

In summary, identified predictors of relapse include exposure to high risk situations such as negative emotional states, interpersonal conflict, social pressure, and drinking-related cues. Other predictors of relapse include the presence of craving, lack of motivation to change, lack of social support, impoverished or unstable lifestyle, and lack of coping skills. Identification of these antecedents of relapse has resulted in the development of specific treatment regimes, and improved outcomes for patients wishing to maintain abstinence. However, relapse rates are still disappointingly high. It appears that there may be other factors, besides those mentioned above that are not targeted in current treatment regimes, but affect the likelihood of relapse.

There is anecdotal evidence to suggest that withdrawal severity may be a predictor of relapse. For example, in the present study some patients reported that specific withdrawal events precipitated drinking. Sleep disturbances, anxiety, depression, pain and temperature fluctuations were all reported as reasons for initiating and maintaining drinking schedules. Indeed, that withdrawal may antedate relapse drinking is congruent with some of the psychosocial findings mentioned above. That is, negative emotional states may result in a 'high risk' situation, craving, and an increased likelihood of relapse. Accordingly, it is feasible that the psychiatric and mood disturbances (negative emotional states) noted during withdrawal may be severe enough in some patients to precipitate drinking.

At this stage, there have been only a few formal research efforts investigating the relationship between withdrawal severity and relapse. O'Connor and colleagues (1991) observed withdrawing alcoholics over a period of the first two weeks of abstinence. The subjects' withdrawal severity was rated on a scale between 0 and 3, and was classified as being either low, or moderate to high. The authors found that subjects experiencing a moderate to high severity of withdrawal were significantly more likely to relapse than the subjects who experienced a low severity of withdrawal. Hershon (1977) observed alcohol withdrawal in subjects over the first 28 days of abstinence. The author noted that withdrawal symptoms of craving, anxiety, depression, panic, guilt, paranoia, restlessness and tremor,

in that order, were most likely to provoke drinking. Indeed, many subjects reported relief from some of these symptoms when drinking was resumed. Further, Bauer (1994) recorded withdrawal-induced changes in EEG and autonomic activity in subjects experiencing alcohol withdrawal. It was noted that subjects who demonstrated greater withdrawal severity were significantly more likely to have relapsed within 3 months. Finally, several investigators have suggested that a particularly intense and protracted withdrawal may cause patients to relapse, presumably through self-medication with alcohol in order to cope with the persistent presence of withdrawal symptoms (Himmelsbach, 1942; Kissin et al., 1959; Kissin, 1979; Meyer, 1989; Satel et al., 1993).

While there is some evidence that withdrawal severity may be a predictor of relapse, it is not completely clear if it is the syndrome as a whole, or specific symptoms within the withdrawal syndrome. Further, past studies of withdrawal severity and relapse predominantly rely on subjective assessment scales of withdrawal severity, thereby increasing variability and error. Finally, there is a paucity of information available on the relationship between withdrawal severity and other antecedents of relapse, such as the psychosocial parameters mentioned above.

Since withdrawal severity may affect relapse, factors that affect withdrawal severity, and the degree of prior alcohol dependence, may also predict the likelihood of relapse. Anecdotally, it appears that this may be the case. That is, patients who have been drinking greater amounts for longer periods of time, and have a history of repeated withdrawal episodes with concomitant complications appear to have more difficulty in maintaining abstinence, possibly because of the greater degree of physiological and/or behavioural disturbance. That predictors of withdrawal severity affect the likelihood of relapse has also been demonstrated systematically. For example, Yates et al. (1993) observed that drinking history as defined by length of heavy drinking, daily intake and the number of previous treatment episodes, positively affected the likelihood of relapse at six months follow-up. Edwards (1987) proposed that a person's dependence on alcohol may be a significant factor in the relapse process. Finally, Bohn et al. (1995) observed that craving for alcohol was strongly related to the degree of alcohol dependence. While craving is not relapse *per se*, the presence of craving increases the likelihood of relapse. Thus, it appears there is some evidence that predictors of withdrawal severity, particularly drinking history may affect relapse. At this stage it is not known how other potential antecedents of withdrawal severity such as kindling and concomitant complications affect relapse. Moreover, it is not known how predictors of withdrawal severity relate to the other

determinants of relapse.

7.1.1 Experimental rationale and aims

The major aim of this study was to investigate withdrawal severity, both as a global syndrome and on an individual symptom level, as a predictor of relapse, using a prospective study design. That is, does the severity of the total syndrome, or the global severity of the physical aspects of the syndrome predict relapse? Further, are there any specific symptoms of the withdrawal syndrome that antedate relapse? Withdrawal severity in this study was determined using objective and standardised measures taken during the acute phase of abstinence (days 1 to 4), and measures taken into the protracted phase of withdrawal (day 14). There were several input measures of withdrawal severity that were investigated for their potential to affect relapse. These were total global withdrawal severity, physical global withdrawal severity, and all the individual symptoms of withdrawal that were assessed in this thesis (depression, anxiety, disturbances to mood, disturbances to components of health, hyperthermia, sleep disturbance, restlessness during the day, and intensity and duration of sweating). Thus, the aim was to investigate the potential of both the acute and protracted withdrawal syndrome (up to day 14) to predict relapse.

The second aim was to determine the potential of factors that affect withdrawal severity to predict relapse. This was based on the rationale that if withdrawal severity was a predictor of relapse, then the factors affecting withdrawal severity may also antedate relapse. Input measures of predictors of withdrawal severity were as proposed in Chapter 5. These included drinking history (number of years spent in heavy drinking, length of most recent drinking bout, daily alcohol intake), kindling (number of prior withdrawal episodes, history of seizures) and concomitant complications (number of current medical conditions, number of prescribed drugs currently taken, number of non-prescribed drugs currently used).

The final aim was to obtain a comprehensive view of the relationship between social factors, withdrawal severity, and factors affecting withdrawal severity, regarding their potential to predict relapse. The rationale for this stemmed from the paucity of information concerning how various predictors of relapse may relate to each other. In this study, certain lifestyle factors were incorporated to reflect the social aspects of relapse, including the presence of social support through a stable partner or spouse, employment, and stability of residential situation. This was the only psychosocial

information available from this sample. Information was not obtained regarding exposure to high risk situations, degree of craving, degree of motivation to change, and presence of coping skills.

7.2 Methodology

The methodology for this chapter is outlined in further detail in Chapter 3 entitled, '*General Methodology*'. In brief, monitor and questionnaire data from all 47 subjects (37 males, 10 females) were utilised to determine the nature of the relationship between withdrawal severity and relapse. Subjects were assessed following initial abstinence to determine the number of days before relapse occurred. Data collection was censored at seventy days. The number of days served as the outcome measure for all analyses in this chapter.

There were five main sections of analysis in this chapter. The first was univariate survival analysis in which different aspects of acute withdrawal severity, measured during days one to four of abstinence, were investigated as potential predictors of time to relapse. These input variables included total global withdrawal severity and physical global withdrawal severity (employed as outcome measures in Chapter 5), severity of depression (BDI) and anxiety (STAI), severity of mood disturbance (POMS), and severity of health disturbance (SF-36), severity of physical symptoms of hyperthermia, sweating, restlessness and sleep disturbance.

The second phase of analysis involved investigation of protracted withdrawal severity to predict relapse, using univariate survival analysis. Protracted withdrawal assessment incorporated measures that were taken from the subjects on day 14 of abstinence. Similar to the investigation of acute withdrawal severity, input variables included total global withdrawal severity and physical global withdrawal severity (day 14), severity of depression (BDI) and anxiety (STAI), severity of mood disturbance (POMS), and severity of health disturbance (SF-36), severity of physical symptoms of hyperthermia, sweating, restlessness and sleep disturbance. The potential of protracted withdrawal severity to affect relapse from measures taken on days 42 and 70 could not be included in this study, since sample sizes were too small because of a loss of subjects to the study through relapse.

The third analysis section involved univariate survival analysis of factors affecting withdrawal severity. Thus, input measures were drinking history, kindling and complications (as in Chapter 5), and the outcome measure was days to relapse.

The fourth analysis section involved univariate survival analysis of lifestyle factors thought to affect relapse drinking. Lifestyle parameters were determined from subjects' casenotes and included whether or not the subject had a stable partner -which was evidence of social support, whether or not the subject was employed, and the type of residence the subject was living in as evidence of

residential stability. The outcome measure was days to relapse.

The fifth and final section was a multivariate survival analysis that incorporated all variables from the previous three sections that were $p \leq 0.10$. The criterion for entering the multivariate analysis was strict, due to the small sample size for an analysis of this kind. Once again, the outcome measure was time to relapse.

7.3 Results

7.3.1 Relapse rate over the first 10 weeks of abstinence

Fig. 7.1 shows the rate of relapse in this sample of drinkers, censored following 70 days of observation. Rate of relapse was most rapid in the first two weeks of sobriety. Of the 47 subjects studied, 100% were abstinent on day 1. By day seven, 7 subjects had relapsed, leaving 85.1% abstinent (n=40). By day fourteen, only 65.9% of the sample remained abstinent (n=31), followed by 61.7% abstinent on day twenty one (n=29). The rate of relapse slowed over the remainder of the period, leaving 27 subjects abstinent on day twenty eight (57.4%), 24 subjects abstinent on day thirty five (51.0%), 21 subjects abstinent on day forty two (44.6%), 20 subjects on day forty nine (42.5%), 19 subjects abstinent on day fifty six (38.29%), and 18 subjects on days sixty three and seventy (38.2%).

Fig 7.1

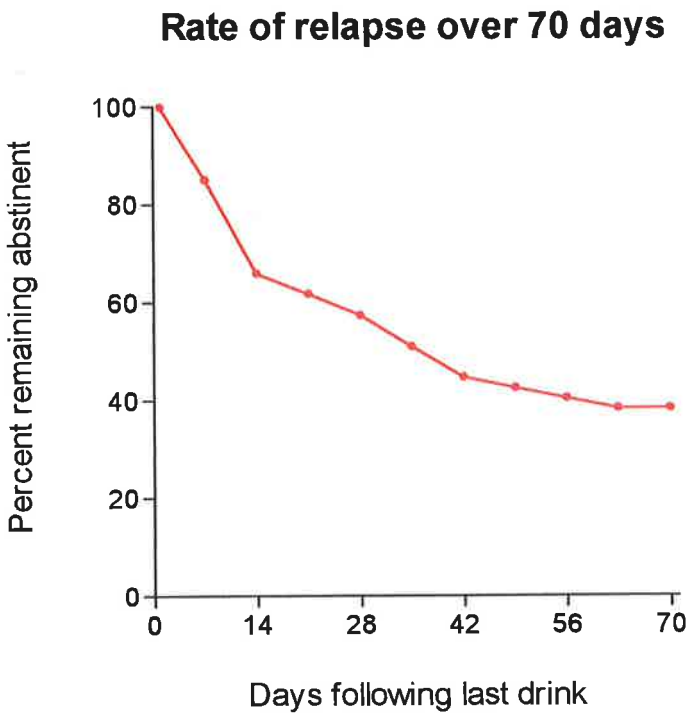


Fig 7.1 Graph showing percent of alcohol withdrawal subjects (n=47) who remain abstinent from week to week, during the seventy day period following their last drink.

7.3.2 Acute withdrawal severity as a predictor of time to relapse (Table 7.1)

The results of the univariate survival analysis of the predictive effects of acute withdrawal severity are shown in Table 7.1. Neither total global withdrawal severity nor physical global withdrawal severity during the inpatient phase were predictive of time to relapse. Depression, as measured by the BDI and anxiety, as assessed by the STAI were not predictive of time to relapse. Components of mood, as assessed by the POMS and comprising the individual parameters of tension/anxiety, depression/dejection, anger/hostility, vigour/activity, fatigue/inertia and confusion/bewilderment, were not significantly predictive of time to relapse. None of the parameters of health, as recorded by the SF-36, were predictive of time to relapse. This included physical functioning, role function physical, role function emotional, social functioning, bodily pain, mental health, vitality and general health.

None of the individual acute physical symptoms of withdrawal during the inpatient period were predictive of time to relapse, including sleep disturbance, hyperthermia between 2pm and 4pm, highest degree of sweating recorded on each day, early morning sweating between 2am and 9am, and restlessness at 1pm.

None of the variables included in this univariate survival analysis were $p \leq 0.10$, and thus were not incorporated into the multivariate survival analysis.

Table 7.1

Univariate survival analysis of various aspects of acute withdrawal severity (global withdrawal and individual symptoms) as predictors of time to relapse

Predictor variable	Significance
Total global withdrawal severity – over days 1 to 4	p = 0.47
Physical global withdrawal severity – over days 1 to 4	p = 0.51
BDI - mean score of days 1 and 4	p = 0.29
STAI - mean score of days 1 and 4	p = 0.48
POMS Tension/Anxiety - mean score of days 1 and 4	p = 0.15
POMS Depression/Dejection - mean score of days 1 and 4	p = 0.29
POMS Anger/Hostility - mean score over days 1 and 4	p = 0.53
POMS Vigour/Activity - mean score over days 1 and 4	p = 0.41
POMS Fatigue/Inertia – mean score over days 1 and 4	p = 0.88
POMS Confusion/Bewilderment – mean score over days 1 and 4	p = 0.89
SF-36 Physical functioning – score on day 1	p = 0.68
SF-36 Role function physical – score on day 1	p = 0.11
SF-36 Role function emotional – score on day 1	p = 0.11
SF-36 Social functioning – score on day 1	p = 0.95
SF-36 Bodily pain – score on day 1	p = 0.12
SF-36 Mental health – score on day 1	p = 0.50
SF-36 Vitality – score on day 1	p = 0.47
SF-36 General health – score on day 1	p = 0.97
Sleep activity – mean activity during sleep over nights 1, 2 & 3	p = 0.55
Skin temperature between 1400 and 1600 – mean over days 1 to 4	p = 0.17
Maximum sweating over 24 hour period – mean over days 1 to 4	p = 0.50
Early morning sweating between 0200 and 0900 – mean over days 1 to 4	p = 0.50
Restlessness – mean activity at 1300 over days 1 to 4	p = 0.29

7.3.3 Protracted withdrawal severity as a predictor of time to relapse (Table 7.2)

The results of the univariate survival analysis of the predictive effects of protracted withdrawal severity are shown in Table 7.2. Neither protracted total global withdrawal severity nor physical global withdrawal severity during day 14 was predictive of time to relapse. Depression, as measured by the BDI and anxiety, as assessed by the STAI were not predictive of time to relapse. Components of mood, as assessed by the POMS and comprising the individual parameters of tension/anxiety, depression/dejection, anger/hostility, vigour/activity, fatigue/inertia and confusion/bewilderment, were not significantly predictive of time to relapse. None of the parameters of health, as recorded by the SF-36, were predictive of time to relapse. This included physical functioning, role function physical, role function emotional, social functioning, bodily pain, mental health, vitality and general health.

None of the individual protracted physical symptoms of withdrawal during day 14 were predictive of time to relapse, including sleep disturbance, hyperthermia between 2pm and 4pm, highest degree of sweating recorded on each day, early morning sweating between 2am and 9am, and restlessness at 1pm.

None of the variables included in this univariate survival analysis were $p \leq 0.10$, and thus were not incorporated into the multivariate survival analysis.

Table 7.2

Univariate survival analysis of various aspects of protracted withdrawal severity (global withdrawal and individual symptoms) as predictors of time to relapse

Predictor variable	Significance
Total global withdrawal severity – day 14	p = 0.30
Physical global withdrawal severity – day 14	p = 0.46
BDI - score on day 14	p = 0.18
STAI - score on day 14	p = 0.35
POMS Tension/Anxiety - score on day 14	p = 0.81
POMS Depression/Dejection - score on day 14	p = 0.24
POMS Anger/Hostility - score on day 14	p = 0.34
POMS Vigour/Activity - score on day 14	p = 0.48
POMS Fatigue/Inertia – score on day 14	p = 0.33
POMS Confusion/Bewilderment – score on day 14	p = 0.28
SF-36 Physical functioning – score on day 14	p = 0.91
SF-36 Role function physical – score on day 14	p = 0.93
SF-36 Role function emotional – score on day 14	p = 0.63
SF-36 Social functioning – score on day 14	p = 0.33
SF-36 Bodily pain – score on day 14	p = 0.24
SF-36 Mental health – score on day 14	p = 0.92
SF-36 Vitality – score on day 14	p = 0.95
SF-36 General health – score on day 14	p = 0.72
Sleep activity – mean activity during sleep on night 14	p = 0.90
Skin temperature between 1400 and 1600 – mean during day 14	p = 0.37
Maximum sweating over 24 hour period – maximum during day 14	p = 0.67
Early morning sweating between 0200 and 0900 – mean during day 14	p = 0.43
Restlessness – mean activity at 1300 during day 14	p = 0.38

7.3.4 Factors affecting withdrawal severity as predictors of time to relapse (Table 7.3)

Drinking history, including length of most recent drinking bout and number of years of heavy drinking, were not predictive of time to relapse. Daily intake was not significant, although tended towards being a positive predictor of relapse ($p = 0.09$). That is, an increased daily intake suggested a higher risk of relapse. Since daily intake was $p \leq 0.10$ it was incorporated into the multivariate survival analysis.

Neither parameters of kindling (number of previous withdrawal episodes and history of seizures) were significantly predictive of relapse, and both had p values greater than 0.10 so were not included in the multivariate analysis.

Complications of withdrawal including number of current medical conditions and number of prescribed medications currently used, were not significantly predictive of relapse, nor were $p \leq 0.10$. However, polydrug use, or number of non-prescribed drugs currently used, was significantly predictive of time to relapse. That is, if other substances were used by the subjects (besides alcohol), the risk of relapse increased. This parameter was incorporated into the multivariate survival analysis. Of the 47 subjects assessed, 8 used alcohol only, 36 also used one other drug (tobacco) and 3 subjects used two other drugs (tobacco and cannabis, tobacco and heroin or tobacco and benzodiazepines).

Table 7.3

Univariate survival analysis of factors affecting withdrawal severity as predictors of time to relapse

Predictor Variable	Significance
Drinking history	
Number of years of heavy drinking	p = 0.20
Number of months spent in most recent drinking bout	p = 0.86
Recent Intake (g/day) during recent drinking bout	*p = 0.09*
Kindling	
Number of previous withdrawal episodes	0.99
History of seizures	0.76
Complications	
Number of current medical conditions	0.97
Number of prescribed drugs currently used	0.35
Number of non-prescribed drugs currently used (including tobacco, but not alcohol)	***0.04***

NB. p values in *italics* were used for multivariate analysis (ie $p \leq 0.10$), p values in **bold** denote statistical significance ($\mathbf{p \leq 0.05}$).

7.3.5 Lifestyle factors as predictors of time to relapse (Table 7.4)

Of the 47 subjects assessed, 15 (31.9%) were involved in a stable relationship with another person. Eight of the total sample was employed (17%), and the remainder unemployed. Ten subjects owned their own home (21.3%), 20 subjects were renting (42.6%), 10 subjects had no fixed address (21.3%), while 7 subjects (14.9%) were living in boarding houses.

Being single (not having a stable partner) was a highly significant predictor of relapse, and was included into the multivariate survival analysis. Whether or not subjects were employed did not appear to affect the rate of relapse. Thus, unemployment was not a significant factor in the analysis.

The style of living arrangement, or type of residence did not appear to be a significant predictor of relapse. However, the trend was such that subjects living in a boarding situation tended to be at greatest risk of relapse followed by subjects with no fixed address, followed by subjects renting, followed by subjects who owned their own home. While not strictly statistically significant, comparison of the most stable residence type (own home) with the least stable (boarding in this sample) resulted in p=0.09 (not shown in Table 7.4). However, type of residence was not included into the multivariate analysis since the overall significance was $p \leq 0.10$.

Table 7.4

Univariate survival analysis of lifestyle factors as predictors of relapse

Predictor	**Significance**
Being single (vs. having a stable partner)	***p = 0.005***
Unemployed (vs. employed)	p = 0.41
Type of residence (boarding vs. no fixed address vs. renting vs. own home)	p = 0.37

NB. p values in *italics* were used for multivariate analysis (ie $p \leq 0.10$), p values in **bold** denote statistical significance ($\mathbf{p \leq 0.05}$).

7.3.6 Multivariate survival analysis of predictors of time to relapse (Table 7.5)

Of the three variables incorporated into the multivariate survival analysis, being single and polydrug use were highly significant as predictors of time to relapse. Calculation of risk ratios indicate that subjects not having a partner were approximately five and a quarter times more likely to relapse, while polydrug users increased their risk of relapse by a factor of 6.56. Daily alcohol intake did not appear to account for any of the variance observed in this sample above the other variables involved, and did not affect the risk of relapse.

Table 7.5

Multivariate survival analysis of predictors determined from univariate analysis of time to relapse

Predictor	**Significance**	**Risk ratio**
Being single (no partner)	**p = 0.005**	5.24
Daily alcohol intake	p = 0.90	1.00
Polydrug use (non medical)	**p = 0.0005**	6.56

NB. p values in **bold** denote statistical significance (**p≤0.05**).

7.4 Discussion

The results from this study show that the likelihood of relapse was not affected by the severity of the total withdrawal syndrome, nor the severity of a physical component of the withdrawal syndrome, during the acute inpatient phase (days 1 to 4). Similarly, protracted withdrawal severity at day 14 did not affect time to relapse. Despite the anecdotal evidence, there were no individual symptoms of acute or protracted withdrawal, such as anxiety or depression that particularly affected time to relapse. Accordingly, most of the factors thought to affect the severity of withdrawal also were not predictive of time to relapse, including duration of drinking (recent and long-term), previous withdrawal episodes, history of seizures, and concomitant medical complications and use of prescribed medications. However, two of the factors that have been shown to affect the severity of withdrawal, also appeared to have an affect on time to relapse. These are discussed in more detail below.

That withdrawal severity, and the majority of its antecedents did not affect time to relapse may be explained by several factors. There was anecdotal evidence from a few of the subjects in this study that withdrawal severity was in fact a predictor of abstinence. These reports came from subjects who were experiencing a particularly severe withdrawal episode. Their rationale was that the memory of having such a bad time made them more determined not to experience withdrawal again, and thus not drink again. Whether these particular subjects actually maintained a greater time to relapse is not known. That a severe withdrawal may actually motivate abstinence in some individuals has also been noted by Taylor et al. (1985).

A second factor that may have contributed to the lack of statistical effect is based on evidence that patients who are better managers of their post acute withdrawal symptoms have an increased chance of maintaining abstinence (Murphy & Hoffman, 1993). This may have been a confounding factor in this study, in that some subjects could have been successfully managing their withdrawal symptoms. It is also possible that the investigator in this study inadvertently contributed to the better management of withdrawal by these subjects. Communicating with the investigator about their symptoms, drinking histories and backgrounds, may have served to 'de-brief' some patients, which may have resulted in their better management of withdrawal symptoms. However, this is one theory as to why no statistical effect was observed, and there is no direct evidence for this proposition.

A third possible explanation for the lack of statistical effect is that the definition of relapse that was utilised for this study may not have been appropriate to identify the changes influenced by withdrawal severity. Other studies have used different relapse criteria. For example, some investigators have stipulated that any alcohol consumption constitutes a relapse (Hunt et al., 1971; Bauer, 1994; Brown et al., 1995). Conversely, Gallant (1992) defined a relapse event as alcohol consumption on four or more days in a week. These relapse criteria may have resulted in an altered relapse rate if they had been utilised in this study, particularly criteria stating that any alcohol use is defined as a relapse. A few of the subjects in the present study did consume a moderate amount of alcohol on one or two days during the follow up period, but did not return to uncontrolled drinking. In fact, they appeared to remain abstinent for the duration of the study, apart from this episode. It appears then that the definition of relapse used in the current study clearly differentiated between controlled use, and a relapse.

Of course, another possible explanation for lack of statistical effect is inadequate sample size and lack of statistical power. Although the power for most of the studies in this thesis was estimated to be between 70% and 90%, the power in this particular study (Chapter 7) may have decreased as the sample size decreased with subsequent relapses.

Despite the above-mentioned potential confounding factors, the most likely explanation appears to be that withdrawal severity and its antecedents have little effect on whether or not relapse will occur. This has also been suggested by other investigators. For example, that withdrawal symptoms do not readily trigger further alcohol consumption has also been proposed by Stockwell (1994). Jin et al. (1998) demonstrated that prior drinking history was not predictive of relapse in a sample of 77 withdrawing male alcoholics. Finally, Heather et al. (1983) investigated an objective measure of alcohol dependence as a potential predictor of relapse. The 'objective' measure of dependence was determined using the Severity of Alcohol Dependence Questionnaire (SADQ), which extracted information on drinking history (frequency and level of consumption), withdrawal phenomena, and relief drinking over the previous month. The authors found that alcohol dependence, as measured by the SADQ, was not predictive of relapse drinking.

Thus, it appears that psychosocial factors indeed may be more important than withdrawal severity, and its antecedents, in determining relapse. This study did find that two of the factors that affect withdrawal severity also appeared to predict relapse drinking. While not strictly statistically

significant, daily intake of alcohol tended towards being a significant predictor of alcohol withdrawal (p=0.09). That is, the greater the amount of alcohol that patients consumed in the period prior to their withdrawal, the shorter the time to relapse. However, when daily intake was investigated along with other factors using multivariate survival analysis, it appeared to have no significant effect on time to relapse.

This study also found that polydrug use of substances of abuse/dependence besides alcohol (e.g. tobacco, cannabis, benzodiazepines, opiates etc.) was a significant predictor of relapse. In this sample polydrug use predominantly referred to the use of tobacco. It may be that polydrug use affected the severity of withdrawal, which in turn affected likelihood of relapse. However, since withdrawal severity itself did not affect relapse, it appears that a psychosocial explanation, expressed in terms of cue exposure, may be more appropriate. That is, the effects of other drugs co-administered with alcohol in the past, may be paired with the pharmacological and social effects of alcohol. When the drug is taken in the future in the absence of alcohol (in the case of an abstinent patient), the drug may serve as a cue for drinking, resulting in increased craving and a consummatory response. This explanation appears to be feasible given that alcohol and tobacco are frequently used concurrently in the population of concern. Multivariate analysis determined that polydrug use increased the risk of relapse by a factor of around 6.5, demonstrating that polydrug use accounted for a significant proportion of the variance.

The results from this study showed that at least one of the psychosocial factors investigated was highly important in predicting relapse. If the patient could access social support because they had a stable partner (either spouse, defacto or steady girlfriend/boyfriend), the likelihood of relapse during the first 70 days was greatly decreased. Multivariate survival analysis determined that patients who did not have this kind of social support were at approximately five times the risk of relapsing within the first seventy days, demonstrating that a lack of social support accounted for a significant proportion of the variance.

While subjects' place of residence was not significant overall, the direction of the trend for predicting relapse showed that people who were boarding with others were at the greatest risk of relapse, followed by persons with no fixed address, followed by renters. People who owned their own home were at least risk of relapse. The reason for this directional trend appears to be due to residential stability, and exposure to social pressure to use alcohol and/or drugs. There is anecdotal

evidence to suggest that subjects who are boarding are generally at greatest risk of exposure to others who are high consumers of alcohol and/or other drugs. While subjects having no fixed address may appear to have a less stable residency than boarders, in this particular study many of the subjects who did not have a fixed address enrolled in a long term therapeutic community, where alcohol and substance use was not permitted. While not strictly statistically significant, there appeared to be a trend for tendency towards increased relapse risk between the least residentially stable subjects (boarders) and subjects who had greatest residential stability and owned their own home.

This study found that unemployment was not a significant risk factor for relapse. While it has been shown that employment may help maintain abstinence (Ellis & McClure, 1992; Murphy & Hoffman, 1993), there is also evidence that relapse risk is related to the quality of the job. For example, if a subject perceives their job as being highly stressful, the risk of relapse may be increased (Smith & Frawley, 1993).

In conclusion, the results from the present study demonstrated that specific symptoms of withdrawal, the withdrawal syndrome as a whole, and its antecedents, were not predictors of relapse. Moreover, they did not contribute to the comprehensive, or total picture of relapse. Daily intake of alcohol appeared to be an important factor, although its effects may be explained by other significant factors, such as polydrug use and social support. These are novel findings, since there are very few studies that have investigated withdrawal as a predictor of relapse, particularly as a total syndrome. Of the studies that have been done in this area, some have tended to rely on subjective, non-standardised scales for assessment of withdrawal severity (Hershon, 1977; O'Connor et al., 1991). This may account for their positive results, and may be an erroneous finding. As mentioned in the introduction, Bauer (1994) found that specific withdrawal-induced changes in EEG and autonomic activity predicted relapse. These symptoms were not incorporated into the present study, so it is difficult to compare the results of the present study with Bauer's study. Indeed it may be that withdrawal-induced changes in EEG and autonomic activity do have an effect on relapse.

The present study appears to be one of the first that has assessed withdrawal using objective and standardised measures, and has incorporated a global withdrawal assessment, a physical global withdrawal assessment, and also individual symptoms as potential predictors of relapse. Further, this study is novel in its comprehensive approach to relapse investigating the relationship between withdrawal severity, factors that affect withdrawal severity, and social factors.

Thus, it can be concluded with more finality that withdrawal severity during the first five days and its antecedents, and the severity of protracted withdrawal at two weeks, are not involved in relapse during the first seventy days. It is not known how the presence and severity of withdrawal affects the likelihood of relapse after this time. As discussed in the methods section of this chapter, protracted withdrawal measures on days 42 and 70 could not be utilised since the sample sizes were inadequate for survival analysis.

Overall, psychosocial factors appear to be more important in the likelihood of relapse. While the finding that lack of social support is a factor in resumption of drinking is already known, that polydrug use is an important factor in predicting relapse is a novel observation, and may account for some of the failure to maintain abstinence from alcohol in current treatment populations.

It was surprising that the withdrawal symptoms of depression and anxiety were not significant predictors of relapse, since there is evidence that negative emotional states may be involved in the resumption of drinking (Loosen et al., 1990; Brown et al., 1991; Schonfield & Dupree, 1991; Brown et al., 1995; Ellis & McClure, 1992; LaBounty et al., 1992). One possible explanation for this lack of effect is that patients successfully managed their withdrawal and had adequate coping skills to maintain abstinence.

These findings have clinical implications. Firstly, psychosocial factors do appear to be highly relevant in maintaining abstinence. Secondly, patients may be identified as being at a greater risk of relapse if they do not have a stable partner, and if they use other substances besides alcohol. Patients who are boarding with others may also be at greater risk of resuming drinking. Patients who meet the criteria for increased risk could receive early intervention, and on going treatment such as support therapy, follow-up and counselling, which may increase the likelihood of maintaining abstinence.

CHAPTER 8

8. GENERAL DISCUSSION

Investigations of alcohol withdrawal over the last fifty years have established that there is a 'syndrome' which occurs with abstinence from alcohol, and that it is characterised by specific signs and symptoms. These include the presence of hyperthermia, sweating, insomnia, restlessness and agitation, fatigue, confusion and disorientation, anxiety and depression, and other psychiatric and mood disturbances, during the first week of abstinence (Victor & Adams, 1953; Wellman, 1954; Isbell et al., 1955; Wellman 1955; Flaherty et al., 1955; Kissin, 1959; Mendelson & La Dou, 1964; Gross & Lewis, 1973; Gross et al., 1974; Feuerlein, 1974; Edwards & Gross, 1976; Sellers & Kalant, 1976; Hershon, 1977; Brown & Schuckit, 1988; Haviland et al., 1988; Clark et al., 1993; O'Connor et al., 1991; Romach & Sellers, 1991; Hemmeter et al., 1993; Murphy & Hoffman, 1993; Schuckit et al., 1994; Brown et al., 1995; Le Bon et al., 1997).

Measurement of physical withdrawal symptoms has predominantly occurred through determination of symptom severity according to subjective rating scales, as assessed by clinicians, researchers, and the patients themselves. The availability of the ambulatory monitor advanced measurement of several physical symptoms of withdrawal. Thus, one of the aims of this thesis was to validate and calibrate the ambulatory monitors for the accurate and reliable recording of alcohol withdrawal symptomatology. The results from the validation studies on the monitors meant that absolute values of temperature in degrees Celsius (°C), sweating in % Relative Humidity (%RH), and activity in 'turns greater than five degrees from the horizontal plane per five minutes' could be derived from the mV output of the monitors. Secondly, the calibration studies of the monitors meant that all six monitors related to each other equally in terms of sensitivity for each of the channels in the measurement of temperature, sweating and activity. Finally, the consistency studies of the monitors meant that there was linearity over a wide range of readings, that is from readings that were at the low end of the spectrum, to readings that were taken at the higher end of the spectrum.

In the present study, and in earlier research, withdrawal symptomatology has been shown to be the most severe, during the first week of abstinence, but markedly improves over the first five to seven days. However, there have been very few details as to what happens immediately after the first

week of withdrawal. Moreover, past investigations are limited by the use of subjective assessments of withdrawal severity, use of unstandardised scales to assess withdrawal severity, use of cross-sectional rather than longitudinal study designs, maintaining a narrow symptom focus, and confusing withdrawal symptomatology with symptoms of recovery from the toxic effects of alcohol. The current study made efforts to counter most of these limitations and fill gaps in the literature regarding the intensity and duration of withdrawal symptomatology.

Chapter 4 demonstrated that indeed, withdrawal symptomatology is most severe in the first week of sobriety. However, it was also found that alcohol withdrawal disturbs diurnal rhythms of temperature, sweating and activity. These symptoms occur even following the administration of benzodiazepines, which was the case for most of the subjects in this sample. Disruption to diurnal rhythms by alcohol withdrawal does not appear to have been recognised previously. Thus, the first week of sobriety is an unpleasant time for most alcohol dependent persons, as they experience a gamut of physical symptoms including increases in temperature, fluctuations in temperature, intense sweating – particularly at night and into the early morning, periods of agitation and restlessness during the day, followed by malaise and tiredness, difficulty sleeping, although feeling fatigued. Physical manifestations of withdrawal are compounded by psychiatric disturbances -severe anxiety, depression and confusion, comparable in severity with a major psychiatric illness. A degree of pain may also be present, accompanied by poor physical and emotional health which interferes with one's ability to perform usual daily activities, including social activities and interactions with others. While symptom improvement does occur, all symptoms are still present in varying degrees, for at least two weeks after drinking has ceased. Over the following four weeks of abstinence (six weeks in total), heightened sweating will resolve, along with feelings of confusion and fatigue. There will be some return to normal functioning, including an improvement in physical health, and an increased ability to execute daily tasks. Social interaction will improve, and bodily pain will lessen. While physically more capable of usual activities, compromised mental health will still interfere with all aspects of life, which may be accompanied by a frustrating awareness of one's own continual poor health. Feelings of depression will begin to resolve, although anxiety will persist. Disruption to diurnal activity rhythms will still be present, although less severe. However, at the end of six weeks, feelings of vitality and vigour will begin to emerge, and hyperthermia and temperature fluctuations will have disappeared.

Over the next four weeks of sobriety (ten weeks in total), insomnia and anxiety will lessen, and tend towards resolution. However, disrupted activity patterns will still be present until at least ten weeks of abstinence, and patients may still feel particularly restless and agitated at certain times of the day. Emotional problems will still interfere with usual daily activities, compounded by compromised mental health. While the ability to interact socially will improve, along with ability to function physically and lessening of bodily pain, at the end of ten weeks overall health status will be comparable with patients that have a minor medical condition.

In conclusion, this study resolved some of the limitations of past investigations, and provided a detailed map of symptom severity occurring in the first ten weeks of abstinence from alcohol, which markedly enhances the current available picture of the withdrawal syndrome. However, some of the symptoms assessed in this study, particularly psychiatric and health disturbances, may reflect recovery from the toxic effects of alcohol, as well as actual symptoms of withdrawal. It is difficult to differentiate absolutely between withdrawal and recovery symptoms, and indeed, is almost impossible in a human population. Finally, the abstinence syndrome appears to last longer than previously has been recognised, and this has implications for treatment extending beyond the first week, in which particular symptoms may be relevant as targets of treatment.

The availability of objective and standardised recordings of withdrawal provided the opportunity to more thoroughly investigate previously identified predictors of the severity of withdrawal that have been determined using more subjective measures. The literature identifies several predictors of withdrawal severity. Predictors include parameters of drinking history, including daily intake, length of most recent drinking bout, and total number of years spent in heavy drinking (Hershon, 1977; Pristach et al., 1983; Gorelick & Wilkins, 1986; Schuckit et al., 1995; Schukit et al., 1998; Shaw et al., 1998). There is also evidence that the number of previous withdrawal attempts has a 'kindling' effect, resulting in more severe withdrawal (Brown et al., 1988; George et al., 1990; Schuckit et al., 1995; Shaw et al., 1998). Finally, concomitant complications may also be involved, including the presence of co-morbid illness (Johnson, 1961; Tavel et al. 1961; Gross et al., 1971; Sellers & Kalant, 1976; Thompson, 1978; Baum & Iber, 1980; Tonneson, 1982; Sheehan, 1983; Gorelick & Wilkins, 1986; Romach & Sellers, 1991), and polydrug use (Schuckit et al., 1993; Schuckit et al., 1995).

Chapter 5 used two outcome measures of withdrawal severity based on data collected for Chapter 4. An extensive search of the literature indicates that this may be one of the first efforts to determine predictors of withdrawal severity using objective and standardised componential measures of withdrawal. Total global withdrawal severity incorporated all the measured components of withdrawal -physical, psychiatric and mood manifestations, and health disturbances. Physical global withdrawal severity incorporated the physical only, since physical withdrawal severity is more relevant as to whether patients require a medical detoxification. It is possible that physical global withdrawal severity may have been a more "pure" measure of withdrawal severity than total global withdrawal severity, since the total global component incorporated symptoms that may have also resulted from direct alcohol toxicity.

Total global withdrawal severity was predicted by drinking history. The length of most recent drinking bout and daily intake were more important than the number of years that the person had been drinking heavily. Kindling and concomitant complications did not appear to be relevant in predicting global withdrawal severity. Conversely, physical global withdrawal severity was best predicted by concomitant complications, particularly the presence of co-morbid illness and resulting prescribed medications. Drinking history and kindling did not appear to play a role. It appears that kindling is not relevant in the withdrawal syndrome as a whole, but may be more relevant for predicting the severity of particular symptoms such as seizures, convulsions and delirium tremens (Brown et al., 1988; Schuckit et al., 1995).

The findings of this study inform and challenge the current understanding of predictors of withdrawal severity, and consequently have several clinical implications. It appears that drinking history does not affect physical withdrawal severity exclusively, but rather the syndrome as a whole. Accordingly, it may be that psychiatric, mood and health disturbances are more affected by drinking history than the physical symptoms of withdrawal, and suggests these features of withdrawal should be more closely monitored and treated in patients with more severe drinking histories. These patients may require less medical supervision, but could respond well to support, and other types of psychosocial treatment. It also appears that the number of years of heavy drinking has little to do with the severity of the overall withdrawal syndrome, but that the length of the most recent drinking bout, and daily intake over that period are more important in this context.

In contrast it appears that patients with co-morbid illnesses are at greater risk of a severe physical withdrawal severity, and thus may be more needy of a medical detoxification. Current knowledge suggests that comorbidity affects only severe withdrawal phenomena, such as convulsions and delirium tremens, but this study indicates that other features of physical withdrawal are affected. It is worth noting that the physical component of withdrawal in this study was comprised of measures of hyperthermia, sweating, agitation and sleep restlessness, which may not require urgent medical attention unless severe (eg. hyperthermia). However, these symptoms may reflect the severity of the physiological disturbances underlying the withdrawal syndrome.

In Chapter 5 it was demonstrated that some aspects of drinking history may determine the intensity of withdrawal a patient will experience once drinking has ceased. However, it is recognised that there may have been some error in the collection of drinking history data, both in this thesis, and in other research efforts that have investigated the effects of drinking history on withdrawal. In brief, the assessment of drinking history is a subjective exercise, in that patients may distort the truth, forget, or be misunderstood by the clinical staff collecting the information. Thus, it is not clear how accurate predictors really are that rely on information collected in this way. For this reason, Chapter 6 investigated the potential of the biological markers GGT, MCV and CDT to predict withdrawal severity. Since these markers are an objective reflection of hazardous alcohol intake over a period of at least one week (Chick et al., 1981; Conigrave et al., 1995; Whitfield, 1991), they may also reflect some aspects of drinking history such as intake and duration of the most recent drinking bout. Thus, they may also indicate physical dependence on alcohol, and hence withdrawal phenomena upon cessation of drinking. The advantage of the present study is that hazardous intake is assessed using objective means, and assessment of withdrawal severity is available based on objective and standardised measures, as determined in Chapter 4. A search of the literature revealed that biological predictors of withdrawal severity had not been examined as objectively or as comprehensively as proposed in Chapter 6.

Total global withdrawal severity was not predicted by any of the biological markers. Physical global withdrawal severity was significantly predicted by CDT, even in the presence of other potentially predictive parameters identified in Chapter 5. GGT and MCV did not predict physical global withdrawal severity. This may be because CDT is a more specific and sensitive marker of alcohol intake than GGT and MCV (Conigrave et al., 1995; Whitfield, 1991). CDT appears to be a better

predictor of the physical symptoms of withdrawal, rather than of the total syndrome which also comprises psychiatric aspects of withdrawal such as depression and anxiety, and disturbances to health.

In conclusion, it appears that CDT is predictive of physical withdrawal severity, as measured by the withdrawal symptoms of hyperthermia, sweating, sleep disturbance and restless. The results from this study may also be interpreted, albeit cautiously, as evidence that CDT is a biological marker for physical dependence on alcohol. However, this is a relatively new area, and further research is warranted. The results from this study also have clinical implications. Since CDT appears to be predictive of physical withdrawal severity, determination of CDT prior to detoxification could be used in conjunction with other information to ascertain the intensity of withdrawal the patient will experience. Because CDT is an objective marker, assessing clinicians could have more confidence in the accuracy of prediction of pending withdrawal severity, and also in the choice of patient-specific treatment.

The availability of objective and standardised recordings of withdrawal provide the opportunity to more thoroughly investigate withdrawal severity as a predictor of relapse, and to determine how withdrawal severity as an antecedent of relapse relates to other predictors of relapse. The factors contributing to relapse are not completely clear. Most of the research into factors that affect relapse is based on psychosocial investigations (Gerard et al., 1962; Rathod et al., 1966; Ludwig & Stark, 1974; Ludwig & Wilker, 1974; Ludwig et al., 1977; Poulos, 1981; Litman et. al., 1984; Marlatt & Gordon, 1985; Macrae et al., 1987; Wilson, 1987; Allsop, 1990; Staiger & White, 1991; Watson, 1991; Gallant, 1992; Johnsen & Herringer, 1992; Klingemann, 1992; Prochaska et al., 1992; Murphy & Hoffman, 1993; Ryan et al., 1995). Identified predictors of relapse include exposure to high risk situations such as negative emotional states, interpersonal conflicts, social pressure, and drinking-related cues. Other predictors of relapse include the presence of craving, lack of motivation to change, lack of social support, impoverished or unstable lifestyle, and lack of coping skills. Identification of these antecedents of relapse has resulted in the development of specific treatment regimes, and improved outcomes for patients wishing to maintain abstinence. However, relapse rates are still high and it appears that there may be other factors, not targeted in current treatment regimes, which may affect the likelihood of relapse.

There is some evidence that withdrawal severity may predict relapse (Hershon (1977; O'Connor et al., 1991; Bauer, 1994), particularly if it persists as protracted withdrawal Kissin (1979).

The concept of withdrawal affecting relapse has not been investigated fully, least of all with objective and standardised measures of withdrawal. If withdrawal severity affects relapse, factors that affect withdrawal severity, particularly drinking history, may also predict the likelihood of relapse, (Edwards, 1987; Yates et al., 1993; Bohn et al., 1995). Thus, Chapter 7 investigated the potential of acute and protracted withdrawal to affect relapse within ten weeks, including total global, physical global and individual symptoms of withdrawal. It also investigated antecedents of withdrawal severity to predict relapse, including those predictors identified in this thesis (Chapter 5) and the work of others (ie. drinking history, kindling and concomitant complications). Finally, psychosocial lifestyle factors were incorporated into the analysis to determine a comprehensive view of the relationship between withdrawal severity, antecedents of withdrawal severity and psychosocial factors.

Withdrawal severity, both acute and protracted, does not appear to be involved in relapse drinking either on a global level or at a specific symptom level, although it should be noted that in some individuals, a severe withdrawal may actually motivate abstinence. Whether or not the patient has access to social support through a partner or spouse is highly predictive of relapse, demonstrating that psychosocial factors are indeed relevant in the risk of relapse. Two of the antecedents of withdrawal severity appeared to be predictive of relapse -daily alcohol intake and polydrug use of other substances of abuse. However, when the variables were viewed comprehensively, in relation to each other, daily intake did not account for any of the variance observed. Lack of social support and polydrug use increase the risk of relapse by around five times and six times respectively. While polydrug use is a putative predictor of withdrawal severity, it appears that a psychosocial explanation, expressed in terms of cue exposure, may be more appropriate. That is, the effects of other drugs co-administered with alcohol in the past, may be paired with the pharmacological and social effects of alcohol. When the drug is taken in the future in the absence of alcohol (in the case of an abstinent patient), the drug may serve as a cue for drinking, resulting in increased craving and a consummatory response. In this sample polydrug use predominantly referred to the use of tobacco. Thus, the psychosocial explanation appears to be feasible given that alcohol and tobacco are frequently used concurrently in the population of concern. These are novel findings, since there are very few studies that have investigated withdrawal as a predictor of relapse, particularly as a total syndrome.

These findings have clinical implications. Firstly, psychosocial factors do appear to be highly relevant in maintaining abstinence. Secondly, patients may be identified as being at a greater risk of

relapse if they do not have a stable partner, and if they use other substances besides alcohol, such as tobacco. Patients who meet the criteria for increased risk may benefit from early intervention, and on going treatment such as support therapy, follow-up and counselling, which may increase the likelihood of maintaining abstinence.

There are several directions that research in the future could follow. The symptom baseline that is available could be used to examine the effects of novel pharmacotherapies and/or psychosocial interventions on withdrawal severity and duration. Of course, increased sample sizes, particularly in the protracted period, would provide a better understanding of withdrawal at this time. Further, subjects could be followed until their symptom severity becomes negligible, to provide improved information on the duration of particular withdrawal symptoms. Another area that would benefit from future research is the use of CDT to predict withdrawal severity. Of particular interest would be determination of CDT cut-off values, and their relationship to appropriate treatment regimes for the withdrawal that will follow. Obviously a much larger sample size is required before cut-off values could be determined. It may also be beneficial to determine the relationship between CDT and other physical withdrawal symptoms, such as gastrointestinal disturbances, tremor, seizure activity, hypertension and cardiac arrythmias. Finally, while this study showed that withdrawal severity was not predictive of relapse, it did not examine the effects of protracted withdrawal severity beyond two weeks. This could be a further research area, by increasing the sample size during the protracted period, to observe the effects of protracted withdrawal on relapse drinking.

APPENDICES

SPSS MACRO FOR MONITOR 1

```
COMPUTE record = a * 1 .
VARIABLE LABELS record 'record number' .
EXECUTE .
COMPUTE temp1mv = c * 1 .
EXECUTE .
COMPUTE sweat1mv = d * 1 .
EXECUTE .
COMPUTE act1mv = e * 1 .
EXECUTE .
COMPUTE tempc = (temp1mv + 18.8484) / 10.6555 .
VARIABLE LABELS tempc 'temperature in degrees centigrade' .
EXECUTE .
COMPUTE sweat1cf = 77.62814 / (sweat1mv + 11.53117) .
VARIABLE LABELS sweat1cf 'correction factor for sweating - mon1' .
EXECUTE .
COMPUTE sweatrh = sweat1mv * sweat1cf .
VARIABLE LABELS sweatrh 'sweating in relative humidity' .
EXECUTE .
COMPUTE mins = record * 5 .
VARIABLE LABELS mins 'minutes (time) graded by 5' .
EXECUTE .
COMPUTE logmins = LG10(mins) .
VARIABLE LABELS logmins 'log 10 of time in minutes' .
EXECUTE .
COMPUTE c1mv = ( - 6.917965 * logmins) + 94.3113 .
VARIABLE LABELS c1mv 'y-intercept for each activity time point' .
EXECUTE .
COMPUTE turn1 = (act1mv - c1mv) / 1.431 .
VARIABLE LABELS turn1 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - incorrected baseline' .
EXECUTE .
COMPUTE turns = (c1mv + turn1) - 20.82 .
VARIABLE LABELS turns 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - corrected baseline' .
EXECUTE .
```

SPSS MACRO FOR MONITOR 2

```
COMPUTE record = a * 1 .
VARIABLE LABELS record 'record number' .
EXECUTE .
COMPUTE temp2mv = c * 1 .
EXECUTE .
COMPUTE sweat2mv = d * 1 .
EXECUTE .
COMPUTE act2mv = e * 1 .
EXECUTE .
COMPUTE tempc = (temp2mv + 7.722104) / 11.13375 .
VARIABLE LABELS tempc 'temperature in degrees centigrade' .
EXECUTE .
COMPUTE sweat2cf = 75.11765 / (sweat2mv + 54.85069) .
VARIABLE LABELS sweat2cf 'correction factor for sweating mon2' .
EXECUTE .
COMPUTE sweatrh = sweat2mv * sweat2cf .
VARIABLE LABELS sweatrh 'sweating in relative humidity'
EXECUTE .
COMPUTE mins = record * 5 .
VARIABLE LABELS mins 'minutes (time) graded by 5' .
COMPUTE minsinv2 = 1 / (mins * mins) .
VARIABLE LABELS minsinv2 'the reciprocal of minutes (mins) squared' .
EXECUTE .
COMPUTE c2mv = (259.5219 * minsinv2) + 137.7869 .
VARIABLE LABELS c2mv 'y-intercept for each activity time point' .
EXECUTE .
COMPUTE turn2 = (act2mv - c2mv) / 2.625 .
VARIABLE LABELS turn2 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - incorrected baseline' .
EXECUTE .
COMPUTE turns = (c2mv + turn2) - 86.06 .
VARIABLE LABELS turns 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - corrected baseline' .
EXECUTE .
```

SPSS MACRO FOR MONITOR 3

```
COMPUTE record = a * 1 .
VARIABLE LABELS record 'record number' .
EXECUTE .
COMPUTE temp3mv = c * 1 .
EXECUTE .
COMPUTE sweat3mv = d * 1 .
EXECUTE .
COMPUTE act3mv = e * 1 .
EXECUTE .
COMPUTE tempc = (temp3mv + 12.434) / 10.83848 .
VARIABLE LABELS tempc 'temperature in degrees centigrade' .
EXECUTE .
COMPUTE sweat3cf = 78.64924 / (sweat3mv + 37.40192) .
VARIABLE LABELS sweat3cf 'correction factor for sweating mon3' .
EXECUTE .
COMPUTE sweatrh = sweat3mv * sweat3cf .
VARIABLE LABELS sweatrh 'sweating in relative humidity' .
EXECUTE .
COMPUTE mins = record * 5 .
VARIABLE LABELS mins 'minutes (time) graded by 5' .
EXECUTE .
COMPUTE logmins = LG10(mins) .
VARIABLE LABELS logmins 'log 10 of time in minutes' .
EXECUTE .
COMPUTE c3mv = ( - 6.863935 * logmins) + 86.8899 .
VARIABLE LABELS c3mv 'y-intercept for each activity time point' .
EXECUTE .
COMPUTE turn3 = (act3mv - c3mv) / 1.325 .
VARIABLE LABELS turn3 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - incorrected baseline' .
EXECUTE .
COMPUTE turns = (c3mv + turn3) - 17.42 .
VARIABLE LABELS turns 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - corrected baseline' .
EXECUTE .
```

SPSS MACRO FOR MONITOR 4

```
COMPUTE record = a * 1 .
VARIABLE LABELS record 'record number' .
EXECUTE .
COMPUTE temp4mv = c * 1 .
EXECUTE .
COMPUTE sweat4mv = d * 1 .
EXECUTE .
COMPUTE act4mv = e * 1 .
EXECUTE .
COMPUTE tempc = (temp4mv + 16.367) / 10.6034 .
VARIABLE LABELS tempc 'temperature in degrees centigrade' .
EXECUTE .
COMPUTE sweat4cf = 77.3755 / (sweat4mv + 95.4354) .
VARIABLE LABELS sweat4cf 'correction factor for sweating mon4' .
EXECUTE .
COMPUTE sweatrh = sweat4mv * sweat4cf .
VARIABLE LABELS sweatrh 'sweating in relative humidity' .
EXECUTE .
COMPUTE mins = record * 5 .
VARIABLE LABELS mins 'minutes (time) graded by 5' .
EXECUTE .
COMPUTE logmins = LG10(mins) .
VARIABLE LABELS logmins 'log 10 of time in minutes' .
EXECUTE .
COMPUTE c4mv = ( - 6.838758 * logmins) + 85.94464 .
VARIABLE LABELS c4mv 'y-intercept for each activity time point' .
EXECUTE .
COMPUTE turn4 = (act4mv - c4mv) / 1.259 .
VARIABLE LABELS turn4 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - incorrected baseline' .
EXECUTE .
COMPUTE turns = (c4mv + turn4) - 14.15 .
VARIABLE LABELS turns 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - corrected baseline' .
EXECUTE .
```

SPSS MACRO FOR MONITOR 5

```
COMPUTE record = a * 1 .
VARIABLE LABELS record 'record number' .
EXECUTE .
COMPUTE temp5mv = c * 1 .
EXECUTE .
COMPUTE sweat5mv = d * 1 .
EXECUTE .
COMPUTE act5mv = e * 1 .
EXECUTE .
COMPUTE tempc = (temp5mv + 21.0663) / 11.36135 .
VARIABLE LABELS tempc 'temperature in degrees centigrade' .
EXECUTE .
COMPUTE sweat5cf = 76.06198 / (sweat5mv + 94.96544) .
VARIABLE LABELS sweat5cf 'correction factor for sweating monitor 5' .
EXECUTE .
COMPUTE sweatrh = sweat5mv * sweat5cf .
VARIABLE LABELS sweatrh 'sweating in relative humidity' .
EXECUTE .
COMPUTE mins = record * 5 .
VARIABLE LABELS mins 'minutes (time) graded by 5' .
EXECUTE .
COMPUTE logmins = LG10(mins) .
VARIABLE LABELS logmins 'log 10 of time in minutes' .
EXECUTE .
COMPUTE c5mv = ( - 8.7147 * logmins) + 92.41494 .
VARIABLE LABELS c5mv 'y-intercept for each activity time point' .
EXECUTE .
COMPUTE turn5 = (act5mv - c5mv) / 1.251 .
VARIABLE LABELS turn5 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - incorrected baseline' .
EXECUTE .
COMPUTE turns = (c5mv + turn5) - 13.77 .
VARIABLE LABELS turns 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - corrected baseline' .
EXECUTE .
```

SPSS MACRO FOR MONITOR 6

```
COMPUTE record = a * 1 .
VARIABLE LABELS record 'record number' .
EXECUTE .
COMPUTE temp6mv = c * 1 .
EXECUTE .
COMPUTE sweat6mv = d * 1 .
EXECUTE .
COMPUTE act6mv = e * 1 .
EXECUTE .
COMPUTE tempc = (temp6mv + 16.4395) / 10.90485 .
VARIABLE LABELS tempc 'temperature in degrees centigrade' .
EXECUTE .
COMPUTE sweat6cf = 76.31056 / (sweat6mv + 86.49857) .
VARIABLE LABELS sweat6cf 'correction factor for sweating mon6' .
EXECUTE .
COMPUTE sweatrh = sweat6mv * sweat6cf .
VARIABLE LABELS sweatrh 'sweating in relative humidity' .
EXECUTE .
COMPUTE mins = record * 5 .
VARIABLE LABELS mins 'minutes (time) graded by 5' .
EXECUTE .
COMPUTE logmins = LG10(mins) .
VARIABLE LABELS logmins 'log 10 of time in minutes' .
EXECUTE .
COMPUTE c6mv = ( - 8.95702 * logmins) + 90.74135 .
VARIABLE LABELS c6mv 'y-intercept for each activity time point' .
EXECUTE .
COMPUTE turn6 = (act6mv - c6mv) / 1.274 .
VARIABLE LABELS turn6 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - incorrected baseline' .
EXECUTE .
COMPUTE turns = (c6mv + turn6) - 14.07 .
VARIABLE LABELS turns 'number of 5degree or greater deflections from the'+
 ' horizontal plane per 5 minutes - corrected baseline' .
EXECUTE .
```

DATA FROM RESULTS SECTION OF CHAPTER 4

Fig. 4.1 Average 24 hour skin temperature (°C), all days. Pp. 85

	Average 24 hour skin temperature, Fig. 4.1			
Day	*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**
1	31.0	0.13	31.0	0.15
2	31.0	0.13	31.2	0.14
3	31.0	0.15	31.2	0.14
14	31.5	0.18	31.0	0.17
42	31.4	0.18	31.0	0.25
70	31.2	0.27	31.1	0.25

Figs. 4.2, 4.3. Diurnal Temperature (°C) in withdrawal and control subjects, Days 1 & 2. Pp 87-88

Time	DAY 1, Fig. 4.2				DAY 2, Fig. 4.3			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	30.4	0.23	30.9	0.13	30.7	0.25	30.6	0.22
1400	31.2	0.29	30.8	0.20	30.9	0.23	30.6	0.28
1500	31.2	0.28	30.5	0.17	31.1	0.22	30.3	0.20
1600	31.1	0.23	30.6	0.24	31.2	0.24	30.6	0.26
1700	31.0	0.27	30.8	0.24	31.0	0.27	30.8	0.24
1800	30.9	0.25	31.1	0.23	31.0	0.24	31.1	0.22
1900	30.7	0.21	31.2	0.22	30.9	0.26	31.3	0.20
2000	30.7	0.24	31.2	0.26	30.7	0.24	31.4	0.24
2100	30.5	0.22	31.0	0.24	30.6	0.20	31.1	0.23
2200	30.6	0.22	31.3	0.25	30.7	0.22	31.1	0.27
2300	30.6	0.23	31.0	0.24	31.1	0.23	31.3	0.27
2400	31.1	0.30	31.4	0.24	31.1	0.26	31.7	0.25
0100	31.7	0.24	31.9	0.22	31.5	0.25	31.7	0.21
0200	31.8	0.27	31.7	0.28	31.9	0.20	32.3	0.19
0300	31.9	0.25	31.7	0.30	32.0	0.16	32.5	0.17
0400	32.0	0.22	31.5	0.26	32.4	0.15	31.6	0.23
0500	31.9	0.19	31.8	0.24	32.2	0.17	31.8	0.22
0600	31.9	0.17	32.0	0.25	31.9	0.26	32.1	0.21
0700	31.8	0.23	31.7	0.21	31.6	0.30	32.1	0.22
0800	31.2	0.28	31.1	0.30	31.3	0.35	31.1	0.38
0900	30.7	0.30	30.1	0.30	30.2	0.34	30.2	0.49
1000	29.9	0.24	29.8	0.29	29.4	0.26	30.3	0.23
1100	30.1	0.25	29.8	0.29	29.4	0.29	30.3	0.24
1200	30.3	0.31	29.8	0.29	30.0	0.26	30.3	0.28

Figs. 4.4, 4.5. Diurnal Temperature (°C) in withdrawal and control subjects, Days 3 & 14. Pp.89, 91

Time	DAY 3, Fig. 4.4				DAY 14, Fig. 4.5			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	30.8	0.30	30.7	0.18	31.2	0.35	30.7	0.21
1400	31.1	0.35	30.6	0.24	31.3	0.33	30.6	0.30
1500	30.6	0.36	30.4	0.18	31.4	0.36	30.4	0.22
1600	30.7	0.33	30.6	0.24	31.6	0.32	30.7	0.29
1700	30.9	0.25	30.8	0.24	31.5	0.31	30.8	0.30
1800	30.7	0.21	31.1	0.23	31.3	0.29	31.0	0.27
1900	30.8	0.24	31.3	0.21	31.2	0.29	31.2	0.23
2000	30.7	0.26	31.3	0.25	31.1	0.30	31.2	0.27
2100	30.7	0.27	31.0	0.24	31.0	0.38	31.0	0.24
2200	30.7	0.28	31.1	0.28	31.1	0.27	31.1	0.28
2300	31.0	0.24	31.4	0.26	31.1	0.23	31.0	0.30
2400	31.1	0.32	31.7	0.25	31.4	0.28	31.3	0.28
0100	31.6	0.27	31.8	0.19	31.8	0.24	31.5	0.22
0200	31.9	0.24	32.3	0.18	32.2	0.24	32.0	0.24
0300	32.3	0.19	32.3	0.20	32.2	0.22	32.1	0.24
0400	32.1	0.16	31.6	0.23	32.5	0.19	31.7	0.24
0500	32.2	0.14	31.9	0.19	32.4	0.22	31.7	0.25
0600	32.2	0.23	32.1	0.22	32.3	0.22	32.0	0.21
0700	31.8	0.31	31.9	0.25	32.4	0.20	32.2	0.18
0800	31.2	0.36	31.1	0.37	31.5	0.34	31.4	0.24
0900	30.3	0.28	30.2	0.49	30.7	0.44	29.9	0.53
1000	29.7	0.21	30.3	0.21	30.1	0.43	29.6	0.33
1100	30.0	0.24	30.2	0.24	30.6	0.38	29.6	0.33
1200	30.1	0.25	30.4	0.27	30.9	0.33	30.1	0.32

Figs. 4.6, 4.7. Diurnal Temperature (°C) in withdrawal and control subjects, Days 42 & 70. Pp. 92-93

Time	DAY 42, Fig. 4.6				DAY 70, Fig. 4.7			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	30.6	0.65	30.6	0.32	31.0	0.50	30.9	0.17
1400	30.8	0.48	30.6	0.35	31.0	0.50	30.8	0.20
1500	31.6	0.52	30.6	0.32	30.9	0.50	30.7	0.30
1600	31.5	0.40	31.1	0.36	31.3	0.51	31.1	0.40
1700	31.8	0.32	31.2	0.41	31.1	0.45	31.2	0.45
1800	31.6	0.31	31.3	0.37	30.5	0.62	31.3	0.40
1900	31.5	0.27	31.0	0.31	31.3	0.38	31.1	0.34
2000	31.2	0.27	30.9	0.33	31.3	0.33	30.8	0.37
2100	31.2	0.34	30.6	0.32	31.0	0.60	30.6	0.34
2200	31.4	0.32	30.7	0.38	31.3	0.39	30.7	0.42
2300	31.0	0.30	30.8	0.41	31.5	0.30	30.8	0.39
2400	31.5	0.28	31.1	0.37	31.5	0.35	31.1	0.38
0100	32.0	0.37	31.4	0.29	31.4	0.28	31.5	0.28
0200	31.8	0.35	31.9	0.30	31.9	0.27	32.1	0.30
0300	31.6	0.36	32.1	0.36	31.9	0.23	32.1	0.37
0400	32.2	0.23	31.7	0.38	31.8	0.25	31.6	0.34
0500	32.4	0.31	31.8	0.39	32.3	0.23	31.8	0.33
0600	32.4	0.27	32.2	0.28	32.2	0.23	32.2	0.21
0700	32.4	0.27	32.2	0.25	31.9	0.39	32.4	0.20
0800	31.6	0.37	31.5	0.32	30.7	0.46	31.9	0.30
0900	30.6	0.49	29.8	0.74	29.9	0.56	30.0	0.82
1000	30.3	0.37	29.6	0.47	29.9	0.51	29.5	0.49
1100	30.6	0.39	29.9	0.46	30.3	0.59	29.9	0.50
1200	31.1	0.52	30.3	0.42	30.5	0.69	30.5	0.41

Fig. 4.8 Average 24 hour sweating %RH, all days. Pp. 94

	Average 24 hour sweating, Fig. 4.8			
Day	*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**
1	28.8	2.84	24.9	1.78
2	28.1	3.34	22.9	2.02
3	25.7	2.89	22.2	1.98
14	26.1	2.12	22.3	1.88
42	22.8	2.73	23.7	2.65
70	24.8	4.34	24.2	2.86

Figs. 4.9, 4.10. Diurnal Sweating (%RH) in withdrawal and control subjects, Days 1 & 2. Pp. 96-97

Time	DAY 1, Fig. 4.9				DAY 2, Fig. 4.10			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	24.5	2.79	21.4	2.50	24.6	3.72	22.0	2.52
1400	22.9	2.99	20.4	2.42	23.3	3.69	20.8	2.44
1500	22.5	2.67	20.2	2.69	23.9	3.93	20.3	2.68
1600	22.1	2.70	19.9	2.77	23.0	4.00	30.0	2.76
1700	20.5	2.80	20.7	2.92	22.6	3.93	20.7	2.91
1800	21.2	3.05	20.0	2.56	23.4	4.16	19.8	2.54
1900	20.8	2.97	20.8	2.75	20.6	3.85	20.4	2.71
2000	20.7	3.07	21.4	2.84	20.4	3.57	21.4	2.83
2100	21.8	3.32	21.3	2.67	19.5	3.41	21.0	2.67
2200	21.6	3.01	18.7	2.34	21.8	3.95	19.9	2.85
2300	22.6	3.14	19.6	1.46	22.4	3.74	21.3	2.86
2400	27.6	3.30	26.1	2.57	24.8	3.74	22.9	2.74
0100	33.0	3.34	28.3	2.45	27.5	3.94	23.0	2.68
0200	33.5	3.49	31.7	2.27	32.3	4.14	28.4	2.76
0300	34.9	3.85	32.3	2.50	35.9	3.91	28.5	2.57
0400	36.2	4.07	31.1	2.57	39.4	4.00	24.6	2.38
0500	36.6	4.13	29.8	2.71	39.2	4.05	25.0	2.07
0600	36.8	4.10	29.1	2.34	36.4	4.10	27.3	2.23
0700	37.4	3.94	30.0	2.29	35.7	3.77	25.3	2.20
0800	36.0	3.97	29.1	2.04	35.3	3.95	23.1	1.89
0900	32.3	3.68	26.3	1.84	31.2	3.90	22.9	1.78
1000	28.8	3.63	28.3	2.77	29.3	3.85	22.9	2.36
1100	27.6	3.68	27.6	2.86	29.4	3.85	26.3	3.08
1200	27.1	3.78	23.9	2.39	25.0	3.74	23.0	2.34

Figs. 4.11, 4.12. Diurnal Sweating (%RH) in withdrawal and control subjects, Days 3 & 14. Pp. 98-99

Time	DAY 3, Fig. 4.11				DAY 14, Fig. 4.12			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	23.3	3.66	21.8	2.49	24.0	3.06	21.2	2.96
1400	24.4	4.18	20.2	2.40	27.6	3.29	20.2	2.84
1500	22.4	3.79	19.5	2.67	24.8	3.58	19.4	2.99
1600	20.0	3.50	18.9	2.79	25.4	3.74	18.4	2.85
1700	20.5	3.79	20.2	2.92	25.2	3.82	19.4	3.07
1800	20.0	3.58	20.5	2.67	21.9	3.01	18.6	2.57
1900	20.3	3.61	20.6	2.77	22.3	2.75	19.6	2.86
2000	20.2	3.69	20.8	2.85	20.5	2.66	20.8	3.26
2100	19.3	3.46	20.5	2.69	19.8	2.67	20.0	3.04
2200	19.2	3.17	19.6	2.85	20.9	3.20	17.9	2.61
2300	20.4	3.07	20.5	2.88	23.5	3.02	16.7	1.32
2400	22.5	3.11	22.1	2.79	24.9	3.05	18.9	1.60
0100	25.2	3.16	22.2	2.72	26.8	2.75	22.3	1.75
0200	31.2	3.62	26.7	2.79	28.3	2.91	26.1	2.01
0300	37.3	4.32	26.0	2.54	29.9	2.99	28.6	1.95
0400	36.3	4.23	22.9	2.34	32.0	3.08	26.0	2.02
0500	35.6	3.73	23.5	2.06	31.9	3.20	25.7	2.13
0600	35.6	3.82	25.9	2.25	30.4	2.94	27.2	2.06
0700	35.7	3.69	23.1	2.14	30.4	2.83	26.3	2.05
0800	32.1	3.46	22.1	1.86	29.3	3.28	25.4	2.05
0900	29.0	3.17	22.2	1.65	26.4	3.22	21.2	1.63
1000	23.9	2.92	23.2	2.41	27.4	2.75	26.5	2.90
1100	24.7	3.46	26.4	3.12	25.3	2.22	26.8	3.30
1200	22.2	3.26	23.0	2.35	25.9	2.46	23.1	2.79

Figs. 4.13, 4.14. Diurnal Sweating (%RH) in withdrawal and control subjects, Days 42 & 70. Pp. 100-101

Time	DAY 42, Fig. 4.13				DAY 70, Fig. 4.14			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	25.7	4.99	22.6	4.52	24.8	6.70	23.7	4.83
1400	25.6	4.42	20.1	4.41	28.6	6.81	20.9	4.73
1500	24.8	4.65	19.8	4.60	28.4	5.89	21.0	4.97
1600	23.1	4.62	19.0	4.50	21.9	5.50	19.4	4.90
1700	21.5	4.56	20.4	4.67	25.6	5.74	19.9	4.99
1800	18.3	4.10	20.0	4.05	26.8	6.06	20.5	4.36
1900	20.2	3.84	21.2	4.42	25.0	5.77	21.6	4.71
2000	21.6	4.46	23.6	4.70	21.7	5.38	23.2	5.07
2100	20.5	4.47	21.9	4.47	24.2	5.64	21.5	4.86
2200	17.1	3.40	19.5	3.90	24.8	6.08	19.3	4.21
2300	18.4	2.77	17.7	1.85	19.2	4.25	17.7	1.95
2400	20.7	2.58	19.6	2.36	18.4	3.02	20.5	2.57
0100	22.2	2.37	21.8	2.23	20.4	3.33	23.5	2.58
0200	25.0	2.65	26.0	2.27	24.6	4.40	27.5	2.57
0300	27.7	2.79	30.9	2.52	26.7	5.42	31.0	2.73
0400	27.3	2.82	28.9	2.82	26.9	4.72	28.6	3.02
0500	27.9	3.15	28.8	2.93	27.8	4.78	28.6	3.14
0600	27.7	3.10	29.4	2.91	28.1	4.68	29.3	3.11
0700	26.8	3.22	28.6	2.96	29.3	4.49	28.5	3.20
0800	23.8	2.96	28.4	2.83	28.4	5.12	28.6	3.08
0900	21.4	3.25	24.8	2.17	28.2	4.68	23.1	2.29
1000	18.7	2.83	26.5	3.36	25.1	5.46	28.7	4.17
1100	16.5	2.09	26.0	4.25	22.4	5.11	28.0	4.92
1200	23.7	4.67	24.0	4.16	26.9	7.00	24.9	4.45

Figs. 4.15, 4.16. Diurnal Sweating (%RH) with and without benzodiazepines in withdrawal subjects, Days 2 & 3. Pp. 102-103

Time	DAY 2, Fig. 4.15				DAY 3, Fig. 4.16			
	Withdrawal + BZD		*Withdrawal no BZD*		*Withdrawal + BZD*		*Withdrawal no BZD*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	22.9	4.05	30.1	9.07	21.9	4.06	26.9	8.16
1400	20.9	3.69	31.4	10.24	22.3	4.59	29.5	9.38
1500	21.3	3.97	32.0	10.50	20.7	4.02	26.6	8.97
1600	20.5	4.06	31.0	10.63	17.7	3.39	25.7	9.02
1700	19.7	3.98	31.9	10.31	18.0	3.57	26.3	9.74
1800	21.1	4.47	30.9	10.13	17.4	3.13	26.1	9.63
1900	17.7	3.90	29.4	9.87	18.0	3.03	25.8	10.04
2000	17.5	3.46	29.3	9.58	17.8	3.22	25.8	10.02
2100	16.1	2.99	29.8	9.78	16.7	2.80	25.4	9.73
2200	19.1	4.08	30.1	9.94	16.9	2.25	24.7	9.45
2300	18.8	3.58	33.4	9.83	18.6	2.20	24.6	9.21
2400	19.2	3.19	41.4	9.42	20.5	2.75	27.4	8.35
0100	23.8	3.90	38.6	9.96	24.1	2.87	27.9	8.56
0200	30.4	4.54	37.8	9.68	29.6	3.54	35.2	9.20
0300	35.0	4.49	38.4	8.46	36.6	4.83	39.0	9.51
0400	39.1	4.74	40.3	7.99	35.8	4.73	37.5	9.34
0500	38.4	4.77	41.8	8.17	34.9	3.95	37.2	8.84
0600	36.2	4.57	36.9	9.58	35.4	4.28	36.2	8.40
0700	35.0	4.09	37.6	9.32	34.6	4.04	38.4	8.36
0800	33.9	4.38	39.5	9.19	30.4	3.65	36.1	8.11
0900	29.4	4.37	36.6	8.74	27.1	3.18	33.7	7.71
1000	26.5	4.25	37.7	8.36	21.5	2.68	29.3	7.33
1100	26.3	4.34	39.0	7.62	21.7	3.46	31.4	8.01
1200	22.7	4.12	31.7	8.42	21.3	3.70	24.6	7.16

Figs. 4.17, 4.18. Diurnal Temperature (°C) with and without benzodiazepines in withdrawal subjects, Days 2 & 3. Pp. 105

Time	DAY 2, Fig. 4.17				DAY 3, Fig. 4.18			
	Withdrawal + BZD		*Withdrawal no BZD*		*Withdrawal + BZD*		*Withdrawal no BZD*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
1300	30.7	0.30	30.6	0.49	30.4	0.28	31.7	0.71
1400	30.9	0.27	30.9	0.49	30.7	0.34	32.1	0.80
1500	31.0	0.26	31.2	0.43	30.4	0.46	31.2	0.52
1600	31.1	0.29	31.5	0.45	30.5	0.44	31.2	0.34
1700	30.9	0.32	31.3	0.45	30.7	0.29	31.4	0.45
1800	31.0	0.29	31.0	0.47	30.7	0.27	30.9	0.34
1900	30.8	0.32	31.2	0.45	30.9	0.27	30.5	0.54
2000	30.7	0.28	30.5	0.46	30.9	0.30	30.2	0.54
2100	30.7	0.25	30.4	0.30	30.8	0.31	30.4	0.57
2200	30.7	0.28	30.9	0.30	30.7	0.38	30.7	0.32
2300	30.8	0.23	32.1	0.46	31.1	0.32	30.8	0.29
2400	30.8	0.28	32.1	0.49	31.1	0.42	31.2	0.39
0100	31.5	0.31	31.7	0.41	31.9	0.33	31.0	0.38
0200	32.0	0.23	31.9	0.38	32.1	0.29	31.3	0.42
0300	32.0	0.20	32.0	0.23	32.5	0.20	31.9	0.42
0400	32.4	0.19	32.5	0.25	32.2	0.18	31.9	0.37
0500	32.1	0.21	32.3	0.27	32.2	0.16	32.3	0.30
0600	32.1	0.32	31.2	0.35	32.3	0.31	32.0	0.24
0700	31.8	0.38	31.0	0.37	31.7	0.42	32.1	0.34
0800	31.5	0.39	30.7	0.83	31.1	0.46	31.3	0.55
0900	30.5	0.41	29.2	0.49	30.3	0.37	30.4	0.41
1000	29.5	0.33	29.2	0.36	29.8	0.29	29.4	0.27
1100	29.6	0.34	28.9	0.54	29.9	0.29	30.2	0.44
1200	30.0	0.32	30.0	0.39	30.1	0.28	30.2	0.58

Fig. 4.19 Average 24 hour activity (turns per 5 minutes), all days. Pp. 106

	Average 24 hour activity, Fig. 4.19			
Day	*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**
1	33.1	3.73	35.7	4.23
2	33.1	4.11	35.0	4.11
3	34.3	3.91	35.0	4.14
14	42.6	4.96	36.4	4.78
42	42.3	5.77	37.9	6.51
70	42.9	7.29	41.5	6.53

Fig. 4.20 Average day activity 8am-11pm (turns per 5 minutes), all days. Pp. 107

	Average day hour activity 8am-11pm, Fig. 4.20			
Day	*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**
1	44.86	3.17	49.53	3.11
2	44.36	2.42	48.23	3.44
3	45.85	2.39	48.16	3.56
14	56.41	4.22	50.44	3.66
42	57.09	4.63	51.76	3.24
70	57.73	4.14	57.24	4.17

Fig. 4.21 Average sleep activity (turns per 5 minutes), all days. Pp. 108

	Average sleep activity, Fig. 4.21			
Day	*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**
1	11.25	2.16	5.49	0.58
2	8.95	1.67	4.76	0.61
3	8.35	1.73	4.76	0.61
14	10.19	1.40	4.90	0.59
42	11.20	2.71	5.51	0.67
70	8.88	1.64	5.86	0.66

Figs. 4.22, 4.23. Diurnal daily activity (turns per 5 minutes) 8am to 11pm in withdrawal and control subjects, Days 1 & 2. Pp. 110

Time	**DAY 1, Fig. 4.22**				**DAY 2, Fig. 4.23**			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
0800	37.6	9.41	27.0	5.06	25.7	7.26	20.5	4.52
0900	42.2	6.09	50.1	10.34	47.3	8.45	47.8	10.61
1000	38.7	5.41	73.9	14.66	56.0	9.57	77.4	19.76
1100	35.5	4.51	68.2	9.89	51.1	5.96	63.4	10.11
1200	42.8	4.71	61.8	11.72	50.8	6.62	64.4	11.78
1300	80.9	11.02	40.7	6.23	59.0	8.53	36.9	6.23
1400	58.2	9.80	41.7	10.16	40.4	5.62	39.9	10.24
1500	47.2	7.36	46.1	5.09	50.5	8.85	43.4	5.09
1600	43.6	6.50	50.8	7.37	39.3	5.09	54.4	8.34
1700	45.6	6.69	58.2	8.69	39.8	4.57	55.6	9.00
1800	61.8	9.13	59.3	6.29	57.5	7.19	57.5	6.27
1900	45.4	6.76	37.7	5.81	40.5	5.01	40.4	5.99
2000	37.2	4.41	47.2	11.12	42.5	5.55	46.0	11.08
2100	34.0	4.19	51.3	9.49	44.2	7.53	47.7	9.34
2200	36.4	5.54	43.7	9.68	37.7	8.09	44.1	9.61
2300	30.6	4.33	34.7	7.05	27.5	4.46	32.2	4.54

Figs. 4.24, 4.25. Diurnal daily activity (turns per 5 minutes) 8am to 11pm in withdrawal and control subjects, Days 3 & 14. Pp 110, 112

Time	DAY 3, Fig. 4.24				DAY 14, Fig. 4.25			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
0800	31.8	8.04	19.9	3.97	25.1	5.09	17.5	5.07
0900	46.6	8.89	49.8	10.74	46.2	11.49	51.0	12.42
1000	50.8	6.16	78.3	19.68	58.8	12.16	78.5	17.02
1100	46.1	6.52	65.9	9.99	79.5	18.13	71.6	11.33
1200	53.7	11.87	64.3	11.78	55.9	7.71	61.9	13.09
1300	64.0	7.45	38.6	6.16	85.7	17.12	41.2	7.44
1400	50.0	6.99	41.4	10.16	78.6	14.76	45.4	12.59
1500	49.3	7.77	43.4	5.10	71.0	14.36	44.5	5.49
1600	50.1	6.63	48.9	7.35	70.2	12.28	55.1	9.19
1700	50.8	7.15	55.8	8.59	58.4	10.82	56.8	10.12
1800	55.1	6.63	57.5	6.33	53.7	7.14	59.4	6.86
1900	44.5	8.32	40.1	6.03	48.8	7.45	41.8	6.85
2000	41.7	6.19	46.7	11.13	49.5	8.67	50.8	13.64
2100	38.8	5.36	47.8	9.32	43.3	6.62	52.1	11.41
2200	34.6	4.60	43.2	9.69	40.3	8.22	49.1	11.73
2300	25.7	3.37	29.0	4.05	37.6	7.49	30.3	4.87

Figs. 4.26, 4.27. Diurnal daily activity (turns per 5 minutes) 8am to 11pm in withdrawal and control subjects, Days 42 & 70. Pp. 112

Time	DAY 42, Fig. 4.26				DAY 70, Fig. 4.27			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
0800	25.2	8.45	20.9	8.07	48.6	11.75	22.9	8.47
0900	66.8	21.16	50.1	18.00	92.1	22.45	56.8	18.79
1000	63.8	18.07	71.1	16.98	62.1	16.80	86.7	18.90
1100	63.0	17.73	70.7	13.81	61.9	15.84	82.8	14.74
1200	74.8	17.97	63.0	18.98	57.6	11.67	74.5	21.24
1300	96.9	25.63	41.2	12.13	89.7	19.46	44.6	12.79
1400	82.9	15.59	54.5	20.53	68.6	19.58	56.9	22.04
1500	63.1	15.27	43.4	8.31	50.1	10.43	46.2	8.59
1600	44.0	7.22	57.5	12.74	54.1	14.77	59.7	13.29
1700	50.5	11.04	54.8	12.66	56.3	16.64	67.3	14.47
1800	50.1	9.43	56.0	8.70	68.5	17.79	64.3	9.54
1900	58.3	8.54	46.9	10.31	46.4	7.82	46.7	10.91
2000	58.2	9.58	45.9	7.10	46.5	8.48	46.5	7.27
2100	44.9	5.01	52.9	13.04	54.4	21.46	57.1	13.44
2200	33.8	6.32	63.8	18.99	37.9	9.27	66.5	20.21
2300	37.2	6.51	35.5	6.76	28.9	5.98	36.4	6.37

Figs. 4.28, 4.29. Diurnal night activity (turns per 5 minutes) 12am to 7am in withdrawal and control subjects, Nights 1 & 2. Pp. 114

Time	NIGHT 1, Fig. 4.28				NIGHT 2, Fig. 4.29			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
2400	24.9	5.17	16.0	4.27	25.2	5.16	18.3	3.66
0100	15.0	4.82	11.9	2.83	7.9	1.90	12.8	3.08
0200	9.6	2.84	7.6	1.85	9.8	3.37	10.4	2.44
0300	7.1	1.80	3.4	0.52	8.0	1.67	4.1	0.74
0400	13.3	3.55	4.5	1.33	6.6	1.91	4.7	0.89
0500	9.3	1.83	9.8	3.46	6.4	2.07	4.5	0.80
0600	9.1	2.12	4.5	1.14	10.3	3.83	5.5	1.52
0700	21.3	6.39	7.5	1.52	15.7	5.23	9.3	2.83

Figs. 4.30, 4.31. Diurnal night activity (turns per 5 minutes) 12am to 7am in withdrawal and control subjects, Nights 3 & 14. Pp. 114-115

Time	NIGHT 3, Fig. 4.30				NIGHT 14, Fig. 4.31			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
2400	22.0	4.50	19.2	3.90	36.7	7.06	19.7	3.94
0100	13.7	4.66	11.4	2.73	16.8	3.21	12.8	3.02
0200	9.3	3.01	7.7	2.20	13.3	3.69	9.5	1.68
0300	6.5	2.05	6.0	1.57	10.6	2.21	4.4	0.69
0400	4.9	1.00	4.1	0.77	8.9	2.70	3.9	0.99
0500	5.9	1.49	4.1	0.82	14.1	4.02	2.8	0.36
0600	8.3	4.01	5.6	1.52	7.8	1.43	7.2	2.08
0700	22.3	5.48	9.6	2.81	8.7	1.70	6.0	0.81

Figs. 4.32, 4.33. Diurnal night activity (turns per 5 minutes) 12am to 7am in withdrawal and control subjects, Nights 42 & 70. Pp. 115

Time	NIGHT 42, Fig. 4.32				NIGHT 70, Fig. 4.33			
	Withdrawal		*Control*		*Withdrawal*		*Control*	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
2400	29.2	7.69	26.2	5.90	19.9	6.39	24.3	6.31
0100	18.5	7.29	17.7	4.62	23.4	8.00	16.3	4.79
0200	9.4	2.78	11.1	2.43	12.5	4.80	10.1	2.60
0300	7.3	1.96	4.6	1.10	6.8	1.44	5.2	1.17
0400	13.8	3.97	5.1	1.59	6.8	2.32	4.8	1.70
0500	7.4	2.04	2.9	0.45	8.5	3.50	3.0	0.50
0600	6.7	1.31	7.7	2.94	13.5	5.45	8.7	3.07
0700	7.9	0.94	6.4	1.16	28.1	12.16	6.7	1.19

Fig. 4.34, 4.35 Average BDI (depression) scores, and STAI (state anxiety scores) all days. Pp.116-117

	Average BDI, Fig 4.34		Average STAI, Fig 4.35	
Day	*Withdrawal – BDI (norm=9)*		*Withdrawal – STAI (norm=36)*	
	Mean	**SEM**	**Mean**	**SEM**
1	26.9	1.45	63.1	2.01
4	15.8	1.49	50.2	2.06
14	14.7	1.69	49.0	2.42
42	9.19	1.99	43.0	2.92
70	8.2	2.09	40.3	3.08

Table 4.1. SEMs for mean item values for BDI, days 1, 4, 14, 42 & 70. Pp. 119

Question number	Corresponding symptoms	SEM DAY 1	SEM DAY 4	SEM DAY 14	SEM DAY 42	SEM DAY 70
1	mood/feeling sad	0.152	0.144	0.124	0.140	0.126
2	pessimism/hopelessness	0.123	0.105	0.135	0.140	0.163
3	sense of failure	0.127	0.128	0.142	0.136	0.168
4	self-dissatisfaction	0.105	0.108	0.119	0.111	0.122
5	guilt	0.132	0.150	0.151	0.140	0.117
6	punishment	0.192	0.183	0.247	0.167	0.221
7	self-dislike	0.124	0.120	0.101	0.111	0.130
8	self-accusations	0.128	0.125	0.106	0.153	0.157
9	suicidal ideas	0.106	0.091	0.088	0.068	0.097
10	crying	0.190	0.180	0.181	0.214	0.277
11	irritability	0.116	0.150	0.186	0.237	0.132
12	social withdrawal	0.121	0.110	0.122	0.140	0.118
13	indecisiveness	0.128	0.131	0.137	0.177	0.121
14	body image	0.125	0.114	0.121	0.167	0.174
15	work difficulty	0.128	0.109	0.130	0.131	0.152
16	insomnia	0.136	0.141	0.194	0.181	0.198
17	fatigability	0.131	0.121	0.133	0.182	0.185
18	loss of appetite	0.161	0.104	0.138	0.115	0.117
19	weight loss	0.170	0.115	0.139	0.102	0.113
20	somatic preoccupations	0.148	0.135	0.157	0.139	0.141
21	loss of libido	0.154	0.120	0.169	0.130	0.152

Table 4.2. SEMs for mean item values for STAI, days 1, 4, 14, 42 & 70. Pp. 121

Question number	Corresponding symptoms	SEM DAY 1	SEM DAY 4	SEM DAY 14	SEM DAY 42	SEM DAY 70
1	not feeling calm	0.115	0.158	0.191	0.188	0.186
2	insecurity	0.155	0.148	0.153	0.206	0.261
3	tension	0.139	0.170	0.208	0.186	0.179
4	strain	0.143	0.154	0.181	0.227	0.193
5	dis-ease	0.131	0.148	0.191	0.203	0.158
6	upset	0.166	0.160	0.190	0.150	0.152
7	worry about possible misfortune	0.152	0.175	0.162	0.234	0.277
8	dissatisfaction	0.152	0.163	0.194	0.190	0.158
9	frightened	0.171	0.157	0.163	0.232	0.122
10	discomfort	0.104	0.164	0.186	0.192	0.230
11	unconfident	0.150	0.146	0.162	0.163	0.174
12	nervousness	0.144	0.145	0.177	0.145	0.184
13	jittery	0.149	0.186	0.195	0.163	0.197
14	indecisive	0.151	0.161	0.189	0.208	0.186
15	not feeling relaxed	0.115	0.160	0.179	0.193	0.251
16	not feeling confident	0.124	0.182	0.185	0.192	0.204
17	worry	0.148	0.174	0.165	0.212	0.257
18	confusion	0.146	0.177	0.171	0.179	0.255
19	unsteady	0.135	0.172	0.134	0.135	0.223
20	unpleasant	0.130	0.170	0.182	0.161	0.203

Fig. 4.36, 4.37 Average POMS scores (depression-dejection, confusion-bewilderment), all days. Pp. 123

	POMS, depression-dejection Fig 4.36		POMS, confusion-bewilderment Fig 4.37	
Day	*Withdrawal (norm=12.5)*		*Withdrawal (norm=7.8)*	
	Mean	**SEM**	**Mean**	**SEM**
1	34.25	2.40	16.92	0.97
4	19.86	2.44	10.39	0.99
14	18.88	2.72	11.49	1.12
42	11.01	3.22	7.56	1.36
70	10.16	3.38	6.06	1.44

Fig. 4.38, 4.39 Average POMS scores (fatigue-inertia, tension-anxiety), all days. Pp. 123-124

	POMS, fatigue-Inertia Fig 4.38		POMS, tension-Anxiety Fig 4.39	
Day	*Withdrawal (norm=6.4)*		*Withdrawal (norm=12.1)*	
	Mean	**SEM**	**Mean**	**SEM**
1	17.31	1.13	26.02	1.26
4	10.76	1.15	16.53	1.29
14	11.94	1.29	14.96	1.48
42	7.53	1.55	10.27	1.82
70	6.27	1.63	8.79	1.93

Fig. 4.40, 4.41 Average POMS scores (anger-hostility, vigour-activity), all days. Pp.124

	POMS, anger-hostility Fig 4.40		**POMS, vigour-activity Fig 4.41**	
Day	*Withdrawal (norm=8.1)*		*Withdrawal (norm=11.4)*	
	Mean	**SEM**	**Mean**	**SEM**
1	13.86	1.68	9.49	1.19
4	6.83	1.28	13.02	1.21
14	10.26	1.93	13.16	1.37
42	7.03	1.55	16.09	1.65
70	7.27	2.22	17.37	1.74

Fig. 4.42, 4.43 Average SF-36 scores (role-function physical, physical functioning), all days. Pp. 126

	SF-36 role-function physical Fig 4.42		**SF-36 physical functioning Fig 4.43**	
Day	*Withdrawal (norm=80.2)*		*Withdrawal (norm=85.4)*	
	Mean	**SEM**	**Mean**	**SEM**
1	19.73	5.35	62.76	3.42
14	39.64	7.87	73.68	3.97
42	71.13	8.11	76.82	4.92
70	75.52	10.03	84.46	5.59

Fig. 4.44, 4.45 Average SF-36 scores (role-function emotional, social functioning), all days. Pp. 127

	SF-36 role-function emotional Fig 4.44		SF-36 social functioning Fig 4.45	
Day	*Withdrawal (norm=87.5)*		*Withdrawal (norm=88.2)*	
	Mean	**SEM**	**Mean**	**SEM**
1	14.03	4.9	31.9	4.28
14	44.45	7.64	54.56	5.28
42	71.7	8.08	78.49	6.51
70	59.3	11.3	85.08	7.19

Fig. 4.46, 4.47 Average SF-36 scores (bodily pain, mental health), all days. Pp. 129

	SF-36 bodily pain Fig 4.46		SF-36 mental health Fig 4.47	
Day	*Withdrawal (norm=77.2)*		*Withdrawal (norm=78.7)*	
	Mean	**SEM**	**Mean**	**SEM**
1	45.52	4.35	33.47	3.33
14	61.30	5.22	54.19	4.12
42	67.98	6.28	70.23	4.93
70	67.78	6.65	68.84	5.24

Fig. 4.48, 4.49 Average SF-36 scores (general health, vitality), all days. Pp. 130

	SF-36 general health Fig 4.48		SF-36 vitality Fig 4.49	
Day	*Withdrawal (norm=73.2)*		*Withdrawal (norm=64.0)*	
	Mean	**SEM**	**Mean**	**SEM**
1	39.57	3.58	27.50	3.31
14	47.88	4.17	42.70	3.45
42	59.90	4.86	62.39	4.85
70	70.02	5.25	64.92	5.44

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