Using actigraphy to assess the effects of psychoactive drugs

by

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Abstract

The effect of psychoactive drugs on sleep is traditionally evaluated with polysomnography (PSG) whereas daytime effects are conventionally assessed with psychometric tests to measure changes in daytime cognition and psychomotor functioning. This thesis examines whether the actigraph, a non-invasive tool, that records rest-activity patterns has the ability to measure drug-induced changes in daytime activity patterns and in sleep.

Two studies were designed to assess the acute effects of psychoactive drugs on daytime activity levels and sleep in a controlled laboratory environment with healthy participants. In the first study participants were randomised to a double-blind, placebo-controlled, crossover trial with lorazepam (LZP), a benzodiazepine sedating hypnotic. Actigraphic activity levels were significantly reduced following LZP dosing (2.5 mg) and these changes were reflected by impairment of cognitive and psychomotor performance.

Participants in the second laboratory study were randomised to a double-blind, placebo-controlled, crossover trial with the sedating antihistamine promethazine. Reduced activity levels reflected changes in significant impairment of cognitive and psychomotor performance. Actigraphy therefore appeared to be sensitive to acute sedating effects and was able to detect changes in sleep behaviour.

Since antidepressants are only effective after chronic administration the effects of treatment was investigated in a third field study. Depressed patients were randomised to a double-blind, parallel group, multi-centre, 14 week study of the antidepressants paroxetine, fluoxetine or sertraline, including abrupt discontinuation. Activity was recorded continuously throughout the whole study. Significant improvement in patients’ subjective mood scales, as depression was alleviated, was reflected in changes in actigraphic sleep and activity profiles.

The findings provide an indication of the usefulness of actigraphy as a diagnostic tool to measure psychoactive drug-induced changes following medication. Further work should concentrate on standardising procedures, study design and algorithms. Actigraphy may thus be a useful sensitive tool in assessing the psychopharmacology of psychoactive medication.
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I wish to thank the many people who have been instrumental in helping me to put this together, but firstly and most importantly my supervisors Prof. Debra Skene and Dr Julia Boyle for their continuing support and invaluable advice throughout. Sincere thanks also go to Prof. Ian Hindmarch and Dr Neil Stanley without whom I would not have had the opportunity to study actigraphy. I would also like to thank Dr Sigurd Johnsen for his help, statistical expertise and advice on the analysis of my data.

I would like to express my sincere thanks to AstraZeneca, Eli Lilly and Servier for permission to use the verum (active control), placebo or study data acquired during clinical studies conducted on their behalf at the Human Psychopharmacology Research Unit (HPRU), (now Surrey Clinical Research Centre) to further my studies into the use of actigraphy in psychopharmacology.

The support of my family and friends goes without saying. I wish to dedicate this thesis to them all, especially my daughters Katie and Kelly, who have listened to my doubts, deliberations and encouraged me when things got tough and provided me with the will to keep going throughout my studies. I would like to convey special appreciation to my mother Dinkie and sister Diann who have been so very understanding when I have not been around to visit and I would like to take this opportunity to remember my late father Donald who would have been so proud.

I hope and trust that my endeavours will be a legacy to my four wonderful grand-daughters Olivia, Daisy, Eleanor and Rosie and that this will encourage them to aim high, and through adversity, perseverance and resilience you can achieve your goals if you put your mind to it.

“Always aim for the Moon, even if you miss, you'll land among the stars.”

W Clement Stone 1902-2002

Last, but by no means least, a great big special thank you goes to my long suffering husband Terry for his everlasting support, patience and encouragement without whom none of this would have been achievable, his love has been an inspiration, always in all ways.
Statement of originality

This thesis and the work to which it refers are the results of my own efforts. Any ideas, data, images or text resulting from the work of other (whether published or unpublished) are fully identified as such within the work and attributed to their originator in the text, bibliography or in footnotes. This thesis has not been submitted in whole or in part for any other academic degree or professional qualification.

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<tr>
<td>AFS</td>
<td>Awakening from sleep (LSEQ)</td>
</tr>
<tr>
<td>AMI</td>
<td>Ambulatory Monitoring Inc.</td>
</tr>
<tr>
<td>ASPS</td>
<td>Advanced sleep phase syndrome</td>
</tr>
<tr>
<td>AST</td>
<td>Actual sleep time = Total sleep time</td>
</tr>
<tr>
<td>AW</td>
<td>Actiwatch</td>
</tr>
<tr>
<td>AWL</td>
<td>Actiwatch-L</td>
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<td>AWM</td>
<td>Average wake movement</td>
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<tr>
<td>AWT</td>
<td>Actual wake time = Wake after sleep onset</td>
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<td>BDI</td>
<td>Beck Depression Index</td>
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<td>BFW</td>
<td>Behaviour following wake (LSEQ)</td>
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<td>BLT</td>
<td>Bright light therapy</td>
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<td>BST</td>
<td>British summer time</td>
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<td>BZD</td>
<td>Benzodiazepines</td>
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<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<td>CFF</td>
<td>Critical Flicker Fusion</td>
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<td>CFQ</td>
<td>Cognitive Failures Questionnaire</td>
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<td>CNL</td>
<td>Cambridge Neurotechnology Ltd.</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<tr>
<td>CRT</td>
<td>Choice Reaction Time</td>
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<tr>
<td>CTT-RT</td>
<td>Continuous Tracking Task – Response time</td>
</tr>
<tr>
<td>CTT-ERR</td>
<td>Continuous Tracking Time – Tracking error</td>
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<tr>
<td>DESS</td>
<td>Discontinuation-Emergent Signs and Symptoms</td>
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<td>DNF</td>
<td>Did not finish</td>
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<td>DSM IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</td>
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<td>GMT</td>
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<tr>
<td>EEG</td>
<td>Electroencephalograph</td>
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<td>GABA</td>
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<td>GENDEP</td>
<td>genome based therapeutic drugs for depression</td>
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<td>GMT</td>
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<td>Major depressive disorder</td>
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<tr>
<td>MML</td>
<td>Mini-Motionlogger</td>
</tr>
<tr>
<td>MRT</td>
<td>Motor Reaction Time</td>
</tr>
<tr>
<td>MSLT</td>
<td>Multiple sleep latency test</td>
</tr>
<tr>
<td>NaSSA</td>
<td>Noradrenergic and specific serotonergic antidepressant</td>
</tr>
<tr>
<td>NAW</td>
<td>Number of awakenings</td>
</tr>
<tr>
<td>NPCRA</td>
<td>Non-Parametric Circadian Rhythm Analysis</td>
</tr>
<tr>
<td>NREM</td>
<td>Non REM</td>
</tr>
<tr>
<td>NS</td>
<td>Non-significant</td>
</tr>
<tr>
<td>PIR</td>
<td>Proportional impairment ratio</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
</tr>
<tr>
<td>QOS</td>
<td>Quality of sleep (LSEQ)</td>
</tr>
<tr>
<td>RA</td>
<td>Relative amplitude</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>REMML</td>
<td>Restricted maximum likelihood</td>
</tr>
<tr>
<td>RLS</td>
<td>Restless leg syndrome</td>
</tr>
<tr>
<td>RMS</td>
<td>Response measure</td>
</tr>
<tr>
<td>RRT</td>
<td>Recognition Reaction Time</td>
</tr>
<tr>
<td>PRT</td>
<td>Peripheral Awareness Task</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical analysis software</td>
</tr>
<tr>
<td>SB</td>
<td>Sleep bouts = number of transitions between sleep and wake</td>
</tr>
<tr>
<td>SBT</td>
<td>Sleep bout time</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Sleep efficiency</td>
</tr>
<tr>
<td>SL</td>
<td>Sleep latency = Sleep onset latency</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
</tr>
<tr>
<td>SMHSQ</td>
<td>St Mary’s Hospital Sleep Questionnaire</td>
</tr>
<tr>
<td>SOL</td>
<td>Sleep onset latency = Sleep latency</td>
</tr>
<tr>
<td>SPT</td>
<td>Sleep period time</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow wave sleep</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TAT</td>
<td>Time above threshold</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td>T1/2</td>
<td>Time taken for concentration of drug to reduce by one half</td>
</tr>
<tr>
<td>TIB</td>
<td>Time in bed</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time to reach peak plasma concentration</td>
</tr>
<tr>
<td>TRT</td>
<td>Total Reaction Time</td>
</tr>
<tr>
<td>TST</td>
<td>Total sleep time = Actual sleep time</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WASO</td>
<td>Wake after sleep onset = Actual wake time</td>
</tr>
<tr>
<td>WB</td>
<td>Wake bouts = transitions from sleep to wake = nocturnal awakenings</td>
</tr>
<tr>
<td>WBT</td>
<td>Wake bout time</td>
</tr>
<tr>
<td>ZCM</td>
<td>Zero crossing mode</td>
</tr>
</tbody>
</table>
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CHAPTER 1 INTRODUCTION

1.1. Introduction

Actigraphy is an objective measure of the sleep wake cycle and is measured by the continuous measurement of activity using an actigraph usually worn on the non-dominant wrist. The development of actigraphy has allowed rest-activity patterns to be measured in different population groups and it provides a more accurate representation of sleep timing and patterns than sleep logs or diaries (Girschik et al., 2012). Whilst polysomnography (PSG) remains the gold standard for assessing sleep, actigraphy has offered a cheaper, less invasive alternative, which has the added advantage of being able to monitor rest and activity patterns for longer periods of time in situations where an intensive in-house assessment of sleep would be difficult. In addition changes in activity can be observed and measured following intervention where other methods would be inappropriate.

1.2. Actigraphy

1.2.1. Uses

Actigraphy is widely accepted as a non-invasive tool for assessing sleep-wake patterns in reviews of a number of different groups (reviewed in Sadeh et al., 1995; Ancoli-Israel et al., 2003; Littner et al., 2003), including, but not exclusive, sleep medicine (Sadeh, 2011), insomnia (Hauri and Wisbey, 1992; Lichstein et al., 2006), sleep-related breathing (Acebo and LeBourgeois, 2006), children (Acebo et al., 2005), restless legs (King et al., 2005), depression (Royant-Parola et al., 1986; Raoux et al., 1994) and circadian rhythm disorders (Lockley et al., 1999; Ancoli-Israel et al., 2003).

The use of actigraphy has been reviewed extensively for clinical and non-clinical use, including assessment of sleep-wake patterns in non-sleep related chronic conditions for patients such as those with poor mental health i.e. Alzheimer’s disease (Van Someren et al., 1999) and psychiatric disorders (Teicher, 1995) as well as patients suffering with cancer (Chevalier et al., 2003). Actigraphy has been specifically used for sleep medicine in various different populations and patient groups as described in the review by Sadeh, (2011) who also outlined many of the issues surrounding the technology including the assessment of ‘wake’ in the sleep period for insomniacs in particular and the different devices and algorithms for calculating the sleep variables. In addition actigraphy has been applied to the sports related field with its use as an activity monitor for daytime activities (reviewed in Matthews et al., 2012).
Diagnosis and treatment of circadian rhythm disorders benefit particularly from the use of actigraphy. Long term analysis of the profiles leads to a better understanding of the 24 h pattern of these and other psychiatric diseases as seen in review (Morgenthaler et al., 2007b) and different methodological approaches have been described (Calogiuri et al., 2013).

1.2.2. History and development

Sleep-wake patterns were historically recorded by observation or through Electro-Encephalograph (EEG) or Polysomnography (PSG) with full body kit by attaching electrodes to the scalp to measure changes in electrical activity, however, these assessments are expensive, time consuming and only offer snapshots of time. The measurement of activity with mechanical monitors, which began in the late 1950’s, was developed to study human activity and sleep-wake patterns with self-winding wrist watches. The first solid state actigraph was described as ‘An ambulatory activity monitor with solid state memory’ in a study by Colburn et al. (1976) and was used to measure movement over 24 h to assess the differences in activity levels in manic-depressives in different episodes of depression. Activity was recorded via a piezo-electric accelerometer which recorded a voltage every time a movement was made which was converted to an activity count and stored in the memory. The accumulated data were downloaded for analysis.

Actigraphs were developed for the purpose of recording continuous activity data and it was shown that low level activity could be manually scored as ‘sleep-like’ in comparison to EEG (Mullaney et al., 1980). This was taken further by Cole et al. (1992) who developed an automatic algorithm which could discriminate between sleep and wake and this enabled the actigraphs to be seen as cheaper alternatives to EEG recording.

The early versions were large and cumbersome and recorded activity for short periods of time. However, these devices have been constantly refined over the years to become the small inexpensive models now available. With the advent of better memory storage and battery life they can record for longer periods up to 180 days depending on the epoch employed. By recording continuously, lower activity levels occurring during the day, which may be associated with naps, tiredness or sedation, can also be detected. These devices have been further developed and coupled to other portable sensors or monitors that also record light, heart rate, sleep, respiration and core body temperature.
1.2.3. Actigraph types

The generic term for an activity monitor is an actigraph; there are many types on the market with various brand names to denote their specificity. All types of actigraphs basically consist of a small device worn on the non-dominant wrist which contains a motion sensor. The sensor or piezo-electric accelerometer generates a signal voltage every time it is moved and this is stored as a count in the memory and recorded as activity. Dedicated software programs are associated with each device and the collection and interpretation of the data. Currently there are devices which have been developed for a variety of specialised uses including monitoring activity and exercise, calorific output and non-movement in bed in the care home scenario as well as prompting the user to respond to commands and subjective ratings. The two most commonly used actigraphs produced are the Mini-Motionlogger and the Actiwatch and these are discussed in more detail (Sections 1.2.3.1 and 1.2.3.2).

1.2.3.1. Mini-Motionlogger

This device, manufactured by Ambulatory Monitoring Inc. (AMI), (731 Saw Mill River Road, P.O. 609, Ardsley, New York. 10502-0609) (Figure 1.1) was originally developed in conjunction with the US Army to monitor fatigue in soldiers. It contains a piezo-electric accelerometer which generates a signal voltage for every movement, this voltage is then compared with a reference signal and the number of times where the movement crosses the reference Zero Crossing Mode (ZCM) or is above the threshold Time Above Threshold (TAT) during a defined epoch is recorded. This reflects the number of movements but not the intensity. This count is stored in the memory unit and the data are downloaded onto a computer and analysed with the ‘Action4’ software program. They are available with different type faces as shown. A typical actogram activity plot from the Action4 software is shown in Figure 1.2.

![Figure 1.1: New versions of the Mini-Motionlogger (2009 catalogue)](image-url)
1.2.3.2. Actiwatch

Developed by Cambridge Neurotechnology Ltd (CNT) (Upper Pendrill Court, Ermine Street North, Papworth Everard, Cambridge, CB3 8UY), this device, now obsolete, was known as the original Actiwatch (Figure 1.3). It houses a piezo-electric accelerometer which digitally integrates the intensity, amount and duration of movement for each epoch and stores this as an activity count, data are downloaded onto a computer and analysed using the proprietary software ‘Sleepwatch’.

The electronics in the device check the amplitude of the signal generated by the accelerometer thirty two times a second and records the highest count in that second, the number of counts being proportional to the intensity. A diagrammatic view to show the mechanism is shown in Figure 1.4. The sum of the highest counts for each individual 1-
second interval is then logged and presented as the number of counts in the epoch period defined by the user. A screen view of the activity plot as an actogram is shown in Figure 1.5.

This Actiwatch 4 Series as described above was used for the studies in this thesis. Since then the rights to the Actiwatch were sold to Philips Respironics (Section 1.2.3.4) who retain the name. Cambridge Neurotechnology has since rebranded as CamNtech ® and developed a newer version called the MotionWatch 8 which is briefly described in the following section (Section 1.2.3.3).

![Diagrammatic view to show the mechanism of the Actiwatch piezo-electric accelerometer](image1)

Figure 1.4: Diagrammatic view to show the mechanism of the Actiwatch piezo-electric accelerometer

![Actogram double plot showing the activity screen using the Actiwatch software](image2)

Figure 1.5: Actogram double plot showing the activity screen using the Actiwatch software

1.2.3.3. MotionWatch 8

This device from CamNtech, as shown in Figure 1.6, works off the same principles as the Actiwatch but with a modern style and with extended battery and memory it is able to store
data for up to 180 days. It connects to a computer via a USB port. A screen view of the activity plot as an actogram is shown in Figure 1.7.

Figure 1.6: MotionWatch 8

Figure 1.7: MotionWatch 8 Actogram screen view

1.2.3.4. Actiwatch 2 and spectrum (Philips)

The devices from Philips are shown in Figure 1.8, they are more stylish than the original Actiwatch and have an inbuilt marker and light sensor. The ‘integrated light sensors in the Spectrum provide irradiance and luminous flux recordings in red, green, and blue colour bands and a white light measurement in lux’ as taken from their brochure.
Early research was conducted using the Gahwiler Monitor (Hombrechtikon, Zurich, Switzerland). This Swiss actigraph was one of the first commercial devices developed however it is no longer available. There are a number of other devices relatively new to the market including GENEActive Sleep (Unit 11, Harvard Industrial Estate, Kimbolton, Cambs, PE28 0NJ), Somnowatch (SOMNOmedics, GmbH & Co. KG, Nonnengarten 8, D-97270, Germany), Body Bug (BodyMedia, Inc., 4 Smithfield Street, 11th Floor, Pittsburgh, PA 15222), ActiGraph (Actigraph, LLC, 709 Anchors Street, NW, Fort Walton Beach, Florida, FL 32528), ActiTrac (MSystmes, 1055 Taylor Avenue, Suite 300, Baltimore, MD 21286) and Vivago (IST, International Security Technology, Melkonkatu 16A, FI-00210 Helsinki, Finland) to name but a few and these devices essentially work in the same way as those previously discussed. However, there are very little published data on these devices and their performance; most research papers quote the use of Actiwatch or Actigraph. Newer versions have been introduced into the daytime activity arena for measuring sport and exercise science related performance and data from their analysis packages have not been published for clinical research.

Measurement of activity with the Actiwatch

Activity is recorded continuously, using various epoch lengths ranging from 0.25 to epochs in excess of 10 minutes. As there is a finite storage capacity in the memory of the Actiwatch used in this thesis, the range of epochs enables the user to store data for different lengths of time from 11 days using the 0.25 min epoch to 90 days using the 2 minute epoch. The shorter 0.25 epoch allows greater differentiation of the movement and to record activity that is high in number of movements such as those seen in Parkinson's or restless legs syndrome (RLS) (King et al., 2005). The longer 1-2 min epoch is useful for studying activity and sleep wake patterns in relation to circadian activity rhythms to define and indicate circadian phase (Ancoli-Israel et al., 2003; Arendt et al., 2006).
The most common epoch setting employed for activity information with the Actiwatch is that of 1 minute where the user can study a continuous pattern of 24 h of rest and wake activity for up to 45 days. For the analysis of sleep and wake in comparison to PSG a 30 sec epoch setting can be used. However, this reduces the overall recording capacity of the memory to 22 days. An epoch setting of 2 minutes can be deployed if a longer recording time is required which will provide reliable rest-activity data for records up to 90 days.

The sensitivity settings can also be altered in the Actiwatch. Medium sensitivity is the default setting which is set at a total score of 40 counts for a 1-minute epoch and is the number of counts to enable the epoch to be scored as ‘awake’. Counts lower than 40 in an epoch may be scored as ‘sleep’ depending on the algorithm. Low sensitivity settings double the activity count in any epoch whereas high sensitivity half the activities count. The Actiwatch is set up via a dedicated reader station connected to a personal computer and following recording data are then downloaded using the reader and the data are stored in the computer, as shown in Figure 1.9.

1.2.5. Algorithms

Traditionally sleep is assessed by PSG which involves attaching electrodes to the scalp, recording and then scoring the brain’s electrical activity to determine the different stages of sleep. However, this is an expensive technique which requires access to sleep laboratories and specialist training, and is therefore very expensive. In order to assess whether sleep could be determined merely by measuring activity levels, PSG recordings were correlated with movement measured by activity monitors throughout the sleep period (Mullaney et al., 1980). By manually scoring each epoch from the activity monitor against the PSG output it was found possible to differentiate between sleep and wake. However, this was very time consuming and in addition periods of ‘quiet wake’ were also difficult to interpret. An automatic algorithm was developed in order to classify whether each individual epoch was scored as wake or sleep, by correlating activity data with PSG recordings and comparing the activity counts of each 1 minute epoch with 4 epochs before and 2 epochs after, (Cole et al., 1992). Nevertheless, this did not account for periods of ‘quiet wake’, where the activity level was very low or the device had been removed which may confound the results. Various scoring algorithms have since been developed which are dedicated to the specific devices and software programs.
1.2.6. Sleep-like minutes

Data recorded during the daytime using the Actiwatch system registers the activity count per epoch. In addition, each activity count is scored by the algorithm when sleep is analysed by the software as either 'sleep' or 'wake'. When the activity count for an epoch of 1 minute falls below 40 counts, using the medium sensitivity setting, it is scored as a 'sleep' epoch. Periods of low activity during the day may therefore be scored as 'sleep-like' where the activity level is very low. This may be the result of a nap, reduced activity as a result of sedation or removal of the device. However few studies have reported on this aspect in clinical trials. A study on the effect of antidepressants on healthy volunteers (n = 12) by Stanley and Hindmarch, (1997) showed reductions in actigraphic daytime activity due to the sedating effect of a single dose of dothiepin 75 mg even at the hourly psychometric test points. Stanley, (1997) also showed a significant reduction in daytime activity in a study using a single dose of the antihistamine promethazine 25 mg in healthy volunteers (n = 24) as well as the time course of its sedating effect over 6 h even with the alerting effects of performing psychometric tests, compared with non-sedating antihistamines and placebo. The sedative effect of both of these studies was evident as a reduction in the activity and not an increase in 'sleep-like’ minutes.

1.2.7. Actigraphic sleep variables

The Actiwatch Sleepwatch software analyses the data and provides a summary of the standard sleep variables common to comparable parameters in PSG, as shown in a screen shot of one analysed sleep period (Figure 1.10). Once the bedtime and wake-up times are set, either automatically using the event marker buttons or by a trained operator, the analysis program provides the various sleep parameters within the sleep period calculated by the
dedicated algorithm. If the markers are not set or the bedtimes are not restricted as in clinical trials participants sleep diaries may also be used to provide the sleep onset and offset. The main sleep variables are described in full in Section 2.4.1.

Although the sleep start and end times are calculated differently by the dedicated algorithm for each device and therefore the resultant data parameters are different, a comparison of the two devices, Actiwatch L and Mini-Motionlogger, found total sleep time (TST), referred to as actual sleep time (AST), to be correlated strongly (Benson et al., 2004).

![Image of Sleep Analysis profile](image_url)

Figure 1.10: Windows view of the Sleep Analysis profile

### 1.2.8. Actigraph comparison with PSG

The first study to compare the two most popular actigraphs against PSG was conducted with healthy participants (n = 12) without sleep disorders who simultaneously wore the Basic Mini-Motionlogger (MML, AMI) and the Actiwatch ® (AW4, CNT) whilst PSG was recorded (Tonetti et al., 2008). The MML data were scored and analysed according to the algorithm developed by Cole et al. (1992) and ‘AW Action W-2® version 3.23 software (AMI). Whilst AW data were analysed by Actiwatch Activity & Sleep Analysis 5® version 5.32 software’, and analysed according to the mathematical model developed and validated by Oakley, (1997). Analysis was conducted for sleep onset latency / sleep latency (SOL/SL), TST, wake after sleep onset / actual wake time (WASO/WT) and sleep efficiency (SE). The authors concluded that both devices performed similarly to each other and PSG on the sleep variables except for SOL which they both underestimated.
The Actiwatch, (Respironics) Sleepwatch (AMI) and Actical (Respironics) an actigraph worn round the waist were compared with PSG in a sleep study with healthy participants (n = 30, male = 19, female = 11) (Weiss et al., 2010). There was a significant correlation between the different devices and PSG for sleep efficiency as shown in Figure 1.11. However all devices underestimated the amount of wake compared with PSG which is particularly important for calculating WASO and TST.

A further comparison study of the basic Motionlogger Watch (AMI) and Actiwatch-64 (Mini-Mitter) to PSG was conducted in young healthy participants (n = 29) and showed that both devices performed as well as each other but that both devices underestimated sleep latency compared with PSG (Rupp and Balkin, 2011). Moreover the researchers stated that they were both ‘reliable and valid tools to evaluate sleep parameters’.

A direct comparison of Actiwatch-L (AWL, Mini-Mitter) and Mini-Motionlogger (MML, AMI) the two most common commercially available actigraphs was conducted in a study with 20 healthy participants who wore both devices on their non-dominant wrist simultaneously for 2 nights. The AWL correlated with the MML at all the sensitivity settings for TST, however where wake measurement is a factor, correlation was poorer for WASO, SL and SE. (Benson et al., 2004).

Although there are limitations, since actigraphy measures activity and not sleep, algorithms have been developed to calculate variables that are similar to both PSG and actigraphy. Moreover actigraphy was positively correlated with PSG in a sleep study of depressed insomniac patients and was validated against PSG (McCall and McCall, 2012). According to the Martin and Hakim, (2011) review ‘actigraphy represents a useful diagnostic tool for the sleep practitioner, allowing for sleep over extended periods of time in the natural sleep environments and appears to provide a valid estimate of TST, sleep percentage, and WASO……and circadian rhythm sleep disorders’. (Wilson et al., 2004b) demonstrated how actigraphy was used to evaluate the effects of two weeks of the hypnotic temazepam 20 mg/day in insomniacs in outcomes of actigraphic sleep variables; significant changes were recorded in fragmentation index, actual sleep time %, actual sleep time and sleep efficiency.

1.2.9. Advantages and disadvantages of actigraphic assessment

The gold standard for sleep recording is PSG, however this has its limitations, it provides a snapshot of one period of sleep usually in a sleep laboratory but also with ambulatory recorders in participant’s homes. Whilst the sleep is an accurate account of the sleep
architecture it does not provide how this fits into a 24 h day, or even over a number of days or weeks. To be wired up for sleep takes 20-30 minutes depending on the number of electrodes by a sleep technician. The electrodes can be uncomfortable to wear and can impact on sleep latency whilst the participant acclimatises to them, often participants feel restricted wearing them when in bed. In addition performing PSG in a sleep laboratory is in unusual surroundings and may also impact on the quality whilst participants become familiarised. When performing clinical studies it is wise to include an acclimation night to remove first night effects. Actigraphy in contrast is unobtrusive, records continuously for 24 hours and allows the participants or patients to sleep unrestricted in their own natural environment over extended time periods than one night (Martin and Hakim, 2011).

Table 3—Pearson correlation coefficients for sleep efficiency from polysomnography (PSG) and actigraphy devices

<table>
<thead>
<tr>
<th>N = 30</th>
<th>PSG</th>
<th>Sleepwatch</th>
<th>Actiwatch</th>
<th>Actical</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG</td>
<td>0.619**</td>
<td>0.651**</td>
<td>0.348</td>
<td></td>
</tr>
<tr>
<td>Sleepwatch</td>
<td>0.619**</td>
<td>0.653**</td>
<td>0.405*</td>
<td></td>
</tr>
<tr>
<td>Actiwatch</td>
<td>0.651**</td>
<td>0.653**</td>
<td>0.820**</td>
<td></td>
</tr>
<tr>
<td>Actical</td>
<td>0.348</td>
<td>0.405*</td>
<td>0.820**</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.001; Sleepwatch, Sleepwatch actigraph (Ambulatory Monitoring, Inc., Ardsley, NY); Actiwatch, Actiwatch actigraph (Respironics, Pittsburgh, PA); Actical, Actical actigraph (Respironics, Pittsburgh, PA)

Actigraphs facilitate the long term continuous objective assessment of changes in rest and activity patterns. Which is one of the reasons why its appeal has grown and it has become a useful adjunct to sleep research with an increase in publications (Sadeh, 2011). The use of actigraphy leads itself to opportunities in which PSG would be expensive and inconvenient as they are non-invasive and are therefore useful for observing changes in sleep wake patterns or sleep profiles following various interventions. These may be drug induced in the case of depression and insomnia; or when using a Continuous Positive Airway Pressure (CPAP) machine in the case of patients suffering from sleep problems associated with sleep apnoea; or for measuring the effectiveness of sleep hygiene advice or cognitive behavioural therapy. An actigraphic study of the rest-activity cycle of psychiatric patients revealed differences and showed that schizophrenics had a more disturbed 24 h pattern with both lower daytime and night-time activity levels than did depressed patients (Berle et al., 2010). Without actigraphy this type of study would not be possible.
Depressed patients (n = 12) were treated with fluvoxamine, home sleep recordings were conducted at baseline and weeks 3 and 12. HAMD and MADRS scores showed patient perceived improvement from baseline following treatment, but objective sleep parameters in increased number of awakenings paradoxically worsened for responders (Wilson et al., 2000), if used actigraphy could have provided a continuous record of changes. A further study was conducted comparing subjective diaries and objective PSG on depressed patients (n = 40) treated with nefazodone or paroxetine over 8 weeks (Argyropoulos et al., 2003). Sleep was recorded on four occasions at baseline, days 3 and 10, then week 8 at patients’ homes. There was a reasonable correlation between the measures of TST and SOL but not number of awakenings. The study was not continuous so unable to report on the effect of medication from day 10 to week 8, whereas actigraphy would have provided a continuous assessment.

Actigraphy is also useful for studying circadian rhythms and disorders such as Delayed and/or Advanced Sleep Phase Syndrome (DSPS and ASPS) (Morgenthaler et al., 2007b), particularly where the use of a diary is cumbersome and compliance is an issue. With the actigraph marker button a participant merely depresses the marker when they have turned off the lights and are trying to fall asleep as opposed to completing a diary the following day which could lead to error. A diary is useful as it enhances the information obtained by actigraphy, so where possible both should be used. In clinical research where participants are advised to follow strict time regimes during the screening period and wash-out phase of a drug trial they are extremely useful for confirming compliance.

Actigraphy has its limitations, as discussed in review by Sadeh, (2011) the biggest disadvantage is that it does not measure sleep, it measures activity which is interpreted as being ‘wake’ or ‘sleep’ depending on the level of activity in each epoch and may therefore present a false indication of sleep since ‘quiet wake’ periods may be scored as sleep. Despite the development of algorithms to minimise the risk of ‘quiet wake’ being incorrectly scored as sleep it is impossible to eradicate this completely and therefore caution is advised when interpreting data from patients/participants where ‘quiet wake’ is seen e.g. in insomnia patients (Hauri and Wisbey, 1992).

There is also variability between activity monitors within the same manufacturer, since each device contains a unique sensor; therefore no one device gives identical results to another. The inbuilt sensors can deteriorate so it is necessary to calibrate the devices regularly to ensure validity of results. For clinical research, in cross-over studies, it is therefore important
to minimise this variation and use the same actigraph for each participant during each treatment period to reduce errors.

One of the main criticisms with actigraphy is with sleep latency however the use of the marker button to indicate lights out as an indicator of intention to sleep is valuable for assessing this and observing difficulty in falling asleep. Although actigraphy does not measure PSG variables it has advantages over sleep diaries which merely measure participant’s perception of sleep timings, number of awakenings and how long it took to get to sleep. Studies have shown that actigraphy closely resembled PSG in terms of sleep disruption, and reported that actigraphy was better than diaries with similar values to PSG for SOL and number of awakenings (Lichstein et al., 2006) in a study of 57 insomniacs. Similar findings were reported in a different study of 54 insomniacs, actigraphy reasonably correlated with PSG in all variables except sleep latency, but sleep logs again recorded worse reports of longer SOL compared with PSG, participant’s perception of sleep was poorer than it actually was (McCall and McCall, 2012).

Diaries are useful for guiding analysis to the correct lights out times if no markers are used or if the marker has been erroneously pressed, and they provide an opportunity to gain further information about the sleep quality and subjective sleep with reasons for poor sleep. Actigraphy showed that in a study of older nocturia patients, participants men (n = 55) and women (n = 92), of nocturnal bathroom visits, sleep efficiency derived from the actigraph was worse than the self-report logs (Zeitzer et al., 2013). Although the sleep logs recorded the subjective disruption, actigraphy recorded reduced sleep efficiency with an increase in number of sleep bouts associated with the higher number of night time voids.

Daytime sedation is traditionally measured with a sleep test known as the Multiple Sleep Latency Test (MSLT) which measures how sleepy an individual is when given the opportunity to sleep which is performed in a sleep laboratory. Actigraphy offers an alternative by measuring reduced daytime activity as naps or the accumulation of low level activity below the threshold of wake as explained in Section 1.2.6.

Despite its limitations of recording activity and not sleep, researchers (Morgenthaler et al., 2007a) in the Practice Parameters for the Use of Actigraphy, encourage the use of actigraphy in depressed patients and concludes that “Actigraphy is indicated as a method to characterize circadian rhythm patterns or sleep disturbances in individuals with insomnia, including insomnia associated with depression” and “Actigraphy is useful for evaluating the
response to treatment for patients with insomnia, including insomnia associated with depressive disorders”.

1.3. Psychopharmacology and CNS drugs

1.3.1. Introduction

Currently the evaluation of psychoactive drug effects has been conducted with healthy participants utilising psychometric test batteries to assess impairments in daytime cognition and psychomotor functioning (Hindmarch, 1980; Fairweather et al., 1996; Kerr et al., 1996; Hindmarch et al., 2005). Tracking and reaction time tasks in particular, are known to be reliable and sensitive to drug effects, and are related to impairment of driving ability (Hindmarch, 1980; Patat, 1998; Ridout et al., 2003a). Night-time sleep following administration of psychoactive drugs is still often evaluated with PSG to assess changes in sleep architecture. This type of study design is possible in Phase I and II studies but the data are limited to a relatively small number of volunteers and may not be relevant to the general population and in particular to the patient groups intended to receive the medication. Although it is not economical or logistically possible to conduct comprehensive in-house assessments in Phase III studies, actigraphy may be of use in the assessment of drug-induced changes in night-time sleep and in daytime activity in large scale patient studies. For example reduction in daytime activity levels may reflect increased sedation, a common side effect of some centrally acting compounds. Psychometric assessments have shown that a number of cognitive functions are adversely affected by increased sedation including information processing, memory and attention (Patat et al., 1987; Hindmarch et al., 2001b; Soo-ampon et al., 2004). However, psychometric tests merely provide indications of impairment at specific time points, often to cover the time of maximum impact of the medication and any hangover effect, but where it is not feasible to measure the continuous effects.

Actigraphy has enabled the continuous measurement of activity in relation to the assessment of a drug and its effect on changes in activity and sleep patterns. It may be useful to reveal that a reduction or change in activity levels following dosing is related to the sedating effect of the medication as indicated in studies examining the effects of psychoactive compounds (Mattmann et al., 1982; Borbély, 1984; Stanley and Hindmarch, 1997). However, there are relatively little data available to show the time-course of drug action. There are also limited data to show that actigraphy can reliably measure the daytime and night-time characteristics of a CNS drug. Whether actigraph technology is sensitive to the sedating effects of
medication and how accurately actigraphy is able to track drug pharmacokinetics and pharmacodynamics remains to be determined.

Previous research has assessed the effect of different drugs on actigraphic sleep and daytime behaviour in small scale studies including sedatives (Mattmann et al., 1982; Borbély et al., 1988), anti-depressants (Fairweather et al., 1996; Stanley and Hindmarch, 1997; Stanley et al., 1999), hypnotics (Borbély et al., 1983; Takahashi et al., 2003), antihistamines (Hindmarch et al., 1999; Roehrs et al., 2000; Shamsi et al., 2001) and stimulants (Hindmarch et al., 2000b). The classes of drugs which are prescribed for inducing sleep, reducing anxiety or reducing a histaminic response have well documented side effects including reduction in activity during wake (Borbély et al., 1983; Takahashi et al., 2003) and impairment of mental ability and alertness in the acute phase following drug administration (Kawahara et al., 2002; Kiang et al., 2003). Drug-induced reduction in activity has been studied in ‘spontaneous’ activity (Kiang et al., 2003) and there are some data to suggest that actigraphy is able to detect “hangover effects” (Borbély, 1984; Borbély et al., 1988; Stanley, 1997; O’Neill et al., 2000; Klösch et al., 2001; Kawahara et al., 2002; Takahashi et al., 2003). Most of these studies, however, have employed different actigraphs and not the Actiwatch system. There are important differences between the devices and the algorithms that are utilized (Section 1.2.5) which means that confirmatory studies using the Actiwatch are required to assess further the utility of ‘actigraphy’ as a tool in psychopharmacology.

Although studies have been conducted on the effects of drugs on sleep and activity, many of these include assessments on patient groups with sleep related disorders. Therefore the studies which have been reviewed in Sections 1.4 Sedative Hypnotics and 1.5 Antihistamines have been limited to include only those which have assessed sleep/wake activity patterns in normal healthy male and female participants. Whereas Section 1.6 Antidepressants reviews studies related to the acute effect of medication on healthy participants and chronic use in depressed patient groups.

1.4. Sedative-hypnotics

Drugs in the benzodiazepine class which act on the CNS are classed as hypnotics to induce sleep or anxiolytics to induce calm and have a sedative effect depending on their duration of action. The shorter acting compounds (e.g. loprazolam, temazepam, nitrazepam) have poorer efficacy but minimal residual effects and are mainly used in the treatment of insomnia (Beaumont, 2000; Nicholson, 2000), whereas the longer acting ones (e.g. alprazolam, diazepam) have good efficacy and are mainly prescribed to treat anxiety (Williams and Smith, 2000).
1.4.1. Mechanism of action

The benzodiazepines (BZD) act on the GABA receptor to increase GABA function and thus promote sedation and sleep. They vary in their duration of action and can be short acting with a $T_{1/2}$ of 2-4 h as in the case of the hypnotic midazolam, or $T_{1/2}$ 8-12 h for lorazepam (LZP) known as an anxiolytic hypnotic, and longer acting $T_{1/2}$ 20-40 h for diazepam used as an anxiolytic, for insomnia and panic attacks. Overall this group of compounds reduce anxiety, induce sedation and reduce the time taken to get to sleep. However caution is advised as they are addictive and should only be used for short-term resolution of sleep problems.

1.4.2. Side effects of sedative-hypnotics

The main side effects of these compounds are sedation and impaired coordination even with the relatively short acting compounds used to treat anxiety resulting in increased risk of motor accidents or when operating machinery. Sedation can be observed as an objective measure with increases in reaction times, reductions in MSLT time or a delay in observation and recognition. Side effects may also be reported as increases in the subjective rating of the sedation component of the Line Analogue Rating Scale (LARS) where participants rate feelings of drowsiness, or not feeling alert the following morning on the awakening from sleep (AFS) and behaviour following wake (BFW) components of Leeds Sleep Evaluation Questionnaire (LSEQ) (Sections 2.6.1 and 2.6.2). Lack of coordination may result in poor performance in psychometric tests and driving skills.

1.4.3. Sedative-hypnotics and cognition and psychomotor function

It is a recognised side effect of psychoactive drugs that they cause impairment of psychomotor function with a lack of coordination and reduced processing ability. The particular tests used in this thesis the Critical Flicker Fusion (CFF), Choice Reaction Task (CRT), and Continuous Tracking Task (CTT) amongst others, are recognised as being ‘sensitive to a wide range of psychoactive compounds’ and are suitable for measuring changes in ‘sensori-motor performance’ (reviewed in Hindmarch, 1980). These cognitive tests, described in full in Section 2.5, are important when measuring effects as they provide useful information on how the psychoactive compounds might impair everyday functions like driving and are used as objective measures of sedation (Sherwood and Kerr, 1993). Subjective questionnaires LSEQ and LARS are used to rate participant’s opinion on the effect of sedating compounds on sleep and sleepiness.
1.4.3.1. Objective psychometric tests

A study was conducted with the short acting benzodiazepine, midazolam, (T½ 2-4 h), compared with placebo. Healthy participants (n = 12) were treated with 4 different doses of midazolam 5, 10, 15 and 20 mg and CFF and CRT were assessed (Gudgeon and Hindmarch, 1983). With respect to CRT all doses of midazolam increased reaction time with peak impairment at 1 h post dose compared with placebo but only the 20 mg dose continued to have an effect 4 h post dose, and there was no hangover effect at 7 h post dose. The 10, 15 and 20 mg doses caused significant impairment in CFF at 1 h post dose and the 15 and 20 mg doses continued to significantly affect CFF to 4 h post dose, as with CRT no impairment was seen at 7 h post dose.

The effect of the medium term acting benzodiazepines LZP 1 mg (T½ 8-12 h) and buspirone 5 mg and 10 mg (T½ 2-3 h) were compared with clobazam 1 mg a non-benzodiazepine anxiolytic (T½ 18 h) and placebo in a 5 way crossover study with healthy female participants (n = 10). Although LZP decreased CFF scores compared with placebo following acute dosing at 1.5 h post dose this was not significant (Alford et al., 1991). Buspirone and LZP both significantly increased the total reaction time of CRT at 1.5 h post dose and LZP increased total reaction time overall for 1.5 – 5 h post dose.

Diazepam 10 mg (T½ 20-40 h), a longer acting benzodiazepine, was compared with LZP 2.5 mg and medazepam 15 mg (T½ 36-200 h), a benzodiazepine derivative, and placebo in a cross-over study to compare the effects of single doses on performance tasks related to driving with healthy participants (n = 10) (Seppälä et al., 1976). Compared with placebo, LZP (T½ 8-12 h) significantly impaired reaction times and CFF up to 12 h, whereas there was no impairment following diazepam and medazepam administration after 5 h. The authors concluded that patients would be safe to drive 5-7 h after diazepam or medazepam administration but not safe for 24 h after LZP.

1.4.3.2. Subjective ratings and sleep questionnaires

The LSEQ and LARS are questionnaires useful for subjective ratings of sleepiness and sedation, and are described in detail in Section 2.6. Sedative-hypnotics are prescribed for insomnia and also for their calming effect in anxiety. A review of studies of benzodiazepines effect on LSEQ by Hindmarch, (1984) showed the usefulness of the scale for measuring drug effects on subjective sleep. LZP 2 mg, used as a sedative hypnotic control, induced feelings of sedation up to 9 h post dose, compared with placebo in a study of the effect of antipsychotics on healthy participants on LARS (Hindmarch and Tiplady, 1994). Participants
felt significantly fatigued as a side effect of LZP 2.5 mg at 7h post dose compared with placebo (Seppälä et al., 1976) in the subjective assessment.

Participants (n = 18) rated their feelings of sedation as being 'groggy' the morning following treatment with flunitrazepam 2 mg, a longer acting benzodiazepine (T½ 18-26 h), compared with placebo, with associated significant residual drug effects in reduced activity (Mattmann et al., 1982). Temazepam 30 mg also induced 'grogginess' the following morning and at midday after a bedtime dose compared with placebo in healthy participants (n = 14) (Borbély et al., 1984). In contrast in a similar study with healthy participants (n = 15) with the short acting benzodiazepines midazolam and triazolam no such effects of residual sedation were reported the following day (Borbély et al., 1983).

1.4.4. Sedative-hypnotics effect on sleep, actigraphic sleep and daytime activity

1.4.4.1. Sleep

This group of compounds aids sleep in general by reducing SOL thereby enabling patients to get to sleep faster. They affect sleep architecture by increasing TST and REM latency, reducing Stage 1, and increasing Stage 2. Healthy participants were each dosed on 2 consecutive nights with flurazepam 30 mg (T½ 40-50 h), LZP 4 mg (T½ 8-12 h) or triazolam 0.5 mg were (T½ 2-4 h) in a 4 way crossover study with placebo (Roth et al., 1980). PSG was recorded and the data for the 2 nights was pooled. All medications significantly affected sleep architecture with decreased stage 1, increased stage 2 but no change in stages 3-4, LZP alone significantly reduced % REM. Participants subjectively felt that they were able to get to sleep significantly faster after flurazepam and LZP, but all treatments significantly improved quality of sleep with less reports of awakenings.

LZP is often used as a verum in comparison clinical studies because of its well-known properties. A study compared LZP with suriclone, a non-benzodiazepine anxiolytic and their effect on sleep architecture, Saletu et al. (1990) confirmed previous research (Roth et al., 1980). In a further study LZP was shown to alter sleep architecture as determined by PSG by reducing sleep latency, number of awakenings, Stage 1 sleep % and REM, whilst increasing TST and Stage 2 sleep in a controlled study with healthy participants. Sleep was recorded over 3 nights and LZP 2.5 mg was administered on night 2 (Grözinger et al., 1998).

1.4.4.2. Actigraphy

The action of benzodiazepines on ‘activity during sleep’ has been assessed using actigraphy in a number of studies (Mattmann et al., 1982; Borbély, 1984; Walsh et al., 1991) as well as
other hypnotic non-benzodiazepines compounds (Borbély et al., 1988; Daurat et al., 2000; Denise, 2003).

The hypnotic action of midazolam 7.5 mg and 15 mg on actigraphic activity during the night taken 30 min before bedtime was compared with triazolam 0.25 mg and 0.5 mg, (Borbély et al., 1983). These researchers found that activity was reduced on all treatments compared with placebo and that this reduction in activity was mainly limited to the first half of the night. In addition there was no significant difference in the levels of spontaneous activity during the first 4 h after waking.

Using a solid state actigraph, hypnotics with a long half-life (flunitrazepam 2 mg, flurazepam 30 mg, temazepam 20 and 30 mg) were compared with those with a short half-life (midazolam 7.5 mg and 15 mg, triazolam 0.25 mg and 0.5 mg) (Borbély, 1984). Following administration 30 min before bedtime, all treatments caused a marked reduction in activity for the first half of the sleep period whereas flunitrazepam and flurazepam reduced motor activity during the whole of the sleep period compared with placebo. In another study (Borbély et al., 1984) the effect of temazepam (20 mg and 30 mg) on actigraphic sleep and on activity levels after waking was studied, although both doses reduced activity during sleep, there was no difference in activity levels during the first 8 h after waking.

The residual effect of three benzodiazepines was studied in a placebo-controlled trial (Mattmann et al., 1982) with a solid state Swiss-type actigraph. Night time activity was significantly reduced for all treatments (triazolam 0.25 mg, triazolam 0.5 mg, triazolam 1.0 mg, nitrazepam 10 mg) compared with placebo. The overall activity level for a 6 h period the following day was found to be significantly reduced by all treatments except for the triazolam 0.25 mg. The hangover effects of triazolam 0.25 mg, flunitrazepam 1.0 mg and quazepam 15 mg were also evaluated in a single-blind study (Takahashi et al., 2003) by recording mean activity levels in 6 h periods with the ActiTrac (IM Systems, Baltimore, MD, USA) wrist actigraph. Significant effect of treatment was shown as a reduction in activity levels for the afternoon block (12:00-18:00 h) following administration with quazepam compared with flunitrazepam and triazolam. In contrast the effect of triazolam on daytime sleep was measured in a study using the wrist activity monitor (AMI actigraph) in a placebo-controlled trial following triazolam 0.25 mg and 0.5 mg dosing after a simulated night shift (Walsh et al., 1991). Total Sleep Time (TST) as measured by actigraphy was significantly increased for participants taking triazolam compared with placebo.
With regard to non-benzodiazepine hypnotics, the effect of zolpidem 10 mg and 20 mg on activity during sleep was compared (Borbély et al., 1988) using a solid state actigraph in a placebo-controlled study and found that only zolpidem 20 mg, a higher dose than normally prescribed, significantly reduced activity during sleep. No reduction in activity for the first 4 h in the daytime following the sleep period was observed. Moreover, activity during sleep was significantly reduced compared with placebo in a study to examine the effects of zopiclone 7.5 mg taken after a westward flight (Daurat et al., 2000). Further work on the effect of zolpidem 10 mg, zopiclone 7.5 mg and flunitrazepam 1 mg on activity during the night in a placebo-controlled crossover study using the Gaehwiler actigraph was studied (Denise, 2003). Activity levels were significantly reduced after treatment on all medications compared with placebo.

These studies have shown that actigraphy is useful when looking at global effects but no studies have been conducted to assess the subtle time-course of action in the benzodiazepine group of compounds combined with the effect on night-time sleep and following daytime activity.

1.5. Antihistamines

This class of compounds is used for treating allergic reactions including allergic rhinitis and urticaria; as an antiemetic for travel sickness; and for their sedative action. Some of the earlier antihistamines were prescribed for their sedative properties and could be purchased in over the counter sleep remedies.

1.5.1. Mechanism of action

Allergic reactions have traditionally been treated with the antihistamine class of drugs known as H1 receptor antagonists which alleviate the symptoms associated with this condition by blocking H1 histamine receptors. Earlier first generation antihistamines (promethazine, diphenhydramine and chlorpheniramine) pass through the blood-brain barrier and are associated with unwanted side effects which cause reduced alertness, drowsiness and psychomotor impairment (Roehrs et al., 1984; Roth et al., 1987; Hindmarch et al., 1999). These side effects are due predominantly to their ability to cross the blood-brain barrier and thus block central H1 receptors, involved in arousal. Second generation antihistamines (loratadine and cetirizine) however slightly cross the blood brain barrier and unwanted side effects of sedation and impaired function are reduced. Newer 3rd generation antihistamines (fexofenadine, levocetirizine and desloratadine) have since been developed which do not cross the blood-brain barrier and are relatively free from sedative side effects. The first
generation antihistamines vary in their duration of action; diphenhydramine has a plasma half-life of 7 h, promethazine 16-19 h, and chlorpheniramine 23 h. In comparison cetirizine has a plasma half-life of 8.3 h and loratadine 8 h, whereas the third generation non-sedating antihistamines levocetirizine, fexofenadine and desloratadine have half-lives of 6-10 h, 14.4 h and 27 h respectively.

1.5.2. Side effects of antihistamines
The first generation antihistamines cause the most side effects of drowsiness and psychomotor impairment. One such antihistamine is promethazine, which is known to induce central nervous system side effects including psychomotor and cognitive impairment as well as possessing sedative effects. Studies have shown that cognitive and psychomotor performance are significantly impaired by promethazine (Clarke and Nicholson, 1978; Parrott and Wesnes, 1987; Hindmarch et al., 1999, 2001a; Nicholson et al., 2003).

1.5.3. Antihistamines and cognitive and psychomotor function
A review of the different antihistamines and their effect on subjective and objective psychometric tests combined enabled indices to be calculated of their relative effects overall as a Proportional Impairment Ratio (McDonald, et al. 2008). As a comparison the PIR’s for a range of the different generations of antihistamines is shown in Table 1.1.

Table 1.1: Comparative PIR ratios for antihistamines

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd Generation</th>
<th>3rd Generation</th>
<th>PIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>diphenhydramine</td>
<td>cetirizine</td>
<td>levocetirizine</td>
<td>1.616</td>
</tr>
<tr>
<td>chlorpheniramine</td>
<td>loratadine</td>
<td>fexofenadine</td>
<td>1.956</td>
</tr>
<tr>
<td>promethazine</td>
<td></td>
<td>desloratadine</td>
<td>2.207</td>
</tr>
</tbody>
</table>

Comparison the PIR’s for a range of the different generations of antihistamines Proportional Impairment Ratio comparison

1.5.3.1. Objective psychometric tests
The psychometric tests CFF and CRT were used to compare possible impairing effects of levocetirizine 5 mg with diphenhydramine 50 mg (as positive control) and placebo in a 3-way, cross-over, repeated measures, study, with healthy participants (n = 18). Treatment was administered each morning for 5 days. Tests were conducted at 1, 2, 3, 5, 12 and 24 h on Day 1 and repeated on Day 5. There was a significant impairment of CFF following
diphenhydramine administration at 1, 2 and 3 h post dose but no effect following levocetirizine. CRT was not impaired for any treatment although reaction times improved following levocetirizine which the authors (Gandon and Allain, 2002) concluded was due to its slight alerting effect which was consistent with the alertness scale on the Bond and Lader’s VAS.

The effect of fexofenadine high dose 360 mg was compared with promethazine and placebo, in a 3-way cross-over study (Hindmarch et al., 2002). Healthy participants (n = 15) received fexofenadine 360 mg, promethazine 30 mg and placebo and the psychometric tests CFF, CRT and CTT were conducted at 1, 3, 5 and 7 h post dose. All tests were significantly impaired following promethazine administration up to 7 h post dose with respect to placebo however there was no effect on performance following fexofenadine administration. Moreover promethazine also significantly increased the sedation component of LARS up to 7 h.

1.5.3.2. Subjective ratings and sleep questionnaires

Subjective sedation is composed of the mean scores of ratings of “tiredness”, “drowsiness” and “alertness”, as described in full in Section 2.6.2, from the components of LARS. A significant effect of treatment was recorded following promethazine 25 mg treatment up to 6 h post dose compared with placebo with healthy participants (n = 24) feeling sedated, in an eight-way, cross-over study of loratadine (10, 20 and 40 mg) and cetirizine (2.5, 5.0 and 10 mg) with promethazine as the active control (Shamsi et al., 2001).

1.5.4. Antihistamines effect on sleep, actigraphic sleep and daytime activity

1.5.4.1. Sleep

Roth and colleagues (1987) conducted sleep and MSLT studies on healthy participants (n = 16) following administration with loratadine (10 and 40 mg in the morning), diphenhydramine (50 mg three times a day) and placebo in a Latin square cross-over design. There was a 5 day wash out between treatments. PSG was averaged over 2 days of treatment. Daytime sleepiness was measured as subjective sleep with the Stanford Sleepiness Scale and the participants sleep latency of the 5 MSLT’s which were conducted every 2 hours. Diphenhydramine significantly reduced latency to sleep on all MSLT’s except the second at 11:00. The mean of the 5 ratings of sleepiness was significantly different from loratadine and placebo with the diphenhydramine participants being sleepier. There was no significant difference between treatments in nocturnal sleep.
1.5.4.2. Actigraphy

The effect of antihistamines on actigraphic activity comparing the sedative properties of promethazine 25 mg, a first generation antihistamine, with the newer generation of antihistamines cetirizine (2.5, 5 and 10 mg) and loratadine (10, 20 and 40 mg) have been studied using the AMI actigraph (Stanley, 1997). Promethazine was found to induce a significant reduction in activity at 5 h post dose compared with all other drugs tested and placebo. There was also a significant overall increase in reaction time in CRT showing impairment on performance with promethazine compared with the other treatments. Actigraphic sleep however was not recorded.

Activity levels were monitored for 24 h with AMI actigraphs following dosing in a study comparing the effects of fexofenadine 80, 120 and 180 mg, loratadine 10 mg, promethazine 30 mg and placebo. The percentage ‘sleep’ and ‘wake’ for the 24 h period including the sleep period was calculated as was the daytime activity until lights out. During the daytime there was a significant increase in the number of epochs scored as ‘sleep’ with promethazine as well as significant impairments in psychomotor performance (Hindmarch et al., 1999). There was also a significantly higher percentage of sleep for the whole period during promethazine treatment compared with the other treatments although there was no significant difference in the amount of sleep during the night.

The effect of diphenhydramine 50 mg, a first generation sedating antihistamine, was found to increase daytime inactivity in a study using AMI actigraphs comparing sleepiness induced by the drug or sleep restriction (Roehrs et al., 2000). These above studies indicate that whilst actigraphy was designed to investigate ‘sleep’ and ‘wakefulness’ the technology was also useful to assess changes in daytime activity following administration of sedating compounds.

1.6. Antidepressants

Compounds used to treat major depressive disorder (MDD) are known as antidepressants. There are three main groups: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). This thesis is focused on the effect of three SSRI antidepressants paroxetine, fluoxetine and sertraline on depressed patients with the same variables used to assess the effect of sedative hypnotics and antihistamines.
1.6.1. Depression

Hippocrates, 460–377 BC defined depression as “Grief and fear, when lingering, provoke melancholia”. Depression is associated with a multitude of underlying negative symptoms including feelings of low mood and self-esteem, anxiety with a loss of interest in daily activities, loss of appetite, coupled with reduced daytime activity and poor sleep. A ‘triad of symptoms clinically characterizes depression: low or depressed mood, ANHEDONIA and low energy or fatigue’ (Wong and Licinio, 2001). In the context of this thesis it is important to review depression as a disease / disorder as depressed patients suffer symptoms which are alleviated with antidepressants and one of the main focuses of this thesis is the chronic effect of treatment on depression by the psychoactive SSRIs.

1.6.1.1. Depression and sleep

Poor sleep quality is a core symptom of depression with patient complaints of difficulty falling asleep, disturbed sleep, and waking early reported in over 90% of patients (Benca and Peterson, 2008; van Mill et al., 2010; Wichniak et al., 2012). These sleep problems are similar to the side effects caused by SSRI antidepressants as will be discussed later. Indeed in many cases as reported in reviews by (Benca and Peterson, 2008) and (Santos Moraes et al., 2011) depression is often associated with insomnia and can be a precursor to and predictor of depression (Baglioni et al., 2011; Baglioni and Riemann, 2012). Depression is also associated with daytime somnolence and reduced daytime activity as detailed in a review by (Burton et al., 2013), as well as subjective reports of reduced mood and lethargy (Armitage et al., 1997a; Rotenberg et al., 2000; Argyropoulos et al., 2003; Bixler et al., 2005) have all also studied the relationship between objective and subjective sleep of patients and found correlation in the sleep duration, sleep latency and number of awakenings.

Typical complaints of depressed patients are about ‘difficulty falling asleep, frequent awakenings and early morning wakening’ (Wichniak et al., 2012). Alteration in the sleep-wake cycle e.g. loss of job, may ‘desynchronize many endogenous rhythms which in turn may lead to depressed state hypothesis’ according to Monteleone and Maj, (2008).

The effect of depression on sleep architecture and the effect of the SSRI antidepressant treatment in particular on the sleep architecture of depressed patients have been thoroughly investigated in reviews (Sharpley and Cowen, 1995; Argyropoulos and Wilson, 2005; Wilson and Argyropoulos, 2005; Holshoe, 2009; Mendlewicz, 2009). Studies have shown that depression is associated with increased sleep latency, increased sleep disruption and fragmentation with more WASO, REM latency and changes in REM distribution as well as
reduction in slow wave sleep in depressed patients compared with healthy controls (Rotenberg et al., 2000; Argyropoulos et al., 2003; Tsuno et al., 2005; Benca and Peterson, 2008; Quera-Salva et al., 2010). The effect of depression on sleep architecture was reviewed in Winokur et al. (2001) and tabulated in Figure 1.12.

<table>
<thead>
<tr>
<th>TABLE 1. Patterns and polysomnographic features of sleep in patients with clinical depression</th>
</tr>
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<tbody>
<tr>
<td>NREM*</td>
</tr>
<tr>
<td>Decreased slow-wave sleep</td>
</tr>
<tr>
<td>Decreased delta sleep in NREM-1 vs. NREM-2</td>
</tr>
<tr>
<td>REM</td>
</tr>
<tr>
<td>Reduced REM latency</td>
</tr>
<tr>
<td>Increased REM during first half of night</td>
</tr>
<tr>
<td>Increased REM density</td>
</tr>
<tr>
<td>Sleep continuity</td>
</tr>
<tr>
<td>Increased sleep latency</td>
</tr>
<tr>
<td>Increased wake time</td>
</tr>
<tr>
<td>Early morning awakenings</td>
</tr>
</tbody>
</table>

*NREM, non-rapid eye movement; REM, rapid eye movement.

Figure 1.12: Sleep parameters of depressed patients (Winokur et al., 2001)

The comparison of sleep architecture of healthy participants and depressed patients is tabulated in Figure 1.13. Studies have produced conflicting results however, differences in PSG between healthy participants and depressed patients were found but depressed patients subjective sleep did not correlate as well with PSG sleep as the healthy controls (Rotenberg et al., 2000). It was reported that depressed patients underestimated the number of awakenings. Whereas a study by Argyropoulos et al., 2003 showed that depressed patients subjective sleep did correlate with objective sleep specifically in TST and SOL.

Depression is linked with insomnia which has been suggested is a risk factor for depression. A study of insomniacs and depressed patients reported that the only differences between their sleep was the latency and % of REM sleep (Benca and Peterson, 2008). Therefore it has been postulated that to improve sleep in depressed patients would hopefully improve depression. Such studies have focused on PSG recordings of single or multiple nights however, less research has investigated the course of depression longer term and the effect on sleep in ambulatory field conditions. An actigraphy study of motor activity during the day and at night showed that depressed hospitalised in-patients who had subjectively rated poorer sleep using the Pittsburgh Sleep Quality Index PSQI questionnaire recorded more nocturnal activity than patients who rated their sleep good (Lemke et al., 1999). It was suggested that
although PSG may be best for measuring objective sleep, an actigraph might be useful for an extended length of time.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sleep variables in healthy subjects and in depressed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Healthy subjects</td>
</tr>
<tr>
<td>Nights</td>
<td>20</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>412 (43)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>0.98 (0.3)</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>3.3 (2.1)</td>
</tr>
<tr>
<td>Slow wave sleep (%)</td>
<td>14.5 (6.5)</td>
</tr>
<tr>
<td>SWS, 1 cycle (min)</td>
<td>26.2 (12.3)</td>
</tr>
<tr>
<td>SWS, 2 cycle (min)</td>
<td>22.6 (13.2)</td>
</tr>
<tr>
<td>SWS, 3 cycle (min)</td>
<td>6.6 (8.7)</td>
</tr>
<tr>
<td>SWS, 4 cycle (min)</td>
<td>4.8 (8.6)</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>89.4 (33.7)</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>19.3 (7.7)</td>
</tr>
<tr>
<td>REM sleep 1 cycle (min)</td>
<td>7.9 (4.5)</td>
</tr>
<tr>
<td>REM sleep 2 cycle (min)</td>
<td>19.7 (9.5)</td>
</tr>
<tr>
<td>REM sleep 3 cycle (min)</td>
<td>22.4 (11.5)</td>
</tr>
<tr>
<td>REM sleep 4 cycle (min)</td>
<td>23.0 (12.3)</td>
</tr>
<tr>
<td>EM density, 1 cycle (min)</td>
<td>2.0 (2.3)</td>
</tr>
<tr>
<td>EM density, 2 cycle (min)</td>
<td>3.6 (1.9)</td>
</tr>
<tr>
<td>EM density, 3 cycle (min)</td>
<td>5.1 (2.6)</td>
</tr>
<tr>
<td>EM density, 4 cycle (min)</td>
<td>5.4 (3.2)</td>
</tr>
<tr>
<td>Awakening</td>
<td>1.0 (1.0)</td>
</tr>
</tbody>
</table>

*P < 0.05. 
**P < 0.02. 
***P < 0.01.

Figure 1.13: Sleep variable comparison between healthy and depressed patients (Rotenberg et al., 2000)

A review of studies (reviewed in Kronfeld-Schor and Einat, 2012) suggested that there is a link between circadian rhythm, sleep and depression as it was shown that a large percentage of the general population with sleep problems were depressed. A further review by Monteleone et al. (2011) highlighted the links between circadian rhythms in depression with changes in mood and sleep-wake cycle. Activity levels were inversely correlated to severity of depression symptoms, patients experienced a significant worsening of depressed mood in the morning compared to the evening although their activity levels were significantly higher in the morning compared to the evening according to Lemke et al. (1997).

The main treatment of MDD is drug therapy and a review to explain the current rise in prescriptions was conducted by Moore et al. (2009). The total number of prescriptions dispensed in 2012 was 50,167,201 for all types of antidepressants up 7.5 per cent on 2011 (when totals were 46,677,813). The cost of antidepressant prescription was £211,145,435 in 2012. Health and Social Care Information Centre, Prescriptions Dispensed in the
Community. Statistics for England (2002-2012). The World Health Organisation predicts that by 2020, depression will be the second leading cause of disability throughout the world.

Clinical trials provide a standardised controlled environment in which to study the acute effect of a drug reviewed in Kirsch et al. (2008) and Sussman, (2007), and have often been used to assess the effects of different classes of antidepressants on sleep reviewed by Mayers and Baldwin, (2005), including the SSRIs.

1.6.2. Selective serotonin reuptake inhibitors (SSRIs) and treatment of depression

Selective serotonin reuptake inhibitors (SSRIs) are widely recognised as treatments for mild to moderate depression. There is evidence to suggest from various reviews that this group of antidepressants affect PSG sleep in laboratory settings (Wilson and Argyropoulos, 2005; Mendlewicz, 2009; Holshoe, 2009) (Table 1.2). Less work however has investigated the long term effect on sleep and activity in ambulatory field conditions with antidepressants (Kasper et al., 2010). The effect of the respective SSRIs on PSG sleep variables is shown in Table 1.2 in comparison with the effect of depression on sleep, data from (Winokur et al., 2001).

Some antidepressants such as the TCAs promote sleep reviewed in Mayers and Baldwin. (2005) whereas the SSRIs are associated with reductions in sleep efficiency, increased latency and sleep disruption. Most antidepressants affect the distribution of REM throughout the night (reviewed in Wilson and Argyropoulos, 2005). The 3 SSRIs listed in Table 1.2 have slightly different profiles and mechanisms of action as well as side effects.

Table 1.2: Effect of SSRI antidepressants paroxetine, fluoxetine and sertraline on sleep variables

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Paroxetine 20 mg/day</th>
<th>Fluoxetine 20 mg/day</th>
<th>Sertraline 50 mg/day</th>
<th>Depressed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Slow wave sleep</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>REM</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>REM Latency</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

The effect of antidepressant treatment and direction of change on sleep variables is shown by the arrows, ↑ = increased, ↓ = decreased, for the antidepressants paroxetine, fluoxetine and sertraline compared with the effect of depression on sleep variables in patients. The SSRI antidepressants reduce REM and increased REM latency (Winokur et al., 2001).
1.6.3. Mechanism of action of selective serotonin reuptake inhibitors (SSRIs)

Lam. (2008) proposed that ‘an ideal antidepressant should combine high short-term clinical efficacy for acute phase treatment with good long-term efficacy and tolerability for the maintenance phase’. Paroxetine, fluoxetine and sertraline belong to the complex group of antidepressants known as the selective serotonin reuptake inhibitors SSRIs which according to (Hiemke and Härter, 2000) have a ‘high affinity to serotonin reuptake sites, low affinity to noradrenaline sites’. However, they have varying affinities for these sites with differing lengths of action which might explain the efficacy differences between them. Fluoxetine has a half-life up to 4 days, whereas paroxetine and sertraline both have comparatively short half-lives of 1 day, moreover, fluoxetine has an active metabolite which continues to be active for 7-15 days whereas sertraline has a low activity metabolite of 66 h, and paroxetine has no active metabolite (Preskhorn, 1996; Nutt et al., 1999; Vaswani et al., 2003).

According to the literature however, four weeks or more of treatment are required to reach steady state following commencement of treatment with fluoxetine, compared with 7-14 days for sertraline and 10-14 days for paroxetine due to their half-lives (Preskhorn, 1996; Hiemke and Härter, 2000). Moreover, dosing with fluoxetine with its active metabolite and extended half-life, can allow for missed or sporadic doses as steady state levels are still reached according to (Preskorn, 1994; Preskhorn, 1996). With regards to wash-out time, worth considering when choosing an SSRI, fluoxetine due to the long half-life of its metabolite is slower to be cleared, taking several weeks. Whereas, the rapid clearance of sertraline and paroxetine of 95% in less than 1 week could therefore account for the higher numbers of reports of discontinuation symptoms associated with rapid withdrawal (Price et al., 1996; Haddad and Anderson, 2007). This might therefore lead to the assumption that for fluoxetine, whilst taking longer to reach maximal effect, having a slower decline also decreases severity of withdrawal and successful end of treatment.

1.6.4. Side effects of selective serotonin reuptake inhibitors (SSRIs)

Nausea, disturbed sleep, dry mouth, changes in appetite and sexual dysfunction are all reported side effects of this group of antidepressants (Ferguson, 2001) however, compared with the other main group of prescribed antidepressants the TCAs, they are well tolerated and do not commonly cause the side effect of daytime sedation which is common to the TCAs. Although malaise and tiredness are some of the most frequently reported side effects in the first month of treatment (Mackay et al., 1999).
It is estimated that up to 44% patients stop taking medication within the first 3 months of treatment due to the side effects (Bull et al., 2002); and between 20-50% are non-compliant and stop taking medication for short periods of time (Rosenbaum et al., 1998). Neither the incidence of adverse side effects nor the use of concurrent medication has been included in this thesis.

1.6.5. Cognitive and psychomotor function and selective serotonin reuptake inhibitors (SSRIs)

The DSM-IV is a coding system used for the diagnosis of depression and comprises 9 symptoms mainly dealing with mood and according to Kerr and Hindmarch, (1996) do not stress the cognitive aspects of major depression although ‘impairment of psychomotor speed and disruption of information processing’ are ‘significant features of major depressive illness’, with 70% of elderly having ‘measurable cognitive deficits’. The symptoms that deal with the cognitive or psychomotor aspects are ‘diminished ability to think or concentrate’ and ‘psychomotor agitation or retardation’. Fava, (2003) also stated that ‘fatigue and cognitive/executive dysfunction are common symptoms in patients with MDD which may either persist due to the disorder despite effective antidepressant treatment or emerge as a side effect of the antidepressant treatment itself’, (MDD = major depressive disorder).

Cognitive and psychomotor retardation manifested in depression has been recognised for many years according to (Widlöcher, 1983) and is associated with depressed mood and melancholia. In his review into the ‘effects of antidepressants on cognitive function’ (Amado-Boccara et al., 1995) stated that it should be considered that there are less adverse effects in long-term antidepressant treatment administration to depressed patients compared with short term effects in healthy volunteers. Also that clinical improvement usually appears in the third week of treatment so to measure improvement in performance in depressed patients might be an indicator of improvement in depression. Although change in depressed mood is diagnosed through questionnaires such as Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD) and ZUNG, changes in psychomotor agitation or cognitive retardation may be measured by changes in performance of cognitive and psychometric tests. In recent reviews (Lee et al., 2012) concluded that cognitive functioning was reduced in patients in their first episode of depression and that early recognition and treatment may alleviate relapse and (Marazziti et al., 2010) that impairments in attention and executive function are key disturbances of MDD which occur in all ages. The tests used to determine the effect of SSRIs on objective cognitive effects in the study conducted in Chapter 5 were CFF and CRT.
1.6.5.1. Objective psychometric tests Critical Flicker Fusion (CFF) and Choice Reaction Time (CRT)

It is important to evaluate impact of cognitive function, as patients age their cognitive ability deteriorates so it is important to consider which antidepressants to use when treating the elderly, according to Variend and Gopal, (2008) some elderly patients develop their first depressive episode as late-onset depression so it is important to prescribe medications that will not have a negative effect on everyday activities. Lane and O’Hanlon, (1999) discuss how SSRIs might affect the depressed elderly and various factors to consider when associated with the cognitive decline related to aging and suggest that more studies are required to assess the effect on this relevant population.

The objective psychomotor tasks relevant to ‘psychomotor function and psychoactive drugs’ (Hindmarch, 1980), the Critical Flicker Fusion (CFF) (Hindmarch, 1982) and Choice Reaction Time (CRT) (Sherwood and Kerr, 1993) were used in Chapter 5 to determine the effect of 12 weeks treatment, on cognitive function. The CFF is a measure of behavioural arousal, with a decrease in threshold indicating an impairment of information processing, and the CRT is a measure of sensorimotor performance (Hindmarch, 1998). These tasks are useful, sensitive, reliable, valid and commonly used tests (Sherwood and Kerr, 1993) which are sensitive to changes in the brain of integrative functioning and reaction time and have been used extensively in research into the effects of CNS drugs.

In single dose acute studies with healthy volunteers, the SSRIs assessed in the study reported in Chapter 5 have been extensively studied in healthy participants and showed improved cognitive function. The comparable behavioural toxicity value of a range of antidepressants, including SSRIs and TCAs was calculated by Hindmarch, (1999) and Kerr and Hindmarch, (1996) from a number of individual healthy volunteer studies by quantitative comparison of administration of a single dose compared with placebo, the relative effect sizes were reported in comparison with placebo. The individual studies with single dose effects were reported in Hindmarch and Harrison, (1988) for paroxetine 30 mg in females (n = 10) mean age 38 years, Hindmarch, (1987) for fluoxetine 40 mg in females (n = 8) mean age 37 years and in Hindmarch and Bhatti, (1988) for sertraline 100 mg in females (n = 10) mean age 34 years.

CFF was significantly elevated for all treatments compared with placebo, which indicated improvements in cognitive function and increased arousal following administration. Sertraline (100 mg/day) showed the greatest increase followed by paroxetine (30 mg/day) and fluoxetine (40 mg/day). The relative values for the medications were documented as paroxetine 1.153, fluoxetine 0.895 and sertraline 1.769, with these compounds producing a
significant elevation of CFF compared with zero for placebo, although the doses were higher than those administered to the patients in Chapter 5 study (Kerr and Hindmarch, 1996; Hindmarch, 1999).

Data from several healthy volunteer studies have provided similar relative drug effect values for CRT, for the medication were documented as paroxetine (30 mg/day) 0.276, fluoxetine (40 mg/day) 0.432 and sertraline (100 mg/day) 0.802 with a significant ‘quickening’ for sertraline and paroxetine compared with zero for placebo suggesting that they have an arousing effect (Kerr and Hindmarch, 1996; Hindmarch, 1999). Although these healthy volunteer studies were not conducted at the same time as double-blind crossover studies, comparisons can be compared, as these are relative effect sizes. What is evident is that the SSRIs have a stimulating effect improving cognitive function which can be measured with the CFF and CRT, and that these tasks, loosely related to driving ability, may be useful in determining driving impairment or improvement. This aspect was also discussed by Brunnauer et al. (2006) who showed an association between driving, psychomotor tests and antidepressants in depressed patients and indicated that SSRIs are preferable to TCAs.

The CFF and CRT were 2 of the tests applied in the review by Amado-Boccara et al. (1995) to compare the effects on cognition of various antidepressant medications. It was concluded that in similar doses to the study in Chapter 5, in single dose healthy volunteer studies, the antidepressants paroxetine and sertraline have a ‘positive cognitive impact’. Paroxetine (20 mg/day) raised CFF threshold and decreased reaction time on CRT, that sertraline (50 mg/day) significantly increased CFF threshold but fluoxetine had no cognitive effect. The long term effects of the medications administered to depressed patients were not reported.

There are relatively few studies which have reported on the chronic long term effects of the SSRI antidepressant treatments assessed in Chapter 5 on the CFF and CRT cognitive and psychomotor tests on depressed patients. Gorenstein et al. (2006), in a study comparing chronic use of sertraline and fluoxetine with other antidepressants in depressed patients treated for > 6 months did ‘observe some impairment at their therapeutic dose’ in reaction times on a similar test to CRT, the visual Foundations I, PSS reaction task, but this was not significant.

A study comparing fluoxetine (20 mg/day) with amitriptyline (75 mg/day), in depressed elderly patients (n = 54) on stable dosing, Kerr et al. (1993) reported that CFF was significantly improved with increased thresholds following fluoxetine treatment from baseline for 6 weeks of medication whilst depression scores were significantly reduced with
both MADRS and HAMD scores. CRT was also significantly improved by week 1 following fluoxetine treatment compared with amitriptyline with a reduction in reaction times. In a similar study comparing dothiepin (75 mg/day) and fluoxetine (20 mg/day) in depressed patients (n = 64) mean age 44, study duration of 6 weeks, Fairweather et al. (1999) found significantly greater improvement in CFF scores following treatment with fluoxetine than in patients treated with dothiepin, no reaction tests were conducted.

A study from Fairweather et al. (1993) in depressed elderly (n = 60) (mean age 70) compared fluoxetine (20 mg/day) with amitriptyline (75 mg/day) over 6 weeks found that there was a significant improvement in CFF scores from patients on fluoxetine from week 1 compared with amitriptyline and a significant reduction in reaction times with CRT. Improvement was also reflected in the HAMD and MADRS scores and quality of sleep from LSEQ variables although not significantly different from amitriptyline.

Hindmarch and Kerr, (1994) administered paroxetine (20 mg/day increasing to 30 mg/day) over 6 weeks to depressed patients (19-65 years) following 1 week placebo washout, CFF threshold was significantly elevated after 2 weeks of treatment and the improvement was maintained for the study duration, CRT was not conducted. Ravindran et al. (1995) compared placebo, and dose escalated treatments with sertraline and desipramine in mild to moderately depressed patients (n = 103) (18 – 65 years) over 6 weeks treatment following 2 weeks placebo wash out. Although there was a trend for improvements in CRT following sertraline administration it was not statistically different from placebo or desipramine.

With respect to paroxetine Alexander et al. (1997) conducted a study in depressed patients compared with dothiepin in an escalated dose regime over 6 weeks. Whilst the HAMD scores were significantly reduced for both medications, there were significant differences between paroxetine and dothiepin recorded for CFF threshold with paroxetine producing a significant improvement in the first 2 weeks following paroxetine treatment. Sleep was also rated significantly better on QOS (LSEQ) compared with dothiepin, but there was no significant difference in reaction times between the treatments.

It is important to consider cognitive side-effects of antidepressants in depressed patients and particularly in the elderly as the consequences of negative cognitive and behavioural side effects can be exacerbated with the likelihood of reduced compliance of treatment and increased accident and injury risk. The older generation of antidepressants the TCAs have known adverse side effects including a sedative action and the comparison studies discussed
above with some of the TCAs have shown that the SSRI antidepressants used in the current study have more positive outcomes in terms of cognitive and psychometric tests.

Although the tests used in the current study have not been correlated with driving performance, according to Verster and Roth, (2012), a tenuous link exists between SSRIs in general and impaired driving ability in depressed patients (Brunnauer et al., 2006; Wingen et al., 2006), and Ravera et al. (2012) commented that in an epidemiological review of motor accidents that there was a ‘statistically significant association with SSRIs’. It was concluded that the impairment seen in driving performance in depressed patients could be attributed to ‘residual depressive symptoms’ rather than the effect of the antidepressant (Wingen et al., 2006). Nevertheless Ramaekers, (2003) suggested that psychometric tests are important as they can provide an early indication and direction of action. They are important measures in regards to drugs that might interfere with CNS activity and impact on safety when patients are taking daily medication. Moreover, although tests are a mere snapshot at any one time-point, to measure response over a long period of time would give an indication of the direction and stability of change and as depressed patients are cognitively impaired treatment should improve and not exaggerate symptoms.

1.6.5.2. Subjective ratings and depression questionnaires

Few studies have reported on the daytime sedating effect of SSRIs, and as SSRIs are known to be activating compounds (reviewed in Wichniak et al., 2012), less daytime sedation as treatment progresses is expected. However some patients do experience ‘daytime sleepiness’ but whether this equates to sleepiness or fatigue has not been determined (reviewed in Wilson and Argyropoulos, 2005). A specific adverse event which suggests daytime sedation is reported as somnolence (Fava et al., 2000, 2002). Additionally there were almost 3 times as many reports of sedation occurring in the first month following paroxetine treatment than there were for fluoxetine or sertraline in a report on the ‘comparability of tolerability’ (Mackay et al., 1999). The questionnaires used to determine the subjective effect of SSRIs on daytime sedation are LSEQ and LARS and the MADRS and HAMD questionnaires are used to determine depression severity and progress and also contain items related to sleep. The MADRS and HAMD are physician administered questionnaires and a similar self-completion questionnaire is the ZUNG.

The LSEQ is an effective tool used to assess the subjective effects of a psychoactive compound on quality of sleep and related behaviour; full details are in Section 2.6.1. The LSEQ has been shown to be an effective assessment tool when used to quantify subjective sleep effects (Parrott and Hindmarch, 1980; Hindmarch, 1984; Zisapel and Laudon, 2003).
Two of the most recognised and widely used diagnostic assessments by clinicians in determining depression severity are the depression rating scales of Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD). Changes in these scales are used to measure the effect of treatment and improvement in the symptoms of the disease. Studies have shown that there is good correlation between the 2 scales (Kearns et al., 1982; Carmody et al., 2006). The MADRS is reported to be more sensitive overtime to changes in symptoms (Mulder et al., 2003) and comparable to identifying placebo to drug differences than HAMD (Khan et al., 2002). Moreover the MADRS was preferred being better for estimating depression symptoms and for clinical trials (Carmody et al., 2006). The HAMD-17 was developed for inpatients and contained several items less suitable for out-patients such as ‘lack of insight’ and ‘agitation’ interpreted as anxiety and was not as useful for the GENDEP study (Uher et al., 2008). The MADRS questionnaire was related to the mental aspects of depression such as sadness, tension and pessimistic suicidal thoughts. Whereas the emphasis of the HAMD was related to psychomotor symptoms and somatic mood, such as work and activities, as well as insomnia, retardation and mood. However, studies have shown that there is good correlation between the 2 scales (Kearns et al., 1982; Carmody et al., 2006)

The criteria for improvement in depression symptoms with the MADRS and HAMD was defined as the ‘time to onset’, the first time point at which a ‘statistically significant and a clinically meaningful difference’ occurs when there is a reduction of ≥ 20% from baseline for the first time, and ‘response to treatment’ when there is a ≥ 50% reduction in the MADRS and HAMD scores (Thompson, 2002). In order to compare the outcome scores for the 2 scales comparable scores have been suggested by (Müller et al., 2000; Müller, 2003) as shown in Figure 1.14.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Suggested severity gradations of the HAMD-17 and the MADRS in moderately to severely depressed inpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recovered</td>
</tr>
<tr>
<td>HAMD-17</td>
<td>0–7&quot;</td>
</tr>
<tr>
<td>MADRS</td>
<td>0–5&quot;</td>
</tr>
</tbody>
</table>

Figure 1.14: Comparable scores for MADRS and HAMD (Müller et al., 2000; Müller, 2003)

1.6.5.3. Subjective sleep questionnaires Leeds Sleep Evaluation Questionnaire (LSEQ) and Line Analogue Rating Scale (LARS)

Studies have found similar improvements as those seen in HAMD or MADRS with LSEQ. In a study comparing fluoxetine (20 mg) (n = 51) with dothiepin (120 mg) (n = 56) it was
reported that over 6 weeks of treatment, following 1 week placebo run-in, newly diagnosed patients were randomised to be treated with fluoxetine or dothiepin (Stephenson et al., 2000). All patients improved not only their LSEQ scores for GTS, QOS and AFS scores but also the HAMD and MADRS depression rating over the 6 weeks of treatment for either fluoxetine or dothiepin, indicating that as patients became less depressed their sleep improved. There was a greater improvement in GTS for the patients treated with fluoxetine, whereas the patients treated with dothiepin felt drowsier.

A trend in favour of a sleep improvement with sertraline treatment (50 mg/day) (n = 88) was shown in a randomised study of newly diagnosed depressed patients compared with fluoxetine (20 mg/day) (n = 79), during the 18 and 24 weeks analysis of treatment on the LSEQ (Sechter et al., 1999). This outcome corresponded with the significant improvement in HAMD scores, however no data or different aspects of the LSEQ were reported. Whilst Bennie et al. (1995) found similar improvements in both LSEQ components and HAMD sleep disturbance in a double-blind study in depressed patients treated with fluoxetine (20 mg/day) (n = 140) or sertraline (50 mg/day) (n = 140). Patients treated with sertraline experienced less difficulty in GTS, but patients treated with fluoxetine felt better on AFS at the end of the 6 week study.

A 6-week double-blind study was conducted in 100 depressed patients (final numbers not reported) treated with paroxetine (20 mg/day) or dothiepin (75 mg/day) with escalated dosing (Alexander et al., 1997). The overall HAMD scale showed that both treatments produced a significant improvement at week 6, with a greater improvement in the patients treated with paroxetine. Moreover the sedative action of dothiepin was more evident in the elevated scores for GTS indicating that patients got to sleep quicker, whilst the elevated scores for QOS and AFS scores for paroxetine indicated better sleep and improved waking.

Improvements in subjective sleep have also been reported following paroxetine treatment (Dorman, 1992; Kerr et al., 1997). Newly depressed patients were randomised to receive paroxetine (20 mg) or dothiepin (75 mg) over 5 weeks following 1 week placebo run-in (Kerr et al., 1997). Results showed that although both treatments improved GTS, QOS and AFS, there was a significant difference between treatments for GTS with dothiepin, a TCA, treated patients getting to sleep quicker, and a trend for greater improvement in QOS with paroxetine. On the other hand, in a 6 week double-blind study in 60 depressed unipolar patients treated with paroxetine (n = 24) (15 mg/day) or mianserin (n = 25) (30 mg/day) reportedly slept better (Dorman, 1992). The HAMD for both groups showed improvement in the depression scores although there was a greater improvement in the paroxetine treated
patients from week 2 onwards. Results for the LSEQ sleep moreover showed that patients treated with paroxetine reported significantly improved GTS, QOS and AFS compared with mianserin.

Studies conducted on the effect of fluoxetine on LSEQ components (Fairweather et al., 1993; Stephenson et al., 2000) have reported on improvements on depressed patients, following fluoxetine treatment. Fairweather et al. (1993) compared the effect of fluoxetine (20 mg/day) and amitriptyline (75 mg/day) on elderly depressed patients (n = 66) for 6 weeks. Significant improvements were recorded for the MADRS and HAMD scores with both treatments relieving depression. With regards to LSEQ both treatments improved QOS and AFS. Although GTS improved for both treatments it was significantly shorter with patients treated with amitriptyline compared with fluoxetine at week 1, which is likely to be the effect of its sedating properties. Depressed patients were randomised to receive fluoxetine (20 mg/day) (n = 50) or dothiepin (150 mg/day) (n = 56) in a randomised double-blind study for 7 weeks reported by (Stephenson et al., 2000) MADRS and HAMD showed that depression symptoms were equally relieved by both treatments at the end of the study; however GTS was improved with fluoxetine treatment in the first week compared with dothiepin, QOS improved gradually for both treatments but there were more reports of disturbed sleep from the dothiepin treated patients.

Sertraline was compared with fluoxetine (Aguglia et al., 1993) in an 8 week double-blind study in 88 patients. Patients with baseline HAMD ≥18 were randomised to receive fluoxetine (20 mg/day) (n = 40) or sertraline (50 mg/day) (n = 48). As discussed in Section 1.6.5.5 significant improvements in the sleep items for HAMD with patients treated with fluoxetine or sertraline were also reported after 56 days compared with baseline which was comparable to the general improvements in LSEQ scores for both treatments.

To record the efficacy of a novel antidepressant agomelatine (Kasper et al., 2010) conducted a randomised double-blind 6-week study comparing depressed patients, with HAMD scores ≥ 22, treated with sertraline (50-100 mg/day) (n = 157) to patients treated with agomelatine (25-50 mg/day) (n = 150). LSEQ questionnaires were completed at baseline then at 2, 4 and 6 weeks. HAMD insomnia items significantly decreased between baseline and final visit indicating an improvement in sleep. There was a greater improvement in patients treated with agomelatine than sertraline at week 2. Similar significant outcomes were recorded for the LSEQ items GTS and QOS as well as AFS and BFW for both treatments with agomelatine again showing a significantly faster response of action at week 2. Improved scores were observed in the agomelatine treated patients at week 6 but the difference
between treatments was not significant. The virtue of the use of the LSEQ for showing improvements in subjective sleep following SSRI treatment, although not sedative in action, is highlighted in a review of comparable studies which shows that in depressed patient studies the SSRIs in the current study all showed improvement in LSEQ variables after a number of weeks (Zisapel and Laudon, 2003).

The LARS has a series of rating scales and is employed as a measure of the subjective effects of psychoactive drugs. The mean components of ‘tiredness’, ‘drowsiness’, and ‘alertness’, presented among several distracter scales, are assessed as a measurement of perceived sedation (Hindmarch and Gudgeon, 1980).

Few studies however have used this scale to indicate daytime sedating effect of SSRIs effects in antidepressant studies. The SSRI paroxetine (20 mg) and noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine (15 mg/30 md nocte) induced healthy participant self-assessed daytime sedation compared with placebo the day following dosing in a study comparing their effects on car driving (Ridout et al., 2003a). Dothiepin (75 mg) a TCA induced self-assessed sedation compared with the SSRI fluvoxamine (50 mg and 100 mg) and placebo in a healthy participant study (Fairweather et al., 1996; Stanley and Hindmarch, 1997). Depressed elderly patients (n = 66) became subjectively less sedated over 6 weeks of medication with either fluoxetine (20 mg/day) or amitriptyline (75 mg/day), although fluoxetine treated patients were significantly less sedated than patients treated with amitriptyline during the first two weeks (Fairweather et al., 1993).

1.6.5.4. Depression questionnaires Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD)

The Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD) are valuable questionnaires to assess the progress of treatment and can provide as estimate of the onset of improvement as well as remission. There are various reports on the time taken to the onset of effect of SSRIs using the HAMD from 3 days (Parker et al., 2000) to 2 weeks, with 80% of studies reporting a greater response in weeks 1 and 2 than later, (Mitchell, 2006). Although Stassen et al. (1997) postulated that abrupt response might be a placebo response, onset of effect was defined by Wade et al. (2009) as a 20% reduction in baseline scores after 2 weeks using the HAMD and ZUNG scales. In a systematic review of 28 trials Taylor et al. (2006) concluded that SSRIs appear to begin to have an effect in the first week of treatment with a ‘likelihood of achieving a 50% reduction’ in HAMD score as confirmed by Katz et al. (2004), although ‘improvement continues at a decreasing rate for at least 6 weeks’.
Other review studies showed that using the MADRS and HAMD the ‘time to onset’ and ‘response to treatment’ occurred within the first 4 weeks of treatment when comparing various SSRIs (Wade et al., 2009; Thompson, 2002).

Similarly other studies reported significant improvements in HAMD and LSEQ following long term administration with sertraline or fluoxetine to depressed patients over 24 weeks and reported that there was no significant difference between treatments (Sechter et al., 1999). Significant improvements were also reported in a randomised patient study in primary care which determined that following a rapid improvement in symptoms after 4 weeks all treatments, (paroxetine, sertraline and fluoxetine) continued to be ‘equally efficacious’ and the sleep item in the Medical Outcomes Study scale (MOS) showed equal improvements over 3 months of treatment (Kroenke, 2001).

A study comparing the efficacy and tolerability of paroxetine, fluoxetine or placebo on MDD patients (Fava et al., 1998) found no significant difference in 21-item HAM D, although all patients improved. However, there were more reports of adverse events following paroxetine or fluoxetine treatment compared with placebo during the 12 weeks. A further study by (Fava et al., 2000) on paroxetine 20 mg day, sertraline 50 mg/day and fluoxetine 20 mg/day treatments in a trial with depressed patients and over 6 weeks, with up titration if necessary and found that all treatments produced significant improvements in the HAMD scores from baseline to endpoint. In a similar study (Fava et al., 2002) not only found significant improvement in overall HAMD but also in the sleep disturbance items with patients reporting less insomnia.

1.6.5.5. Depression questionnaires Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD) sleep items

The HAMD and MADRS both have questions related to sleep and these are useful when comparing PSG studies for subjective effects of medication. The HAMD items are related to the occurrence of insomnia early, middle or late, with early insomnia related to patients having difficulty in falling asleep, similar to LSEQ GTS. Trivedi et al. (1999) showed that HAMD sleep items conversely improved in a study of fluoxetine whilst PSG sleep was disrupted, study reported in Section 1.6.6.

The MADRS sleep item is related to the amount of sleep and how fragmented it is. Lader et al. (2005) reported that the SSRIs citalopram (20 to 40 mg/day) and escitalopram (10 to 20 mg/day) significantly improved MADRS sleep Item 4 compared with placebo at 6 weeks of
treatment with depressed patients (n = 1321). In the study, a significant improvement in Item 4 score in patients was reported from ≥ 4 at the start of the study to < 3 at 4 weeks and < 2 at 8 weeks compared with placebo, assessments were conducted at 1, 2, 4, 6 ad 8 weeks.

1.6.5.6. ZUNG Depression Inventory

The ZUNG Depression Inventory questionnaire was designed by William Zung (ZUNG, 1965) and published in 1965 to be used as a self-completion tool for assessing depression in patients, on the basis that it should be ‘short and simple, quantitative rather than qualitative’. It was felt at the time that the scales that were available were too lengthy and time consuming for depressed patients and that they were not completed by the patient. The ZUNG questionnaire consists of 20 sentences which the patient completes giving a value between 1 and 4, depending on whether the sentence is worded positively or negatively. The values, which relate to the current time, are recorded as 1 for ‘a little of the time’, 2 ‘for some of the time’, 3 for ‘a good part of the time’ and 4 for ‘most of the time’. The higher the score the more depressed is the patient with 80 being the maximum score. The score ranges relate to the values 20-44 normal range, 45-59 mildly depressed, 60-69 moderately depressed and 70 and above severely depressed.

The ZUNG depression scale was utilised in a study to compare the effect of treatment in depressed patients (Stassen et al., 1997). Although scores were not reported, 93% of patients (n = 44) treated with oxaprotiline, and 98.3% of patients (n = 58) treated with amitriptyline had improved by day 28. Improvement onset of was defined as a reduction of baseline scores by 20% at day 28. There was more than 90% concordance in a comparison between HAMD observer rated and Zung patient rated assessments.

1.6.5.7. Cognitive Failures Questionnaire (CFQ)

According to the literature depression is associated with negative thoughts and that depressed patients report deficits in cognition and concentration which result in lapses of memory and impaired attention. The Cognitive Failures Questionnaire (CFQ) was developed by Broadbent et al. (1982) to provide a measure of the frequency of patient’s errors when completing everyday tasks, and consisted of 25 questions associated with the 3 categories of memory, attention and psychomotor function.

Little commercial data is available on CFQ use in pharmacological studies so for comparable baseline values other studies were reviewed. A study of SAD patients versus controls by Michalon et al. (1997) gave baseline values of 38 for controls and 57 for SAD patients. CFQ
scores of 38 for controls and 59 for depressed patients was recorded in a study of depressed and normal UK military personnel (Farrin et al., 2003). These CFQ values provide a basis for evaluating improvement in symptoms in the pharmacological studies.

A study comparing the effects of fluoxetine and dothiepin on CFQ and other cognitive variables on depressed patients (n = 84) was conducted with a series of assessment visits over 6 weeks of treatment by Fairweather et al. (1999). Patients were randomized to receive either fluoxetine (20 mg/day) or dothiepin (75-150 mg/day). Assessments also included LSEQ and HAMD. At baseline Day 0 the CFQ scores were 51 and 56 for fluoxetine and dothiepin respectively, following 6 weeks of treatment scores were 42 and 47 respectively. Unfortunately the HAMD results were not reported although it was stated that 36 patients responded to treatment with a 50% reduction in HAMD, however the CFQ results included all patients.

1.6.6. Effect of selective serotonin reuptake inhibitors (SSRIs) on sleep

The group of SSRI antidepressants do not improve objective sleep, indeed they may actually induce a negative effect on sleep in general, by increasing sleep latency, increasing REM onset latency, reducing REM and disrupting sleep as described in reviews of healthy participants and depressed patient studies (Oswald and Adam, 1986; Vasan et al., 1994; Feige et al., 2002; Bell et al., 2003; Jindal et al., 2003; Argyropoulos and Wilson, 2005). A significant reduction in REM, and an increase in REM onset latency following acute dosing with paroxetine in healthy volunteers was reported (Oswald and Adam, 1986; Wilson et al., 2004a). Similar effects have also been reported after a single dose of fluoxetine administration to healthy volunteers (Feige et al., 2002). Due to their deleterious effects they may be co-prescribed with hypnotics to aid sleep (Jindal and Thase, 2004).

A study reported by Hicks et al. (2002) showed that moderate to severely depressed patients’ treated with paroxetine had increased PSG sleep latency on days 3 and 10 and week 8, increased number of awakenings on day 10 and reduced sleep efficiency which correlated with subjective ratings of the St Mary’s Hospital Sleep Questionnaire (SMHSQ).

Following fluoxetine treatment, patients demonstrated significant increases in number of awakenings and REM latency with reduced sleep efficiency at week 8 compared with baseline but with conversely a significant improvement in the HAMD insomnia sleep items (Gillin et al., 1997). Trivedi et al. (1999) conducted a study of the effects of fluoxetine on EEG on depressed outpatients (n = 58) with HAMD ≥ 17 at inclusion and aged between 18 and 50 years. It was reported that in the acute phase and up to 10 weeks fluoxetine increased
Stage 1 sleep, REM latency and REM density but decreased total REM and Stage 2 sleep whilst HAMD and HAMD sleep items conversely improved.

Sertraline was found to increase sleep latency and suppress REM in depressed patients following acute dosing at week 2 and week 12 of treatment respectively on sertraline which resulted in outcomes of increased sleep latency, reduced sleep efficiency and a decrease in total sleep time. However subjective PSQI scores reported an improvement from baseline to week 12 (Jindal et al., 2003).

Although PSG studies report poorer sleep architecture with SSRI administration paradoxically patients felt that they slept better. Depressed patients treated with SSRIs subjectively felt that their sleep was significantly improved according to LSEQ and HAMD sleep item outcomes according to a review of antidepressants and their effect on sleep (Mayers and Baldwin, 2005). Fava et al. (2002) investigated the HAMD insomnia items in (n = 284) depressed untreated patients who had been diagnosed with MDD on the DSM-V criteria for at least 1 month. After 10 to 16 weeks of treatment with fluoxetine, sertraline or paroxetine patients felt that their insomnia had significantly improved as shown by reductions in the HAMD insomnia item scores for all treatments.

1.6.7. Actigraphy and depression

Insomnia co-exists as a symptom of depression and has been known as a precursor for a number of years (reviewed in Baglioni et al., 2011; Baglioni and Riemann, 2012), therefore to measure changes in the sleep wake pattern during the course of treatment with actigraphy might provide a non-invasive diagnostic method of revealing improvements in symptoms. These symptoms of depression are described as extended sleep latency, increased number of awakenings, more time awake after sleep onset and daytime sleepiness (Mendlewicz, 2009), which could be determined with actigraphy, as well as alterations in the sleep architecture. Over the years various studies have used a variety of activity recording devices to compare different patient groups.

In his Harvard review Teicher, (1995) discussed the usefulness of ‘Actigraphy and motion analysis’ in studies in psychiatric disease and summarised the early studies which indicated that ‘rest-activity levels were altered’ depending on the disorder and that these changes could be useful in objectively measuring the diagnosis and response to treatment. The early studies in actigraphy and depression focused on raw activity levels and showed that elevated activity levels at night were predictors of depression (Mendlowicz et al., 1999). Patients wore the Gaehwiler actigraph for 5 days and depression was correlated with sleep latency, WASO and
TST. Foster and Kupfer, (1975) showed that, using an early motion sensing device, actigraphic night-time activity was more disrupted in a group of hospitalised depressed patients where there was an increase in number of awakenings in sleep coupled with less time asleep, compared with acute cognitive disorganisation (ACD) patients.

The 24 h activity data of a group of melancholic depressed patients (n = 10) who were hospitalized for a mean of 30 days was compared with normal controls pre and post therapy by Ueda et al. (2005). Data were subdivided into 4 periods of 6 hours. Depressed patients pre-therapy exhibited significantly higher activity in the period from 12:00 to 18:00 than normal controls. Following imipramine therapy during the relief period activity levels were significantly reduced compared with pre-therapy levels, which were similar to the activity levels of control participants. There was a positive correlation between the activity data and the self-depression scale (SDS). Although not significant the data also shows that the melancholic patients were less active during the period from 06:00 to 12:00 than pre-therapy.

Volkers et al. (2002) also used the Gachwiler actigraph and reported an increase in the daytime mean, of three 24 h days of half hour activity, of 25 in-patients treated with the TCA imipramine for 4 weeks compared with before treatment, the increase in activity corresponded to an improvement in the HAMD score (Figure 1.15). Moreover there was a significant effect of increased sleep fragmentation following 4 weeks of imipramine treatment which the authors suggest may be attributed to movement disorders or agitation or akathisia, which is also a known side-effect of SSRIs according to Vaswani et al. (2003).

![Figure 1.15: Plot of 24 h activity distribution counts between treatment free and imipramine (Volkers et al., 2002)](image-url)
Similarly Royant-Parola et al. (1986) recorded 24h activity to assess clinical improvement over 30 days in depressed hospitalised patients, (medication not reported) and reported that there was an increase in the actigraphy profile of daytime activity in the last 8 days by the end of hospitalisation which correlated with an improvement in MADRS and HAMD.

This increase in daytime activity was also reported by Raoux et al. (1994) who showed that in an in-patient study of 26 patients over 26 days of treatment with TCAs daytime activity increased between the 3 days at treatment onset to 3 days prior to discharge, again this was correlated with improvements in MADRS. Cosinor analysis was also performed which revealed not only a significant increase in the mesor and amplitude but a delay in the acrophase of 15 min, although not significant. Joffe and colleagues. (1987) also showed that the 24 h mean of 3 days of daytime activity levels of the depressed patients that responded to treatment increased following carbamazepine escalated dosing (200 - 1600 mg/day), which is used to treat epilepsy and bipolar disorder.

Stanley et al. (1999) reported that actigraphy could measure the difference in the mean 24 h activity between 2 antidepressants, recorded over 10 days. Fourteen depressed out-patients wore AMI Actigraphs, 7 were treated with fluoxetine 20 mg/day and 7 with dothiepin 75 mg/day escalating to 150 mg/day after the first week. Activity levels were lower from patients treated with dothiepin which was attributed to the sedating effect of medication.

Recent studies, with the advent of more sensitive sophisticated actigraphs, have employed algorithms to calculate sleep variables which are comparable to PSG sleep variables (McCall and McCall, 2012). A study by Winkler et al. (2005) used actigraphy in SAD patients treated with light therapy and demonstrated how useful actigraphy could be in determining the benefit of treatment and showed that SAD patients normalised to healthy control activity levels after 4 weeks of light treatment and in improved sleep efficiency, increased daytime activity, a reduced cosine peak and 1 h phase delay which brought them into line with healthy controls.

1.6.8. Actigraphy and antidepressants

Most actigraphic studies of the effects of antidepressants have recorded snapshots of time by selecting various weeks or blocks of days to compare sleep changes or to show changes in activity levels rather than continuous measures. An early study recorded the motor activity of in-patients receiving a variety of antidepressant medications for 72h using the Actometer (Zak, Germany) (Lemke et al., 1997). This study showed that the activity levels of depressed inpatients was significantly greater in the morning (07:00 to 08:00) compared with the
evening (20:00 to 21:00) although depressive symptoms were greater in the morning than the evening. Lemke et al. (1997) also reported that melancholic unipolar depressed patients exhibited more activity during the night indicating that their sleep was more disturbed and fragmented before treatment. Actigraphy activity data were negatively correlated with subjective Multiple Affective Adjective Checklist (MAACL) which measures intensity of subjective symptoms.

Todd et al. (2009) conducted a longitudinal 4 week study of quantity and intensity of movement in depressed patients (n = 27) treated with quetiapine (50-100 mg/day dose adjusted) and healthy controls (n = 27) in conjunction with HAMD using Actiwatches. Following 2-day baseline, actigraphy was recorded for 2, 7-day periods at period 1 (days 1-7) and period 2 (days 22-29). Patients that improved in response to the HAMD were included in the analysis. The analysis showed that patients’ locomotor activity levels significantly increased during the day (08:00 to 20:00) following 4 weeks treatment to normalised healthy controls. The actigraphy sleep variable data were reported by Todd et al. (2006). It was demonstrated that actual sleep time and sleep efficiency were significantly higher after 4 weeks of treatment with quetiapine in both the clinically improved and non-improved patients as well as there being a shorter sleep latency in the clinically improved patients. However although it was reported that actiwatches were worn continuously only the data for weeks 1 and 4 were reported.

A study of female patients (n = 15 aged matched with n = 15 controls) with panic disorder were treated with the SSRI escitalopram 5 mg/day for 4 weeks (Todd and Baune, 2010). Actigraphy data were continuously measured, although only the data for the untreated week versus week 4 treated was presented. The data showed that there was a significant improvement in sleep efficiency at week 4 compared with week 1 which was mirrored, although not significant, in the improvement in the PSQI. A trend was detected in patients who improved with a ≥ 50% reduction in Hamilton Anxiety Scale (HAM-A) and showed a reduction in the actigraphic mean activity score in sleep and increase in actual sleep percent.

However very few studies have monitored the long term effects of antidepressants to track the time-course of treatment to measure sleep and / or daytime changes in the community according to the review by Burton et al. (2013). In fact only the Kasper et al. (2010) study conducted continuously for 6 weeks on patients treated with agomelatine or sertraline shows any similarity to the present study in Chapter 5. The study by Kasper et al. (2010) reported on sleep variables, daytime activity and circadian rhythm in depressed patients. This was a randomised parallel, double-blind study of depressed patients (HAMD ≥ 22) treated with
agomelatine (25 – 50 mg/day) (n = 133) or sertraline (50 – 100 mg/day) (n = 129). HAMD and LSEQ data were collected weekly. Actiwatches were worn throughout and data were analysed for changes in the rest-activity cycle with assessment of NPCRA and the actigraphic sleep parameters which were calculated weekly. There were significant differences between treatments for sleep efficiency, sleep latency and mean length of wake bouts, but no significant effect of time for either treatment was reported. Sleep efficiency decreased over time in the sertraline treated patients whilst sleep latency and the number of wake bouts increased over the 6 weeks. The contrasts with the current study will be further discussed in Chapter 5.

1.6.9. Circadian analysis

The rest-activity rhythm is associated with the internal circadian timing system which conforms to a general stable rhythm. Irregular behaviour such as shift work, or an illness such as Alzheimer’s or insomnia affects sleep and alters the circadian structure. Various options to reset the rest-activity pattern have been suggested and one of the mechanisms for characterising, measuring, assessing and reviewing restoration of the rhythm is provided by actigraphy. Studies have shown a disrupted rhythm from Alzheimer’s patients (Van Someren et al., 1999) and that bright light might be useful in enabling depressed elderly to maintain a 24 h circadian rhythm (Most et al., 2010). Different methods have been used to show disruption and resumption of the circadian rhythms and the two commonly used with actigraphy are Cosinor analysis and Non Parametric Rhythm Analysis (NPCRA). The cosinor program was developed by Minors et al. (1986) and the NPCRA analysis was developed by Van Someren et al. (1999). These programs have been used extensively for studying circadian timing in a variety of conditions but few studies have explored these methods for the long term evaluation of drug effects.

Wehr et al. (1979) hypothesised ‘phase advancing the circadian sleep wake cycle as an antidepressant’ to reset the rhythm but few studies have reported on this aspect. Sleep deprivation and light studies to reset the circadian rhythm have been proposed (Benedetti et al., 2005). The disturbances in the circadian rhythm in depression are well known and multifactored (Germain and Kupfer, 2008) including changes in daytime activity and sleep disturbances. In his review paper Gorwood. (2010) suggested that ‘restoring circadian rhythms might be a new way to successfully manage depression’. To record and review the progress of the circadian rhythm by actigraphy in a non-invasive way therefore would be useful in the process of normalising and restoring the disruption caused by depression.
The 24 h activity profile mean of 3 days following treatment with the antipsychotic imipramine was recorded, with the Gaehwiler actigraph, pre and post 4 weeks of treatment. Patients (n = 52) activity was shown to increase during the day and reduce at night compared with no treatment (Volkers et al., 2002). Data were also associated with improvement in HAMD.

A study reported on rest-activity disturbances in SAD patients (Teicher et al., 1997) with the time of the peak of the circadian rhythm, 1 h delayed in SAD patients compared with controls. This was taken a step further whereby SAD patients versus matched normal controls, were treated with light therapy (Winkler et al., 2005). The acrophase time of peak activity was significantly phase advanced by almost 1 h after 4 weeks of bright light therapy (BLT) treatment and almost matched healthy control subjects. Furthermore it has been postulated that the simple method of recording 24 h activity data may be a suitable method to evaluate antidepressant efficacy (Benoit et al., 1985) and test new therapies, as it has been established that depressed patients have a lower 24 h activity and a more fragmented rhythm than healthy controls (Berle et al., 2010).

Cosinor and NPCRA variables may be a reliable non-invasive method to understand changes in circadian rhythmicity during treatment and there are merits to both methods as discussed by Calogiuri et al. (2013). Other markers of circadian phase include melatonin and cortisol but the collection of these are more labour intensive relying on timed blood or urine samples collected over long periods of time that would impact on the activity pattern of individuals by controlling events. Further these bio-markers do not give any indication of the sleep and wake activity pattern.

1.6.9.1. Cosinor analysis

Circadian rhythm activity can be likened to a cosine curve, where there are perfect peaks of activity during the day and troughs of activity during the night. These patterns follow a rhythmic pattern close to the shape of a cosine curve and if the daily pattern was perfectly fitted to this cosine curve, the percentage rhythm would be expressed as 100%. However, as activity data are not perfect, estimates for the variation to the best fit are calculated using an analysis program based on fitting the data to the cosine curve by the method of least means squares (Nelson et al., 1979; Minors et al., 1986), the better the fit the more robust the cosine rhythm is. Other variables were calculated to provide the peak activity of the curve (amplitude), the mean activity value of the curve (mesor), and the time of the peak of activity (acrophase time). Subtle changes and variations over long periods of time could therefore be measured.
Cosinor analysis has been used for many years and Brown et al. (1990) conducted one of the early studies which showed that there was a pattern of activity throughout the 24 h cycle in normal healthy volunteers. A study of the effect of one hour of bright light in the afternoon on hospitalised Alzheimer’s patients showed evidence of a more stable rhythm compared with controls (Dowling et al., 2005).

1.6.9.2. Non-parametric circadian rhythm analysis (NPCRA)
Non-parametric circadian rhythm analysis (NPCRA) provides an alternative more sensitive method of analysis to cosinor, the data variables are assumed to be more meaningful as they are not fitted to a cosine curve. The NPCRA variables are described in Section 5.4.8 and shown in Figure 1.16. The NPCRA developed by Van Someren et al. (1999) has been particularly useful in recording the 24 h behaviour of Alzheimer’s patients and of depressed elderly (Most et al., 2010). However few studies have been conducted of the use of NPCRA in drug studies. The activity is calculated for the mean activity of the 6 minute blocks during the 10 most active hours (MIO) and the mean activity of the 6 minute blocks during the 5 least active hours (L5).

![Figure 1.16: Example of NCPRA rhythm](image)
The profile of 7 days of activity combined to show a 24 h mean. The 10 h of maximum activity is presented as the blue line and the 5 h of least activity as the red line. The time of M10 onset is 07:00 and the time of L5 onset is 01:00.
Circadian activity was recorded with the Actiwatch in a study of depressed out-patients treated with either agomelatine or sertraline for 6 weeks (Kasper et al., 2010). Changes in the NPCRA Relative Amplitude (RA), the M10 and the L5 were reported. RA remained fairly constant whereas M10 increased and L5 decreased between the baseline and post-baseline week 6. Neither the data for the individual weeks or the time course was presented. The authors reported a faster improvement in circadian variables with outpatients treated with agomelatine (25-50 mg/day) (n = 133) compared with sertraline (50-100 mg/day) (n = 129), in line with improvement in HAMD (Kasper et al., 2010).

Although a double-blind randomised, placebo controlled study of the effect of 2 weeks temazepam 20 mg/day on 38 insomniacs failed to show any significant effect of treatment in most of the NPCRA variables, the significant increase in L5 activity during withdrawal was associated with a significant reduction in sleep efficiency compared with placebo. The authors Wilson et al. (2004b) stated that as the participants were in work that it was unlikely that obvious changes in NPCRA would be recorded.

Baune et al. (2006) studied the effect of the antidepressant quetiapine on changes in daytime activity in hospitalised unipolar (n = 8) and bi-polar (n = 2) depressed patients and showed that there was an improvement in activity levels with an increase at week 4 compared with week 1 in M10 regardless of clinical improvement but no difference in L5 activity at night. The L5 levels of non-responders to treatment however, were higher compared to the responders at both weeks 1 and 4, and they had significantly lower sleep efficiency and TST.

1.6.10. Discontinuation of selective serotonin reuptake inhibitors (SSRIs)

One of the many problems associated with any long term treatment is the likelihood of patients missing doses, and the potential for the emergence of discontinuation symptoms. Apart from forgetting to take medication and instances like holidays with medication left at home, van Geffen et al. (2005) found that the main reasons for abrupt discontinuing were 'feeling better 45%, side effects 24%, no need for antidepressant 15%', in a follow-up questionnaire of 74 patients discontinuing SSRI treatment. However such is the problem with discontinuing that it was classified as a syndrome in 1996 by a panel of experts (Schatzberg, 1997) with the following definition:

- It is not attributable to other causes.
- It emerges upon abrupt discontinuation, frequent noncompliance (missed doses), and, less often after dose reduction.
- It is generally mild and short-lived but can be distressing.
- It can be reversed by the reintroduction of the original medication or one that is pharmacologically similar.
- It is minimized by a slow taper or by using a drug that has an extended half-life.

The problem with abrupt discontinuation is the likelihood of the emergence of discontinuation symptoms which were well documented in a discontinuation study (Judge et al., 2002) and reviewed in Demyttenaere and Haddad, (2000). These symptom may include dizziness, nausea, sleep-disturbances, stomach aches, flu-like symptoms, headache and fatigue to name but a few, which can occur shortly after stopping treatment (Haddad, 2001). The emergence of these symptoms, which differ from the side effects of SSRIs, appear to be related to the short half-life of the treatment, with many more reports of symptoms occurring after 1-5 days of paroxetine discontinuation (Black et al., 2000), than with other SSRIs.

Price et al. (1996) reported that in a comparison of SSRI post marketing safety from the UK database of adverse drug reactions, discontinuation symptoms following paroxetine withdrawal accounted for 5% of the reports compared with < 1% for sertraline and fluoxetine. Nevertheless, a review by Montgomery et al. (1994) reported that in a meta-analysis it was found that ‘significantly fewer patients withdraw from treatment of major depression with SSRIs than from TCAs’. Recognising the symptoms and subsequent management of discontinuation is a key factor in treating patients (Haddad and Anderson, 2007) and the use of tapering and reducing dosages has been suggested by van Geffen et al. (2005).

Rosenbaum et al. (1998) conducted a discontinuation study with 242 depressed patients on SSRIs, where the treatment of patients on maintenance medication was interrupted and substituted with 5-8 days of placebo. Symptoms were measured with MADRS, HAMD28 and the Discontinuation-Emergent Signs and Symptoms (DESS) checklist. There were significantly higher adverse outcomes following paroxetine and sertraline withdrawal compared with fluoxetine, although most symptoms resumed to pre-discontinuation levels on re-stabilisation of treatment. The incidence of symptoms was significantly higher with patients treated with paroxetine 66% (n = 82) and sertraline 60% (n = 79) compared with fluoxetine 14% (n = 81) according to the Discontinuation-Emergent Signs and Symptoms questionnaire (DESS). The percentage of patients who reported having trouble sleeping from
DESS, reported by ≥ 10% of patients, was greater following paroxetine withdrawal than fluoxetine or sertraline with 39, 22 and 9, respectively.

In a similar study with a 5 day placebo substitution, by Michelson et al. (2000), significantly higher numbers of adverse events were reported with functional impairment after paroxetine withdrawal compared with sertraline or fluoxetine. Patients (n = 77) on long term antidepressant treatment with the SSRIs and with a HAMD score ≥ 10 were recruited. There was a significantly shorter onset time of new symptoms in the Patient Rated Adverse Events Scale, occurring within 2 days following paroxetine withdrawal but no significant effect in either sertraline or fluoxetine even after 4 days. The ‘time to onset of symptoms’ is shown in Figure 1.17 (Michelson et al., 2000).

Interestingly Michelson et al. (2000) also reported on the plasma concentrations at the end of the placebo substitution disruption, the mean percentage reduction of active treatment was 29.7% for fluoxetine, 73.5% for sertraline and 86.7% for paroxetine although this did not correlate with the emergence of new symptoms. With respect to these and other reported effects of discontinuation it has been suggested that tapering instead of abrupt withdrawal might be preferable (Rosenbaum and Zajecka, 1997; Haddad, 2001).

![Figure 1.17: Time to onset of discontinuation symptoms (Michelson et al., 2000)](image)

1.6.10.1. Objective tests Critical Flicker Fusion (CFF) and Choice Reaction Times (CRT)

Only one study by (Hindmarch et al., 2000a) has investigated the effect of brief discontinuation of the SSRIs paroxetine, fluoxetine, sertraline or citalopram treatment on cognitive functioning of depressed patients and the effect of time on CRT and CFF. Depressed patients (n = 87) on maintenance therapy for at least 3 months and with a
MADRS score of ≤ 12 were recruited. Patients on treatment with either paroxetine, n = 22 (20 mg/day), fluoxetine, n = 22 (20 mg/day), sertraline n = 22 (50 mg/day) or citalopram, n = 21 (20 mg/day) had their treatment disrupted for 4-7 days (Hindmarch et al., 2000). Cognitive and psychomotor function was assessed with LARS, CFF, CRT, LSEQ and CFQ as well as the depression scales of MADRS and ZUNG at screening Day 0, Day 5 baseline, Day 10 post withdrawal and Day 15 after 5 days re-introduction of SSRI treatment. Brief treatment discontinuation of 4-7 days had no overall effect on CFF for any treatment, although a slight non-significant decrease in threshold was observed following paroxetine withdrawal (Hindmarch et al., 2000a). Although reaction time increased on CRT following withdrawal of all treatments, this was only significant for paroxetine.

1.6.10.2. Leeds Sleep Evaluation Questionnaire (LSEQ)

As previously stated only one other study has reported on the effect on (Leeds Sleep Evaluation Questionnaire) LSEQ items following withdrawal of SSRI treatment (Hindmarch et al., 2000a). In the study reported and described in the previous Section 1.6.10.1 there was a slight impairment of sleep assessed with LSEQ items following paroxetine, fluoxetine and sertraline withdrawal.

Although all GTS scores increased for all treatments following discontinuation the effect was not significant. Scores for QOS following paroxetine withdrawal significantly increased with a worsening of symptoms and poorer sleep quality, and QOS scores were also adversely affected with fluoxetine withdrawal. Discontinuation from paroxetine or sertraline worsened with an increase, but not significant, in scores for AFS, with patients feeling less refreshed, whereas scores following fluoxetine withdrawal slightly increased and therefore exerted no adverse effect on AFS. The effect of discontinuation on BFW worsened following withdrawal from paroxetine, increased scores indicated that patients felt worse upon awakening and that their behaviour and functioning was impaired. Data suggests therefore that withdrawal from paroxetine caused disruption in GTS, QOS, AFS and BFW, whereas discontinuation from fluoxetine or sertraline does not affect patients to the same degree (Hindmarch et al., 2000a). Rosenbaum et al. (1998) also reported that paroxetine caused more 'fatigue' than either sertraline or fluoxetine during placebo substitution.

1.6.10.3. Line Analogue Rating Scale (LARS)

The trend for a worsening of symptoms during abrupt discontinuation from paroxetine was repeated in the LARS in the previously described Hindmarch et al. (2000a) study, who reported an increase in sedation scores following paroxetine withdrawal. Rosenbaum et al.
(1998) also reported that paroxetine caused more ‘fatigue’ according to the DESS, than either sertraline or fluoxetine during placebo substitution.

1.6.10.4. Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD)

In the 4 week multicentre study reported in Section 1.6.10 there was a significant change in both MADRS and HAMD28 scores following interruption in the paroxetine and sertraline groups but not in the patients treated with fluoxetine as shown in Figure 1.18 (Rosenbaum et al., 1998). As reported previously, Michelson et al. (2000) conducted a similar study of a 5 day placebo-blind withdrawal of SSRIs in patients, there was a statistically significant increase at the end of the withdrawal, in the HAMD21 scores, for patients treated with paroxetine which occurred after the 2nd day of replacement with placebo, but not for patients treated with either fluoxetine or sertraline.

Figure 1.18: Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD) during discontinuation (Rosenbaum et al., 1998)

Depression severity was also assessed in the discontinuation study reported in Section 1.6.10.1 (CFF and CRT) (Hindmarch et al., 2000a). At screening patients were included with a MADRS score ≤ 12. At the end of the withdrawal period there was a statistically significant increase, in the MADRS scores, for patients treated with paroxetine but not for patients treated with either fluoxetine or sertraline. Results of the withdrawal are shown in Figure 1.19. This significant effect was also reported following abrupt discontinuation of paroxetine treatment on HAMD.
Other researchers, Judge et al. (2002), also found that there was a statistically significant increase at the end of the withdrawal, in the HAMD21 scores, for patients treated with paroxetine but not for patients treated with either fluoxetine or sertraline in study with a 3-5 day placebo abrupt withdrawal of SSRIs in patients. The differences in the MADRS and HAMD scores for the discontinuation period between paroxetine and sertraline or fluoxetine are likely to be due to the difference in their pharmacokinetics. As described in Section 1.6.3 fluoxetine has a longer half-life of 1-3 days with the half-life of its metabolite of 4-16 days, concentration levels decline at a slower rate which helps to reduce severity of symptoms. This contrasts with paroxetine with a short half-life of 21 h and no active metabolite, and sertraline with a half-life of 26 h and a low activity metabolite of 66 h and maybe why more discontinuation symptoms are recorded for paroxetine than for the other SSRIs in the current study according to reviews (Price et al., 1996; Black et al., 2000).

1.6.10.5. 
ZUNG

The ZUNG scores worsened in self-rated depression following paroxetine withdrawal in the study reported by Hindmarch et al. (2000a), a significant discontinuation effect was observed. The scores reported increased from 38.3, 40.9 and 38.3 before discontinuation to 48.6, 42.8 and 40.6 after 5 days of discontinuation for paroxetine, fluoxetine and sertraline respectively, showing that paroxetine had caused a significant effect (Figure 1.20).
1.6.10.6. Cognitive Failures Questionnaire (CFQ)

The study by Hindmarch et al. (2000a), previously reported, also showed a significant increase in the CFQ score during the week following abrupt discontinuation from paroxetine and a trend for impairment following sertraline withdrawal as shown in Figure 1.21.

1.7. Aims and Objectives

Since actigraphy measures rest-activity patterns the overall aim of the studies was to investigate whether it is possible using actigraphy to identify and measure drug-induced changes in activity following acute administration of different classes of psychoactive drugs (sedative hypnotics and antihistamines). The time course of action of these CNS drugs will be investigated in relation to the changes in activity patterns in conjunction with changes in psychomotor function to determine whether actigraphy is suitably sensitive to detect drug-induced effects.
Whether actigraphy can be used to measure drug-induced changes in sleep behaviour during the sleep period and changes in the sleep profile following drug administration will also be evaluated. In addition, whether actigraphy can distinguish changes in motor activity the following morning and therefore any hangover effect of the drug will also be determined.

The sensitivity of the actigraph technology to the sedating effects of medication and how accurately actigraphy is able to track drug pharmacokinetics and pharmacodynamics will also be investigated.

The chronic effects of antidepressant administration will also be investigated to determine the usefulness of the actigraphy technology in monitoring patient groups in their own home environment following long term administration of medication to evaluate changes in activity and sleep patterns.

1.8. Hypotheses

Since two different types of studies were being conducted, namely the short acting effects of psychoactive compounds on healthy volunteers and the longer acting effects of antidepressant treatment on depressed patients the different hypotheses are:

Acute studies:
   i. Acute administration of psychoactive compounds will impair cognition and psychomotor performance in healthy participants greater than placebo and these sedative changes in activity and sleep will be measurable by actigraphy.
   ii. Actigraphy will determine whether the administration of psychoactive compounds causes motor impairments throughout the treatment period.
   iii. The null hypotheses for acute studies are that the hypnotic sedative lorazepam and the antihistamine promethazine will have no effect on arousal, attention, and sleep as assessed by the cognitive and psychomotor tests, actigraphy and subjective questionnaires.

Chronic study:
   i. Changes in activity, the sleep wake and circadian profile of depressed patients treated with chronic SSRI antidepressants will be measureable by actigraphy.
   ii. Changes in the sleep wake and circadian profile of depressed patients following abrupt discontinuation of treatment will be detectable by actigraphy.
iii. For statistical purposes the null hypotheses for the chronic study is that the SSRI antidepressant treatment will have no effect on sleep wake and circadian activity of depressed patients as measured by actigraphy.

For specific hypotheses refer to relevant sections in the respective chapters.
CHAPTER 2 GENERAL METHODS

This thesis reports on three separate studies, methods common to each study are described in this chapter, with specific methods of each of the studies described in the respective chapters.

2.1. Participants

Participants, as healthy volunteers or patients, were recruited to the relevant studies, according to the strict criteria in the clinical trial protocols and the inclusion/exclusion restrictions. Written informed consent was obtained from all participants together with the consent of their medical practitioner to participate in the trials. Participants were sequentially randomised to receive study medication. The participants in the studies referred to in Chapters 3 sedative hypnotics and Chapter 4 antihistamines were conducted on healthy volunteers whereas the participants in the antidepressant study Chapter 5 were depressed patients.

2.2. Study Design

The studies were randomised, double-blind investigations into the effects of treatment on actigraphic sleep variables, subjective sleep and aspects of cognitive and psychomotor performance. The full details of each study design are in the relevant chapters. Studies were approved by the relevant Ethics Committees.

2.3. Actigraphy

The Actiwatch AW4 (Cambridge Neurotechnology Ltd., Cambridge, UK) was worn by the participants continuously on their non-dominant wrist for the duration of each study to record activity.

2.4. Activity

Actigraphy records activity in counts per epoch so drug-induced changes in activity may be observed and measured. Data were recorded in either 1 or 2 minute epochs depending on the study. Actiwatches were set up to record using the manufacturer's proprietary default medium setting and activity data were stored in 1 minute epochs. Prior to download the marker buttons were pressed to confirm that the internal timer was correct against the previously checked computer clocks.
To obtain the actigraphic sleep variables the Actiwatch Activity and Sleep Analysis Version 5 (Sleepwatch Version 5.51) (Figure 2.1) was used to calculate the variables from lights off to lights on. The Sleepwatch proprietary algorithm was used to compare the activity data of epochs 10 minutes either side and in a series of linked calculations epochs were scored as ‘sleep’ or ‘wake’. Epochs with a value of 40 counts per 1 minute or more were scored by the algorithm as wake, anything less being scored as sleep.

![Figure 2.1: Actiwatch screen view of Version 5.51](image)

To show version of software used for analysis.

For each study the sleep start and sleep end times were calculated from the lights out and lights on times set by the marker or operator and checked for consistency. Sleep analysis was performed using the automated proprietary software algorithm and the sleep variables were calculated. Summary data were exported to Excel for statistical analysis.

2.4.1. Actigraphic sleep variables

In each study the actigraphic sleep variables for the sleep period were automatically calculated with the internal Sleepwatch algorithm and software. The analysis window was set before and after the ‘lights out’ and ‘lights on’ to cover the whole sleep period.

Four of the 17 Sleepwatch variables [sleep period time (SPT), wake after sleep onset (WASO), sleep efficiency (SE) and sleep onset latency (SOL)] are common and considered to be comparable to PSG (Oakley, 1997). For the purpose of statistical analysis all times were calculated in decimal minutes.
The validated sleep variables calculated for the purpose of the studies comprised the following:

- **Time in bed (TIB)** – Lights out to lights on
- **Assumed sleep time / Sleep period time (SPT)** – Assumed sleep time from sleep start to sleep end similar to sleep period time, from sleep start to sleep end including any wake time
- **Actual sleep time / Total sleep time (AST/TST)** – The total amount of sleep in the sleep period minus any wake time
- **Actual awake time / Wake after sleep onset (AWT/WASO)** – The amount of time spent awake in the sleep period
- **Sleep efficiency (SE)** – The percentage of time spent asleep whilst in bed
- **Sleep latency (SOL/SL)** – The latency before sleep onset following bed time, the time taken to fall asleep from lights out
- **Sleep bouts (SB) and wake bouts (WB)** – The number of episodes of continuous sleep or continuous wake, and therefore the number of transitions from sleep to wake
- **Sleep bout time (SBT) and wake bout time (WBT)** – The mean time of an episode of sleep or wake
- **Fragmentation index (FI)** – The addition of the percentages of moving time and 1 minute immobility phases, which is used as an indicator of restlessness.
- **Average wake movement (AWM)** – Mean activity count per epoch during the preceding day, from sleep end to sleep start.
- **Total activity counts in sleep**

2.4.2. **Sleep-like activity**

A method of analysing data for measuring low activity during the day which can be classed as ‘sleep-like’ or ‘sedation’ was suggested by Stanley and Hindmarch, (1997). In the current studies each epoch was scored as sleep or wake according to the algorithm whereby activity epochs with less than 40 counts recorded per 1 min epoch are defined as sleep-like, and over 40 counts / min as wake. It was therefore possible to determine whether a treatment had induced ‘sedation’.

2.4.3. **Cosinor analysis**

This is described in detail in Sections 1.6.9.1 and 5.4.8.1.
2.4.4. Non-parametric circadian rhythm analysis (NPCRA)
This is described in detail in Section 5.4.8.3.

2.5. Cognitive and psychomotor tests
Various cognitive and psychometric performance tests were conducted in each of the studies. For the purpose of reference all tests are described in this methods section. The tests included Choice Reaction Time (CRT), Continuous Tracking Task (CTT) and Critical Flicker Fusion (CFF). These tests are known to be sensitive to the impairing effects of psychotropic compounds (Sherwood and Kerr, 1993; Hindmarch, 1999, 2002; Hindmarch et al., 2002, 2005). To standardise the procedure and for calibration and validation purposes the tests were put together collectively in a test battery known as the Leeds Psychomotor Tester (LPT). Individually they are useful for comparing the pharmacodynamics effects of different classes of medication. Different tests were used in the various studies in this thesis.

2.5.1. Choice Reaction Time (CRT)
The CRT task is sensitive to a variety of psychoactive agents (Alford et al., 1991; Baselt, 2001; Hindmarch, 1981; Hindmarch and Parrott, 1978) and is used as an indicator of sensorimotor performance (Hindmarch, 1975, 1980), assessing the ability to attend and respond to a critical stimulus (Sherwood and Kerr, 1993). The CRT equipment is shown in Figure 2.2. Participants placed the index finger of their preferred hand on a central starting button, and were instructed to extinguish one of six equidistant red lights, illuminated at random, by pressing the response button immediately in front of the light as quickly as possible. The mean of 50 consecutive presentations was recorded as a response measure of three components of reaction time: recognition, motor and total reaction time. Recognition reaction time (RRT) is the time it takes for the participant to notice the light, being the time between stimulus onset and the participant lifting their finger from the start button. Motor reaction time (MRT) indexes the movement component of this task, and is the time between the participants lifting their finger from the start button and touching the response button. Total reaction time (TRT) is the sum of RRT and MRT. All results were recorded electronically.

2.5.2. Critical Flicker Fusion (CFF)
The CFF task provides an index of central nervous system activity or “cortical arousal”. More specifically, the CFF assesses the ability to distinguish between discrete sensory events. Participants were required to discriminate flicker from fusion and vice versa in four light emitting diodes (LEDs) arranged in a one-centimetre square on a black background.
The participant was instructed to sit one metre away from the diodes. Individual thresholds were determined by the psychophysical method of limits on four ascending (flicker to fusion) and four descending (fusion to flicker) scales (Woodworth and Schlosberg, 1958). CFF has been shown to be sensitive to a variety of psychoactive compounds (Smith and Misiak, 1976; Hindmarch, 1975, 1982, 1994). A decrease in the CFF threshold is indicative of a reduction in the overall integrative activity of the central nervous system (Fairweather et al., 1997). Moreover CFF is able to show improvement in cognitive function with an increase in the CFF threshold being indicative of an improvement in overall integrative activity (Kerr et al., 1991, 1993; Alexander et al., 1997). All results were recorded electronically.

Figure 2.2: Choice reaction test platform

2.5.3. Continuous Tracking Task (CTT)

The CTT interactive task of psychomotor function entails using a mouse to keep a cursor in alignment with a moving target on a VDU screen. The movement of the target is a function of an irregular sine wave. The response measure is the mean difference between the centres of target and cursor in pixels, sampled 5 times per second, over the 5-minute test. Lower scores are indicative of more accurate tracking (CTT-ER). A peripheral awareness task (PRT) was included in which the participant responded to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking test. The mean reaction (CTT-RT) time in milliseconds to these stimuli over the trial period was taken as the response measure for this component of the divided attention task. Data were captured electronically.
2.6. Questionnaires

A variety of questionnaires were used in the studies, the most common were Leeds Sleep Evaluation Questionnaire (LSEQ) and Line Analogue Rating Scale (LARS), descriptions of which are provided below. Other questionnaires, Montgomery-Åsberg Depression Rating Scale (MADRS) Appendix I, Hamilton Depression Rating Scale (HAMD) Appendix II, ZUNG Appendix III and Cognitive Failures Questionnaire (CFQ) Appendix IV were specifically used in the depression study and are described in detail in Chapter 5.

2.6.1. Leeds Sleep Evaluation Questionnaire (LSEQ)

The Leeds Sleep Evaluation Questionnaire LSEQ (Appendix V) assesses the effects of psychoactive compounds on sleep and early morning behaviour (Hindmarch, 1984; Zisapel and Laudon, 2003). It has been shown to be an effective assessment tool when used to quantify subjective sleep effects (Parrott and Hindmarch, 1980; Hindmarch, 1984; Zisapel and Laudon, 2003). The questionnaire consists of ten questions on aspects of subjective sleep and early morning behaviour and is grouped into four categories: ‘getting to sleep’ (GTS), ‘quality of sleep’ (QOS), and any hangover effect the following morning in feelings on ‘awakening from sleep’ (AFS) and ‘behaviour following wake’ (BFW). It was employed in Chapter 5.

Participants marked a series of 100 unit line analogue scales to indicate the direction and magnitude of changes in sleep following the administration of a drug in relation to their normal non-drug performance (Parrott and Hindmarch, 1980). The questionnaire was presented in the studies as a paper-based test. The participants marked each question by placing a vertical mark on the 100 mm line with a pen to indicate the extent of the effect they were experiencing with regards to a midpoint. This midpoint represented their normal state of mind before treatment began. The response was scored by measuring the distance in millimetres between the left end of the line and the participant’s mark.

For the purpose of the current studies it was useful to compare objective actigraphic variables and subjective sleep, and with regards to the LSEQ GTS was compared with sleep latency and QOS was compared with sleep efficiency, percentage sleep and movement within the sleep period.

A LSEQ score of 50 indicated no change compared with how participants had slept prior to drug treatment. A lower score (< 50) indicated a perception of improved sleep, i.e. easier to get to sleep, more restful sleep, and improved early morning behaviour, for example easier to
wake up and feeling less clumsy than usual. A higher score (> 50) indicated a perceived worsening in sleep quality or behaviour the next morning.

2.6.2. Line Analogue Rating Scales (LARS).

The Line Analogue Rating Scale (LARS) (Appendix VII) was used to assess patients’ present feeling with that before drug treatment by marking on a series of 100 mm visual analogue scales, the midpoint represented their normal state of mind. The scale consists of 10 components: Dizzy, Clumsy, Anxious, Relaxed, Tired, Drowsy, Alert, Energetic, Sad, and Depressed. The mean scores of ratings of ‘tiredness’, ‘drowsiness’, and ‘alertness’, presented among several distracter scales, are taken as a measurement of perceived sedation (Hindmarch and Gudgeon, 1980). The lower the score (in millimetres), the more alert and less tired and drowsy the participant feels. Depending on the study the LARS was completed following dosing, in the morning or at the out-patient visits. The response was scored by measuring the distance in mm between the left end of the line and the participant’s mark.

2.6.3. Montgomery-Åsberg Depression Rating Scale (MADRS)

This is described in detail in Section 5.4.9.7.

2.6.4. Hamilton Depression Rating Scale (HAMD)

This is described in detail in Section 5.4.9.8.

2.6.5. ZUNG Depression Inventory

This is described in detail in Section 5.4.9.10.

2.6.6. Cognitive Failures Questionnaire (CFQ)

This is described in detail in Section 5.4.9.11.

2.7. Statistical methods

The data for this thesis were extracted from each of the larger respective studies and analysed separately. Data were analysed as a two-treatment data set, for the verum and placebo data, in the case of Chapter 3 Sedative Hypnotics and Chapter 4 Antihistamines or as a three-treatment data set for all treatments for Chapter 5 Antidepressants.

The analysis for each study was conducted as an analysis of variance with each variable e.g. mean activity, test or questionnaire as the dependent variable; drug treatment and study period as fixed effects, and time (within participant and study period) as a repeated measure
and with spatial power SP(POW) variance-covariance matrix, with participant as a random effect.

Individual treatment versus placebo or baseline comparisons were performed using the LSMEANS option for estimating differences of SAS PROC MIXED (Statistical Analysis Software SAS® PC, Version 9.1, SAS Institute, North Carolina, USA) which provided information on estimates, 95% confidence limits, and P-values for each time point. No test multiplicity significance adjustment was made at any stage in the analysis. The results were analysed by the restricted maximum likelihood ‘REML’ method in SAS PROC MIXED with ‘treatment’ and ‘period’ as fixed effects and ‘participant’ as a random effect, whereby any non-missing observations for participants with any missing values were used in the estimation.
CHAPTER 3 SEDATIVE HYPNOTICS

3.1. Introduction

Lorazepam (LZP), a second generation hypnotic benzodiazepine, is prescribed to alleviate anxiety and aid sleep. LZP is usually prescribed in small doses (1 mg) during the day to reduce anxiety and is also given in a single dose at night (2.5 mg) to initiate sleep. The pharmacokinetics of LZP show that it is readily absorbed reaching a peak concentration approximately 2 h after dosing with an elimination half-life of about 12 h (Kyriakopoulos et al., 1978). A dose of 2.5 mg LZP has been shown to increase total sleep time and change sleep architecture at night (Grözinger et al., 1998; Röschke et al., 2000), induce subjective daytime sleepiness (van Laar et al., 2001), and reduce anxiety symptoms (Laakmann et al., 1998). Previous studies have also shown that it impairs daytime psychomotor performance and memory (Baselt, 2001).

The effects of benzodiazepines in healthy participants and patients are detailed in Section 1.4. As the daytime impairment effects of LZP have been well documented it was considered appropriate to use LZP as a tool to assess how well actigraphy maps onto changes in cognitive and psychomotor function. Permission was received from Servier to use the placebo and LZP verum data.

3.2. Aims

The aim of the study was to evaluate the effect of a single dose (2.5 mg) of LZP, compared with placebo, on actigraphic motor activity in association with cognitive and psychomotor function in healthy participants kept in laboratory conditions. The ability of actigraphy to detect LZP-induced changes in both spontaneous and controlled activity was assessed. In addition, whether actigraphy could distinguish changes in the sleep profile and any hangover effect of the drug was also determined.

3.3. Hypotheses

i. Lorazepam will reduce actigraphic activity levels, increase daytime ‘sleep-like activity’ and increase actigraphic sleep variables compared with placebo.

ii. Lorazepam will impair cognitive and psychomotor performance compared with placebo.

iii. The null hypothesis is that compared to placebo, LZP will have no effect on cognitive and psychomotor performance, actigraphic activity, or actigraphic sleep variables.
3.4. Methods

3.4.1. Study design

Participants were randomised to a double-blind, placebo-controlled, crossover design study where each volunteer acted as their own control. The data presented here were taken from a larger clinical trial and for the purpose of this investigation only the results of the study treatments of placebo and LZP are presented. Volunteers received either LZP (2.5 mg) or placebo on two consecutive days, in a Latin Square design so that each volunteer received each treatment. All treatments were supplied in identical capsules and each oral dose was taken at 18:00 h on Day 1 and Day 2 of each study period as shown in schedule (Figure 3.1). Each of the study periods was separated by a six day washout.

![Study schedule](image)

Figure 3.1: Study schedule
Legend, A = Admit participants to unit, X = dosing with placebo or LZP (2.5 mg), D = discharge from unit

3.4.2. Participants

Twenty four healthy male and female Caucasian volunteers were recruited onto the study; one participant was withdrawn after Night 1. Twenty three participants completed at least one of the treatments and are therefore are included in the analysis, 21 participants (10 males, 11 females) completed both study treatments. The age (mean ± SD) of the 23 participants was 27.3 ± 5.3 years and the mean height, weight and body mass index (BMI) of the participants at screening were 1.72 ± 0.08 m, 70.0 ± 9.7 kg and 23.7 ± 2.2 kg/m², respectively.
All participants were in good health without any clinical history of physical or mental illness as assessed by a physician. No participants were taking any concomitant medication (except oral contraceptives) likely to interfere with the study measures. Following a medical history, participants underwent a medical examination (including 12-lead electrocardiogram, urinalysis, haematology, biochemistry, alcohol breath test and drugs of abuse screen). Written informed consent was obtained from all volunteers together with the consent of their medical practitioner to participate in the trial. The study was approved by the Ethics Committee of the South West Surrey Health Authority.

Participants were instructed to avoid late-nights and adhere to their usual bedtime (minimum 6 - 8 h sleep) before each of the study periods. In order to ensure compliance to the sleep wake restriction they were required to wear actigraphs continuously from the screening visit to study completion (maximum 8 weeks). The use of alcohol, nicotine and products containing caffeine were prohibited for 24 h before and on study days.

3.4.3. Study procedures

Participants attended the unit on Day -1, a breath alcohol reading was taken and a urine sample obtained for drugs of abuse screening. The actigraph was removed, downloaded, checked for compliance and reattached. Participants were familiarised with the study procedures and trained on the standard battery of psychometric tests (Section 2.5) at the start of the trial in order to minimize learning effects during the study (Parkin et al., 1997).

The psychometric test battery was performed at 07:00 h on Day 1 of each study period in order to obtain pre-treatment baseline recordings. Treatment (placebo or LZP) was administered at 18:00 h. After dosing on Day 1 the standard battery of psychomotor and cognitive tests was conducted at 1, 2, 3, 4 and 14 h post dose. During the study periods food consumption was strictly controlled and mealtimes were regulated, breakfast was consumed at 09:00 h; lunch at 12:00 h; a snack at 16:00 h; and dinner at 20:00 h on Day 1 and at 17:45 h on Day 2 and Day 3.

Bedtime (participants’ supine in the dark in a standardised controlled environment) was from 23:00 - 07:00 h and participants were prevented from napping during the day. Blood samples were taken hourly at 15 min past the hour from 18:00 - 22:00 h on Day 2 to assess the pharmacokinetic profile of the drug (data not permitted to be presented).
3.4.4. Actigraphy

Volunteers were required to wear Actiwatches AW4 (Cambridge Neurotechnology Ltd., Cambridge, UK), which were set to record at 1 min epoch, on their non-dominant wrist for the duration of each study period (4 days), to monitor rest and activity. Actigraphy records activity in counts per epoch so drug-induced changes in activity may be observed and measured. Actiwatches were also worn from the screening visit to the start of the study (up to 30 days) and during the washout period of at least 6 days between each study period to ensure volunteer compliance and maintenance of a regular bedtime.

All procedures were strictly controlled with relation to times. The sleep analysis sleep period was set from lights off at 23:00 to lights on at 06:59. Sleep analysis was not performed when participants were out of the unit, but the actograms and data were reviewed prior to each period to ensure that participants sleep and wake times were within the study protocol restrictions.

3.4.4.1. Analysis procedure for sleep like minutes and activity

Data were downloaded onto a computer via an Actiwatch Reader Station. The data were then analysed using the internal Sleepwatch analysis program. The 24 h window of analysis for sleep was set from 07.00 to 06.59 for all days. Parameters for sleep were set from 23:00 to 06:59 (in accordance with ‘lights off’ and ‘lights on’ times). The resultant activity data for Day 1 and Day 2 was then extracted and exported into Excel as activity data, in counts per one minute epoch, and sleep data whereby each minute was scored as sleep (S) or wake (W) as determined by the Sleepwatch algorithm. The excel files were saved according to the Treatment Number and Period number. The original *.xls files were saved in a folder labelled ‘original’.

Data epoch points indicating that the Actiwatch had been removed, with a zero in the cell, were edited from the excel sheets and replaced with a full stop, to ensure that these times were not included in the analysis. These periods correlated to times of removal as confirmed by the ‘Removal log’ completed by the volunteers, and confirmed by the reviewer. The edited *.xl data files were saved into a folder labelled ‘edited’.

A macro was performed which calculated the mean activity and the total number of sleep epochs per half hour. The edited .xl file was saved into a folder labelled ‘macrod’ and the resultant spread sheet containing all the relevant data were saved as ‘emsacti.xls’. This
spread sheet was checked against the original excel files together with the Sleepwatch files. The checked spread sheets were initialled and dated.

The mean activity for each 30 min time interval on Day 1 was calculated from dosing at 18:00 h for 24 h. Each 30 min period before the psychometric tests was classified as “spontaneous activity” and each 30 min period during which the tests were performed was classified as “controlled activity”. The evening data on Day 1 consisted of 5 hours from 18:00 to 23:00, as all dosing was conducted simultaneously. Dosing on Day 2 was staggered so post-dose actigraphy participant data were aligned and covers 4 h post dose. The mean activity for each 30 min time interval on Day 1 and Day 2 was calculated from dosing at 18:00 h for 24 h including the sleep period. The activity for the morning following dosing on both Days 1 and 2 was calculated from 07:00 to 08:30 to measure any hangover effects of the medication.

3.4.4.2. Missing data
A log of missing data were compiled for times when the Actiwatch was removed in excess of 30 mins including participant removal and faulty data to ensure that it was not included in the analysis panel.

3.4.4.3. Sleep variables
The actigraphic sleep variables (Section 2.4.1) were automatically calculated with the internal Sleepwatch algorithm and software. The analysis window was set 15 min before and after the ‘lights out’ and ‘lights on’ to cover the whole sleep period. The 8 h window of analysis for sleep was from 23:00 to 06:59 for all days. Parameters for sleep were set from sleep start at 23:00 to sleep end at 07:00 (in accordance with ‘lights off’ and ‘lights on’ times). The resultant summary data for Days 1 and 2 was exported into Excel as the sleep variables. The resultant excel files were saved according to the Treatment Number and Period number and the bespoke SAS program calculated the statistical significance.

3.4.5. Cognitive and psychomotor function
Cognitive and psychomotor performance was measured in a 30 min test battery which included Choice Reaction Time (CRT); Continuous Tracking Task (CTT) and paper-based Line Analogue Rating Scales (LARS). The test battery was conducted at pre-dose 07:00, then 1 h post dose at 19:00, followed hourly at 20:00, 21:00 and 22:00. These tests are known to be sensitive to the impairing effects of psychotropic compounds (Hindmarch et al., 2005). Other tests were performed but are not reported.
3.4.5.1. Choice Reaction Time (CRT)

This test, described in full in Section 2.5.1, was used as a reaction task which is sensitive to a variety of psychoactive agents (Alford et al., 1991; Baselt, 2001; Hindmarch, 1981; Hindmarch and Parrott, 1978). Participants were required to place the index finger of their preferred hand on a central starting button, and were instructed to extinguish one of six equidistant red lights, illuminated at random, by pressing the response button immediately in front of the light as quickly as possible. The response measure is the time in ms of each of the three components of reaction time: recognition (RRT), motor (MRT) and total reaction time (TRT). All results were recorded electronically.

3.4.5.2. Continuous Tracking task (CTT)

This test is described in full in Section 2.5.3, and is a divided attention interactive task of psychomotor performance (Hindmarch, 1987; Kerr et al., 1996; Parkin et al., 1998). Participants were required to keep a cursor in alignment with a moving target on a computer screen using a mouse, whilst simultaneously responding to a peripheral stimulus. The response measure of the tracking component of the task was the mean deviation in pixels, with lower scores indicative of more accurate tracking (CTT-ER). The mean reaction time in milliseconds was taken as the response measure of the peripheral awareness task (RT) component. All data were captured electronically.

3.4.5.3. Line Analogue Rating Scale (LARS)

The LARS (Hindmarch, 1980; Hindmarch and Gudgeon, 1980) was employed as a measure of the subjective effect of the medication and is explained in full in Section 2.6.2. Volunteers were required to indicate their present feeling, where the mid-point on a 10 cm scale represented their normal state of mind before treatment began. The mean scores of ratings of the 'tiredness', 'drowsiness' and 'alertness' factors were taken as a measurement of perceived sedation. LARS was performed on Day 2 at 07:00 h; 17:00 h; 19:00 h; 20:00 h; 21:00 h and 22:00 h and then on Day 3 at 08:00 h.

3.4.6. Statistical analysis

The data for the placebo and LZP were extracted from the larger four-way treatment study and analysed separately as a two-treatment data set. Baseline values, taken prior to each study period, were used as a covariate to minimise any order effects in the study periods. The statistical analysis is described in full in Chapter 2 Methods Section 2.7.
Comparison of the effect of LZP and placebo on activity, conducted separately for each day, was divided into 3 time intervals, 0 to 5 h (18:00-23:00 h) for acute effects of the medication, 5-13 h (23:00-07:00 h) for evaluation during the overnight sleep period and 13-14.5 h (07:00-08:30 h) post dose for residual effects.

A Pearson’s Correlation Matrix was produced to identify any relationship between the activity levels and the psychomotor performance. As data were taken from a larger four treatment study, a test for significance as an explanatory variable of sequence category effect was performed, however no statistical significance was found.

3.5. Results

3.5.1. Participants

One participant removed the actiwatch during night 2, 2 participants completed only one of the treatment periods, 1 each for LZP and placebo; one participant did not complete either treatment. The data for 23 participants is included in the analysis.

3.5.2. Actigraphy

The Actiwatch was used to collect activity data. The data were analysed for activity counts, sleep-like minutes and sleep variables. Faulty and missing data were removed.

3.5.2.1. Wake activity

There was a significant main effect of treatment following dosing (0 to 5 h, 18:00 – 23:00) on the first day of treatment Day 1 ($F_{(1,85,4)} = 6.86$, $P = 0.0104$) for LZP compared with placebo and a significant effect of time ($F_{(9,311)} = 15.92$, $P < 0.0001$) (Figure 3.2A). Post-hoc analysis revealed that there was a significant effect of treatment on ‘spontaneous’ activity counts per epoch (mean ± SEM) at 3 h (20:30 – 21:00) post dose, with LZP reducing activity compared with placebo (191 ± 8 versus 257 ± 11; $P = 0.0061$), in the 30 minutes prior to the test point at 21:00. There was a trend for significance at 5 h ($P = 0.0542$) post dose just prior to bedtime (22:30 – 23:00) with LZP reducing activity compared with placebo (272 ± 15 versus 318 to ± 21). On Day 2, activity levels 0-4 h post dose, were also reduced following LZP administration however this effect was not statistically significant (Figure 3.2B).

The morning following Day 1, (residual effects) there was a significant effect of treatment on activity immediately following the 8 h sleep period ($F_{(1,63,3)} = 6.55$, $P = 0.0129$) which occurred between 13:00 – 14:30 h post dose (07:00 – 08:30) with a significant effect of time ($F_{(2,82,6)} = 8.65$, $P = 0.0004$). Compared with placebo, LZP produced a significant reduction
in activity in the hours after waking, suggesting a hangover effect after LZP administration (Figure 3.2A).

Figure 3.2: Time course of effect of placebo (■) and LZP 2.5 mg (□) on daytime actigraphic activity. There was an overall significant effect of treatment on Day 1 (P < 0.02), post-hoc tests revealed a significant effect at 3 h post dose (*P < 0.01) compared with placebo and an overall significant effect of treatment on morning after Day 1 (P < 0.02). A = Day 1, B = Day 2. Data are presented as mean ± SEM (n = 23) (# = psychometric test point, controlled activity). Data are presented as mean ± SEM (n = 21).

Following a second evening dose of LZP on Day 2, although activity in the morning was again reduced there was no overall significant effect of treatment 13:00 – 14:30 h post dose (07:00 – 08:30), although there was a significant effect of time (F(2,72.5) = 13.57, P < 0.0001) (Figure 3.2B).

3.5.2.2. ‘Sleep-like’ minutes during wake

Each individual activity epoch was scored as ‘sleep’ or ‘wake’ by the Sleepwatch algorithm, using the Sleepwatch medium sensitivity setting where an activity count of less than 40 is scored as sleep, ‘sleep-like activity’ was pooled into 30 min blocks. There was a statistically significant effect of time P < 0.0001. Although there was an increase in the number of sleep-like epochs overall during the 5 h period following LZP administration on Day 1, this was not statistically significant (Figure 3.3).
3.5.2.3. Sleep activity

Activity was also continuously monitored during the 8 h sleep periods (23:00 – 07:00 h) on Day/Night 1 and Day 2/Night 2. There was a significant effect of treatment on Night 1 \( F(1,9) = 7.11, P = 0.015 \), LZP reduced half hourly activity compared with placebo and with a significant effect of time \( F(5,630) = 4.66, P < 0.0001 \). Post-hoc analysis revealed that LZP produced a significant reduction in activity at the beginning of the sleep period at 5.5 h post dose compared with placebo (23:00 – 23:50) \( P = 0.0001 \), (Figure 3.4A) with LZP reducing mean activity counts from 38 ± 4.9 (placebo) to 19 ± 3.1 (LZP).

A similar effect of LZP treatment was observed on activity levels during the sleep period on Night 2, LZP \( F(1,147) = 11.58, P = 0.0009 \) reduced half hourly activity compared with placebo and with a significant effect of time \( F(15,534) = 5.28, P < 0.0001 \). Post-hoc analysis revealed that LZP again produced a significant reduction in activity at the beginning of the sleep period at 5.5 h post dose compared with placebo (23:00 – 23:50) \( P < 0.0001 \) (Figure 3.4B) with LZP reducing mean activity counts per epoch from 40 ± 4.7 (placebo) to 16 ± 3.0 (LZP).
There was an overall significant effect of treatment on Night 1 (P = 0.0151), post-hoc tests revealed a significant effect at 5.5 h post dose (\(*\ P < 0.001\)) compared with corresponding placebo. On Night 2 there was a significant effect of treatment (P = 0.0009), post-hoc tests also revealed a significant effect at 5.5 h post dose (\(*\ P < 0.001\)) compared with corresponding placebo. 5 – 5.5 h post dose corresponds to 23:00 – 23:30 h. A = Day 1, B = Day 2. Data are presented as mean ± SEM (n = 23).

3.5.2.4. Actigraphic sleep variables

The effect of LZP on the main sleep variables is shown in Table 3.1. Compared with placebo, LZP produced a statistically significant reduction in the number of sleep bouts \((F_{(1,18)} = 11.63, P = 0.0031)\), \((22 \pm 2\) versus \(28 \pm 2\), respectively), with longer sleep bout times following LZP compared with placebo \((23 \pm 2\) min compared with placebo \(17 \pm 2\) min). There was an indication that LZP reduced fragmentation index, with a trend for a significant reduction \((F_{(1,18)} = 3.92, P = 0.06)\) on the first night after dosing \((26 \pm 2\) versus \(21 \pm 2\) placebo versus LZP respectively). LZP significantly increased actual sleep percent \((F_{(1,18)} = 6.73, P = 0.0183)\) (LZP versus placebo, \(91\% \pm 1\) versus \(88\% \pm 1\)) and had a similar significant effect on sleep efficiency \((F_{(1,18)} = 12.81, P = 0.002)\) (LZP versus placebo, \(90\% \pm 1\) versus \(86\% \pm 1\)).

Similarly on the second night after dosing LZP again reduced activity shown as a significant reduction in the number of sleep bouts \((F_{(1,17)} = 7.74, P = 0.0128)\), LZP versus placebo \((22 \pm 2\) versus \(27 \pm 2\) bouts respectively). The sleep bout times were longer following LZP \(24 \pm 2\) min compared with \(18 \pm 2\) min for LZP versus placebo. However there was no significant effect for the fragmentation index on Night 2. LZP significantly increased actual sleep percent.
percent \( \left( F(1,17) = 8.03, P = 0.0115 \right) \) to 92 (± 1) % compared with 89 (± 1) % for placebo and sleep efficiency \( \left( F(1,17) = 13.44, P = 0.0019 \right) \) to 91 (± 1) % compared with 87 (± 2) % for placebo.

Table 3.1: Effect of LZP and placebo on the main actigraphic sleep variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Night 1</th>
<th>Night 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Actual Sleep (%)</td>
<td>88 ± 1</td>
<td>91 ± 1 *</td>
</tr>
<tr>
<td>Number of Sleep Bouts</td>
<td>28 ± 2</td>
<td>22 ± 2 **</td>
</tr>
<tr>
<td>Fragmentation Index</td>
<td>26 ± 2</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>86 ± 1</td>
<td>90 ± 1 **</td>
</tr>
<tr>
<td>Mean Sleep Bout Time (mins)</td>
<td>17 ± 1</td>
<td>23 ± 2 **</td>
</tr>
<tr>
<td>Sleep Latency (mins)</td>
<td>9 ± 2</td>
<td>4 ± 1</td>
</tr>
</tbody>
</table>

Sleep variables calculated with Sleepwatch Algorithm and presented as mean ± SEM \((n = 23)\). * \( P < 0.05 \), ** \( P < 0.01 \) versus corresponding placebo.

3.5.3. Psychometric tests

Subjective and objective assessments of sedation were measured with psychometric tests. The subjective test was LARS, and the objective assessments CRT (TRT), and CTT. The effect of LZP on those assessments is shown below and presented in Figure 3.5.

3.5.3.1. Line Analogue Rating Scale (LARS)

The perception of sedation was increased, LZP caused a main effect of treatment \( \left( F(1,65.3) = 4.58, P = 0.0361 \right) \) when compared with placebo and a significant treatment by time interaction \( \left( F(4,158) = 3.08, P < 0.0179 \right) \). *Post-hoc* analysis revealed a significant effect at 4.5 h post dose only \( (P < 0.0001) \) (mean ± SEM) with subjective sleepiness increasing following LZP from \((50 ± 2)\) to \((59 ± 2)\) placebo versus LZP respectively (Figure 3.5A). Participants felt drowsier following LZP dosing but this was limited to 4.5 h post dose and subjects did not experience any hangover effect the following morning.

3.5.3.2. Choice Reaction Time (CRT) and Total Reaction Time (TRT)

Analysis of the Total Reaction Time (TRT) component of the CRT task revealed that LZP caused an overall significant increase in reaction times \( \left( F(1,52.6) = 39.37, P < 0.0001 \right) \), with a statistically significant effect of time \( \left( F(4,150) = 5.87, P = 0.0002 \right) \), and a treatment by time
interaction \(F_{(4,150)} = 4.2, P = 0.003\). Post-hoc analysis revealed a significant effect of LZP compared with placebo on the individual time points at 2.5 h \((740 \pm 34.2, P < 0.0001)\), 3.5 h \((774 \pm 35.6, P < 0.0001)\), 4.5 h \((776 \pm 31.9, P < 0.0001)\) post dose as well as the following morning at 14.5 h \((712 \pm 20.8, P = 0.0127)\) compared with placebo \((635 \pm 18.6, 648 \pm 25.2, 638 \pm 23.0, 651 \pm 17.8, \text{at } 2.5, 3.5, 4.5 \text{ and } 14.5 \text{ h respectively}) (\text{mean} \pm \text{SEM})\) as shown in Figure 3.5B. LZP impaired reaction times by increasing participant’s time taken to complete the task compared with placebo.

![Figure 3.5: Time course of effect of placebo (■) and LZP 2.5 mg (□) on cognitive function](image)

**Figure 3.5:** Time course of effect of placebo (■) and LZP 2.5 mg (□) on cognitive function

Time course of effect of placebo (■) and LZP 2.5 mg (□) on (A) sedation component of LARS, (B) total reaction time of CRT (C) reaction time of CTT and (D) tracking error of CTT.  
* P < 0.05, ** P < 0.02 compared with corresponding placebo. Data are presented as mean ± SEM \((n = 21)\)

### 3.5.3.3. Continuous Tracking Task – Reaction Time (CTT-RT)

There was a main effect of treatment with an increase in response time to the peripheral stimulus component of the continuous tracking task (CTT) with LZP \(F_{(1,43.7)} = 26.58, P < 0.0001\), a main effect of time \(F_{(1,137)} = 6.94, P < 0.0001\) and treatment by time interaction
(F(1,137) = 5.22, P = 0.0006) compared with placebo. Post-hoc analysis revealed a significant effect of LZP compared with placebo on the individual time points at 2.5 h (628 ± 36.3, P = 0.009), 3.5 h (689 ± 46.1, P < 0.0001), 4.5 h (781 ± 70.2, P < 0.0001) h post dose as well as the following morning at 14.5 h (654 ± 47.2, P = 0.026) compared with placebo (502 ± 21.0, 505 ± 23.5, 513 ± 20.6, 542 ± 28.3 at 2.5, 3.5, 4.5 and 14.5 h respectively) as shown in Figure 3.5C. LZP impaired reaction times by causing a significant increase in time taken compared with placebo.

3.5.3.4. Continuous Tracking Task – Tracking Error (CTT-ERR)

There was a main effect of treatment on tracking performance, with impaired tracking accuracy increase in CTT-ERR with LZP (F(1,54.41) = 19.83, P < 0.0001), a main effect of time (F(4,15.0) = 4.47, P = 0.0019) and treatment by time interaction (F(1,137) = 5.22, P = 0.0023) compared with placebo. Post-hoc analysis revealed a significant effect of LZP compared with placebo on the individual time points at 2.5 h (31 ± 5.1, P = 0.0116), 3.5 h (35 ± 5.8, P = 0.013), 4.5 h (44 ± 8.1, P < 0.0001) post dose compared with placebo (19 ± 2.1, 19 ± 2.5, 19 ± 2.0, at 2.5, 3.5, and 4.5 h respectively) (mean ± SEM) as shown in Figure 3.5D. LZP impaired tracking performance by increasing the error in following the moving target.

3.5.4. Correlation of actigraphic actigraphy with cognitive performance

There was no significant correlation between actigraphic activity at 3 h (20:30 – 21:00) post dose where the difference in activity levels was significant and the 3.5 h (21:00 – 21:30) post dose time point of the cognitive performance tests, as detailed in the Pearson’s Correlation Matrix although activity levels and CTT-ERR approached significance (P = 0.08).

3.6. Discussion

There is relatively little literature on the actigraphic profile of sedative hypnotics. Some authors (Roehrs et al., 2000; Kiang et al., 2003; Takahashi et al., 2003) have reported that the derived actigraph data show significant reductions in activity after dosing with various compounds, using a variety of time blocks ranging from 6 to 24 post dose. Although these studies have provided an indication that actigraphy may be able to detect changes in behavioural activity following medication, the use of large analysis time episodes may not be sufficient to provide a discrete profile of the drug and of its time course of effect on activity and pharmacodynamics.

One of the first early studies to investigate the use of actigraphy as a new technology compared the effect of 3 hypnotic benzodiazepines on subjective sleep, MSLT, psychomotor
tests and motor activity (Mattmann et al., 1982). The study examined the effects of triazolam (0.25, 0.5 and 1 mg), nitrazepam (10 mg) and flunitrazepam (2 mg) in a double blind crossover study on activity at night. Eighteen participants slept in their own homes and activity was recorded overnight with an early generation actigraph, subjective sleep was assessed by questionnaire and a typing test was employed as a measure of psychomotor performance. The study showed that nocturnal motor activity was reduced by all the hypnotics with a 10% significant reduction after dosing with triazolam 0.25 mg to a significant 31% reduction following dosing with triazolam 1 mg relative to placebo. Additionally reductions in daytime activity were substantiated by subjective sleepiness and impaired performance.

A further study from the same group using a similar protocol (Borbély et al., 1983) examined the hypnotic and residual effects of triazolam and midazolam. Activity data were again calculated in 7.5 min epochs overnight to 4 h post waking. Night-time activity was significantly reduced by > 10% overall compared with placebo after dosing with triazolam (0.5 mg) and midazolam (15 mg) most of the reduction occurring in the first half of the night. Neither treatment affected daytime activity however psychomotor performance (typing test) was significantly impaired after triazolam (0.5 mg). There was no significant effect on subjective sleep by either treatment.

These studies reported above used actigraphy periods much larger than the current study and did not map the half-hourly effect of the hypnotic as is reported here where activity was recorded in 1 min epochs. Nevertheless they were able to show that actigraphy had the potential to identify differences in activity levels and activity in sleep following psychoactive medication.

The time intervals for analysis in the current study were such that it was possible to differentiate between ‘controlled’ activity during the 30 min test points and ‘spontaneous’ activity between the test points thereby removing the stimulating effects of the tests and avoiding confounding data by including periods where activity levels were dictated by protocol required tasks. The reduction in ‘spontaneous’ activity levels during the 5 h period after LZP dosing closely followed the cognitive impairment observed in the psychometric tests suggesting that actigraphy is able to detect a drug-induced effect. The current data also showed that LZP reduced activity levels even whilst tests were being conducted and that therefore the ‘sedating’ effect of LZP was observed even when activity was fairly prescribed.
LZP (2.5 mg single dose) significantly impaired psychometric and cognitive effects at 4.5 h post dose in the current study. This data confirms the findings of Allen et al. (1993) that LZP (2 mg) in healthy participants induced impairment up to 5 h post dose in DSST and pursuit rotor performance, the latter being similar to CTT. A similar study by O’Neill et al. (2000) showed that LZP 0.5 mg/day significantly impaired psychometric performance on the CRT at 4 h post dose in healthy subjects.

Daytime actigraphy data may also be interpreted as ‘sleepiness’ or ‘sleep-like’ behaviour by using the propriety sleep analysis software algorithm to score each epoch as either ‘sleep’ or ‘wake’. Various studies (Roehrs et al., 2000; Kawahara et al., 2002; Kiang et al., 2003) have successfully used this method to calculate overall ‘sleep-like’ behaviour during the day. In the present study, although no overall significant effect of treatment was found on the overall number of ‘sleep-like’ epochs during the 5 h period post dose, it is worthy to note that there was a post-hoc significant difference in the 30 min interval at 4 h, 21:30 – 22:00 post dose. This was during the half hour just prior to the 4.5 h 22:00 – 22:30 test point which also showed the greatest impairment in performance on the psychometric tests and when the subjective rating of sedation in the LARS showed that participants actually felt significantly more sedated and drowsy.

LZP has been shown to alter sleep architecture as determined by PSG (Grözinger et al., 1998; Saletu et al., 1990) by reducing sleep latency, number of awakenings, Stage 1 and REM sleep, whilst increasing TST and Stage 2 sleep. Whilst actigraphy is not able to identify changes in sleep stages / architecture the present study showed that the actigraphic analysis of the sleep period revealed significant reductions in the activity levels at the beginning and end of the sleep period indicating more restful sleep. These findings are consistent with previous findings of reduced sleep latency and increased TST (Grözinger et al., 1998). The actigraphic sleep parameters confirm this improvement in sleep showing an increase in the actual sleep percent and longer mean sleep bout times, reductions in the number of wake bouts and the fragmentation index. This clearly indicates that the actigraphy data were consistent with previous PSG findings of the effect of LZP and provides a less expensive, non-invasive alternative for detecting changes in sleep due to the effect of a drug.

Previous studies have used actigraphy for recording activity during sleep and calculating the sleep variables which are common to PSG. In a study by Kawahara et al. (2002) investigating the effects of benzodiazepine and non-benzodiazepine compounds brotizolam (0.25 mg) and zopiclone (7.5 mg) showed that sleep time (TST) was significantly longer following both hypnotic drugs.
Actigraphy is a useful non-invasive tool to assess CNS drug effects in the field or in a patient's natural environment. As psychoactive drugs have varied durations of efficacy, it is important to establish the maximum duration of impairment in order to provide safety data when prescribing. If a hypnotic taken to aid sleep has residual or hangover effects in the morning clearly this may be a safety hazard. As in the present study reported here previous studies (Mattmann et al., 1982; Borbély et al., 1988; Takahashi et al., 2003) have also shown that actigraphy is useful in providing data on residual effects through a reduction in activity levels following dosing.

In addition to demonstrating reduced activity levels following dosing the present study showed that actigraphy is able to detect a significant reduction in activity in the hour immediately following the sleep period (first hour of wake) therefore suggesting the presence of residual impairment the morning after dosing known as the ‘hangover’ effect. This coincided with impairment observed by the psychomotor assessments the morning following LZP compared with placebo. Interestingly subjective assessments (LARS) did not show that participants taking LZP felt drowsy in the morning compared with placebo. This is of concern as although subjects did not feel impaired their cognitive data suggests significant impairment on cognitive and psychomotor tasks.

Similar effects to those described above were seen following a repeated dose of LZP. There was a significant reduction in activity in the 5 h period immediately following dosing, as well as residual effects the following morning. The actigraphic sleep showed a similar profile following the second dose of LZP again with improved sleep and reduced movement.

The present study has endorsed previous findings and shown that psychomotor performance impairment and reduced processing skills, and subjective assessment of sedation are mirrored by actigraphy (Stanley, 1997; Stanley and Hindmarch, 1997; Stanley et al., 1999).

3.7. Limitations

The current study has limitations and recommendations for improvement. As the present analysis was taken from a larger clinical trial the study was not specifically designed for measuring the effect of treatment with actigraphy and therefore may not have been adequately powered. It was necessary to compartmentalise the actigraphy data to avoid the confounding effect of the psychometric testing and pharmacokinetic sampling. This may have further reduced the statistical power of the study. Having stated that, the analysis was able to show an effect on daytime activity and sleep.
3.8. Conclusion

This study provides evidence that actigraphy is sensitive not only to the sedating effects of LZP, as measured by a reduction in behavioural activity, but also to the residual effects of the drug the morning after dosing. The study also confirms that the actiwatch is able to detect the effects of a hypnotic on sleep and is able to provide an indication of the clinical effects of medication. Moreover this study, following the recommendation of Roehrs and colleagues (2000), adds further evidence that actigraphy can provide a reliable and sensitive indicator of the time course of action of psychoactive drugs.
CHAPTER 4 ANTIHISTAMINES

4.1. Introduction

First generation antihistamines have well known sedative effects and impair cognitive function which are reviewed in detail in Section 1.5 (Baselt, 2001; McDonald et al., 2008). These antihistamines, one of which is promethazine, are known to induce central nervous system side effects including psychomotor and cognitive impairment as well as possessing general sedative effects. Promethazine passes through the blood-brain barrier, blocks histamine from binding to its receptors and inducing a stimulating effect, causing the central side effect of sedation and reducing wake behaviour.

Studies have shown that cognitive and psychomotor performance are significantly impaired by promethazine (Clarke and Nicholson, 1978; Parrott and Wesnes, 1987; Hindmarch et al., 2001a, 1999; Nicholson et al., 2003). In addition it has been shown that sedation induced by these antihistamines can also be detected as a reduction in wrist actigraphic ‘activity’ and an increase in actigraphic ‘sleep-like’ minutes (Stanley, 1997; Kamei et al., 2012). Previous work by the author on benzodiazepines has demonstrated that reductions in actigraphic activity mirror impairment of psychomotor performance (Dawson et al., 2008) and Chapter 3. The aim of this work was to assess whether the algorithm applied to detect LZP induced impairment of activity could be applied to other psychoactive drugs with a different mechanism of action.

A clinical trial, conducted between February and March 2005, was used to investigate the effects of three different doses of a novel antihistamine, against the first generation antihistamine promethazine (active control) and placebo. The primary objective of the study was to assess the effect on cognitive and psychomotor function of the novel antihistamine compared with placebo and promethazine. A secondary objective was to assess the efficacy of the novel antihistamine on histamine-induced wheal and flare. The placebo and verum (promethazine) data from this trial has been extracted for analysis.

Promethazine an impairing antihistamine has a T\textsubscript{max} of 4.39 h (range 2 – 8 h) and T\textsubscript{1/2} of 18.6 h (range 9.5 – 29.7 h) (Strenkoski-Nix et al., 2000). It has been shown to specifically impair CTT, CFF and CRT (Baselt, 2001), and induce subjective sleepiness between 2 and 5.5 h post dose (Clarke and Nicholson, 1978) with a performance decrement profile 3 - 8 h post dose (Hindmarch et al., 2001a; Nicholson et al., 2003; Paul et al., 2005).
4.2. Aims

The purpose of the study was to evaluate the appropriateness of the Sleepwatch algorithm and methods developed by the author to assess the effect of a single dose of the antihistamine promethazine 25 mg compared with placebo on motor activity assessed by actigraphy in healthy volunteers kept in controlled laboratory conditions. The analysis was designed to investigate whether actigraphy could accurately reflect the psychometric evidence of sedation associated with promethazine.

4.3. Hypotheses

i. Promethazine will reduce actigraphic activity levels, increase ‘sleep-like’ minutes and increase actigraphic sleep variables compared with placebo. Compared with placebo, promethazine will impair cognitive and psychomotor performance.

ii. The null hypothesis is that there will be no difference between promethazine and placebo in actigraphic activity, actigraphic sleep or cognitive and psychomotor performance.

4.4. Methods

4.4.1. Study design

The original clinical trial was a randomised, double-blind, double dummy, five way crossover, single dose study to examine the effects of 3 different doses of a novel antihistamine compound on cognitive and psychomotor performance function compared with placebo and promethazine. Promethazine 25 mg, is an antihistamine known to produce psychomotor and cognitive impairment as well as possessing sedative side effects was used as an active control (verum). As the purpose of this investigation was the use of actigraphy and the associated performance tests, only the placebo and promethazine results have been used for further/original analysis.

Procedures, including the baseline assessment for psychometric tests, pharmacokinetic samples and wheal and flare, were carried out pre-dose and then at selected time points up to 24 h following administration. Each study treatment period was followed by a wash-out period of between 6-10 days. The study was approved by a COREC approved Ethics Committee and the Quorn Research Review Committee, Quorn Research Review Committee, 25 Church Lane, Old Dalby, Leicestershire, LE14 3LB. During the study participants were required to wear an Actiwatch throughout each study treatment period to measure their overall motor activity 0-12 hours post dose and for sleep during the subsequent 8 hour sleep period, to assess objective measures of sedation and actigraphic sleep. Validated
psychometric tests were performed at +1, +3, +6, +9, +12 h and + 24 h time points to assess objective levels and cognitive and psychomotor impairment and at the same test points the Line Analogue Rating Scales (LARS) was also conducted to assess subjective levels of sedation.

4.4.2. Participants
Healthy adult males ($n = 19$) aged 18-45, were randomised to receive the study medication. The mean ($\pm$ SD) age of the participants was $28.9 \pm 6.7$ years and the mean height, weight and body mass index (BMI) of the participants at screening were $1.77 \pm 0.07$ m, $76.00 \pm 9.14$ kg and $24.16 \pm 2.61$ kg/m$^2$, respectively.

Following informed consent all participants underwent a full medical screening to ensure that they were within the study inclusion/exclusion criteria. The inclusion criteria for the study required that participants were healthy males, non-smokers, 18-45, BMI $>18$ and $<30$ kg/m$^2$ of minimum 50 kg weight, with normal resting ECG, a positive response to histamine-induced wheal and flare by skin prick and a normal sleep-wake cycle. Study restrictions included abstinence from caffeine containing beverages or food, e.g. coffee, tea, chocolate and soft drinks for 24 hours, alcohol for 48 hours and grapefruit and/or grapefruit juice for 72 hours prior to and during the study visit. All participants were tested for alcohol and drugs of abuse at screening and on admission to each treatment period.

4.4.3. Study procedures
Participants were admitted on Day -1 when a wrist actigraph (Actiwatch®) was attached to the participant’s non-dominant wrist. During the evening prior to the first treatment period participants underwent a minimum of 3 training sessions on the psychometric tests. Bedtime (participants’ supine in the dark in a standardised controlled environment) was from 23:00 to 07:00 h. On Day 1 of each study period participants were woken at 07:00 h. Baseline medical checks, including resting 12-lead ECGs, pulse and blood pressure, were performed prior to dosing at 07:15 h, and the psychometric tests were conducted at 07:30 h to obtain pre-dose baseline levels. A pre-dose baseline blood sample was also obtained at 07:25 h and the wheal and flare test (Section 4.4.7) was administered at 08:00 h with the skin test measurement at 08:10 h. Following the baseline procedures during study period 1, participants were assigned a randomisation code. Dosing was performed at 08:30 h. Due to the complexity of the study all procedures were staggered and conducted relative to the drug dosing time to allow for management of the study procedures by the clinical team.
Psychometric tests, including the LARS as a measure of subjective sedation, were conducted at +1, +3, +6, +9, +12 h and +24 h post dose each period followed immediately by the wheal and flare tests. Blood samples were also obtained for pharmacokinetic analysis at +1, +3, +6, +9, +12 h and +24 h post dose. The principles of the psychometric tests are described in full detail in Chapter 2.

Figure 4.1: Study design
Plan to illustrate the study protocol. Drug administration, placebo or promethazine 25 mg (X), arrival (A), departure (D), sleep period 23:00 – 07:00 h, continuous actigraphy (↔), psychometric testing (P) and wheal and flare (W)

Breakfast was administered at +2 h, lunch at +4.5 h and dinner at +11 h post dose. Lights out was at 23:00 h. The following day participants were woken at 07:00 h and the study procedures were repeated at +24 h post dose. After thorough medical examination participants were required to complete a sleep questionnaire (LSEQ), (data not included), and the wrist actigraph was removed and they were discharged from the unit. The study design and timing of the procedures is shown in Figure 4.1.

4.4.4. Actigraphy

Volunteers were required to wear Actiwatch®s, AW4 (Cambridge Neurotechnology Ltd., UK), on their non-dominant wrist for the duration of each study period (2 days) to monitor rest and activity. The Actiwatch was set at the manufacturer’s default medium setting and activity data were captured in 1 min epochs. As dosing was staggered the activity data files clock times were adjusted and synchronised to study time and pooled into 15 minute blocks to control for the confounding activity of the study procedures and analysed with means for 15 mins, 30 mins and 60 mins.
To investigate the effects of treatment when activity was unrestricted and spontaneous, activity data were identified for the times during which the test procedures were not being conducted and the activity of the participants was uncontrolled. To ensure consistent comparative data of the hourly effects for up to 12 h post dose, the last 15 minutes of activity for each hour was extracted and analysed. Data were further subdivided into 4 h sections, 0-4 h, 5-8 h and 9-12 h post dose so that the time course of action of promethazine could be investigated and so that the time period around the $T_{\text{max}}$ of promethazine (2 to 8 h) could be identified and assessed.

The Sleepwatch algorithm was used to score each individual one minute epoch as either 'sleep-like' as 'S' whereby activity counts below 40 were designated as sleep, or 'wake' as 'W'. The addition of the 'S' minutes provided an estimation of the 'sedative' effects of the drug, although it is worth noting that objective psychometric assessments and / or actigraphically measured impairment might not be equivalent to subjective feelings of sedation. As with activity counts, data were pooled into 15 minute blocks and analysed by 15 mins, 30 mins and 60 mins.

4.4.5. Actigraphic sleep variables

Using the Sleepwatch algorithm the sleep period from 23:00 h to 07:00 h was analysed for various sleep summary variables including sleep percentage time, sleep efficiency, sleep bouts, and fragmentation index (Section 2.4.1).

4.4.6. Cognitive and psychomotor function

Cognitive and psychomotor performances were measured in a test battery, which included Choice Reaction Time (CRT); Continuous Tracking Task (CTT) and Line Analogue Rating Scales (LARS) Chapter 2 Sections 2.5.1, 2.5.3 and 2.6.2. The mean scores of ratings of the 'tiredness', 'drowsiness' and 'alertness' factors were taken as a measurement of perceived sedation (Gudgeon and Hindmarch, 1983). These tests are known to be sensitive to the impairing effects of psychotropic compounds (Hindmarch et al., 2005). The test battery was conducted at pre-dose 07:30, then 1 h post dose, followed by 3 h post dose, 6 h post dose, 9 h post dose, 12 h post dose and 24 h post dose the following morning at 08:30. The first two subjects were dosed at 08:30 followed by a 15 minute stagger for subsequent pairs of participants.
4.4.7. Wheal and flare

The wheal and flare test was used to assess skin reactivity to histamine. When a small area of skin is injured, there is local vasodilatation which elicits reddening of the skin. This is followed by a swelling (a wheal) which is localised to the site of the injury and its immediate surroundings. The original site of injury is then surrounded by a much wider area of less intense vasodilatation known as the flare.

The wheal and flare test was performed at designated time points for 24 h following drug administration to assess the clinical effectiveness of the antihistamine. A drop of solution containing 10 mg/mL histamine solution was placed on the volar surface of the forearm. The skin was pricked through the droplet using ALK Lancet (B D Microfine U 100) and then blotted. After ten minutes the areas of the wheal and flare were marked and measured respectively. For the duration of each wheal and flare assessment participants were required to rest their arms (with underside uppermost) on a table in front of them, therefore their activity was restricted.

4.4.8. Statistics

The data for the placebo and promethazine were extracted from a larger five-way treatment study and analysed separately as a two-treatment data set. Baseline values, taken prior to each study period, were used as a covariate to minimise any order effects in the study periods.

Comparison of the effect of promethazine and placebo was conducted separately for each day which was separated into 3 time intervals, 0 to 12 h post dose (08:30 - 20:30 h) for acute effects of the medication, 14.5 – 22.5 h post dose (23:00 - 07:00 h) for evaluation during the overnight sleep period and 22.5 – 23.5 h post dose (07:00 - 08:00 h) post dose for residual effects.

A test for the effect of any carryover of treatment was conducted on the activity data. However no statistical significance was found.

4.5. Results

4.5.1. Actigraphy

Wrist actigraphy measured the activity of the participants 0-12 hours post dose, for the 8 hour sleep period plus the hour after waking. Data from 19 participants were included in the analysis, 17 participants completed all treatments, 1 participant completed 4 visits and 1
participant only 1 visit. As the data were taken from a larger five way crossover study a test for a carryover effect was carried out, nonetheless there was no significant effect of carryover for any of the activity or sleep-like minute time blocks for 12 h post dose ($P > 0.25$).

The purpose of the analysis reported here was to investigate the usefulness of the actigraphy device and to determine whether actigraphy was able to mirror the pharmacodynamics of a drug. Therefore only verum and placebo data are reported. The raw actigraphy files were analysed blind according to the algorithm and the subsequent data analysed by the methods developed in the previous chapter (Section 3.4.4) and are prescribed as a two-way crossover for the comparison between promethazine, the active control, and placebo.

4.5.2. Activity

To account for the interference of the effect of the controlled activity test points, data were further divided and analysed in 15, 30 and 60 min time blocks to determine whether any significant effects were evident.

There was no significant main effect of treatment for promethazine compared with placebo for the 15, 30 or 60 min activity data blocks 0 - 12 h post dose, neither was there any significant effect of treatment for the sleep period (23:00 – 07:00) nor for residual effects following sleep (07:00 – 08:00) for any of the time blocks. The activity profile of the activity counts per minute of the 60 min blocks for 12 h post dose is shown in Figure 4.2.

![Figure 4.2: Time course of effect of placebo (■) and promethazine 25 mg (□) on 12 h activity. Activity presented as mean activity counts per 1 min per hour blocks. There was no overall significant effect of promethazine versus placebo. Tests were conducted at +1 h, +3 h, +6 h, +9 h and +12 h as shown by #. Data are presented as mean ± SEM (n = 19).](image-url)
In order to reduce any confounding effect of restricted activity periods post-hoc analysis was conducted on the last 15 minutes of activity for each hour, (prior to the test points), when activity was spontaneous. Extracted data were further subdivided into 4 h sections, 0-4 h, 5-8 h and 9-12 h post dose in order to cover the $T_{\text{max}}$ to $T_{\frac{1}{2}}$ post dose of promethazine (2.5 to 12 h).

There was no overall significant effect of treatment for the 12 h analysis with regards to reductions in spontaneous activity. Neither was there an effect of treatment for the time sections 0-4 h nor 9-12 h for the last 15 minutes of each hour. Analysis of the 5-8 h post dose period revealed a significant effect of treatment with promethazine reducing activity ($F_{(1,44,1)} = 5.72, P = 0.0378$). Post-hoc analysis revealed a significant effect of treatment at 6 h ($P = 0.0112$), promethazine reduced activity (Mean ± SEM) to 152 (± 19) compared with placebo 293 (± 78) as shown in Figure 4.3.

![Figure 4.3](image_url)

**Figure 4.3:** Time course of effect of placebo (■) and promethazine 25 mg (□) on spontaneous activity. ‘Spontaneous activity’ was taken as the last 15 minutes of every hour, up to and including 12 h post dose. There was an overall significant effect of treatment in the time section 5-8 h post dose ($P < 0.05$). Post-hoc tests revealed a significant effect at 6 h post dose ($* P < 0.02$) compared with placebo. Data are presented as mean ± SEM (n = 19).

There was no effect of treatment on activity during the sleep period (23:00 – 07:00) or for residual effects following sleep (07:00 – 08:00) for any of the different time blocks.

### 4.5.3. Residual effects

There was a significant effect of treatment for promethazine compared with placebo for the 15 min sleep-like activity data blocks 0 - 12 h post dose ($F_{(1,397)} = 7.19, P = 0.0077$), where
promethazine increased sleep-like activity relative to placebo. Post-hoc analysis revealed a significant effect of treatment at time point 23, 6.5 – 6.75 h post dose, $P = 0.0163$, and at time point 42, 11.25 – 11.5 h, post dose $P = 0.0045$.

There was also a significant main effect of treatment for promethazine compared with placebo for the 30 min sleep-like activity data blocks 0 - 12 h post dose with a significant effect of treatment ($F_{(1,202)} = 4.16$, $P = 0.0427$) with promethazine. Post-hoc analysis revealed a significant effect of treatment at time point 10, 4.5 – 5.0 h post dose, $P = 0.0284$; at time point 12, 6.5 – 7.0 h post dose, $P = 0.0257$; at time point 21, 10.0 – 10.5 h post dose, $P = 0.0150$; and at time point 23, 11.0 – 11.5 h post dose $P = 0.0301$, promethazine increased sleep-like activity relative to placebo.

There was a similar significant main effect of treatment for the 60 min sleep-like activity data bins 0 - 12 h post dose ($F_{(1,114)} = 4.92$, $P = 0.0285$) with promethazine increasing sleep-like activity. Post-hoc analysis revealed a significant effect of treatment at time point 5, 4.0 to 5.0 h post dose, $P = 0.0343$; at time point 6, 6.0 – 7.0 h post dose, $P = 0.0288$; and time point 11, 11.0 – 12.0 h post dose, $P = 0.0214$. Promethazine increased sleep-like minutes at time points 5, 6 and 11 to 0.16 (± 0.03), 0.28 (± 0.04) and 0.19 (± 0.4) compared with 0.10 (± 0.2), 0.21 (± 0.4) and 0.11 (± 0.3) compared with placebo respectively (Mean ± SEM) (Figure 4.4).

There was no significant effect of treatment for sleep-like minutes in any of the 4 h blocks up to 12 h post dose for the 15 minute periods of spontaneous activity.

As with the reduction in activity the data showed that the ‘sleep-like’ activity of participants was significantly increased following promethazine treatment compared with placebo and that this occurred between the $T_{\text{max}}$ and $T_{0.25} - 12$ h post dose.
4.5.4. Sleep variables

There was no significant effect of promethazine on any of the actigraphic sleep variables including percentage sleep, number of sleep bouts, fragmentation index or sleep efficiency during the post dose night sleep period from 23:00 to 07:00 hours. The values for each of the variables are shown in Table 4.1.

Table 4.1: Actigraphic sleep variables night one

<table>
<thead>
<tr>
<th>Variable</th>
<th>Promethazine 25mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage Sleep</td>
<td>88 ± 1</td>
<td>89 ± 1</td>
</tr>
<tr>
<td>Number of Sleep Bouts</td>
<td>26 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Fragmentation Index</td>
<td>26 ± 2</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>87 ± 1</td>
<td>87 ± 2</td>
</tr>
</tbody>
</table>

Data are provided as sleep variables calculated with the Sleepwatch Algorithm and presented as mean ± SEM (n = 19).

4.5.5. Cognitive and psychomotor function

4.5.5.1. Choice Reaction Time (CRT) – Total Reaction Time (TRT)

There was a significant main effect of treatment with promethazine increasing Total reaction time (TRT) compared with placebo ($F_{(1,46.7)} = 30.86, P < 0.0001$). *Post-hoc* analysis revealed a significant effect of promethazine 25 mg with an increase in reaction times compared with...
placebo on the individual time points at 1 h (600 ± 36.9, \(P = 0.0076\)), 3 h (669 ± 42.7, \(P < 0.0001\)), and 6 h (617 ± 31.4, \(P < 0.0001\)) post dose compared with placebo (563 ± 23.4, 558 ± 23.2, 552 ± 26.2 at 1, 3, and 6 h respectively) (mean ± SEM) as shown in Figure 4.5B.

4.5.5.2. Continuous Tracking Task – Reaction time (CTT-RT)

There was a significant main effect of treatment with promethazine increasing the response time to the peripheral stimulus component of the CTT-RT compared with placebo (\(F_{(1,40.8)} = 8.49, P = 0.0058\)). Post-hoc analysis revealed a significant effect with increased response times following promethazine 25 mg at the individual time points 3 h (701 ± 16.9, \(P < 0.0001\)) and 6 h (702 ± 19.0, \(P < 0.0001\)) post dose compared with placebo (656 ± 11.6 and 663 ± 16.1 at 3 and 6 h respectively) (mean ± SEM) as shown in Figure 4.5C.

4.5.5.3. Continuous Tracking Task – Tracking error (CTT-ERR)

There was a significant effect of treatment with promethazine increasing the number of tracking error on CTT compared with placebo (\(F_{(1,33.9)} = 13.57, P = 0.0008\)). Post-hoc analysis revealed a significant effect of promethazine compared with placebo with on the individual time points at 3 h (15.6 ± 3.1, \(P < 0.0001\)) and 6 h (13.84 ± 2.2, \(P < 0.0001\)) post dose compared with placebo (9.1 ± 0.9 and 8.9 ± 0.8 at 3 and 6 h respectively) (mean ± SEM) as shown in Figure 4.5D.

4.5.5.4. Line Analogue Rating Scales (LARS).

There was a significant effect of treatment on subjective perception of sedation, with higher sedation scores following treatment with promethazine compared with placebo (\(F_{(1,49.1)} = 55.14, P < 0.0001\)). Post-hoc analysis revealed a significant effect of promethazine compared with placebo on the individual time points at 1 h (61.4 ± 2.3, \(P < 0.0001\)), 3 h (71.8 ± 2.5, \(P < 0.0001\)), 6 h (70.7 ± 2.6, \(P < 0.0001\)) and 9 h (57.4 ± 1.4, \(P = 0.0339\)) post dose compared with placebo (52.8 ± 0.9, 55.0 ± 2.1, 53.3 ± 1.7 and 51.9 ± 1.1 at 1, 3, 6 and 9 h respectively) (mean ± SEM) as shown in Figure 4.5A. Participants treated with promethazine scored higher on the sedation component of LARS compared with placebo, higher scores indicate impairment/sedation.
Figure 4.5: Time course of effect of placebo (■) and promethazine 25 mg (□) on cognitive function. Time course of effect of placebo (■) and promethazine 25 mg (□) on (A) sedation component of LARS; (B) total reaction time (TRT) of CRT; (C) response time of CTT-RT and (D) tracking error CTT-ERR. There was an overall significant effect of treatment on LARS and TRT (P < 0.0001), CTT (P < 0.01) and CTT-ERR (P < 0.001) on the psychometric tests. Post-hoc tests revealed significant effects for all tests at 3 h and 6 h post dose (*** P < 0.0001, ** P < 0.01, *P < 0.05) compared with placebo. Data are presented as mean ± SEM (n=19).

4.6. Discussion

The purpose of this study was to compare changes in actigraphic activity following a single dose of promethazine (25 mg) or placebo with changes in cognition and psychomotor performance. The validated cognitive psychomotor or subjective tests used were the CRT (Hindmarch, 1980), CTT (Hindmarch et al., 1983) and LARS (Hindmarch and Gudgeon, 1980) which are known to be sensitive to the CNS effects of the antihistamine promethazine (Hindmarch et al., 2001a, 1999). Promethazine is commonly prescribed not only for allergic reactions but as an anti-emetic in motion-sickness and as a paediatric sedative at night. The side effects associated with this compound are important to note because patients taking these compounds may find that it impacts on their daily activities including driving or operating machinery with associated safety risks. In addition it is important to assess whether
Actigraphy can detect daytime sedation / impairment as this might be useful in predicting relative safety risks of novel, newly developed antihistamine medications.

Psychometric tests were performed at specific time points across the day in order to profile the pharmacodynamic effects of the drug. However since the tests themselves take time to perform the number of tests used in the study was limited and this may have excluded critical time points of interest. In contrast to the psychometric tests actigraphy provides an unobtrusive continuous measurement of activity and therefore any changes in activity associated with the effects of a drug may be measured in a more time-specific manner. Previous work has shown that promethazine 25 mg reduced daytime activity measured by actigraphy and was associated at 6 h post dose (Stanley, 1997; Hindmarch et al., 1999) with significant subjective sedation, as measured by LARS, and decrements in psychomotor performance in antihistamines.

In the current study there was evidence of significant impairment in cognitive and psychomotor performance 0 – 9 h following a single dose of promethazine (25 mg) compared with placebo. Activity levels were not statistically significantly reduced. However when the level of ‘sleep-like minutes’, (i.e. 1 min activity epochs < 40 counts assessed by the algorithm as ‘sleep’) were assessed, promethazine was shown to significantly increase the amount of sleep-like activity during the 0 – 12 h post dose period with significant effects at 5 h and 6 h post dose (Figure 4.4) coinciding with the $T_{\text{max}}$ to $T_{1/2}$ of the drug. The reason for this dissociation in time between activity levels and cognitive performance is unclear. It could be attributed to the confounding factor of restricted activity during the wheal and flare assessments and psychometric assessments.

To assess whether the potentially confounding time periods, where the activity of participants was either standardised (psychometric testing) or restricted (wheal and flare), impacted on the output, activity was selected from the data panels when the tests were not being performed and activity was not controlled. This enabled ‘spontaneous activity’, as the last 15 minutes of each hour, to cover the whole of the treatment period, to be measured. Analysis showed that there was a significant reduction in activity levels at 5 – 8 h post dose (Figure 4.3).

Promethazine is known to effect sleep variables (Adam and Oswald, 1986) when given 1 h prior to sleep at night by increasing TST and reducing number of awakenings. However, no effect was observed during the sleep period 23:00 to 07:00 h for any of the actigraphic sleep variables in the current study. This could be due to the fact that promethazine was
administered in the morning over 14 h before the sleep period, and past the T½ of 12 h so any
effect was diminished. There was a reduction in the fragmentation index indicating less
movement during sleep, although this was not statistically significant.

This study clearly demonstrates the importance of study design when using actigraphy.
During residential laboratory studies more data are needed to correct for periods when
activity is controlled or restricted as this can confound results. As with the previous study on
the benzodiazepine LZP (Chapter 3), actigraphy was able to show reduced activity due to the
effect of the sedating treatment. In the present study only 15 min of spontaneous activity was
available compared with 30 min in the LZP study. However, as actigraphy recording is
continuous it allows for the investigation of times when activity is not restricted or affected
by other activities unlike cognitive and psychomotor tests that are performed at precise time
points to try and measure the effect of greatest impairment.

Although the length of assessment at each time-point was greater in this study the frequency
of the tests in the current study at +1, +3, +6, +9, and +12 post dose was less compared with
the LZP study where tests were conducted hourly. This scheduling of tests allowed
participants to have more ‘spontaneous’ time. During this time it was found that activity
epochs reduced to very low levels which were calculated as being ‘sleep-like’ with under 40
counts per 1 min epoch. From the data it was clear that promethazine increased the amount
of sleep-like behaviour and that this persisted for up to 6 h post dose.

This study confirms previous evidence (Stanley, 1997) that actigraphy is able to measure
‘sedation’, with significant reductions in activity, up to 6 h post dose following promethazine
administration being observed. Thus actigraphy appears useful for studying the subtle effects
of sedating compounds. Furthermore, in the current study significant reductions were also
observed at 11 h post dose, which might translate to a residual effect of medication in the
morning if given at night.

4.7. Limitations

The current study has similar limitations and recommendations for improvement to the
previous study in Chapter 3. The data for the present analysis were taken from a larger
clinical trial which was not specifically designed for measuring the effect of treatment with
actigraphy. It was again necessary to compartmentalise the actigraphy data to avoid the
confounding effect of the psychometric testing, weal and flare assessments and
pharmacokinetic sampling.
4.8. Conclusions

As in the previous study, the data showed that it was possible to detect changes in daytime activity and sleep due to the psychoactive effect of medication. Actigraphy appears to be useful as an adjunct to clinical studies to measure the effect of sedating medication on activity even when confounding assessments are being performed. This study provides further evidence that actigraphy is sensitive not only to the sedating effects of LZP (Chapter 3) but to the effect of the sedating antihistamine promethazine as measured by an increase in ‘sleep-like’ behaviour.

Although psychometric tests were being performed at distinct time-points, actigraphy was able to show the time-course of promethazine in relation to its pharmacokinetic profile. The activity profile showed a significant reduction in ‘spontaneous’ activity levels during the \( T_{\text{max}} \) to \( T_{\frac{1}{2}} \) of the drug between 5 to 6 h post dose. In addition, by using the algorithm to score the activity epochs as sleep or wake, actigraphy was also able to show a significant increase in ‘sleep-like’ behaviour during the \( T_{\text{max}} \) to \( T_{\frac{1}{2}} \) at 6 h post dose. These detrimental changes in activity mirrored the significant impairment observed in the cognitive and psychomotor function tests from 1 to 6 h post dose. Although these effects occurred earlier than the activity, they are not continuous but only snapshots of the impairing effect. Furthermore, the reduction in activity and the increase in sleep-like activity supported the participants’ subjective feeling of being sedated as shown by the increase in LARS scores.
CHAPTER 5 ANTIDEPRESSANTS

5.1. Introduction

5.1.1. Chronic antidepressant administration

Actigraphy, used in a study of patients with depression in their own home environment would provide a 'real-life' assessment of the effects of a drug on patients. It would be difficult to evaluate the chronic effect of antidepressant medication with patients living in the laboratory since this would not only depend on the time taken to reach the stable dose with different medications but would also not provide an indication of the effect of the drug on the disease in everyday living.

Due to the reported effects of discontinuation of SSRI treatment discussed in Section 1.6.10 it was therefore necessary to study not only the early phases of the treatment but also the long term effects including a discontinuation phase which would highlight the effects of missing or skipping doses.

5.1.2. Selective serotonin reuptake inhibitors (SSRIs) and treatment of depression

Selective serotonin reuptake inhibitors (SSRIs) are widely recognised as treatments for mild to moderate depression and are discussed in detail in Section 1.6. There is evidence to suggest from various reviews that this group of antidepressants affect sleep in laboratory settings with PSG (Wilson and Argyropoulos, 2005; Mendlewicz, 2009; Holshoe, 2009) (Table 1.2). Less work however has investigated the long term effect on sleep in ambulatory field conditions with antidepressants (Kasper et al., 2010). The effect of the respective SSRIs on PSG sleep variables is shown in Table 1.2 in comparison with the effect of depression on sleep, data from (Winokur et al., 2001).

Some antidepressants such as the TCAs promote sleep (Mayers and Baldwin, 2005) whereas the SSRIs are associated with reductions in sleep efficiency, increased latency and sleep disruption. Most antidepressants affect the distribution of REM throughout the night (reviewed in Wilson and Argyropoulos, 2005). The 3 SSRIs listed above have slightly different profiles and mechanisms of action as well as side effects. They also have different half-lives; fluoxetine has a half-life up to 4 days, whereas paroxetine and sertraline both have comparatively short half-lives of 1 day. The active metabolite of fluoxetine continues to be active for 7-15 days, the metabolite of sertraline is active for 66 h, whereas paroxetine has no active metabolite (Nutt et al., 1999; Vaswani et al., 2003; Preskhorn, 1996).
5.2. Aims
The aim of this study was to assess the effect of three non-sedating antidepressant SSRI antidepressants, paroxetine, fluoxetine and sertraline measured in a 12 week single treatment parallel study to assess whether actigraphy could detect changes in activity and sleep associated with treatment and on a week of abrupt discontinuation. The study also explored the relationship of long term anti-depressant medication on sleep and activity cycles as well as cognitive and psychomotor function and subjective ratings of sleep and mood.

To investigate the effect of 3 SSRI antidepressant treatments (paroxetine, fluoxetine and sertraline) on the time course and duration of action on actigraphic sleep and wake variables, subjective sleep quality, depression rating and psychomotor and cognitive performance in depressed patients.

5.3. Hypotheses
i. Paroxetine, fluoxetine and sertraline will affect actigraphic daytime activity, actigraphic sleep, the sleep wake cycle and circadian activity equally for 12 weeks of treatment, and during treatment discontinuation.

ii. Paroxetine, fluoxetine and sertraline will improve depression rating and cognitive and psychomotor performance up to 12 weeks of treatment, and during treatment discontinuation.

iii. The null hypothesis is that paroxetine, fluoxetine and sertraline will have no effect on actigraphic daytime activity, actigraphic sleep, the sleep wake cycle and circadian activity up to 12 weeks of treatment, and during treatment discontinuation.

iv. The null hypothesis is that paroxetine, fluoxetine and sertraline will have no effect on depression rating or cognitive and psychomotor performance up to 12 weeks of treatment, and during treatment discontinuation.

5.4. Methods
5.4.1. Design
This was a phase IV, randomised, double-blind, parallel group, multi-centre study in which depressed patients Montgomery-Åsberg Depression Rating Scale (MADRS ≥20) diagnosed as requiring antidepressant treatment were randomised to receive either paroxetine, fluoxetine or sertraline antidepressants.

The study was given a favourable ethical opinion from the local ethics committees of South West Surrey and the University of Surrey, together with the Cornwall Local Research Ethics
Committee which covered the area of the GP investigators in the Cornwall Clinical Research Group who carried out the study. Following study initiation GPs were trained to ensure consistency of scoring the MADRS and other questionnaires, study administration, actigraph set up and psychometric procedures.

The MADRS, designed to be sensitive to the changes and treatment effects (Montgomery and Asberg, 1979) of antidepressants, was used to assess eligibility in this study by the GP at the clinical interview visit 1, to record depression scores prior to randomisation. Baseline scores, whereby patients rated with a score of ≥ 20, and matched the inclusion eligibility criteria were entered into the study.

5.4.2. Patients

Patients (n = 99) (18 years and over) diagnosed with depression, defined as requiring treatment for depression on clinical grounds with a Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥ 20 (moderate-severe) (Snaith et al., 1986) at screening Visit 1 (Day 0), were recruited onto the study provided that the patients were able and willing to give informed consent, and were willing to fulfil the study obligations and restrictions including attending all the study visits, performing all the assessments and wearing an Actiwatch throughout.

Recruitment was conducted over 5 months at 9 centres by approximately 12 general practitioners (GPs) as local site investigators. The number of patients ranged from 1 to 24 at each centre. It was anticipated that to obtain 75 completed patients, 100 patients would be required to ensure 25 patients in each treatment group to test the null hypothesis that paroxetine, fluoxetine and sertraline have the same effects on rest-activity up to 12 weeks of treatment and upon discontinuation.

Patients were excluded from recruitment if they had received drug treatment for depression within the previous 3 months, had a history of drug allergy, or serious cardiovascular disease, serious psychological or neurological disorders, history of cancer, were shift-workers or were any patient that the physician or investigator felt was unsuitable.

5.4.3. Study design

The study was a randomised, double-blind, parallel group, multi-centre investigation conducted in general practice. There was no baseline period as patients were randomised to treatment at the first visit (Visit 1). There was no placebo dosing comparator as it was
considered unethical not to dose patients with active drug when efficacious treatments were available.

Cognitive and psychomotor assessments were conducted at each visit throughout the study and are described in detail in section 2.5. Patients were required to wear an Actiwatch (AW4 Cambridge Neurotechnology) continuously throughout the study to measure their rest-activity patterns. At a pre-determined time, from Visit 12 to Visit 13, treatment was discontinued abruptly for 7 days with the substitution of placebo for the active drug to compare the effect of each medication discontinuation. The timing of the discontinuation was blind both to the investigators and patients. All visits were scheduled to occur at approximately the same time of day and patients were advised to take their medication at the same time each day, morning or evening.

Patients were assessed at 14 visits on Days 0, 1, 2, 3, 5, 7, 10 and 14 for Visits 1 to 8, and then at weeks 4, 8, 11, 12, 13 and 14 for Visits 9, 10, 11, 12, 13 and 14, respectively. The study visit schedule is shown in Figure 5.1. Cognitive and psychomotor tests, questionnaires and depression rating scales were assessed at each visit as well as clinical efficacy, safety, and quality of life measures. To ensure patients were assessed according to the visit schedule there were allowable windows for each visit from week 2 Visit 8 of ± 2 days.

During routine clinic appointments, patients suffering from depression were identified as potential participants in the study by their GP and given the informed consent document to review. If following due consideration they were willing to participate in the study they were invited to return and attend Visit 1 for informed consent. At this visit eligibility was confirmed with the inclusion/exclusion criteria and baseline assessments were performed. A unique patient number was assigned, the investigational medication kit was allocated and the first Actiwatch, set to record at 1 min epoch was dispensed.

Further packs of medication were dispensed at Visits 6, 8, 9, 10, 11, 12 and 13. For 12 weeks the patients received the allocated medication, this was followed by a one week period when they received placebo followed by a further week when they again received study medication. Neither the patient nor the investigator was aware of which medication the patient was receiving or the timing of the placebo treatment.
Figure 5.1: Study visit schedule
To show the relationship of study duration with number of days, weeks and visits in relation to the Actiwatch schedule and discontinuation/withdrawal of treatment phase. Actiwatch 1, set at 1 min epoch, was dispensed at Visit 1 and worn for 4 weeks from Visit 1 to Visit 9; Actiwatch 2, set at 2 min epoch, was worn for 8 weeks from Visit 9 to Visit 12; and Actiwatch 3, set at 1 min epoch was worn for 2 weeks from Visit 12 to Visit 14. The medication was discontinued abruptly and replaced by placebo from Visit 12 to Visit 13, weeks 12 to 13.

5.4.4. Study medication
Study medication consisted of fluoxetine (20mg capsules), paroxetine (20mg capsules) or sertraline (50mg capsules), together with matching placebo for the discontinuation phase. The treatment pack for each patient contained 8 boxes one of each to be dispensed at Visits 1, 6, 8, 9, 10, 11, 12 and 13 (Weeks 0, 1, 2, 4, 8, 11, 12 and 13). Each box contained blister strips of medication for oral administration. Patients were to take their medication on a daily basis at the same time each day.

At the first visit patients were sequentially randomised to receive fluoxetine (20 mg/day), paroxetine (20 mg/day) or sertraline (50 mg/day). The patient and investigator were not informed of the timing of the 7-day placebo substitution period, which took place between visits 12 and 13, i.e. placebo treatment started after all assessments had been completed at Visit 12. At Visit 12 (Week 12) patients were dispensed with a pack of placebo to replace medication to simulate one week of abrupt discontinuation.

5.4.5. Study measures
To investigate the effects of paroxetine, fluoxetine and sertraline on aspects of actigraphic sleep, wake and mood depression rating scales, quality of sleep questionnaires and cognitive and psychomotor performance assessments were conducted. The assessments to measure the effects of medication on cognitive function and psychomotor performance included Critical Flicker Fusion (CFF) (Section 5.4.9.2), Choice Reaction Time (CRT) (Section 5.4.9.1), Cognitive Failures Questionnaire (CFQ) (Section 5.4.9.11), and Line Analogue Rating Scale (LARS) (Section 5.4.9.5). These tests are referred to in more detail in Chapter 2.
actigraphic sleep was assessed using the Actiwatch (Sections 5.4.6 and 5.4.7) and the Leeds Sleep Evaluation Questionnaire (LSEQ) (Sections 2.6.1 and 5.4.9.4) was used to assess subjective quality of sleep. Depression severity was measured by the physician with the MADRS (Section 5.4.9.7) and the Hamilton Depression Scale (HAMD) (Section 5.4.9.8) and the patient-rated ZUNG Depression Inventory (Section 5.4.9.10). At the final assessment (Visit 14) the investigator was required to determine whether continuation of treatment with an SSRI was warranted and if so an antidepressant of choice was prescribed.

5.4.6. Actigraphy

Patients were required to wear Actiwatches AW4 (Cambridge Neurotechnology Ltd., Cambridge, UK) on their non-dominant wrist for the duration of the study to monitor rest and activity. Actigraphy records activity in counts per epoch so changes in activity may be observed and measured and therefore provides a continuous measure. The maximum storage of the Actiwatch was 45 days at 1 minute epoch. As the duration of the study was 98 days actigraphy was recorded in three separate files.

When a suitable patient was screened and consented, an appointment for Visit 1 was made. A request was placed by the prescribing GP for the first Actiwatch (AW1) to be set up and sent same day from one of the two GP set-up surgeries, for dispensing and attached at Visit 1. After 4 weeks at Visit 9, AW1 was returned to the GP by the patient (week 4). Actiwatch (AW2), set to record at 2 min epoch, was set up and sent to the GP from University of Surrey to coincide with Visit 9. At the end of 8 weeks at Visit 12, AW2 was returned to the GP by the patient (week 12). Actiwatch (AW3) sent from University of Surrey, set to record at 1 min epoch, was attached. AW3 was returned at the final visit, Visit 14. At the end of each phase the Actiwatches were sent back to the University of Surrey from the investigator site to be downloaded (Figure 5.1).

In order to cover the study duration with as few Actiwatches as possible different epochs were used. To cover the critical periods during the first 4 weeks of medication and the discontinuation phase of the last 2 weeks the Actiwatch epoch was set at 1 minute. Since the maximum data storage duration set at 1 min epoch was 45 days, to reduce the number of changes and cover the middle period, the epoch was set at 2 min to cover the 8 weeks from week 4 to week 12 (Visits 9-12).

As the patients were living at home not in a controlled environment, and they slept to their own habitual bedtimes, they were requested to press the event marker on the Actiwatch to record when they put the lights out to go to sleep in the evening and again in the morning.
when they woke up to indicate the end of their sleep period. They were advised to remove the Actiwatch when bathing. Patients were required to complete a daily diary (Appendix VIII) which was a simple log to record bedtimes and wake times and also daytime activities.

The Actiwatches were purchased specifically for the study and were calibrated prior to delivery. If the Actiwatch failed to download or the actogram when downloaded appeared to exhibit an abnormal reduction of overall activity or unusual activity patterns, then the Actiwatches were returned to the manufacturer for data retrieval or validity and verification. Any obvious data considered not suitable for inclusion in the analysis was rejected, this included sensor faults. Data were captured electronically.

5.4.7. Actigraphy analysis

5.4.7.1. Data download and preparation procedures

Prior to download to ensure that the actual times registered were correct the computer clock at the University of Surrey was synchronised to the correct real time (GMT or BST) using a radio controlled clock. As a check to determine whether the internal clock of the Actiwatch was accurate the event marker was pressed and the time was recorded in a log, after a few minutes the data from the Actiwatch was downloaded and the event marker check time was compared with the actual time of pressing the marker, differences were noted in the individual participant logs.

Following download the actogram was reviewed for any obvious discrepancies and these irregularities were noted in a log including any marker time errors. These observations included non-compliance issues such as shift work patterns, missing data and abnormal activity related to an Actiwatch sensor fault. The actograms and event marker record were printed off, signed and dated. The actograms were also reviewed for the overall sleep window to determine the sleep analysis start and end times. By checking the marker at download it was discovered that the internal computer clocks at the 2 surgeries, where the first Actiwatches (AW1) were set up, were incorrect. One surgery, organised to set up most of the Actiwatches, was approximately 1.5 hours in advance of real time and the other surgery was approximately 1 hour in advance. It was therefore necessary prior to analysis to adjust the start times of the *.awd data files to correct the time errors by opening the file in notepad and amending the start time.

Prior to analysis the epochs of the first and third *.awd data files were changed to 2 min epoch in order to harmonize and analyse all data files with the same epoch length, for
accurate comparison of outputs across the datasets and not to introduce errors by forcing the 2 minute data into 1 minute epochs. The activity and sleep/wake variables were automatically calculated using the Sleepwatch® software (version 5.51) set at the manufacturer’s default medium setting. In addition where necessary, to adjust for clock time changes from Greenwich Mean Time (GMT) to British Summer Time (BST) to ensure that data files were correct to actual time, separate *.awd data files were created for pre and post the clock change.

5.4.7.2. Sleepwatch analysis procedures

The Sleep Analysis window was opened, then from the Sleep Diary dropdown menu the analysis window was set to broadly cover the patient’s sleep period with all the sleep start and end times, as pre-determined by visual inspection of the actogram. The ‘read markers’ button was activated and the markers, if set by the patient, were selected and the automatic calculation of the sleep variables was conducted using the internal algorithm. Following the automatic analysis each day was visually checked to confirm the presented analysis, or manually adjusted by resetting the sleep and end times and recalculated if markers were not set or not appropriate. The manual sleep start and sleep end times were captured as observed by a reduction in activity prior to sleep start and the resumption of activity after waking. Nights when the Actiwatch was not worn were not included.

The panel of sleep variables for each of the sleep files were saved as an AWS summary file and each summary was exported to Excel 2003. The three summary files for AW1, AW2 and AW3 were amalgamated into one Excel workbook, and then joined to form one worksheet where the study and visit days from Visit 1 Day 1 to Visit 14 Day 96 were identified. Some Actiwatches were attached after Visit 1, therefore the excel files were adjusted to take account of this by inserting blank nights to ensure that visit dates corresponded to dates from the excel output to allow accurate statistical analysis from Day 1 Visit 1. The extracted sheets were checked to confirm that all days were included in the summary, since the program just exported analysed nights. Extra blank nights were inserted if there were missing data to ensure that all dates were included and the file continuous. Extra rows were added to convert the values presented from clock time to decimal time for ease of analysis, so when the times occurred after midnight, the midnight value as 00:00 h was converted to 24.00 h and 01:30 h converted to 25.50 h.

The data for the first 24 h in each panel were adopted as the baseline in order to assess change across time. The excel data panel for each participant was extracted to a SAS data file and a SAS program (SAS®Version 9.1 Statistical Analysis Software, SAS Institute,
North Carolina, USA) written by Dr Sigurd Johnsen (University of Surrey) was used to extract the weekly means for each individual variable. This resulted in an output file for each of the treatments for each variable calculated as weekly means. A further SAS program calculated the statistical significance between the treatments, and between the study weeks.

5.4.7.3. Sleepwatch variables

The variables analysed for this study are as fully described in Section 2.4.1. The variables calculated for this study with the 2 minute epoch were:

- Time in bed (TIB)
- Assumed sleep time / Sleep period time (SPT)
- Actual sleep time / Total sleep time (AST/TST)
- Actual awake time / Wake after sleep onset (AWT/WASO)
- Sleep efficiency (SE)
- Sleep latency (SOL/SL)
- Sleep bouts (SB)
- Sleep bout time (SBT)
- Total activity counts in sleep
- Average wake movement (AWM)

5.4.8. Circadian rhythm analysis

Circadian rhythm activity was determined by 2 methods namely Cosinor analysis (Nelson et al., 1979) and Non-parametric circadian rhythm analysis (NPCRA) (Van Someren et al., 1999). For both analyses the first Actiwatch files were adjusted for the clock error by editing the start time of the recording by opening the text file in the ‘Notepad’ program and amending the time. Since the Actiwatch files were of different epochs and lengths all Actiwatch files were also converted to a common 1 minute epoch. In addition files were adjusted for GMT and BST time, and separate files created where necessary.

5.4.8.1. Cosinor analysis

Cosinor analysis is explained in full in Section 1.6.9.1 (Dowling et al., 2005; Calogiuri et al., 2013). The values calculated were:

- Amplitude: Difference between the mesor and peak activity
- Mesor: Mean activity value
- Rhythm %: Percentage of data points that fit the cosine curve
- Acrophase time: Time of peak activity during the biological day
5.4.8.2. Cosinor analysis procedure

A macro provided by Dr Rob Meadows (University of Surrey) was used to extract the 24 h mean activity values for each day for each of the Actiwatch awd files. Data cells were excluded where the Actiwatch had been removed and the mean hour values were adjusted to account for the clock change from Greenwich Mean Time (GMT) to British Summer Time (BST) where the Actiwatch had been worn across the time change weekend. The mean hour values were grouped into weeks, aligned with the visit dates, if there was a visit deviation, and then averaged. The averaged data were then fitted to a cosinor model using a program provided by Dr D Minors (Nelson et al 1979; Minors and Waterhouse, 1989), and the circadian rhythm variables, as described in Section 5.4.8.1 for activity, were calculated.

5.4.8.3. Non-parametric circadian rhythm analysis (NPCRA)

Non-parametric circadian rhythm analysis (NPCRA) is explained in Section 1.6.9.2. The following NPCRA variables for activity were calculated:

- Average: The mean activity of the 6 minute blocks over the 24 h period.
- Amplitude: The difference between the daily averages for the activity during the 10 hours with the most activity (M10) and the 5 hours with the least activity (L5). This provides an indication of the circadian rhythm.
- Interdaily Stability (IS): The stability of the rhythm which ranges from 0 to 1. If a patient had the same schedule every day with activities and rest at exactly the same times the stability would be 1. A normal value is considered to be approximately 0.6.
- Intradaily Variability (IV): Provides an indication of the fragmentation of the rhythm ranging from 0 to 2 where 2 is indicative of an unstable rhythm. The normal value would be approximately 1.
- M10: Mean activity of the 6 minute blocks during the 10 most active hours.
- M10 onset time: the start time of the 10 hours of maximum activity (M10).
- L5: Mean activity of the 6 minute blocks during the 5 least active hours.
- L5 onset time: the start time of the 5 hours of least activity (L5).
- Relative Amplitude: Calculated by dividing the amplitude with the sum of M10 and L5, provides a range from 0 to 1 where higher values are indicative of a higher amplitude (Kasper et al., 2010).
5.4.8.4. Non-parametric circadian rhythm analysis (NPCRA) analysis procedure

The Actiwatch files were adjusted for the clock error by editing the start time of the recording by opening the text file in the ‘Notepad’ program and changing the time. All Actiwatch files were then converted to a common 1 minute epoch. As the macro was not written for files longer than 30 days the 8 week files were split into manageable 30 day sub-files. The activity data were then analysed in weekly blocks using an excel macro (provided by Prof. Eus Van Someren) whereby the start dates and times were entered. Any days or parts identified as unreliable or missing, e.g. due to non-compliance where patients had omitted to wear the Actiwatches, were entered in whole 24 h periods and were removed from the analysis.

5.4.9. Cognitive and psychomotor function

Cognitive and psychomotor performance was measured by the Leeds Psychomotor Tester, which comprised the Choice Reaction Time (CRT) and Critical Flicker Fusion (CFF). These tests are known to be sensitive to the impairing effects of psychotropic compounds (Röschke et al., 2000; Hindmarch et al., 2005). CRT and CFF tests have previously been described in Sections 2.5.1 and 2.5.2, respectively. The patients completed the tests at all Visits 1 to 14, however, only the data from Visits where depression was also assessed are presented which were Visits 1 (baseline), 7, 8, 9, 10, 11, 12, 13 and 14 (corresponding to study weeks 0, 1, 2, 4, 8, 11, 12, 13 and 14).

5.4.9.1. Choice Reaction Time (CRT)

The CRT, as described in detail in Section 2.5.1, was conducted at each visit. The components of the test, Recognition Reaction Time (RRT) and Motor Reaction Time (MRT) were individually measured and combined to provide the Total Reaction Time (TRT).

5.4.9.2. Critical Flicker Fusion (CFF)

The CFF, as described in detail in Section 2.5.2, was conducted at each visit. Patients were required to discriminate flicker from fusion, and vice versa, in a set of four light emitting diodes arranged in a one centimetre square.

5.4.9.3. Questionnaires

Questionnaires were used to evaluate patients’ subjective ratings of the effects of the antidepressants. The Line Analogue Rating Scale (LARS) (Appendix VI) was employed to measure perceived daytime sedation. The mean scores of ratings of ‘tiredness’, ‘drowsiness’, and ‘alertness’, presented among several distracter scales, were taken as a measurement of
perceived sedation. Subjective sleep quality was assessed using the Leeds Sleep Evaluation Questionnaire (LSEQ) (Appendix V), cognitive impact was assessed with the Cognitive Failures Questionnaire (CFQ) (Appendix IV), and depression with the ZUNG (Appendix III). Depression rating was also evaluated using the physician rated depression scales of MADRS (Appendix I) and HAMD (Appendix II) as detailed in the following sub-sections.

5.4.9.4. Leeds Sleep Evaluation Questionnaire (LSEQ)
The LSEQ, described in detail in Section 2.6.1, was used to assess the subjective rating of sleep of the patients and was completed at each visit by the patient to record changes in perceived sleep quality. At Visit 1, for the baseline night, patients were required to compare their sleep for ‘last night’ with ‘sleep in the past week’. The polarity of some of the individual lines was reversed to ensure that patients read the scales correctly. For all subsequent Visits patients were required to compare their sleep ‘using the medication’ to normally ‘without the medication’. The questionnaire was completed by the patients at all visits but only the data for weeks 0, 1, 2, 4, 8, 11, 12, 13 and 14 were used in the analysis.

5.4.9.5. Line Analogue Rating Scale (LARS)
The LARS as described in detail in Section 2.6.2 was used to assess patients’ present feelings with that before treatment. Subjective evaluation of perceived sedation was obtained from the mean scores of ratings of “tiredness”, “drowsiness” and “alertness”. The questionnaire was completed by the patients at all visits but only the data for weeks 0, 1, 2, 4, 7, 8, 11, 12, 13 and 14 were used in the analysis.

5.4.9.6. Depression scales
Three depression rating scales MADRS, HAMD and ZUNG were used in the study to assess the subjective effect of SSRI treatment on patients’ depression and subsequent improvement. The MADRS and HAMD were completed by the GP and the ZUNG by the patient. The questionnaires were completed at weeks 0 (baseline), 1, 2, 4, 8, 11, 12, 13 and 14 (corresponding to visits 7, 8, 9, 10, 11, 12, 13 and 14) to monitor the level of depression and efficacy of treatment. During the first weeks there were frequent assessments to cover the early onset of the relief of depressive symptoms from visit 1 prior to treatment, then at 1, 2 and 4 weeks. Questionnaires were administered at week 13 following the discontinuation week and at week 14, following one week of treatment resumption.

The MADRS, designed to be sensitive to the changes and treatment effects (Montgomery and Asberg, 1979) of antidepressants, was used to assess eligibility in the current study by
the GP at the clinical interview visit 1, to record depression scores prior to randomisation. The HAMD was shorter in time to administer than the MADRS. To improve inter-rater variability the GPs were trained on administering the questionnaires during the study initiation. In addition, as the study was a clinical trial patients were their own control and therefore change across the study and within each patient was measured.

It was important to monitor and capture the outcomes of these questionnaires during the first 4 weeks of treatment on the current study more intensely to determine when the onset and response of treatment occurred.

5.4.9.7. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS questionnaire was originally designed as a rating scale to be sensitive to change and treatment effects (Montgomery and Åsberg, 1979) and was related to the mental aspects of depression such as sadness, tension and pessimistic suicidal thoughts. The MADRS (Appendix I) consists of 10 items related to depressive feelings (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thought and suicidal thoughts) with each item graded 0 to 6.

The ratings were based on a clinical interview completed by the same GP at each visit. The total of the scores for the ten items was an indicator of the severity of depression, 0 to 6 normal to recovered, 7 to 19 mild, 20 to 34 moderate and 35 to 60 severe (Bhatt et al., 2011). A subset of item 4 for reduced sleep which represented the experience of reduced duration or depth of sleep compared with patient’s own pattern when well was also evaluated. Baseline scores, whereby patients rated with a score of ≥ 20, and matched the inclusion eligibility criteria were entered into the study. Patients were included in the study if their score was > 20 at baseline Visit 1.

The sleep subset of Question 4, on reduced sleep (Lader et al., 2005) was used in the analysis to specifically review changes in perceived sleep duration, the subset was marked out of 6 whereby 0 was scored for no change, 1-2 slight difficulty dropping off to sleep or slightly reduced, 3-4 indicated reduced sleep by at least 2 hours and 5-6 indicated less than 2-3 h sleep (Appendix I MADRS).
5.4.9.8. Hamilton Depression Rating Scale (HAMD)

The Hamilton Depression Rating Scale (Hamilton, 1960) (Appendix II) was designed to measure the severity of depression in patients already diagnosed as suffering from depressive illness. The HAMD scale was completed by the same GP at each of the study visits 1, 7, 8, 9, 10, 11, 12, 13 and 14, and was used to assess the state of the patient’s current condition with that over the preceding few days. There are various versions of the HAMD which originated in 1960 (Hamilton, 1960) and in this study the 17 item version of the questionnaire was used. According to the scoring patients severity is assessed from 0-7 normal, 8-13 mild, 14-18 moderate, 19-22 severe, > 23 very severe depression.

The HAMD consists of 17 items which relate to depressive feelings (mood, guilt, suicide, insomnia, work and activities, retardation, agitation, anxiety, somatic symptoms, loss of libido, hypochondriasis, weight loss and insight), with the items being rated according to severity either on a 0-2 point or a 0-4 point scale. The total of the scores for the 17 items was used in the analyses. In addition further analysis of the sleep questions was conducted. A sleep subset of items 4-6 relating to insomnia (difficulty getting to sleep, restlessness, waking in the night and waking early) and a further subset for item 4 relating to insomnia occurring early in the night (difficulty getting to sleep) was evaluated.

5.4.9.9. MADRS and HAMD sleep items

As previously stated poor sleep or insomnia is a major factor in depression (Benca and Peterson, 2008) and both of the depression questionnaires have scales related to questions on sleep which is useful for comparison with other objective and subjective ratings of sleep duration or quality. The sleep question in MADRS Item 4, comprised a scale of 1 to 6 on aspects of sleep duration or ‘reduced sleep’ from 0 = sleep as usual, through to ‘slight difficulty dropping off’ or ‘fitful sleep’ = 2, ‘sleep broken or reduced by 2 hours’ = 4 to the extreme ‘less than 2 or 3 hours sleep’ = 6. ‘Sleep disturbance’ according to previous literature is a score of 2 or more (Williamson et al., 2006) in bipolar patients. The full questionnaire is shown in Appendix I.

The HAMD sleep questions relate to issues of insomnia. Question 4 relates to insomnia occurring early in the night rated as 0 = ‘no difficulty falling asleep’ = 0, ‘occasional difficulty’ = 1 and ‘nightly difficulty’ = 2. Similarly for question 5 which relates to middle of the night insomnia where ‘patient complains of being restless and disturbed’ = 1, and waking during the night and getting out of bed’ = 2. Question 6 relates to early waking, ‘waking in early hours but gets back to sleep’ = 1 and ‘waking but unable to fall back to sleep again’ =
2. The maximum score for insomnia occurring early, middle and late was therefore 6 (Fava et al., 2002). The full questionnaire is shown in Appendix II.

5.4.9.10. ZUNG Depression Inventory

The ZUNG Depression Inventory (ZUNG, 1965) (Appendix III) was a subjective questionnaire completed by the patient in contrast to the MADRS and HAMD which were completed by the GP. It was developed to be self-completed by the patient to indicate their own feelings during drug treatment and consisted of 20 sentences which the patient scored out of 4 quantitative terms: ‘none or a little of the time’, ‘some of the time’, ‘good part of the time’, ‘most or all of the time’. The 20 sentences related to mood, somatic symptoms, irritability and agitation, indecisiveness, suicide, worthlessness, fatigue and weight changes. The answers were scored 1 - 4, the lower the score the better the outcome for that sentence, 80 being the worst overall score. The total of the scores for the 20 sentences was used in the analysis. The questionnaires were completed by the patients at weeks 0, 1, 2, 4, 8, 10, 11, 12, 13 and 14, corresponding to study visits 1, 7, 8, 9, 10, 11, 12, 13 and 14. Values for depression severity were < 50 (normal), 50 to 59 (mild), 60 to 69 (moderate), and > 69 (severe) (Passik et al., 2002) with most people with depression scoring between 50 and 69 (Cusin et al., 2010).

5.4.9.11. Cognitive Failures Questionnaire (CFQ)

To measure the effects of treatment in the present study patients were also required to rate their feelings for self-reported, cognitive failures in perception, memory and motor function in everyday activities using the CFQ. The Cognitive Failures Questionnaire (CFQ) was a measure of self-reported cognitive failure in perception, memory and motor function, developed by (Broadbent et al., 1982) comprising 25 possible failures covering the three general areas (Appendix IV).

Participants self-rated how often they had experienced each problem since the last visit, using a five point scale ranging from ‘never’ (0) to ‘very often’ (4). The lower the score the better, the maximum impairment score for cognitive failures was 100. Higher scores have been shown to correlate significantly with depressive symptoms (Hohman et al., 2011; Farrin et al., 2003) with values of 38 for controls and 59 for depressed patients, lower values indicating less anxiety. The questionnaire was completed by the patients at weeks 1, 2, 4, 8, 11, 12, 13 and 14 corresponding to study visits 1, 7, 8, 9, 10, 11, 12, 13 and 14.
5.4.10. Statistical analysis

All results were analysed using a linear mixed model (SAS®Version 9.1) with fixed effects for participant and treatment, and time as a repeated measure. Tests were used to determine which times or treatments were significantly different. Pairs of treatments were statistically contrasted within visits, where appropriate, estimates, 95% confidence limits and P-values, unadjusted for test multiplicity, being examined. Pairs of visits were also statistically contrasted within treatments, estimates, 95% confidence limits and P-values, unadjusted for test multiplicity, being examined. A trend towards statistical significance was shown by ‘=’ if the P-value was < 0.1.

5.5. Results

The data presented here were taken from the larger clinical trial and for the purpose of this investigation only the results of those participants that completed the study and consistently wore the Actiwatch were analysed and are presented. The data were analysed using the methods developed in Chapter 2 to determine whether there were any statistically significant effects of the SSRIs on the time course of treatment of the variables measured; whether there was any statistical difference between treatments; and to determine whether actigraphy was sensitive enough to measuring the effect of the SSRIs on activity and sleep. The results are presented in sub-sections for the full study weeks 0 to 14, for the treatment period weeks 1 to 12 and for the withdrawal and discontinuation period weeks 12 and 13.

5.5.1. Demographics

The total number of patients that were randomised to the study was 99 with 33 patients in each treatment group. Vital signs (blood pressure and heart rate), weight, date of birth and sex were recorded and completed on the Informed Consent page in the Case Report Form (CRF) at Visit 1. The average age of all patients in the study (n = 99) was 43.5 (± SEM 1.3) years, with a range of 19 - 84 years. The mean MADRS score overall was 29.3 (± SEM 0.8) with a score range from 20.0 to 40.0, a score of 7 to 19 being mild, 20 to 34 moderate and 35 to 60 severe (Table 5.1).

For the purpose of this study in order to compare actigraphy data with cognitive and psychomotor assessments and depression rating scales only patients (n = 56) that completed either the whole study of 14 weeks (n = 54) or up to and including the discontinuation week of 13 weeks (n = 2) and consistently wore the Actiwatch were eligible and therefore analysed (Table 5.2). Fifty six patients were included in the final analysis having completed at least 13 visits, including the discontinuation phase Visits 12 to 13. In order to be included patients
were also required to have been compliant with wearing the Actiwatch for the duration of the study. Patients were not included in the analysis if they were withdrawn due to adverse event or did not complete all visits (n = 8, n = 7, n = 10 for paroxetine, fluoxetine and sertraline, respectively) as shown in study flow chart Figure 5.2. Further, patients were excluded if they had not consistently worn the Actiwatch, were shift workers or had unusual sleep/wake patterns (n = 5, n = 8, n = 5 for paroxetine, fluoxetine and sertraline, respectively).

Table 5.1: Summary of demographics for the full data set at randomisation before treatment

<table>
<thead>
<tr>
<th></th>
<th>Paroxetine 20 mg/day</th>
<th>Fluoxetine 20 mg/day</th>
<th>Sertraline 50 mg/day</th>
<th>All treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 33</td>
<td>N = 33</td>
<td>N = 33</td>
<td>N = 99</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>11</td>
<td>6</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Females</td>
<td>22</td>
<td>27</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>44.9 (2.3)</td>
<td>43.6 (2.5)</td>
<td>42.0 (2.2)</td>
<td>43.5 (1.3)</td>
</tr>
<tr>
<td>Min</td>
<td>19</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Max</td>
<td>76</td>
<td>84</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>MADRS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>29.0 (0.8)</td>
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<td>29.7 (0.7)</td>
<td>29.3 (0.8)</td>
</tr>
<tr>
<td>Min</td>
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<td>37.0</td>
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<td>40.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Patients were required to have a physician rated MADRS score $\geq$ 20 at screening, in order to be included in the study, a score of 7 to 19 = mild; 20 to 34 = moderate; and 35 to 60 = severe depression. MADRS = Montgomery-Åsberg Depression Rating Scale.

The average age of all patients in the completer’s dataset was 46.0 ± 12.1 years, with a range of 21.4 – 83.6 years. The demographics of these patients are presented in Table 5.2. The mean age in the three treatment groups was 48.1 ± 9.9, 45.2 ± 13.4 and 44.6 ± 13.3 years for paroxetine (20 mg/day), fluoxetine (20 mg/day) and sertraline (50 mg/day), respectively. Of those, 20 patients (6 male) received paroxetine, 18 (1 male) received fluoxetine and 18 (5 male) received sertraline. Two patients (1 male, 1 female) from the paroxetine group who completed up to and including Visit 13 week 13 were also included in the analysis. The study flow chart of patient randomisation is shown in Figure 5.2.

The mean MADRS score overall was 28.7 (± 0.6), and in the three treatment groups was 28.8 (± 1.1), 28.3 (± 1.1) and 29.0 (± 0.9) for paroxetine 20 mg/day, fluoxetine 20 mg/day and sertraline 50 mg/day, respectively.
Table 5.2: Patient randomisation demographics and numbers for dataset of completers

<table>
<thead>
<tr>
<th>Completers dataset</th>
<th>Paroxetine 20 mg/day N = 20</th>
<th>Fluoxetine 20 mg/day N = 18</th>
<th>Sertraline 50 mg/day N = 18</th>
<th>All treatments N = 56</th>
</tr>
</thead>
<tbody>
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<td>Gender</td>
<td>Males</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>14</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SEM)</td>
<td>48.1 (2.2)</td>
<td>45.2 (3.2)</td>
<td>44.5 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>33</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>65</td>
<td>84</td>
<td>74</td>
</tr>
<tr>
<td>MADRS score</td>
<td>Mean (SEM)</td>
<td>27.9 (1.7)</td>
<td>24.9 (1.8)</td>
<td>26.5 (1.8)</td>
</tr>
<tr>
<td></td>
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Patients were required to have a physician rated MADRS score ≥ 20 at screening, in order to be included in the study, a score of 7 to 19 = mild; 20 to 34 = moderate; and 35 to 60 = severe depression. MADRS = Montgomery-Åsberg Depression Rating Scale

Figure 5.2: Study flow chart of patient randomisation and completion numbers
Patients who did not finish treatment (DNF)
5.5.2. Analysis rationale

Sleep variables were analysed for the full 14 weeks of the study using Visit 1 (Day 1 / Night 1) as the baseline and results are presented as change relative to this baseline. The first night of the study, however, might not be medication-free, given that the time of dosing was not recorded. Patients were provided with medication to commence from the very first day and consequently could have dosed either in the evening before the first night or the following morning. The first night was therefore included in the 14 week analysis as one baseline night for comparison, as there was no placebo control or placebo run-in for the study. All other weeks were analysed as the mean of 7 days. The 14 week study moreover included one week discontinuation.

To take account of this anomaly, and for clarity for direction of change, the sleep variables were further analysed without using the first night as baseline for the 12 weeks of chronic medication. The results for the 12 week study are therefore presented as relative to week 1.

Further analysis was conducted for weeks 12 and 13 separately, which was the week prior to and the discontinuation week. Only statistically significant results are presented. For both cosinor and NPCRA the analysis was conducted using the weekly means with the first day included in the first week, results are therefore presented as change relative to week 1.

The cognitive and psychometric tests and rating scales were conducted on Day 1 Visit 1 prior to treatment and were therefore medication free, these results were analysed both as relative to, and change from, Visit 1 baseline.

5.5.3. Actigraphy

The overall Sleepwatch mean values and significance results for weeks 0 to 14 are summarised by week and treatment group, differences between weeks, and on discontinuation withdrawal and re-introduction of treatment in Tables 5.3 and 5.4, and in Figures 5.3 – 5.7. The Actiwatch activity sleep analysis is based on the completers dataset $n = 56$, (those compliant with wearing actiwatch and completing discontinuation) with paroxetine, fluoxetine and sertraline $n = 20$, $n = 18$ and $n = 18$ respectively. The first values for each treatment and variable were recorded as week 0 the night of Visit 1 for all the sleep variables or the day following Visit 1 for the average wake movement. Analysis showed no significant difference between the three treatment groups, or treatment by time interaction for any of the Sleepwatch variables. There were, however, overall significant effects of time for some of the Sleepwatch variables as detailed in the relevant sub-sections.
The analysis for the actigraphy variables from week 1 to week 12 was conducted on the 7 day weekly means excluding Night 1, as previously stated, it was not documented when patients took their first dose of medication and if taken on the first night could have affected the sleep data. The different antidepressant treatments were further analysed for the effect of time, and for each week relative to week 1 for weeks 1 to 12, the chronic treatment phase. Further analysis was conducted for the effect of the withdrawal of medication during the discontinuation period, from week 12 to week 13, between the means for weeks 12 and 13, the week before discontinuation on stable treatment and the week of abrupt discontinuation. An example of each of the Actograms for a single patient covering the full treatment period is shown in Appendix (VfX).

5.5.4. Actigraphic sleep variables

5.5.4.1. Sleep time - time in bed

The mean (± SEM) time in bed (TIB) for each treatment recorded on the night of Visit 1 was 509 (± 14), 484 (± 22), and 489 (± 24) minutes (8h28m, 8h04m and 8h09m) for paroxetine, fluoxetine and sertraline, respectively. Analysis of TIB showed no statistically significant difference between the treatment groups, however, there was a significant effect of time (F(14, 718) = 3.49, P < 0.0001). All three treatments showed an increase in TIB (Figure 5.3A). For paroxetine there was a significant effect of time (F(14, 257) = 1.84 P < 0.05) with increases in the TIB for weeks 1, 2, 3, 4, 6, 7, 8, 9, 11 and 14 compared with week 0 Visit 1. Fluoxetine showed a trend approaching significance over time (F(14, 224) = 1.63 P = 0.07). Post-hoc analysis revealed that for sertraline there was a significant effect of time (F(14, 237) = 2.36 P < 0.05) for weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12 and 14 compared with Visit 1.

Analysis of the TIB from week 1 to week 12, i.e. to the end of the 12 week treatment phase, showed no significant difference between the three treatment groups or across time. There was however a statistically significant effect of time between week 12 compared with week 13, during discontinuation, with a reduction in TIB for all treatments (F(1, 52.5) = 5.89, P < 0.05). Post-hoc analysis showed that this was significant for sertraline (F(1,17) = 5.84, P < 0.05).

5.5.4.2. Sleep time - sleep period time

The mean (± SEM) sleep period time (SPT) (duration of time from sleep start to sleep end, also known as actigraphic assumed sleep time) for each treatment recorded at Visit 1 was 485 (± 15), 448 (± 23) and 461 (± 23) minutes (8h05m, 7h28m and 7h41m) for paroxetine,
fluoxetine and sertraline, respectively. There was an overall significant effect of time ($F_{(14, 718)} = 2.14, P < 0.01$), with an increase in sleep duration (Table 5.4 and Figure 5.3B). *Post-hoc* analysis revealed that there was a significant effect of time for sertraline ($F_{(4, 237)} = 1.75, P < 0.05$) for weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, 11 and 12 compared with Visit 1.

The mean (± SEM) SPT for each treatment recorded for week 1 was 510 (± 18), 463 (± 12) and 479 (± 9) minutes for paroxetine, fluoxetine and sertraline, respectively. Analysis of the SPT from week 1 to week 12, showed no significant difference between the three treatment groups nor a significant effect of time. There was however, a significant difference between week 12 compared with week 13 during discontinuation overall with a reduction in SPT for all treatments ($F_{(1, 52)} = 4.52, P < 0.05$). *Post-hoc* analysis showed that this was statistically significant for sertraline ($F_{(1, n)} = 6.71, P < 0.05$).

The mean (± SEM) TST for each treatment recorded at Visit 1 was 424 (± 16), 397 (± 21) and 398 (± 22) minutes (7h04m, 6h37m and 6h38m) for paroxetine, fluoxetine and sertraline, respectively (Table 5.3 and Figure 5.4A), there was no significant difference between the three treatment groups, however there was a trend towards a significant effect of time, ($F_{(14, 718)} = 1.61, P = 0.07$), with sleep time reducing. Patients on paroxetine, also exhibited a trend towards a significant reduction in minutes ($F_{(4, 257)} = 1.62, P = 0.07$). There was also a significant reduction in TST for patients on paroxetine for the 12 week analysis ($F_{(11, 204)} = 2.13, P > 0.05$).

![Figure 5.3: Effect of antidepressant treatment on actigraphic TIB and SPT.](image)

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on actigraphic sleep variables (mean ± SEM) on A. TIB and B. SPT. Week 0 is the value recorded on the night of Visit 1.

5.5.4.3. **Sleep time – total sleep time**

The mean (± SEM) total sleep time (TST) (sleep start to sleep end, less any wake time) for each treatment recorded at Visit 1 was 424 (± 16), 397 (± 21) and 398 (± 22) minutes (7h04m, 6h37m and 6h38m) for paroxetine, fluoxetine and sertraline, respectively (Table 5.3 and Figure 5.4A), there was no significant difference between the three treatment groups, however there was a trend towards a significant effect of time, ($F_{(14, 718)} = 1.61, P = 0.07$), with sleep time reducing. Patients on paroxetine, also exhibited a trend towards a significant reduction in minutes ($F_{(14, 257)} = 1.62, P = 0.07$). There was also a significant reduction in TST for patients on paroxetine for the 12 week analysis ($F_{(11, 204)} = 2.13, P > 0.05$).
5.5.4.4. Sleep efficiency %

The mean (± SEM) sleep efficiency % (SE) for each treatment recorded at Visit 1 was 83.4 (± 2.1), 81.8 (± 1.7) and 81.9 (± 2.7) % for paroxetine, fluoxetine and sertraline, respectively (Figure 5.4B and Table 5.3). There was also an overall significant effect of time ($F_{(14, 718)} = 2.37, P < 0.01$). For paroxetine there was a significant effect of time with a reduction in sleep efficiency ($F_{(4, 257)} = 2.19, P < 0.01$) for weeks 3, 4, 5, 6, 7, 8, 9, 11, 12, 13 and 14 compared with Visit 1.

Analysis of the sleep efficiency from week 1 to week 12 showed a significant effect of time with a reduction in sleep efficiency overall across time ($F_{(11, 566)} = 2.21, P < 0.05$). The mean (± SEM) for each treatment recorded for week 1 was 81.9 (± 1.7), 83.6 (± 1.1), and 82.1 (± 2.3) % for paroxetine, fluoxetine and sertraline, respectively (Table 5.4). There was a trend towards a decrease in sleep efficiency with paroxetine ($F_{(11, 204)} = 1.74, P = 0.07$) with a significant effect at weeks 3, 4, 5, 6, 7, 8, 9, 10 and 12 compared with week 1. Similarly with fluoxetine ($F_{(11, 175)} = 1.76, P = 0.06$) there was a significant effect at weeks 6, 8, 10, 11 and 12 compared with week 1. There was no significant difference between the three treatment groups or effect of time in sleep efficiency from week 12 to week 13.

Figure 5.4: Effect of antidepressant treatment on actigraphic TST and SE

The effect of paroxetine (■) ($n = 20$), fluoxetine (●) ($n = 18$) and sertraline (▲) ($n = 18$) on actigraphic sleep variables (mean ± SEM) on A. TST and B. SE. Week 0 is the value recorded on the night of Visit 1.
Table 5.3: Effect of antidepressant treatment on actigraphic sleep variables by treatment and time

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<th>Sleep efficiency (%)</th>
<th>Sleep latency (min)</th>
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Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each treatment is shown by time. Week 0 is the value recorded on the night of Visit 1. Significance for individual weeks within each respective treatment compared with week 0 are denoted in weeks by *** <0.0001, ** <0.01, * <0.05. A trend towards statistical significance is denoted as *, if the P-value, in the individual treatment time column, was <0.1. Mean values are expressed at each time point (± SEM).
5.5.4.5. Sleep latency

The mean (± SEM) sleep latency (SL) for each treatment recorded at Visit 1 (Table 5.3) was 16 (± 3), 29 (± 5) and 17 (± 3) minutes for paroxetine, fluoxetine and sertraline, respectively. There was no significant effect between treatments for sleep latency (Figure 5.5A) however, the effect of time approached significance (F(4, 718) = 1.56, P = 0.08). For paroxetine there was a significant effect of time with an increase in sleep latency (F(14, 257) = 1.84, P < 0.05) for weeks 3, 4, 5, 7, 9, 10, 11 and 14 compared with baseline Visit 1. There was no significant difference between the three treatment groups nor effect of time in sleep latency from weeks 1 to 12 or from weeks 12 to 13 during discontinuation.

5.5.4.6. Sleep bouts

The mean (± SEM) number of sleep bouts (SB) for each treatment recorded at Visit 1 was 14 (± 2), 14 (± 1), and 14 (± 2) for paroxetine, fluoxetine and sertraline, respectively (Table 5.4). There was an overall significant effect of time for the number of sleep bouts (F(4, 718) = 7.4, P < 0.0001) indicating that sleep was more restless with increased sleep disturbance. Analysis showed that there were significant effects of time (Figure 5.5B) with increases in the number of sleep bouts with paroxetine (F(14, 257) = 4.80, P < 0.0001) in weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 compared with Visit 1; with fluoxetine (F(14, 224) = 3.21, P < 0.001) for weeks 7, 9, 10, 11, 12, 13 and 14 compared with Visit 1 and with sertraline (F(14, 237) = 1.76, P < 0.05) for weeks 3, 4, 6, 7, 8, 10, 11, 12 and 14 compared with Visit 1.

Figure 5.5: Effect of antidepressant treatment on actigraphic SOL and sleep bouts.

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on actigraphic sleep variables (mean ± SEM) on A. SL and B. sleep bouts. Week 0 is the value recorded on the night of Visit 1.
Analysis of the number of sleep bouts for weeks 1 to 12 showed a significant effect of time ($F(11, 566) = 6.13, P < 0.0001$) with an increase in the number of sleep bouts indicating more restless sleep and increased sleep disturbance. The mean ($\pm$ SEM) number of sleep bouts for each treatment recorded for week 1 was 16 ($\pm$ 1), 14 ($\pm$ 1), and 14 ($\pm$ 1) for paroxetine, fluoxetine and sertraline, respectively. There was a significant effect of time for paroxetine ($F(11, 204) = 3.89, P < 0.0001$) in weeks 4 to 12 inclusive compared with week 1; for fluoxetine ($F(11, 175) = 2.53, P < 0.01$) for weeks 5 to 12 inclusive compared with week 1 and for sertraline ($F(11, 187) = 2.03, P < 0.05$) for weeks 2 to 12 inclusive compared with week 1. Analysis showed no significant difference between the three treatment groups nor effect of time in number of sleep bouts during the discontinuation from weeks 12 to 13.

5.5.4.7. Sleep bout time

The mean ($\pm$ SEM) sleep bout time recorded at baseline Visit 1 for each treatment was 38 ($\pm$ 5), 34 ($\pm$ 4) and 37 ($\pm$ 8) minutes for paroxetine, fluoxetine and sertraline, respectively (Table 5.4). Analysis showed no significant difference between the three treatment groups nor effect of time on sleep bout time from weeks 0 to 14 during the overall period (Figure 5.6A), from weeks 1 to 12 the active period, or from weeks 12 to 13 during the discontinuation period.

5.5.4.8. Wake after sleep onset

The mean ($\pm$ SEM) wake after sleep onset time (WASO) (number of minutes spent awake from sleep start to sleep end) for each treatment recorded at baseline Visit 1 was 61 ($\pm$ 11), 51 ($\pm$ 7) and 63 ($\pm$ 11) minutes for paroxetine, fluoxetine and sertraline, respectively (Table 5.4). The effect of time approached significance ($F(14, 718) = 1.54, P = 0.09$) with the number of minutes awake increasing (Figure 5.6B). There was a significant effect of time for fluoxetine ($F(14, 224) = 2.24, P < 0.01$) with significant increase in WASO for weeks 7, 10, 11, 12, 13 and 14 compared with Visit 1. Analysis showed no significant difference between the three treatment groups nor effect of time on WASO from weeks 1 to 12 or during the period of discontinuation week 12 to 13.

5.5.4.9. Total activity counts in sleep

The mean ($\pm$ SEM) total number of activity counts during the SPT for each treatment recorded at Visit 1 was 6337 (8h05m) ($\pm$ 1156), 5024 (7h28m) ($\pm$ 771) and 5649 (7h41m) ($\pm$ 928) for paroxetine, fluoxetine and sertraline respectively (Table 5.4). There was an overall significant effect of time ($F(14, 718) = 1.72, P < 0.05$) with an increase in the number of activity counts during sleep indicating restless sleep (Figure 5.7). However, post-hoc analysis failed
to reveal an effect of time for any treatment. Analysis showed no significant difference between the three treatment groups nor effect of time on the number of total activity counts in sleep from weeks 1 to 12 or from weeks 12 to 13 during the discontinuation period.

A. B.

Figure 5.6: Effect of antidepressant treatment on actigraphic sleep bout time and WASO. The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on actigraphic sleep variables (mean ± SEM) on A. sleep bout times and B. WASO. Week 0 is the value recorded on the night of Visit 1.

5.5.4.10. Average wake movement (AWM)

The mean (± SEM) average wake movement calculated as the activity counts per 2 minute epoch during the day (sleep end to sleep start), for each treatment recorded on day 2 was 431 (± 51), 627 (± 77) and 623 (± 75) for paroxetine, fluoxetine and sertraline, respectively (Table 5.4). There was an overall significant effect of time (F(14, 718) = 1.77, P < 0.05) with wake activity levels increasing over time (Figure 5.7). For paroxetine there was a trend approaching significance (F(4, 258) = 1.61, P = 0.07) with significantly increased activity for weeks 7, 8, 9, 10, 11, 12, and 13 compared with day 2.

Analysis of the average wake movement for weeks 1 to 12 showed a trend towards an overall significant effect of treatment (F(2, 531) = 2.56, P = 0.09) with lower overall wake activity levels for paroxetine during the day. The mean (± SEM) average wake movement for each treatment recorded for week 1 was 462 (± 52), 651 (± 62) and 616 (± 67) for paroxetine, fluoxetine and sertraline, respectively (Table 5.4).
Table 5.4: Effect of antidepressant treatment on actigraphic sleep variables by treatment and time (continued)

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<tr>
<td>Sertraline</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>Sertraline</td>
<td>63</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total activity counts in sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>6337</td>
<td>7104</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5024</td>
<td>6206</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5649</td>
<td>6190</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average wake movement (counts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>431</td>
<td>462</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>627</td>
<td>631</td>
</tr>
<tr>
<td>Sertraline</td>
<td>623</td>
<td>616</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each treatment is shown by time. Week 0 is the value recorded on the night of Visit 1. Significance for individual weeks within each respective treatment compared with week 0 are denoted in weeks by ***<0.0001, ** <0.01, * <0.05. A trend towards statistical significance is denoted as *, if the P-value, in the individual treatment time column, was <0.1. Mean values are expressed at each time point (± SEM).
There was a significant difference between week 12 compared with week 13 overall with an increase in daytime wake activity (F(1, 50.7) = 20.11, P < 0.0001) during the discontinuation period for all treatments (Figure 5.7B). Analysis showed that there was a significant increase in daytime wake activity for fluoxetine (F(1, 15.6) = 21.53, P < 0.01) and a trend towards significance for sertraline (F(1, 17) = 4.33, P = 0.05) in week 13.

![Figure 5.7: Effect of antidepressant treatment on total activity counts and average wake movement. The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on actigraphic sleep variables (mean ± SEM) on A. Total activity counts in sleep (x 10^3) and B. Average wake movement. Week 0 is the value recorded on the night of Visit 1.](image)

5.5.4.11. Summary of actigraphic sleep variables

A summary of the direction of the statistically significant effect of time of antidepressants on actigraphic sleep variables for the full study for weeks 0 to 14, the treatment phase for weeks 1 to 12 and for the last week of treatment week 12 compared with the discontinuation withdrawal week 13, is presented in Table 5.5. The arrows show the direction of change of the variables that were statistically significant with ↑ = increased and ↓ = decreased.

5.5.5. Cosinor

The overall mean cosinor values and significance results are summarised by week and treatment group, and differences between weeks, on discontinuation and re-introduction of treatment is shown in Table 5.6 and Figures 5.12 to 5.15. The first chart in each section shows the mean scores for each treatment and cosinor variables recorded. The second chart shows the change with respect to the first week, week 1 as baseline. There were some significant effects between treatments, but no treatment by time interaction for any of the cosinor variables. There were significant effects of time for some of the variables as detailed in relevant sub-sections. The individual treatments were also analysed for the effect of time
overall and for individual weeks compared with baseline for weeks 1 to 12, the treatment phase and a further analysis for weeks 12 and 13, the maintenance treatment and abrupt discontinuation weeks, respectively. The Actiwatch cosinor analysis was conducted on the completers dataset n = 56, (those compliant with wearing actiwatch and completing discontinuation) with paroxetine, fluoxetine and sertraline n = 20, n = 18 and n = 18 respectively.

5.5.5.1. Amplitude

The mean (± SEM) amplitude of activity, at the peak (acrophase) of activity of the cosine curve less the mesor, for each treatment recorded at week 1 was 9026 (± 1264), 12658 (± 1333) and 11863 (± 1315) for paroxetine, fluoxetine and sertraline, respectively (Table 5.6). There was a trend towards significance between treatments for amplitude (F(2, 53) = 2.70, P = 0.08); with lower values for paroxetine as shown in Figure 5.8.

Figure 5.8: Effect of antidepressant treatment on cosinor amplitude

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on the amplitude cosinor variable (mean ± SEM) on A. Amplitude and B. Amplitude change relative to baseline week 1. Data are presented as activity counts x 10^3. There was a trend towards a significant effect of treatment for amplitude (P < 0.1).

Analysis showed no significant difference between the three treatment groups nor effect of time on the amplitude from weeks 1 to 12. There was a trend towards a significant difference between weeks 12 and 13 during the discontinuation period with an increase in amplitude overall (F(1, 50) = 3.93, P = 0.05) and a trend towards significance for fluoxetine (F(1, 14.3) = 3.96, P = 0.07).
Table 5.5: Summary of the statistically significant effects of duration of antidepressant treatment on actigraphic sleep variables

<table>
<thead>
<tr>
<th>Sleep Variable</th>
<th>Weeks 0 to 14 Full Study</th>
<th>Weeks 1 to 12 Treatment phase</th>
<th>Weeks 12 and 13 Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td>P&lt;0.05</td>
<td>P=0.07</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Sleep period time (min)</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>P=0.01</td>
<td>P=0.07</td>
<td>P&lt;0.07</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>P=0.07</td>
<td>P&lt;0.01</td>
<td>P=0.09</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>P&lt;0.01</td>
<td>P&lt;0.01</td>
<td>P&lt;0.09</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>P=0.08</td>
<td>P&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sleep bouts</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P=0.01</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Wake after sleep onset</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>P=0.09</td>
<td>P&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total activity counts in sleep</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>P&lt;0.05</td>
<td>P=0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average wake movement</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>P&lt;0.05</td>
<td>P=0.07</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table shows the statistically significant effect of duration of antidepressant treatment and direction of change on actigraphic sleep variables as shown by the arrows, ↑ = increased, ↓ = decreased, for the full study weeks 0-14, the treatment phase weeks 1-12 and the last week of treatment week 12 compared with discontinuation week 13. A trend towards statistical significance is shown by *" if the P-value was <0.1.
Table 5.6: Effect of antidepressant treatment on cosinor variables by treatment and time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cosinor Variable</th>
<th>Mean (SEM)</th>
<th>P-value</th>
<th>Time</th>
<th>Treatment</th>
<th>Time</th>
<th>Treatment by time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (weeks)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Amplitude</td>
<td>Paroxetine</td>
<td>9026</td>
<td>(1264)</td>
<td>9576</td>
<td>(1214)</td>
<td>10356</td>
<td>(1304)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>12658</td>
<td>(1333)</td>
<td>12702</td>
<td>(1280)</td>
<td>13061</td>
<td>(1388)</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>11863</td>
<td>(1315)</td>
<td>12608</td>
<td>(1266)</td>
<td>13164</td>
<td>(1359)</td>
</tr>
<tr>
<td>Mesor</td>
<td>Paroxetine</td>
<td>9499</td>
<td>(1250)</td>
<td>9690</td>
<td>(1192)</td>
<td>10198</td>
<td>(1250)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>13646</td>
<td>(1320)</td>
<td>13531</td>
<td>(1258)</td>
<td>13845</td>
<td>(1334)</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>12010</td>
<td>(1305)</td>
<td>13079</td>
<td>(1248)</td>
<td>13777</td>
<td>(1303)</td>
</tr>
<tr>
<td>Rhythm %</td>
<td>Paroxetine</td>
<td>69.6</td>
<td>(3.0)</td>
<td>72.1</td>
<td>(2.4)</td>
<td>70.4</td>
<td>(3.0)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>74.5</td>
<td>(3.1)</td>
<td>77.6</td>
<td>(2.5)</td>
<td>73.8</td>
<td>(3.2)</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>71.8</td>
<td>(3.1)</td>
<td>78.6</td>
<td>(2.5)</td>
<td>74.5</td>
<td>(3.2)</td>
</tr>
<tr>
<td>Acrophase time (h)</td>
<td>Paroxetine</td>
<td>13.62</td>
<td>(0.26)</td>
<td>13.68</td>
<td>(0.24)</td>
<td>13.93</td>
<td>(0.24)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>13.84</td>
<td>(0.27)</td>
<td>13.67</td>
<td>(0.26)</td>
<td>13.77</td>
<td>(0.26)</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>13.46</td>
<td>(0.26)</td>
<td>13.43</td>
<td>(0.25)</td>
<td>13.52</td>
<td>(0.26)</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. Means (± SEM) are expressed at each time point.
5.5.5.2. Mesor

The mean (± SEM) mesor of activity for each treatment recorded at week 1 was 9499 (± 1250), 13846 (± 1320) and 12610 (± 1305) (Table 5.6) for paroxetine, fluoxetine and sertraline, respectively. There was a significant effect between treatments for the mesor, mean level of activity, (F(2, 53) = 3.46, P < 0.05) with lower levels of activity for paroxetine compared with either fluoxetine or sertraline (Figure 5.9).

Analysis showed a significant difference between the three treatment groups for the mesor mean level of activity from weeks 1-12, (F(2, 53.4) = 3.21, P < 0.05). There was a trend towards a significant difference between weeks 12 and 13 during the discontinuation period with an increase in mesor overall shown as an increase in mean activity (F(1, 50.4) = 6.73, P = 0.05) and for fluoxetine (F(1, 14.7) = 5.94, P < 0.05).

5.5.5.3. Rhythm percentage %

The mean (± SEM) percentage rhythm for each treatment recorded at week 1 was 69.9% (± 3.0), 74.5% (± 3.1) and 71.8% (± 3.1) for paroxetine, fluoxetine and sertraline, respectively (Table 5.6). There was a trend towards significance for the effect of time (F(13, 37.5) = 1.86, P = 0.07) with an increase in percentage rhythm with time compared with week 1 as shown in Figure 5.10.

Analysis showed a significant effect of time overall (F(11, 39.8) = 2.22, P < 0.05) with an indication of an increase in in the percentage rhythm for the treatment phase weeks 1 to 12.
There was a significant difference between weeks 12 and 13 for fluoxetine ($F(1,15.8) = 11.75$, $P < 0.01$) with an increase in the percentage rhythm during the abrupt discontinuation week.

5.5.5.4. Acrophase time

The mean ($\pm$ SEM) time of the acrophase (peak) of the activity rhythm for each treatment recorded at baseline week 1 was 13.62 ($\pm$ 0.26), 13.84 ($\pm$ 0.27) and 13.46 ($\pm$ 0.26) hours (13:37, 13:50 and 13:27 hh:mm) for paroxetine, fluoxetine and sertraline, respectively (Table 5.6). There was a trend towards an overall significant effect of time ($F(3,36.7) = 1.92$, $P = 0.06$) with the acrophase time being delayed and occurring slightly later in the biological day for the middle weeks (Figure 5.11).

![Figure 5.10: Effect of antidepressant treatment on cosinor percentage rhythm.](image)

The effect of paroxetine (■) ($n = 20$), fluoxetine (●) ($n = 18$) and sertraline (▲) ($n = 18$) on the percentage rhythm cosinor variable (mean $\pm$ SEM) on A. Percentage rhythm and B. Percentage rhythm change relative to baseline week 1. There was a trend towards a significant effect of time for percentage rhythm ($P < 0.1$).

For the treatment phase weeks 1 to 12, analysis showed that there was a trend towards significance for the effect of time overall ($F(11,38.2) = 1.87$, $P = 0.08$) with a slight delay in the timing, occurring later in the day during the middle weeks. There was also a trend towards a significant difference between weeks 12 and 13 overall with a delay in the acrophase time occurring later in the biological day ($F(1,51.1) = 9.06$, $P < 0.01$). There was also a significant effect of time for fluoxetine ($F(1,15.3) = 7.41$, $P < 0.05$) between weeks 12 and 13.
Figure 5.11: Effect of antidepressant treatment on cosinor acrophase time.
The effect of paroxetine (■) (n = 20), fluoxetine (○) (n = 18) and sertraline (▲) (n = 18) on the acrophase time cosinor variable (mean ± SEM) is represented as dec.h. There was a trend towards a significant effect of time for acrophase time (P < 0.1).

5.5.5.5. Summary of cosinor variables
A summary of the direction of the statistically significant effect of duration of antidepressants on cosinor variables for the full study for weeks 0 to 14, the treatment phase for weeks 1 to 12 and for the last week of treatment week 12 compared with the discontinuation withdrawal week 13, is presented in Table 5.7. The arrows show the direction of change of the variables that were statistically significant with ↑ = increased and ↓ = decreased. The effect of timing on M10 and L5 onset is shown as delayed or advanced.

5.5.6. Non-parametric circadian rhythm analysis (NPCRA)
The NPCRA mean values and significance results are summarised by week and treatment group, differences between weeks, on discontinuation and re-introduction of treatment in Tables 5.8 and 5.9 and Figures 5.16 to 5.20. The mean scores for each week of treatment for the NPCRA variables were recorded with the first values for the scores recorded during the first week of treatment. The Actiwatch NPCRA analysis was conducted on the completers dataset n = 56, (those compliant with wearing actiwatch and completing discontinuation) with paroxetine, fluoxetine and sertraline n = 20, n = 18 and n = 18 respectively.

5.5.6.1. Average activity
The mean (± SEM) average activity for each treatment recorded at week 1 was 159 (± 21), 228 (± 22) and 212 (± 22) for paroxetine, fluoxetine and sertraline, respectively (Table 5.8). As shown in Figure 5.12, there was a trend towards a significant effect between treatments.
overall for average activity with paroxetine activity levels lower than fluoxetine or sertraline ($F_{(2, 53.2)} = 3.03, P = 0.06$). There was also an overall significant effect of time ($F_{(13, 36.8)} = 5.05, P < 0.0001$) with an increase in activity over time.

Analysis showed no significant difference between the three treatment groups or effect of time on NPCRA average activity from weeks 1-12. There was a significant effect of time overall on average activity between week 12 and week 13 ($F_{(1, 49.8)} = 1.93, P < 0.01$) with an increase in activity during the abrupt discontinuation week. There was also a significant effect for fluoxetine ($F_{(1, 15.1)} = 9.74, P < 0.01$) with an increase in activity in week 13 compared with week 12.

![Figure 5.12](image.png)

Figure 5.12: Effect of antidepressant treatment on NPCRA average activity.
The effect of paroxetine (■) ($n = 20$), fluoxetine (●) ($n = 18$) and sertraline (▲) ($n = 18$) on NPCRA variables (mean ± SEM) on A. Average activity and B. Average activity change relative to baseline week 1. There was significant effect of time on average activity ($P < 0.0001$) and a trend towards a significant effect of treatment ($P < 0.1$).

5.5.6.2. Amplitude

The mean (± SEM) amplitude for each treatment recorded at week 1 was 273 (± 37), 383 (± 38) and 363 (± 38) for paroxetine, fluoxetine and sertraline, respectively (Table 5.8). There was a trend towards a significant effect between treatments ($F_{(2, 53.2)} = 2.65, P = 0.08$) with lower overall activity levels for paroxetine compared with fluoxetine or sertraline (Figure 5.13). Analysis showed no significant difference between the three treatment groups nor effect of time on NPCRA amplitude from weeks 1-12.

There was a significant effect of time overall on amplitude between week 12 and week 13 ($F_{(1, 49.1)} = 4.04, P = 0.05$) with an increase in overall amplitude on week 13. This was also seen in the fluoxetine group with a significant effect of time ($F_{(1, 14.3)} = 7.64, P < 0.05$) with
an increase in amplitude in week 13 in the abrupt discontinuation week compared with week 12.

A.

![Graph A](image)

B.

![Graph B](image)

Figure 5.13: Effect of antidepressant treatment on NPCRA amplitude. The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. Amplitude and B. Amplitude change relative to baseline week 1. There was significant effect of time on average activity (P < 0.0001) and a trend towards a significant effect of treatment (P < 0.1).

5.5.6.3. M10 onset time

The mean (± SEM) M10 onset time of the 10 hours of maximum activity for each treatment recorded at week 1 was 8.7 (± 0.3), 8.4 (± 0.3) and 8.1 (± 0.3) (08:42, 08:24 and 08:06 hh:mm) for paroxetine, fluoxetine and sertraline, respectively (Table 5.8). There was a trend towards a significant effect of time overall, shown in Figure 5.14, for the M10 onset time (F(2, 53.2) = 2.52, P = 0.07) with a delay occurring later in the biological day relative to week 1.

For the treatment phase weeks 1 to 12, there was a trend towards significance for the effect of time overall on the M10 onset time (F(11, 40.1) = 1.93, P = 0.06) with a slight delay in the timing, occurring later in the day. This was also seen in the sertraline group with a significant effect of time (F(11, 6.96) = 3.31, P = 0.07) for weeks 2, 5 and 10 compared with week 1. Analysis showed no significant difference between the three treatment groups nor effect of time on M10 onset time between weeks 12 and 13.

5.5.6.4. M10 average activity

The mean (± SEM) activity of the 6 minute blocks for the 10 hours of maximum activity for each treatment recorded at week 1 was 286 (± 37), 396 (± 39) and 375 (± 39) for paroxetine, fluoxetine and sertraline, respectively (Table 5.8). There was a trend towards a significant
effect of treatment ($F(2, 51.2) = 2.52, P = 0.09$) with lower activity levels for paroxetine compared with fluoxetine and sertraline (Figure 5.15).

A. B.

Figure 5.14: Effect of antidepressant treatment on NPCRA MIO onset time.
The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. MIO onset time and B. MIO onset time change relative to baseline week 1. There was a trend towards a significant effect of time ($P < 0.1$).

A. B.

Figure 5.15: Effect of antidepressant treatment on NPCRA MIO average activity.
The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. MIO activity and B. MIO activity change relative to baseline week 1. There was a trend towards a significant effect of treatment ($P < 0.1$).

Analysis showed no significant difference between the three treatment groups nor effect of time on MIO average activity between weeks 1 and 12. There was a significant effect of time overall on MIO activity between week 12 and week 13 ($F(1, 49) = 4.01, P = 0.05$) with an increase in MIO overall activity for the 10 hours of maximum activity in week 13 compared with week 12. This was also seen in the fluoxetine group ($F(1, 14.2) = 7.52, P < 0.05$) with an increase in MIO activity in week 13 discontinuation week compared with week 12.
Table 5.7: Summary of the statistical significant effect of duration of antidepressant treatment on cosinor variables

<table>
<thead>
<tr>
<th>Cosinor Variable</th>
<th>Weeks 0 to 14 Full Study</th>
<th>Weeks 1 to 12 Treatment phase</th>
<th>Weeks 12 and 13 Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Effect of time</td>
<td>Overall</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Amplitude</td>
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<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P&lt;0.05</td>
<td></td>
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</tr>
<tr>
<td>Rhythm %</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>P=0.07</td>
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<tr>
<td>Acrophase time (h)</td>
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</tr>
<tr>
<td></td>
<td>Delayed</td>
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<tr>
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<td>P=0.06</td>
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<td>Delayed</td>
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<tr>
<td></td>
<td>P=0.08</td>
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</tbody>
</table>

The statistical significant effect of time of antidepressant treatment and direction of change on cosinor variables is shown by the arrows, ↑ = increased, ↓ = decreased, for the full study of weeks 0-14, the treatment phase for weeks 1-12 and for the last week of treatment week 12 compared with the discontinuation withdrawal week 13. A trend towards statistical significance is shown by ‘*’ if the P-value was <0.1.
Table 5.8: Effect of antidepressant treatment on NPCRA variables by treatment and time

<table>
<thead>
<tr>
<th>NPCRA Variable</th>
<th>Mean (SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Time (weeks)</td>
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<tr>
<td>Paroxetine</td>
<td>159 (21) 162 (19.5) 161 (20) 163 (18) 177 (20) 172 (19) 176 (18) 182 (19) 185 (19) 179 (18) 184 (20) 180 (18) 176 (18) 196 (19) 180 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>228 (22) 221 (20) 237 (21) 224 (19) 229 (20) 223 (19) 233 (20) 239 (20) 213 (19) 227 (19) 235 (20) 223 (19) 264 (20) 251 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Sertraline</td>
<td>212 (22) 218 (20) 228 (21) 220 (19) 215 (20) 222 (19) 211 (20) 218 (19) 212 (20) 210 (19) 219 (20) 203 (19) 226 (20) 219 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Amplitude</td>
<td>273 (37) 279 (36) 270 (36) 275 (32) 288 (36) 288 (34) 306 (35) 315 (37) 297 (33) 309 (39) 301 (35) 321 (33) 303 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>393 (38) 379 (36) 398 (36) 379 (34) 381 (37) 373 (36) 395 (35) 354 (37) 376 (38) 398 (38) 448 (42) 431 (37) 35 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>363 (38) 380 (36) 390 (34) 393 (37) 386 (36) 367 (35) 371 (34) 364 (38) 357 (34) 378 (36) 352 (35) 366 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8.7 (0.3) 8.7 (0.3) 8.9 (0.3) 8.6 (0.3) 9.3 (0.3) 9.1 (0.3) 9.3 (0.3) 9.0 (0.3) 9.0 (0.3) 8.5 (0.2) 8.8 (0.2) 9.0 (0.3) 9.0 (0.3) 8.9 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8.4 (0.3) 8.6 (0.3) 9.0 (0.3) 8.2 (0.3) 8.8 (0.3) 8.9 (0.3) 9.0 (0.3) 9.1 (0.3) 9.1 (0.3) 8.8 (0.2) 9.0 (0.3) 8.9 (0.3) 9.0 (0.3) 8.9 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Sertraline</td>
<td>8.1 (0.3) 8.6 (0.3) 8.4 (0.3) 8.6 (0.3) 8.6 (0.3) 8.5 (0.3) 8.7 (0.3) 8.5 (0.3) 8.5 (0.3) 8.9 (0.2) 8.8 (0.3) 8.5 (0.3) 8.9 (0.2) 8.9 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>286 (37) 292 (36) 285 (36) 289 (35) 313 (36) 302 (34) 312 (36) 322 (34) 336 (34) 313 (33) 323 (34) 314 (33) 330 (33) 319 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>396 (39) 390 (37) 410 (38) 394 (35) 394 (37) 386 (36) 408 (37) 409 (36) 377 (38) 391 (35) 411 (37) 402 (36) 461 (37) 445 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Sertraline</td>
<td>375 (36) 391 (37) 405 (38) 400 (36) 398 (36) 376 (35) 383 (37) 375 (38) 388 (34) 389 (34) 363 (37) 378 (35) 379 (34)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. A trend towards statistical significance is shown if the P-value was <0.1. Means (± SEM) are expressed at each time point.
5.5.6.5. L5 onset time

The mean (± SEM) onset time for the 5 hours of least activity for each treatment recorded at week 1 was 0.8 (± 0.3), 1.0 (± 0.3) and 0.6 (± 0.3), (00:48, 01:00 and 00:36 hh:mm) for paroxetine, fluoxetine and sertraline, respectively (Table 5.9) as shown in Figure 5.16. However, there was no significant effect for treatment or time for weeks 1 to 14.

Analysis showed that there was no effect of treatment nor time on L5 onset time overall for weeks 1 to 12. However, there was a significant effect of time for paroxetine ($F_{(11,8,1)} = 4.92, P < 0.02$) with a significant effect at week 7, shown as a delay in timing, L5 onset occurring later in the night. There was a significant effect of time for the L5 onset overall with an advance in the L5 onset between week 12 and week 13 occurring earlier in the night ($F_{(1,49,2,1)} = 5.7, P < 0.05$).

![Figure 5.16: Effect of antidepressant treatment on NPCRA L5 onset time.](image)

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. L5 onset time and B. L5 onset time change relative to baseline week 1.

5.5.6.6. L5 Activity

The mean (± SEM) activity counts per 6 minute epoch for the 5 hours of least activity, for each treatment recorded at week 1, and shown in Figure 5.17, was 13 (± 2), 13(± 2) and 12 (± 2), for paroxetine, fluoxetine and sertraline, respectively (Table 5.9). Analysis showed that there was no significant effect for treatment or time for weeks 1 to 14.

There was no significant effect of time or treatment overall on the L5 activity for weeks 1 to 12, however there was a significant effect of time with sertraline causing a reduction in L5 activity ($F_{(11, 7,1)} = 4.08, P < 0.05$). Analysis showed no significant difference between the three treatment groups nor effect of time on L5 mean activity between weeks 12 and 13.
Table 5.9: Effect of antidepressant treatment on NPCRA variables by treatment and time (continued)

<table>
<thead>
<tr>
<th>NPCRA Variable</th>
<th>Variable</th>
<th>Time (weeks)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<th>11</th>
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<td></td>
</tr>
<tr>
<td>L5 onset time</td>
<td>Paroxetine</td>
<td>0.8 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.1 (0.3)</td>
<td>0.9 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.8 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.3 (0.3)</td>
<td>0.9 (0.3)</td>
<td>1.0 (0.3)</td>
<td>1.2 (0.3)</td>
<td>0.9 (0.3)</td>
<td>0.7 (0.3)</td>
<td></td>
</tr>
<tr>
<td>(decimal h)</td>
<td>Fluoxetine</td>
<td>1.0 (0.3)</td>
<td>0.9 (0.3)</td>
<td>1.0 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.4 (0.3)</td>
<td>0.9 (0.3)</td>
<td>1.6 (0.3)</td>
<td>1.1 (0.3)</td>
<td>1.6 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.3 (0.3)</td>
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<td>1.4 (0.3)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
<td>0.9 (0.3)</td>
<td>0.8 (0.3)</td>
<td>0.7 (0.3)</td>
<td>1.0 (0.3)</td>
<td>1.2 (0.3)</td>
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<td>0.6 (0.3)</td>
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<tr>
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<td>13 (2)</td>
<td>15 (2)</td>
<td>15 (2)</td>
<td>14 (2)</td>
<td>14 (2)</td>
<td>15 (2)</td>
<td>15 (2)</td>
<td>14 (2)</td>
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<td>14 (2)</td>
<td>15 (2)</td>
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<tr>
<td></td>
<td>Fluoxetine</td>
<td>13 (2)</td>
<td>10 (2)</td>
<td>12 (2)</td>
<td>15 (2)</td>
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<tr>
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<td>Sertraline</td>
<td>12 (2)</td>
<td>11 (2)</td>
<td>12 (2)</td>
<td>13 (2)</td>
<td>12 (2)</td>
<td>12 (2)</td>
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<td>11 (2)</td>
<td>12 (2)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IS (Range 0 to 1)</td>
<td>Paroxetine</td>
<td>0.57 (0.03)</td>
<td>0.56 (0.03)</td>
<td>0.54 (0.03)</td>
<td>0.57 (0.03)</td>
<td>0.55 (0.03)</td>
<td>0.57 (0.03)</td>
<td>0.59 (0.03)</td>
<td>0.60 (0.03)</td>
<td>0.59 (0.03)</td>
<td>0.57 (0.03)</td>
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</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>0.64 (0.03)</td>
<td>0.65 (0.03)</td>
<td>0.64 (0.03)</td>
<td>0.63 (0.03)</td>
<td>0.62 (0.03)</td>
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<td>0.64 (0.03)</td>
<td>0.64 (0.03)</td>
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<tr>
<td></td>
<td>Sertraline</td>
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<td>0.64 (0.03)</td>
<td>0.66 (0.03)</td>
<td>0.63 (0.03)</td>
<td>0.67 (0.03)</td>
<td>0.65 (0.03)</td>
<td>0.64 (0.03)</td>
<td>0.63 (0.03)</td>
<td>0.62 (0.03)</td>
<td>0.62 (0.03)</td>
<td>0.62 (0.03)</td>
<td>0.63 (0.03)</td>
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</tr>
<tr>
<td>IV (Range 0 to 2)</td>
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<td>0.73 (0.04)</td>
<td>0.81 (0.04)</td>
<td>0.77 (0.04)</td>
<td>0.82 (0.04)</td>
<td>0.80 (0.04)</td>
<td>0.72 (0.04)</td>
<td>0.75 (0.04)</td>
<td>0.80 (0.04)</td>
<td>0.78 (0.04)</td>
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<td></td>
<td>Fluoxetine</td>
<td>0.65 (0.05)</td>
<td>0.71 (0.05)</td>
<td>0.68 (0.05)</td>
<td>0.73 (0.05)</td>
<td>0.71 (0.05)</td>
<td>0.71 (0.05)</td>
<td>0.67 (0.05)</td>
<td>0.67 (0.05)</td>
<td>0.69 (0.05)</td>
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<td>0.64 (0.05)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Sertraline</td>
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<td>0.68 (0.05)</td>
<td>0.71 (0.05)</td>
<td>0.64 (0.05)</td>
<td>0.67 (0.05)</td>
<td>0.63 (0.05)</td>
<td>0.65 (0.05)</td>
<td>0.66 (0.05)</td>
<td>0.67 (0.05)</td>
<td>0.68 (0.05)</td>
<td>0.64 (0.05)</td>
<td>0.62 (0.05)</td>
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<tr>
<td>RA (Range 0 to 1)</td>
<td>Paroxetine</td>
<td>0.90 (0.01)</td>
<td>0.90 (0.01)</td>
<td>0.89 (0.01)</td>
<td>0.88 (0.01)</td>
<td>0.89 (0.01)</td>
<td>0.90 (0.01)</td>
<td>0.90 (0.01)</td>
<td>0.90 (0.01)</td>
<td>0.90 (0.01)</td>
<td>0.89 (0.01)</td>
<td>0.91 (0.01)</td>
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</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>0.94 (0.01)</td>
<td>0.94 (0.01)</td>
<td>0.94 (0.01)</td>
<td>0.92 (0.01)</td>
<td>0.94 (0.01)</td>
<td>0.93 (0.01)</td>
<td>0.93 (0.01)</td>
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</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>0.93 (0.01)</td>
<td>0.94 (0.01)</td>
<td>0.92 (0.01)</td>
<td>0.93 (0.01)</td>
<td>0.93 (0.01)</td>
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</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. A trend towards statistical significance is shown if the P-value was <0.1. Means (± SEM) are expressed at each time point.
Figure 5.17: Effect of antidepressant treatment on NPCRA L5 activity. The effect of paroxetine (■) \((n = 20)\), fluoxetine (●) \((n = 18)\) and sertraline (▲) \((n = 18)\) on NPCRA variables (mean ± SEM) on A. L5 activity and B. L5 activity change relative to baseline week 1.

5.5.6.7. Interdaily Stability (IS)

The IS value, which is an indication of the stability of the rhythm, ranges in theory between values of 0-1, for each treatment, with lower levels indicating less stable rhythm. The mean IS value (± SEM) recorded at week 1 was 0.57 (± 0.03), 0.64 (± 0.03) and 0.65 (± 0.03), for paroxetine, fluoxetine and sertraline, respectively (Table 5.9). There was no significant effect of treatment overall or time, during the 14 week study although there were lower values for paroxetine, as shown in Figure 5.18, indicating a less stable rhythm. Analysis showed no significant effect of time on IS between weeks 1 and 12 but there was a significant trend for a treatment effect \((F(2,51,7) = 2.72, P = 0.08)\).

There was a trend towards a significant effect of time with a decrease in IS overall between week 12 and week 13 with a reduction in IS between week 12 and week 13 \((F(1,49,1) = 3.12, P = 0.08)\). This was also seen in the fluoxetine treatment group with a significant effect of time \((F(1,14,2) = 4.03, P = 0.06)\) and a reduction in IS in week 13 the abrupt discontinuation week compared with week 12.

5.5.6.8. Intradaily Variability (IV)

The IV value, which is an indication of the fragmentation of the rhythm, ranges in theory with values between 0-2 with higher values indicates a more fragmented rhythm. The mean IV value (± SEM) for each treatment recorded at week 1 was 0.81 (± 0.4), 0.65 (± 0.5) and 0.70 (± 0.5), for paroxetine, fluoxetine and sertraline, respectively (Table 5.9). There was a trend towards a significant difference between treatments \((F(2,52,9) = 2.94, P = 0.06)\), overall
there were higher values for paroxetine indicating a more disrupted rhythm as shown in Figure 5.19.

Analysis showed no significant difference between the three treatment groups nor effect of time on IV between weeks 1 to 12. Analysis showed no significant difference between the three treatment groups nor effect of time on IV between weeks 12 to 13.

A.

Figure 5.18: Effect of antidepressant treatment on NPCRA IS activity.
The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. IS and B. IS change relative to baseline week 1.

B.

Figure 5.19: Effect of antidepressant treatment on NPCRA IV activity.
The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. IV and B. IV change relative to baseline week 1. There was a trend towards a significant effect of treatment (P < 0.1).
5.5.6.9. Relative Amplitude (RA)

The RA value, ranges in theory with values between 0-1 with higher values indicating a rhythm of higher amplitude. The mean RA value (± SEM) for each treatment recorded at baseline week 1 was 0.90 (± 0.1), 0.94 (± 0.1) and 0.93 (± 0.1), for paroxetine, fluoxetine and sertraline, respectively (Table 5.9). There was a significant effect, as shown in Figure 5.20, between treatments (F(2, 53.2) = 3.68, P < 0.05) with lower values for paroxetine overall indicating a rhythm with less amplitude.

Analysis showed no significant difference between the three treatment groups nor effect of time on RA between weeks 1 to 12. Analysis also showed no significant difference between the three treatment groups nor effect of time on RA between weeks 12 to 13.

![Figure 5.20: Effect of antidepressant treatment on NPCRA RA.](image)

The effect of paroxetine (■) (n = 20), fluoxetine (•) (n = 18) and sertraline (▲) (n = 18) on NPCRA variables (mean ± SEM) on A. RA and B. RA change relative to baseline week 1. There was a significant effect of treatment (P < 0.05).

5.5.6.10. Summary of NPCRA variables

A summary of the direction of the statistically significant effect of duration of antidepressants on NPCRA variables for the full study for weeks 0 to 14, the treatment phase for weeks 1 to 12 and for the last week of treatment week 12 compared with the discontinuation withdrawal week 13, is presented in Table 5.10. The arrows show the direction of change of the variables that were statistically significant with ↑ = increased and ↓ = decreased. The effect of timing on M10 and L5 onset is shown as delayed overall for weeks 0 - 14 and 1 - 12, occurring later in the biological day. Whereas the effect of timing on L5 onset time overall was advanced during the abrupt discontinuation between weeks 12 and 13.
Table 5.10: Summary of the statistically significant effects of duration of antidepressant treatment on NPCRA variables

<table>
<thead>
<tr>
<th>NPCRA Variable</th>
<th>Weeks 0 to 14 Full Study</th>
<th>Weeks 1 to 12 Treatment phase</th>
<th>Weeks 12 and 13 Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Effect of time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average activity</td>
<td>↑ P&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M10 onset time (h)</td>
<td>Delayed P=0.07</td>
<td>Delayed P=0.06</td>
<td>Delayed P=0.06</td>
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<tr>
<td>M10 activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5 onset time (h)</td>
<td></td>
<td>Delayed P&lt;0.05</td>
<td>Advanced P&lt;0.05</td>
</tr>
<tr>
<td>L5 activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
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<td>IV</td>
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<tr>
<td>RA</td>
<td></td>
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</tbody>
</table>

The statistical significant effect of duration of antidepressant treatment and direction of change on NPCRA variables is shown by the arrows, ↑ = increased, ↓ = decreased, for the full study for weeks 0-14, the treatment phase for weeks 1-12 and for the last week of treatment (week 12) compared with discontinuation withdrawal week 13. Significance with respect to clock time is shown as a delay or advance where applicable. A trend towards statistical significance is shown by ‘~’ if the P-value was <0.1.
5.5.7. Cognitive and psychomotor function

The overall mean values and statistical results for the psychometric tests are summarised by week and treatment group, in Tables 5.11 and 5.12 with the mean change from baseline shown in Figures 5.21 and 5.22. The mean baseline scores for each treatment and test variables were recorded at the first visit and are valid baselines as these results were obtained prior to antidepressant dosing. There was no significant effect between treatments, or treatment by time interaction for any of the test variables for the 14 week period.

5.5.7.1. Choice Reaction Time (CRT)

The CRT results are summarised by visit and treatment group in Table 5.11 for the individual components Recognition Reaction Time (RRT); Motor Reaction Time (MRT) and Total Reaction Time (TRT) (ms).

At baseline, Visit 1 week 0 the mean RRT (± SEM) was 457 (± 24), 534 (± 25) and 447 (± 25) ms for paroxetine, fluoxetine and sertraline respectively (Table 5.11). There was a significant effect of time overall for all treatments ($F_{(5, 45)} = 3.66, P < 0.01$) with an improvement in reaction time across time. Analysis showed a trend towards a significant effect of time for fluoxetine ($F_{(5, 10)} = 2.62, P = 0.08$) with improved performance at weeks 8 and 11 compared with baseline Visit 1 week 0 (Figure 5.21A). Analysis of RRT from Visit 1 to Visit 12, i.e. to the end of twelve weeks of treatment, showed in general an improvement with reductions in reaction time across time. There was a significant effect of time overall for all treatments ($F_{(6, 48)} = 4.79, P < 0.01$) with a trend towards a significant effect of time for fluoxetine ($F_{(6, 12)} = 2.39, P = 0.09$) and sertraline ($F_{(6, 12)} = 2.61, P = 0.08$). Further analysis showed no significant difference between the three treatment groups nor effect of time on RRT between weeks 12 and 13 during discontinuation of treatment.

At baseline, Visit 1 week 0 the mean MRT (± SEM) was 322 (± 15), 339 (± 16) and 333 (± 16) ms for paroxetine, fluoxetine and sertraline respectively (Table 5.11). The analysis of the change in MRT from week 1 to week 14 did not reach significance between the three treatment groups (Figure 5.21B). Analysis of MRT from week 1 to week 12 showed no significant difference for time overall however there was a trend towards an overall significant effect of time for sertraline ($F_{(6, 12)} = 2.61, P = 0.08$) with a reduction in reaction times across time. Further analysis showed no significant difference between the three treatment groups or effect of time on RRT between weeks 12 and 13.
Figure 5.21: Effect of antidepressant treatment on RRT and MRT on change from baseline.

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on variables of cognitive and psychomotor function (mean ± SEM) on mean change from baseline for A. RRT and B. MRT (ms). There was a trend towards a significant effect of time for RRT for sertraline (P < 0.1).

At baseline the mean TRT (± SEM) was 778 (± 34), 872 (± 36) and 779 (± 36) ms for paroxetine, fluoxetine and sertraline, respectively (Table 5.11). There was a significant effect of time overall for all treatments (F(8, 46.1) = 3.20, P < 0.01) with a reduction in reaction time (Figure 5.22A). There was an overall significant effect of time for TRT for paroxetine (F(8, 11.8) = 3.42, P < 0.05) with a significant reduction for weeks 1, 2, and 4 compared with baseline Visit 1 week 0. There were trends toward overall significance of time for TRT for fluoxetine (F(8, 10.0) = 2.61, P = 0.08) with a significant reduction for weeks 8 and 11 compared with baseline Visit 1 week 0 and for sertraline (F(8, 10.0) = 2.44, P = 0.09) with a significant reduction for week 2 compared with baseline Visit 1 week 0. Analysis of the change in TRT from week 1 to week 12 showed that there was an overall effect of time (F(6, 48.0) = 4.16, P < 0.01) and a trend towards significance for sertraline (F(6, 12) = 2.76, P = 0.06).

Analysis of the change in TRT from week 12 to week 13, i.e. during discontinuation of treatment, did not reach statistical significance for all treatments. However, discontinuation from paroxetine showed a within group significant decrease with an impairment during week 13 compared with week 12 with an increase in TRT (F(1, 19) = 4.96, P < 0.05).
Table 5.11: Effect of antidepressant treatment on cognitive and psychomotor function by treatment and time:

<table>
<thead>
<tr>
<th>Cognition Variable</th>
<th>Time (weeks)</th>
<th>Mean (SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Variable</td>
<td>Time</td>
<td>Treatment</td>
<td>Time</td>
</tr>
<tr>
<td>RRT (ms)</td>
<td>457 (24)</td>
<td>416 (36)</td>
<td>408 (21)</td>
</tr>
<tr>
<td></td>
<td>534 (25)</td>
<td>512 (38)</td>
<td>466 (22)</td>
</tr>
<tr>
<td></td>
<td>447 (25)</td>
<td>429 (38)</td>
<td>413 (22)</td>
</tr>
<tr>
<td>MRT (ms)</td>
<td>322 (15)</td>
<td>313 (17)</td>
<td>315 (16)</td>
</tr>
<tr>
<td></td>
<td>339 (16)</td>
<td>323 (18)</td>
<td>335 (17)</td>
</tr>
<tr>
<td></td>
<td>333 (16)</td>
<td>315 (18)</td>
<td>307 (17)</td>
</tr>
<tr>
<td>TRT (ms)</td>
<td>778 (34)</td>
<td>729* (43)</td>
<td>723** (30)</td>
</tr>
<tr>
<td></td>
<td>872 (36)</td>
<td>834 (46)</td>
<td>801 (32)</td>
</tr>
<tr>
<td></td>
<td>779 (36)</td>
<td>744 (46)</td>
<td>720* (32)</td>
</tr>
<tr>
<td>CFF (Hz)</td>
<td>27.8 (0.6)</td>
<td>29.7*** (0.6)</td>
<td>29.8*** (0.7)</td>
</tr>
<tr>
<td></td>
<td>29.3 (0.7)</td>
<td>29.7 (0.6)</td>
<td>30.5 (0.7)</td>
</tr>
<tr>
<td></td>
<td>28.5 (0.7)</td>
<td>28.7** (0.6)</td>
<td>28.4 (0.7)</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. Significance for individual weeks within each respective treatment compared with week 0 are denoted in weeks by *** = <0.0001, ** = <0.01, * = <0.05. A trend towards statistical significance is denoted as *, if the P-value, in the individual treatment time column, was <0.1. Means (± SEM) are expressed at each time point. Values have been rounded up.
Figure 5.22: Effect of antidepressant treatment on TRT and CFF on change from baseline. The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on variables of cognitive and psychomotor function (mean ± SEM) on mean change from baseline for A. TRT (ms) and B. CFF (Hz). There was a trend towards a significant effect of time for TRT (ms) for sertraline (P < 0.1) on change from baseline relative to Day 0. For CFF there was a significant effect of time overall (P = 0.05) and a trend towards a significant effect of time for fluoxetine and sertraline (P < 0.1) on change from baseline relative to Day 0.

5.5.7.2. Critical Flicker Fusion (CFF)

The CFF results are summarised by visit and treatment group in Table 5.11. The mean CFF (± SEM) recorded at baseline, Visit 1, for the individual means were 27.8 (± 0.6), 29.3 (± 0.7) and 27.5 (± 0.7) Hz for paroxetine, fluoxetine and sertraline, respectively. There was a significant effect of time for all treatments (F(5, 46, 1) = 3.00, P < 0.01) with an overall improvement in integrative function as measured by CFF as shown in Figure 5.22B. For paroxetine there was an overall significant effect of time (F(5, 11, 6) = 6.08, P < 0.01) with a significant improvement for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1 week 0. For sertraline, there was an overall significant effect of time (F(5, 10, 6) = 3.19, P < 0.05), with a significant improvement for weeks 1 4, 8 and 12 compared with baseline Visit 1 week 0.

Analysis of weeks 1 to 12 showed that CFF was improved overall (F(5, 48, 1) = 3.85, P < 0.01) for all treatments with an improvement in integrative function over time. There was a significant effect of treatment for paroxetine (F(5, 14) = 7.66, P = 0.01), and a trend towards a significant effect of time for fluoxetine (F(5, 12) = 2.85, P = 0.07) and sertraline (F(5, 12, 1) = 2.56, P = 0.08). A higher score indicates improved functioning.

Analysis of the change in CFF from week 12 to week 13, i.e. during discontinuation of treatment, did not reach statistical significance for all treatments. Paroxetine and sertraline
showed a decrease in CFF from Visit 12 to Visit 13, whilst fluoxetine showed an increase during this period. However this reduction was only significant in CFF for sertraline ($F_{(1, 17)} = 5.43, P < 0.05$) at week 13 compared with week 12 showing a within group impairment in integrative function during treatment discontinuation.

5.5.7.3. Summary of cognitive and psychomotor function variables

A summary of the direction of the statistically significant effect of duration of antidepressants on cognitive variables for the full study for weeks 0 to 14, the treatment phase for weeks 1 to 12 and for the last week of treatment (week 12) compared with the discontinuation withdrawal week 13, is presented in Table 5.12. There was a significant improvement in RRT, TRT and CFF during the 12 week and 14 week study. However, there was a significant worsening of TRT following paroxetine withdrawal and CFF following sertraline withdrawal during the abrupt discontinuation between weeks 12 and 13.

5.5.7.4. Leeds Sleep Evaluation Questionnaire (LSEQ)

The LSEQ is divided into four sub-sections, getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS) and behaviour following wake (BFW) which are covered in detail below. At Visit 1, for the baseline night, patients were required to compare their sleep for ‘last night’ with ‘sleep in the past week’. For all further visits in weeks 1 to 14 patients were required to compare their sleep ‘with the medication’ to normally ‘without the medication’ where a score of 50 indicates no change.

The individual mean LSEQ scores (± SEM) for GTS recorded at baseline, Visit 1 were 53.8 (± 3.4), 51.1 (± 3.6) and 49.1 (± 3.6) for paroxetine, fluoxetine and sertraline, respectively Table 5.13. Analysis of the change in GTS from week 0 (Visit 1) to week 14, did not reach statistical significance between treatments or for time Figure 5.23A. However, GTS was significantly improved overall ($F_{(6, 48)} = 2.24, P = 0.055$) for the treatment period weeks 1 to 12.

The individual mean LSEQ scores (± SEM) for QOS recorded at baseline, week 0 Visit 1 for the baseline night, when patients were required to compare their sleep for ‘last night’ with ‘sleep in the past week’ were 63.3 (± 3.7), 51.6 (± 3.9) and 45.5 (± 3.9) for paroxetine, fluoxetine and sertraline respectively, where a score greater than 50 indicated poorer sleep Table 5.13. For the change from week 0 Visit 1 to week 14, analysis did not reach statistical significance between treatments Figure 5.23B. There was, however, a significant effect of time overall for all treatments ($F_{(8, 45.8)} = 2.47, P < 0.05$) with an improvement in quality of
sleep across time. For the treatment period week 1 to week 12 the QOS analysis showed a significant improvement across time for all treatments ($F_{(6,\ 48)} = 2.69, \ P < 0.05$) with a significant improvement in QOS for paroxetine ($F_{(6,\ 14)} = 2.84, \ P = 0.05$).

Analysis did not show an effect of treatment for QOS for the discontinuation phase between weeks 12 and 13, however there was a trend towards a significant treatment by time interaction ($F_{(2,\ 53)} = 2.87, \ P = 0.07$). QOS was significantly improved for fluoxetine ($F_{(1,\ 17)} = 5.01, \ P < 0.05$) and a trend was observed for sertraline ($F_{(1,\ 17)} = 3.76, \ P = 0.07$) with a reduction in QOS scores at week 13 during the discontinuation period compared with week 12.

The mean LSEQ scores (± SEM) for AFS recorded at baseline, Visit 1, were 50.8 (± 3.9), 49.5 (± 4.1) and 42.3 (± 4.1) for paroxetine, fluoxetine and sertraline, respectively Table 5.13. Analysis did not show any significant effects of treatment or time for the 14 weeks study Figure 5.24A, the treatment period from week 1 to week 12 or the abrupt discontinuation from week 12 to week 13.

![Figure 5.23: Effect of antidepressant treatment on GTS and QOS on change from baseline.](image)

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on LSEQ components (mean ± SEM) on mean change from baseline for A. Getting to sleep (GTS) and B. Quality of sleep (QOS). There was a significant difference of treatment for QOS ($P < 0.05$). The charts indicate a worsening of effect of paroxetine on GTS and QOS occurring during the withdrawal period (week 13).
Table 5.12: Summary of the statistically significant effects of duration of antidepressant treatment administration on cognitive and psychomotor function

<table>
<thead>
<tr>
<th>Cognition Variable</th>
<th>Weeks 0 to 14 Full Study</th>
<th>Weeks 1 to 12 Treatment phase</th>
<th>Weeks 12 and 13 Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect of time</td>
<td>Overall</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>RRT (ms)</td>
<td>Improved P&lt;0.01</td>
<td>Improved P=0.08</td>
<td>Improved P&lt;0.01</td>
</tr>
<tr>
<td>MRT (ms)</td>
<td>Improved P&lt;0.01</td>
<td>Improved P=0.08</td>
<td>Improved P&lt;0.01</td>
</tr>
<tr>
<td>TRT (ms)</td>
<td>Improved P&lt;0.01</td>
<td>Improved P=0.08</td>
<td>Improved P&lt;0.01</td>
</tr>
<tr>
<td>CFF (Hz)</td>
<td>Improved P&lt;0.01</td>
<td>Improved P=0.05</td>
<td>Improved P&lt;0.01</td>
</tr>
</tbody>
</table>

The statistically significant effect of duration of antidepressant treatment and direction of change on cognitive function, for the full study of weeks 0-14, treatment phase of weeks 1-12 and for the last week of treatment (week 12) compared with discontinuation withdrawal week 13. A trend towards statistical significance is shown by ‘-’ if the P-value was <0.1.
The individual means for LSEQ scores (± SEM) for BFW recorded at baseline, Visit 1, were 55.9 (± 3.2), 57.0 (± 3.4) and 53.5 (± 3.4) for paroxetine, fluoxetine and sertraline, respectively indicating that the patients were less confused and sleepy after waking than the previous week since scores were on average greater than 50 Table 5.13. For the week 1 to 14 study period, analysis showed a significant trend for improvement over time ($F(8, 458) = 2.04, P = 0.06$) with a reduction in scores indicating that the patients felt more refreshed on waking (Figure 5.24B). Analysis showed a significant trend of improvement over time for the 12 week study period for BFW ($F(6, 48) = 2.81, P < 0.05$) with a reduction in scores, and a significant trend for paroxetine ($F(6, 14) = 2.42, P = 0.08$). Analysis did not show any significant effect of treatment nor time for the abrupt discontinuation from week 12 to week 13.

Figure 5.24: Effect of antidepressant treatment on AFS and BFW on change from baseline. The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on LSEQ components (mean ± SEM) on change from baseline for A. Awakening from sleep (AFS) and B. Behaviour following wake (BFW).

5.5.7.5. Line Analogue Rating Scale (LARS)

The subjective evaluation of sedation was obtained from the mean score (in millimetres) for the combined ratings of “tiredness”, “drowsiness” and “alertness” from the LARS questionnaire. The individual mean scores (± SEM) for the three treatment groups at baseline Visit 1 prior to treatment were 68.1 (± 3.4), 65.7 (± 3.6) and 58.8 (± 3.6) for paroxetine, fluoxetine and sertraline, respectively, patients indicated that they felt more sleepy and less alert than the previous week (Table 5.13).
### Table 5.13: Effect of antidepressant treatment on Leeds Sleep Evaluation Questionnaire and Line Analogue Rating Scale by treatment and time

<table>
<thead>
<tr>
<th>Questionnaire Variable</th>
<th>Mean (SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>Time</td>
</tr>
<tr>
<td><strong>LSEQ Getting to sleep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>53.8</td>
<td>43.0</td>
</tr>
<tr>
<td>(3.4)</td>
<td>(3.1)</td>
<td>(3.1)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>51.1</td>
<td>39.9</td>
</tr>
<tr>
<td>(3.6)</td>
<td>(3.3)</td>
<td>(3.2)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>49.1</td>
<td>43.8</td>
</tr>
<tr>
<td>(3.6)</td>
<td>(3.3)</td>
<td>(3.2)</td>
</tr>
<tr>
<td><strong>LSEQ Quality of sleep</strong></td>
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<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>63.3</td>
<td>39.4</td>
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<tr>
<td>(3.7)</td>
<td>(3.4)</td>
<td>(4.1)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>51.6</td>
<td>42.7</td>
</tr>
<tr>
<td>(3.9)</td>
<td>(3.5)</td>
<td>(4.4)</td>
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<tr>
<td>Sertraline</td>
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<td>40.2</td>
</tr>
<tr>
<td>(3.9)</td>
<td>(3.5)</td>
<td>(4.4)</td>
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<td><strong>LSEQ Awakening from sleep</strong></td>
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</tr>
<tr>
<td>Paroxetine</td>
<td>50.8</td>
<td>46.7</td>
</tr>
<tr>
<td>(3.9)</td>
<td>(3.7)</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>49.5</td>
<td>50.0</td>
</tr>
<tr>
<td>(4.1)</td>
<td>(3.9)</td>
<td>(3.9)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>42.3</td>
<td>43.9</td>
</tr>
<tr>
<td>(4.1)</td>
<td>(3.9)</td>
<td>(3.9)</td>
</tr>
<tr>
<td><strong>LSEQ Behaviour following wake</strong></td>
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<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>55.9</td>
<td>48.1</td>
</tr>
<tr>
<td>(3.2)</td>
<td>(3.0)</td>
<td>(3.1)</td>
</tr>
<tr>
<td>Fluoxetine</td>
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<td>47.9</td>
</tr>
<tr>
<td>(3.4)</td>
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<tr>
<td>Sertraline</td>
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</tr>
<tr>
<td>(3.4)</td>
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<td>(3.3)</td>
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<td><strong>LARS (Sedation)</strong></td>
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<tr>
<td>Paroxetine</td>
<td>68.1</td>
<td>46.0**</td>
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<tr>
<td>(3.4)</td>
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<td>58.8</td>
<td>48.3</td>
</tr>
<tr>
<td>(3.6)</td>
<td>(4.4)</td>
<td>(4.2)</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. Significance for individual weeks within each respective treatment compared with week 0 are denoted in weeks by ***, **, * < 0.0001, ** < 0.01, * < 0.05. A trend towards statistical significance is denoted as *, if the P-value, in the individual treatment time column, was < 0.1. The reduction in scores indicate improved quality of sleep, with patients feeling less drowsy and more alert on waking and less sleepy during the day. Means (± SEM) are expressed at each time point.
Analysis of the 14 week study showed that there was a significant effect of time overall for all treatments ($F(8, 45.7) = 7.10, P < 0.0001$), with patients indicating an improvement and feeling less drowsy and tired, and more alert as shown in mean change from baseline in Figure 5.25. For paroxetine there was an overall significant effect of time ($F(8, 11.3) = 5.36, P < 0.01$), with a significant decrease in scores for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1 week 0. Similarly there was an overall significant effect of time ($F(8, 10.0) = 4.18, P < 0.05$) for fluoxetine, with a significant decrease in scores for weeks 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1 week 0.

Analysis for the 12 week treatment period showed a significant effect of time overall for all treatments ($F(6, 48) = 8.92, P < 0.0001$), indicating an improvement and in feeling less drowsy and tired and more alert with significant improvements for paroxetine ($F(6, 14) = 6.74, P < 0.01$) and fluoxetine ($F(6, 12) = 5.06, P < 0.01$). There was a significant trend with an increase in scores with paroxetine ($F(1, 19) = 4.05, P = 0.06$) indicating patients felt more drowsy and sedated during the discontinuation week 13 compared with week 12.

![Figure 5.25: Effect of antidepressant treatment on LARS on change from baseline.](image)

The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on LARS (mean ± SEM) on mean change from baseline. There were no statistically significant effects. The chart indicates a worsening of effect occurring during the withdrawal period week 13 for paroxetine.

### 5.5.7.6. Summary of the sleep questionnaire variables

A summary of the improvement of the statistically significant effect of duration of antidepressants on the sleep questionnaire variables for the full study for weeks 0 to 14, the treatment phase for weeks 1 to 12 and for the last week of treatment (week 12) compared with the discontinuation withdrawal week 13, is presented in Table 5.14. There was a significant improvement in patient’s perception of the quality of their sleep according to the LSEQ. Moreover, they felt significantly less drowsy and more alert according to the LARS during the 12 week and 14 week study. However, there was a significant worsening of LARS.
following paroxetine withdrawal during the abrupt discontinuation between weeks 12 and 13.

5.5.7.7. Montgomery-Åsberg Depression Rating Scale (MADRS)

The overall MADRS results for the 14 week study are summarised by visit and treatment group, and differences between visits, on discontinuation and re-introduction of treatment in Table 5.15. The maximum achievable score for severe depression on the MADRS scale is 60 whereas the mean MADRS score (± SEM) for each treatment recorded at baseline Visit 1 was 27.9 (± 1.8), 24.9 (± 1.8) and 26.5 (± 1.8) for paroxetine, fluoxetine and sertraline, respectively corresponding to moderate to severe depression MADRS (25-30). There was no significant effect between treatments or for treatment by time interaction for the MADRS score as shown in Figure 5.26. There was, however, an overall significant effect of time ($F(8, 45.6) = 32.87, P < 0.0001$) with substantial improvements in depression rating.

All treatments showed an improvement in depression rating observed as a decrease in MADRS scores. For paroxetine there was a significant effect of time ($F(8, 11.2) = 18.9, P < 0.0001$) with a decrease in depression severity for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with the baseline Visit 1. Fluoxetine showed a significant effect of time ($F(8, 10.0) = 6.93, P < 0.01$) for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with the baseline Visit 1. For sertraline there was also a significant effect of time ($F(8, 10.0) = 31.42, P < 0.0001$) with a decrease in depression scores for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with the baseline Visit 0. Patients improved from being moderately depressed (MADRS 25-30) to not being clinically depressed with scores less than 15 (mild depression MADRS 15-24), scoring 7.5 (± 2.0), 8.8 (± 2.1) and 9.1 (± 2.1), for paroxetine, fluoxetine and sertraline, respectively at week 14.

Analysis of the 12 week treatment period from week 1 to week 12 showed MADRS depression scores were significantly reduced indicating an improvement in depression rating overall for MADRS across time ($F(6, 48) = 45.34, P < 0.0001$). There were significant improvements for each treatment with paroxetine ($F(6, 14) = 24.88, P < 0.01$), fluoxetine ($F(6, 12) = 9.72, P < 0.01$) and sertraline ($F(6, 12) = 44.04, P < 0.0001$) with a reduction in depression scores. Analysis did not show any significant effect of treatment nor time during the abrupt discontinuation from week 12 to week 13.
Figure 5.26: Effect of antidepressant treatment on MADRS on mean change from baseline.
The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on MADRS score (mean ± SEM) on change from baseline. There was a significant effect of time on MADRS overall (P < 0.0001), for paroxetine and fluoxetine (P < 0.01), and for sertraline (P < 0.0001). The chart indicates a worsening of effect during the withdrawal period week 13 for paroxetine and sertraline but a continued improvement for fluoxetine.

5.5.7.8. Montgomery-Åsberg Depression Rating Scale (MADRS) sleep item

The question relating to the sleep component was analysed independently as a MADRS sleep subset. Results are summarised by week and treatment group, and differences between visits, on discontinuation and re-introduction of treatment as shown in Table 5.15. The maximum score for severe sleep impairment is 6. The mean MADRS sleep component (± SEM) for each treatment recorded at baseline Visit 1 was 3.6 (± 0.4), 2.8 (± 0.4) and 2.9 (± 0.4) for paroxetine, fluoxetine and sertraline, respectively suggesting that sleep was impaired due to the patients’ depression. There was an overall significant effect of time (F(8, 45.8) = 7.17, P < 0.0001) but no significant effect between treatments nor for treatment by time interaction on the MADRS sleep subset. Although scores were reduced for all treatments, as shown in Figure 5.27 there was only a significant effect of time for paroxetine, (F(8, 11.7) = 6.38, P < 0.01) with significant reductions on the MADRS sleep score for weeks 1, 2, 4, 8, 11, 12, 13 and 14 (P < 0.0001) compared with baseline Visit 1.
Table 5.14: Summary of the statistically significant effects of duration of antidepressant treatment administration on Leeds Sleep Evaluation Questionnaire and Line Analogue Rating Scale

<table>
<thead>
<tr>
<th>Questionnaire Variable</th>
<th>Weeks 0 to 14</th>
<th></th>
<th></th>
<th>Weeks 1 to 12</th>
<th></th>
<th></th>
<th>Weeks 12 and 13</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect of time</td>
<td>Overall</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
<td>Overall</td>
<td>Paroxetine</td>
<td>Fluoxetine</td>
<td>Overall</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>LSEQ Getting to sleep</td>
<td></td>
<td></td>
<td>Improved</td>
<td>P=0.055</td>
<td>Improved</td>
<td>P=0.05</td>
<td></td>
<td>Improved</td>
<td>P=0.07</td>
</tr>
<tr>
<td>LSEQ Quality of sleep</td>
<td>Improved</td>
<td>P&lt;0.05</td>
<td></td>
<td></td>
<td>Improved</td>
<td>P=0.05</td>
<td>Improved</td>
<td>P=0.08</td>
<td>Improved</td>
</tr>
<tr>
<td>LSEQ Awakening from sleep</td>
<td></td>
<td></td>
<td>Improved</td>
<td>P=0.06</td>
<td>Improved</td>
<td>P=0.05</td>
<td></td>
<td>Improved</td>
<td>P=0.01</td>
</tr>
<tr>
<td>LSEQ Behaviour following wake</td>
<td>Improved</td>
<td>P&lt;0.0001</td>
<td>Improved</td>
<td>P&lt;0.05</td>
<td>Improved</td>
<td>P&lt;0.01</td>
<td>Improved</td>
<td>P&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>LARS (Sedation)</td>
<td>Improved</td>
<td>P&lt;0.01</td>
<td>Improved</td>
<td>P&lt;0.05</td>
<td>Improved</td>
<td>P&lt;0.01</td>
<td>Improved</td>
<td>P&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

The statistically significant effect of duration of antidepressant treatment and direction of change on Leeds Sleep Evaluation Questionnaire (LSEQ) and Line Analogue Rating Scale (LARS), for the full study of weeks 0-14, the treatment phase of weeks 1-12 and for the last week of treatment (week 12) compared with discontinuation withdrawal week 13. A trend towards statistical significance is shown by ‘#’ if the P-value was <0.1.
Figure 5.27: Effect of antidepressant treatment on MADRS sleep component on change from baseline. The effect of paroxetine (■) (n = 20), fluoxetine (●) (n = 18) and sertraline (▲) (n = 18) on MADRS sleep component (mean ± SEM) on change from baseline. There was a significant effect of time on MADRS sleep component overall and sertraline (P < 0.01), and a trend for sertraline (P < 0.1). The chart indicates a worsening of effect during the withdrawal period week 13 for paroxetine and sertraline.

Analysis of the 12 week treatment period from week 1 to week 12 showed that the MADRS sleep component depression scores were significantly reduced indicating an improvement in the sleep aspect of depression (F(6, 48) = 9.84, P < 0.0001). There were significant improvements for each treatment for MADRS sleep for paroxetine (F(6, 4) = 7.18, P < 0.01), with a trend towards significance for fluoxetine (F(6, 12) = 2.38, P = 0.09) sertraline and (F(6, 12) = 2.97, P = 0.05). Analysis showed a significant effect of time during the abrupt discontinuation from week 12 to week 13 with a significant increase in the MADRS sleep component scores indicating a deterioration during discontinuation (F(1, 53) = 4.77, P < 0.05), however, this was significant only for paroxetine (F(1, 19) = 3.57, P = 0.07) and sertraline (F(1, 17) = 3.57, P = 0.08).

5.5.7.9. Hamilton Depression Rating Scale (HAMD)

The overall HAMD results are summarised by week and treatment group, and differences between visits, on discontinuation and re-introduction of treatment in Table 5.15. The mean HAMD score (± SEM) for each treatment recorded at baseline Visit 1 was 20.7 (± 1.2), 19.8 (± 1.3) and 20.8 (± 1.3) for paroxetine, fluoxetine and sertraline, respectively being mild to moderate depression (HAMD 18-24). There was no significant effect for treatment nor treatment by time for the HAMD score. There was, however, an overall significant effect of time (F(8, 45.8) = 32.17, P < 0.0001). All treatments showed substantial improvements in the HAMD depression rating observed as a decrease in scores as shown in Figure 5.28.
Table 5.15: Effect of antidepressant treatment on Montgomery-Åsberg (MADRS) and Hamilton (HAMD) Depression Rating Scales by treatment and time

<table>
<thead>
<tr>
<th>Questionnaire Variable</th>
<th>Mean (SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Variable</td>
<td>Time (weeks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>MADRS (Range 0-60)</td>
<td>Paroxetine</td>
<td>27.9</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>24.9</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>26.5</td>
</tr>
<tr>
<td>HAMD Sleep (Range 0-6)</td>
<td>Paroxetine</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>2.9</td>
</tr>
<tr>
<td>HAMD (Range 0-52)</td>
<td>Paroxetine</td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>20.8</td>
</tr>
<tr>
<td>HAMD Sleep (Range 0-6)</td>
<td>Paroxetine</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>3.2</td>
</tr>
<tr>
<td>HAMD Insomnia Early (Range 0-2)</td>
<td>Paroxetine</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. Significance for individual weeks within each respective treatment compared with week 0 are denoted in weeks by *** <0.0001, ** <0.01, * <0.05. A trend towards statistical significance is denoted as *, if the P-value, in the individual treatment time column, was <0.1. Means (± SEM) are expressed at each time point.
For paroxetine there was a significant effect of time \( (F_{(8,11.4)} = 17.09, P < 0.0001) \) with a decrease in depression severity for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. Fluoxetine showed a significant effect of time \( (F_{(8,10.0)} = 8.02, P < 0.01) \) for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. For sertraline there was also a significant effect of time \( (F_{(8,10.0)} = 13.7, P < 0.001) \) with a decrease in depression scores for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. Patients improved from being moderately depressed (18-24) to being not clinically depressed with scores less than 7 (mild depression 7-17), with mean scores of 5.2 \((± 1.2)\), 5.3 \((± 1.2)\) and 6.6 \((± 1.2)\), for paroxetine, fluoxetine and sertraline, respectively at week 14.

![Figure 5.28: Effect of antidepressant treatment on HAMD on change from baseline. The effect of paroxetine (■) \((n = 20)\), fluoxetine (●) \((n = 18)\) and sertraline (▲) \((n = 18)\) on HAMD (mean ± SEM) on change from baseline for HAMD score. There was a significant effect of time on HAMD overall \( (P < 0.0001) \), and for paroxetine and sertraline \( (P < 0.05) \) with a trend for fluoxetine \( (P < 0.1) \).](image)

Analysis of the 12 week treatment period showed that the HAMD depression scores were significantly reduced indicating an improvement in depression rating overall for HAMD \( (F_{(6,48)} = 42.39, P < 0.0001) \). There were significant improvements for treatments paroxetine \( (F_{(6,14)} = 24.61, P < 0.0001) \), fluoxetine \( (F_{(6,12)} = 9.76, P < 0.001) \) and sertraline \( (F_{(6,12)} = 18.43, P < 0.0001) \). Analysis of the HAMD depression scores for weeks 12 to 13 showed a trend towards a significant increase in scores for paroxetine \( (F_{(1,19)} = 3.18, P = 0.09) \) from 5.7 \((± 1.4)\) to 7.5 \((± 1.4)\) with a rebound effect on the depression rating during the discontinuation period.

5.5.7.10. Hamilton Depression Rating Scale (Insomnia) sleep item

The HAMD sleep subset component for insomnia was made up of the total score of the 3 components of early, middle and late insomnia, the maximum score for severe insomnia being 6. Results are summarised by week and treatment group, and differences between
visits, on discontinuation and re-introduction of treatment in Table 5.15. The mean HAMD sleep subset score (± SEM) for each treatment recorded at baseline Visit 1 was 3.7 (± 0.7), 4.4 (± 0.7) and 3.2 (± 0.7) for paroxetine, fluoxetine and sertraline, respectively indicating that patients were experiencing sleep problems. There was no significant effect of treatment nor treatment by time interaction for the HAMD sleep score. There was, however, an overall significant effect of time (F(8, 450) = 5.32, P < 0.001) as shown in Figure 5.29. All treatments showed improvements in the sleep component of the depression rating observed as a decrease in scores to 1.3, 0.9 and 1.4 for paroxetine, fluoxetine and sertraline, respectively at week 14. However, there was only a significant effect of time for paroxetine (F(8, 109) = 4.02, P < 0.05) with a decrease in severity on sleep for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1.

![Figure 5.29: Effect of antidepressant treatment on HAMD sleep score on change from baseline.](image)

HAMD sleep scores for the 12 week period were significantly reduced indicating an improvement in the sleep component rating overall across time (F(6, 48) = 7.35, P < 0.0001). There was a significant improvement for paroxetine (F(6, 14) = 5.77, P < 0.01). Analysis of the sleep component showed no significant effect during the discontinuation weeks.

5.5.7.11. Hamilton Depression Rating Scale (Early Insomnia) sleep item

A further component of the HAMD was analysed for early insomnia, which is comparable with sleep latency, the time taken to get to sleep, the maximum score for severe early insomnia is 2. Results are summarised by week and treatment group, and differences between visits, on discontinuation and re-introduction of treatment in Table 5.15. The mean HAMD sleep subset score (± SEM) for early insomnia for each treatment recorded at the
baseline Visit 1 was 1.1 (± 0.2), 0.9 (± 0.2) and 1.0 (± 0.2) for paroxetine, fluoxetine and sertraline, respectively indicating occasional difficulty falling asleep of less than 30 minutes. There was an overall significant effect of time ($F(8, 45.4) = 4.69, P < 0.001$). For fluoxetine there was a significant effect of time ($F(8, 10.0) = 2.91, P = 0.06$) for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1 (Figure 5.30). All treatments showed improvements in early insomnia, the sleep latency component of the depression rating observed as a decrease in scores to 0.2 (± 0.1), 0.3 (± 0.1) and 0.3 (± 0.1) for paroxetine, fluoxetine and sertraline, respectively at week 14 indicating little difficulty falling asleep.

![Figure 5.30](image-url)

Figure 5.30: Effect of antidepressant treatment on HAMD early insomnia on change from baseline. The effect of paroxetine (■) (n = 20), fluoxetine (•) (n = 18) and sertraline (▲) (n = 18) on HAMD early insomnia components (mean ± SEM) on change from baseline. The chart indicates a worsening of effect during the withdrawal period week 13 for paroxetine and sertraline.

Analysis of the 12 week period showed that the HAMD scores for the early insomnia aspect were significantly reduced ($F(6, 48) = 5.93, P < 0.001$), indicating an overall improvement with a significant improvement for paroxetine ($F(6, 14) = 4.14, P < 0.05$). Analysis of the discontinuation weeks for early insomnia showed no significant effect, however, there was a trend towards a worsening of the early insomnia score for sertraline ($F(1, 17) = 3.4, P = 0.08$) with an increase in scores between weeks 12 and 13 indicating that patients took longer to get to sleep during the discontinuation week.

5.5.7.12. ZUNG Depression Inventory

The overall ZUNG results are summarised by week and treatment group, and differences between visits, on discontinuation and re-introduction of treatment in Table 5.16. The maximum self-completed score for the severest depression is 80. The mean ZUNG score (± SEM) for each treatment recorded at baseline Visit 1 was 56.5 (± 1.7), 54.4 (± 1.8) and 53.7 (± 1.8) for paroxetine, fluoxetine and sertraline, respectively being mild to moderate depression (50-59). There was no significant effect between treatments nor treatment by time.
interaction for the ZUNG score; however, there was significant effect of time overall ($F_{(8, 45.5)} = 14.94, P < 0.0001$) Figure 5.31. All treatments showed improvements in the depression rating observed as a decrease in scores. For paroxetine there was a significant effect of time ($F_{(8, 11.2)} = 5.25, P < 0.01$) with a decrease in depression severity at weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with the baseline Visit 1. Fluoxetine showed a significant effect of time ($F_{(8, 10.0)} = 9.78, P < 0.01$) for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. For sertraline there was also a significant effect of time ($F_{(8, 10.0)} = 9.91, P < 0.01$) with a decrease in depression scores for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. All treatments showed improvements in the depression rating observed as a decrease in scores to 35.9 ($± 2.4$), 36.7 ($± 2.5$) and 37.5 ($± 2.5$) for paroxetine, fluoxetine and sertraline, respectively at week 14 which is in the normal ZUNG score range of 20-49.

Figure 5.31: Effect of antidepressant treatment on ZUNG on change from baseline. The effect of paroxetine (■) ($n = 20$), fluoxetine (•) ($n = 18$) and sertraline (▲) ($n = 18$) on ZUNG (mean $±$ SEM) on change from baseline. There was a significant effect of time on ZUNG score overall ($P < 0.0001$), and for sertraline ($P < 0.01$), and paroxetine and fluoxetine ($P < 0.05$).

Analysis of the 12 week period showed that the ZUNG depression scores were significantly reduced indicating an improvement in self-rated depression overall ($F_{(6, 48)} = 20.72, P < 0.0001$). There were significant improvements for each treatment, for paroxetine, fluoxetine and sertraline ($F_{(6, 14)} = 7.94, P < 0.01$), ($F_{(6, 12)} = 10.26, P < 0.01$) and ($F_{(6, 12)} = 15.47, P < 0.0001$) respectively. Analysis showed no significant effect during the discontinuation weeks for the ZUNG depression rating.

5.5.7.13. Cognitive Failures Questionnaire (CFQ)

The overall CFQ is a self-reported questionnaire on failures in perception, memory and motor function. The overall CFQ results are summarised by week and treatment group, and differences between visits, on discontinuation and re-introduction of treatment in Table 5.16.
The maximum score is 100. The mean CFQ score (± SEM) for each treatment recorded at baseline Visit 1 was 58.9 (± 3.7), 57.6 (± 3.9) and 66.4 (± 3.9) for paroxetine, fluoxetine and sertraline, respectively indicating a mild level of impairment.

There was no significant effect of treatment nor treatment by time interaction for the CFQ score. There was, however, an overall significant effect of time \( F(8, 45.2) = 7.68, P < 0.0001 \) as shown in Figure 5.32. There was a significant effect of time overall for sertraline \( F(8, 10) = 3.76, P < 0.05 \) with an improvement in cognitive function for weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. Whereas for paroxetine \( F(8, 11) = 2.39, P = 0.09 \) and fluoxetine \( F(8, 10.0) = 2.53, P = 0.09 \) there was a trend towards significance for time overall with improvements at weeks 1, 2, 4, 8, 11, 12, 13 and 14 compared with baseline Visit 1. All treatments showed a reduction in perceived failures after 14 weeks, observed as a decrease in scores to 35.0 (± 4.5), 39.1 (± 4.8) and 41.1 (± 4.8) for paroxetine, fluoxetine and sertraline, respectively at Week 14 which are within the normal range of 40-45.

![Figure 5.32: Effect of antidepressant treatment on CFQ on change from baseline.](image)

Analysis of the 12 week period showed that CFQ scores were significantly reduced indicating an improvement in self-rated cognitive function overall \( F(6, 48) = 10.46, P < 0.0001 \). There were significant improvements for each treatment individually, for paroxetine, fluoxetine and sertraline \( F(6, 14) = 3.64, P < 0.05 \), \( F(6, 12) = 3.96, P < 0.05 \) and \( F(6, 12) = 5.58, P < 0.01 \) respectively. Analysis showed no significant effect during the discontinuation weeks for the CFQ.
Table 5.16: Effect of antidepressant treatment on the ZUNG depression inventory and the Cognitive Forms Questionnaire (CFQ) by treatment and time

<table>
<thead>
<tr>
<th>Questionnaire Variable</th>
<th>Mean (SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (weeks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>ZUNG</strong>&lt;br&gt;(Range 0-80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>56.5</td>
<td>44.9***</td>
</tr>
<tr>
<td>(1.7)</td>
<td></td>
<td>(2.0)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>54.4</td>
<td>45.8***</td>
</tr>
<tr>
<td>(1.8)</td>
<td></td>
<td>(2.1)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>53.7</td>
<td>44.6***</td>
</tr>
<tr>
<td>(1.8)</td>
<td></td>
<td>(2.1)</td>
</tr>
<tr>
<td><strong>CFQ</strong>&lt;br&gt;(Range 0-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>58.9</td>
<td>46.7**</td>
</tr>
<tr>
<td>(3.7)</td>
<td></td>
<td>(4.4)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>57.6</td>
<td>46.6**</td>
</tr>
<tr>
<td>(3.9)</td>
<td></td>
<td>(4.5)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>66.4</td>
<td>54.9**</td>
</tr>
<tr>
<td>(3.9)</td>
<td></td>
<td>(4.5)</td>
</tr>
</tbody>
</table>

Overall significance is shown for treatment, time and treatment by time. NS denotes not significant. Overall significance for each individual treatment is shown by time. Significance for individual weeks within each respective treatment compared with week 0 are denoted in weeks by *** = <0.0001, ** = <0.01, * = <0.05. A trend towards statistical significance is denoted as *, if the P-value, in the individual treatment time column, was <0.1. Means (± SEM) are expressed at each time point.
5.5.7.14. Summary of the depression questionnaire variables

A summary of the improvement of the statistically significant effect of duration of antidepressants on the depression questionnaire variables for the full study for weeks 0 to 14, the treatment phase for weeks 1 to 12 and for the last week of treatment (week 12) compared with the discontinuation withdrawal week 13, is presented in Table 5.17. There was a significant improvement in the GP’s and patient’s perception of the severity of their depression according to the MADRS, HAMD and ZUNG during the 12 week and 14 week study. Moreover, they felt significantly less clumsy according to the CFQ. However, there was a significant worsening of the MADRS sleep and HAMD insomnia early following paroxetine withdrawal during the abrupt discontinuation between weeks 12 and 13.

5.5.7.15. Overall summary of significant variables

For comparison a summary of the significant variables for weeks 1 to 12 and the discontinuation week 12 to 13 is shown in Table 5.18.

5.6. Discussion

5.6.1. Introduction

The treatment of depression for the patients in the current study was with the group of the most widely prescribed antidepressants known as the SSRIs, which are prescribed to treat depression (Taylor and Stein, 2006). This is the first study to investigate and compare the effect of 3 SSRI antidepressant treatments (paroxetine, fluoxetine and sertraline) on the time course and duration of action on actigraphic sleep and wake variables, actigraphic circadian variables, subjective sleep quality, depression rating and psychomotor and cognitive performance in depressed patients in a 14 week randomised, double-blind, study. For the purpose of comparison with other studies reference is made mainly to the effects of the SSRIs detailed in this study on depressed patients and not healthy participants, since the effect of antidepressants and the mechanism of action may vary depending on the length of treatment, their health status and their sleep. Depressed patients experience more sleep (Wichniak et al., 2012) and circadian disruption (Germain and Kupfer, 2008) than healthy participants, disturbed sleep being one of the diagnostic criteria of depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of depression, and with sleep disturbance being reported by > 90% of patients (Wichniak et al., 2012).
Table 5.17: Summary of the statistically significant effects of duration of antidepressant treatment administration on depression rating scales MADRS, HAMD, ZUNG and CFQ

<table>
<thead>
<tr>
<th>Questionnaire Variable</th>
<th>Weeks 0 to 14 Full Study</th>
<th>Weeks 1 to 12 Treatment phase</th>
<th>Weeks 12 and 13 Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect of time</td>
<td>Overall</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>MADRS (Range 0-60)</td>
<td>Improved</td>
<td>P&lt;0.0001</td>
<td>Improved</td>
</tr>
<tr>
<td>MADRS Sleep (Range 0-6)</td>
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<td>P&lt;0.0001</td>
<td>Improved</td>
</tr>
<tr>
<td>HAMD (Range 0-52)</td>
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<td>P&lt;0.0001</td>
<td>Improved</td>
</tr>
<tr>
<td>HAMD Sleep (Range 0-6)</td>
<td>Improved</td>
<td>P&lt;0.001</td>
<td>Improved</td>
</tr>
<tr>
<td>HAMD Insomnia Early</td>
<td>Improved</td>
<td>P&lt;0.001</td>
<td>Improved</td>
</tr>
<tr>
<td>Zung</td>
<td>Improved</td>
<td>P&lt;0.0001</td>
<td>Improved</td>
</tr>
<tr>
<td>CFQ</td>
<td>Improved</td>
<td>P&lt;0.0001</td>
<td>Improved</td>
</tr>
</tbody>
</table>

The statistical significant effect of duration of antidepressant treatment and direction of change on depression rating scales, for the full study of weeks 0-14, the treatment phase of weeks 1-12 and for the last week of treatment (week 12) compared with discontinuation withdrawal week 13. A trend towards statistical significance is shown by ‘−’ if the P-value was <0.1.
Table 5.18: Summary of the statistically significant variables of antidepressant treatment overall

<table>
<thead>
<tr>
<th>Sleep Variable</th>
<th>Weeks 1 to 12 Treatment phase</th>
<th>Weeks 12 and 13 Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>↓ P&lt;0.05</td>
<td>↓ P&lt;0.05</td>
</tr>
<tr>
<td>Sleep period time (min)</td>
<td>↓ P&lt;0.05</td>
<td>↓ P&lt;0.05</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>↓ P&lt;0.05</td>
<td>↓ P&lt;0.05</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>↑ P&lt;0.02</td>
<td>↑ P=0.07</td>
</tr>
<tr>
<td>Number of sleep bouts</td>
<td>↑ P=0.001</td>
<td>↑ P=0.001</td>
</tr>
<tr>
<td>Average wake movement</td>
<td>↑ P&lt;0.001</td>
<td>↑ P&lt;0.01</td>
</tr>
<tr>
<td>Amplitude</td>
<td>↑ P&lt;0.05</td>
<td>↑ P&lt;0.07</td>
</tr>
<tr>
<td>M10 onset time (h)</td>
<td>Delayed P=0.06</td>
<td>Delayed P=0.06</td>
</tr>
<tr>
<td>M10 activity</td>
<td>↑ P&lt;0.05</td>
<td>↑ P&lt;0.05</td>
</tr>
<tr>
<td>LS onset time (h)</td>
<td>Delayed P=0.05</td>
<td>Advanced P&lt;0.05</td>
</tr>
<tr>
<td>LS activity</td>
<td>↓ P&lt;0.05</td>
<td>↓ P&lt;0.01</td>
</tr>
<tr>
<td>IS</td>
<td>↓ P=0.06</td>
<td>↓ P=0.06</td>
</tr>
<tr>
<td>MADRS (Range 0-60)</td>
<td>Improved P=0.0001</td>
<td>Improved P=0.0001</td>
</tr>
<tr>
<td>MADRS Sleep (Range 0-6)</td>
<td>Improved P=0.0001</td>
<td>Improved P&lt;0.01</td>
</tr>
<tr>
<td>HAMD (Range 0-52)</td>
<td>Improved P&lt;0.0001</td>
<td>Improved P&lt;0.001</td>
</tr>
<tr>
<td>HAMD Sleep (Range 0-6)</td>
<td>Improved P=0.0001</td>
<td>Improved P&lt;0.01</td>
</tr>
<tr>
<td>HAMD Insomnia Early (Range 0-2)</td>
<td>Improved P&lt;0.0001</td>
<td>Improved P&lt;0.001</td>
</tr>
<tr>
<td>Zung</td>
<td>Improved P=0.0001</td>
<td>Improved P&lt;0.05</td>
</tr>
<tr>
<td>CFQ</td>
<td>Improved P=0.0001</td>
<td>Improved P&lt;0.05</td>
</tr>
<tr>
<td>LSEQ Getting to sleep</td>
<td>Improved P=0.055</td>
<td>Improved P&lt;0.05</td>
</tr>
<tr>
<td>LSEQ Quality of sleep</td>
<td>Improved P=0.05</td>
<td>Improved P=0.05</td>
</tr>
<tr>
<td>LSEQ Behaviour following wake</td>
<td>Improved P=0.05</td>
<td>Improved P=0.05</td>
</tr>
<tr>
<td>LARS (Sedation)</td>
<td>Improved P=0.0001</td>
<td>Improved P&lt;0.01</td>
</tr>
<tr>
<td>RRT (ms)</td>
<td>Improved P=0.01</td>
<td>Improved P&lt;0.09</td>
</tr>
<tr>
<td>MRT (ms)</td>
<td>Improved P=0.01</td>
<td>Improved P&lt;0.06</td>
</tr>
<tr>
<td>TRT (ms)</td>
<td>Improved P=0.01</td>
<td>Improved P&lt;0.06</td>
</tr>
<tr>
<td>CFF (Hz)</td>
<td>Improved P=0.01</td>
<td>Improved P&lt;0.01</td>
</tr>
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The statistically significant effect of duration of antidepressant treatment and direction of change on all significant variables for the treatment phase weeks 1 to 12; and for the discontinuation withdrawal week 12 to 13. A trend towards statistical significance is shown by ‘=' if the P-value was < 0.1. ↓↑ indicates direction of change.
For the purpose of this study patients were treated as whole groups, and not segregated into sub-groups, on how well they responded to treatment or whether they were depressed anxious and agitated, or depressed melancholic and lethargic, as has been the case in other reported studies (Sechter et al., 1999). This might be an issue when comparing SSRI treatments as there are differing response times depending on the type of depression, according to Nutt et al. (1999) with improvement in depression with SSRI treatment being faster than in anxiety disorders.

The present study set out to investigate whether the use of actigraphs would provide an objective measure of the ‘in the field’ long term chronic effects of medication compared with the use of actigraphy for short duration, well-controlled, residential, studies as detailed in Chapters 3 and 4, where it was used to show changes in daytime activity and differences in sleep variables following one night of medication. In order to determine whether actigraphy would be able to contribute to the measurement of the long term chronic effects of medication it was necessary to examine the outcomes of the other well-known established diagnostic assessments of antidepressants such as depression and sleep questionnaires as well as cognitive and psychomotor assessments. It was important to assess whether the outcomes described above showed changes with the depression status of the patients, and if any changes correlated with the actigraphy data.

5.6.2. Effect of depression on sleep
As described in Section 1.6.1.1, poor sleep is a core symptom of depression, with recognised changes in sleep architecture including increased sleep latency, sleep disruption and fragmentation and in REM distribution.

5.6.3. Effect of treatment on depression questionnaires
5.6.3.1. Effect of treatment on Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD)
At baseline, patients were rated as being moderately depressed on the MADRS questionnaire with a mean score of 26.5 (18-34), which compares with the mean HAMD score at baseline of 20.4 moderate (≥ 16) using the comparison scores by Müller et al. (2000). In the current study the MADRS scores showed that all patients responded well to treatment, and a significant improvement in depression scores was observed by week 2 with the ‘onset of response’ of the antidepressant, as defined as a ≥ 20% both MADRS and HAMD scores when compared with baseline scores (Wade et al., 2009). This is in agreement with other
studies (Parker et al., 2000; Mitchell, 2006; Wade et al., 2009; Stassen et al., 1997) that also found significant improvement at 2 weeks.

By week 8 the MADRS scores for all treatments were significantly further improved with a ‘response’ of $\geq 50\%$ reduction to $< 18$ with scores of 10.4, 11.9 and 8.0 for paroxetine, fluoxetine and sertraline, respectively which signified that patients’ depression scores had improved from moderately severe to mild depression (mild depression 18-34). ‘Remission of depression’ with scores $\leq 10$ is considered to be the cut off for clinical depression severity, patients therefore almost reached remission at week 12, with scores of 7.0, 10.8 and 10.1 for paroxetine, fluoxetine and sertraline, respectively.

The HAMD overall depression scores in the present study were similarly improved, from $\sim 20$ (mild to moderate 18-24) at baseline to mild $\leq 7$ at week 14 with significant reductions in depression severity. The ‘onset of response’ as defined by Wade et al. (2009) was evident by week 2 with a $\geq 20\%$ compared with from baseline, for all treatments. By week 8 depression scores had decreased by $\geq 50\%$ response with all patients now classified as only mildly depressed MADRS ($< 15$). Patients were deemed to be in remission by week 14 with a MADRS score $< 10$, (complete remission MADRS $< 5$).

Although all three treatment groups showed a significant mean decrease in MADRS and HAMD scores there was no significant difference between treatments for either MADRS or HAMD. These results are consistent with the findings of similar studies by Fava et al. (2000; 2002) in which a comparable three-arm treatment of paroxetine (20 mg/day), fluoxetine (20 mg/day) or sertraline (20 mg/day) was administered to depressed patients for between 10 to 16 weeks (average 11 weeks). Similarly, although depression severity was significantly reduced no differences were found between treatments, with HAMD scores for all treatments approximately 25 at baseline, reducing to $< 10$ at study endpoint (Fava et al., 2000).

The study reported in this thesis also supports the evidence of De Wilde et al. (1993) who compared the effect of paroxetine and fluoxetine on HAMD on depressed patients for 6 weeks and highlighted that patients treated with paroxetine responded faster than those with fluoxetine. A significant difference between the treatments at 3 weeks was reported. A similar effect was seen in the current study with a greater response observed on MADRS between the paroxetine and fluoxetine treated patients at 4 weeks, and although significantly different from baseline, it was not significant between the 2 treatments. In contrast, however,
no difference was observed in the present study on the HAMD, both treatments being significantly different from baseline at week 4.

Van Moffaert et al. (1995) conducted a similar study in patients treated with fluoxetine or sertraline with baseline MADRS scores of 28.1 and 29.5 respectively and reported that for both the MADRS and HAMD there was a decrease in scores of 43% and 45% respectively at 8 weeks compared with baseline. The current study showed a greater response with a >50% reduction in scores at week 8 compared with baseline. The reasons for this could be that the patients were recruited from 15 psychiatric centres, were removed from psychotropic medication for one week or two if taking MAOIs, and permitted use of chloral hydrate or short acting benzodiazepines. In contrast patients in the current study were not and had never been prescribed any of the study drugs and were not permitted to use any psychotropic medication during the study. Therefore the use of other psychotropic medication in the Van Moffaert et al. (1995) study could have delayed response.

5.6.3.2. Effect of treatment discontinuation on MADRS and HAMD

As previously discussed the symptoms experienced following abrupt discontinuation were defined by (Schatzberg, 1997) and are a recognised outcome of SSRI withdrawal. This can be quite serious with a rebound effect leading to resumption of the depression symptoms, and other somatic effects such as nausea, insomnia, dizziness and agitation.

In the current study even though mean MADRS and HAMD scores increased slightly during the abrupt discontinuation week 13 by > 25% for paroxetine and > 5% for sertraline compared with week 12 (after 12 weeks of continuous treatment), post-hoc analysis did not reveal any statistically significant effect between treatments or over time. This differs to the finding by Rosenbaum et al. (1998), whereby in a study of 242 depressed patients on continuous antidepressant treatment for > 4 but < 24 months, both the mean MADRS and HAMD scores of patients treated with paroxetine or sertraline, after one week treatment disruption, were significantly higher compared with fluoxetine. However, as in the present study, patients responded to re-introduction as shown by the reduction in MADRS and HAMD scores.

A further difference in outcomes was reported by Hindmarch et al. (2000a) with a significant effect of a 5 day abrupt discontinuation following withdrawal from paroxetine treatment whereby scores were at the upper limit of the mild depression range with a mean of 16.5 compared with the current study where the mean was 8.8, pre-discontinuation treatment
means for both studies were similar with 6.9 and 7.0 for Hindmarch and current studies, respectively. The mean scores of patients treated with sertraline in both studies was 11.6 after disruption, with 8.7 and 10.1 for Hindmarch and the current study, respectively, prior to disruption. Interestingly, in the current study, MADRS scores during discontinuation for patients treated with fluoxetine continued to improve with a further reduction in scores whereas mean scores increased both the other studies (Rosenbaum et al., 1998; Hindmarch et al., 2000a).

In the current study patients did not show any ‘regression’ as defined by Wade et al. (2009) in their MADRS depression symptoms during discontinuation as the mean scores were still \( \leq 12 \) and within the low mild depression cut off point of scores below 9-17. These scores clearly showed that patients were perhaps in remission before discontinuation. Moreover, apart from the MADRS score for paroxetine, the mean scores from the present study following reintroduction were even lower than those at week 12 and in agreement with Rosenbaum et al. (1998) who commented on the ‘enhanced benefit after restarting active treatment of relief from discontinuation discomforts after resuming treatment’ and worthy of further investigation. It has been reported that prompt resumption of treatment reverses the emergence of discontinuation symptoms (Haddad and Anderson, 2007).

As seen in MADRS, post-hoc analysis of HAMD revealed that there was a slight increase in depression scores during the discontinuation week 13 compared with week 12 for both paroxetine and sertraline. Contrary to other findings (Rosenbaum et al., 1998), these changes were not regarded as clinical deteriorations as depression scores remained within the mild depression range (7-17). The current study reported here indicates that there was a rebound worsening and increase in HAMD scores during discontinuation following paroxetine and sertraline withdrawal. This was, however, not statistically significant, although there was a trend towards significance for paroxetine (\( P = 0.09 \)). In a similar discontinuation study, however, it was reported that there was a statistically significant worsening of HAMD symptoms which occurred after the 2nd day of replacement with placebo following paroxetine withdrawal compared with that of sertraline and fluoxetine (Michelson et al., 2000). A study comparing the antidepressant agomelatine with paroxetine (Montgomery et al., 2004) also reported a significant rise in symptoms of depression occurring in the first week of discontinuation of treatment with paroxetine. The reason why there were no statistically significant findings in the current study compared with the literature is unclear but might be because the other studies referred to were conducted with previously depressed patients on long term stable treatment, for at least 4 months when recruited, whereas the
current study was conducted with recently diagnosed treatment naïve patients. Moreover the effect of discontinuation was recorded after 7 days which was longer than any of the other studies reported and it is likely that the effect of discontinuation was reducing.

The findings in the current study are also in agreement with the discontinuation study reported by Judge et al. (2002) which also showed that the MADRS revealed a significant increase in scores following paroxetine withdrawal compared with fluoxetine. Depressed patients (n = 141 completed) who had been on open-label chronic treatment > 4 but < 24 months were given placebo substitution for 3-5 days. It was suggested that the deterioration during the discontinuation may be related to the short half-life of paroxetine (t½, 21 h) as the period of discontinuation was 3-5 days compared with 7 days in the current study. Judge et al. (2002) also reported on the significant effect of paroxetine withdrawal compared with fluoxetine on the Discontinuation-Emergent Signs and Symptoms (DESS) questionnaire with patients experiencing more discontinuation emergent symptoms. Moreover, although not strictly a sleep questionnaire, Rosenbaum et al. (1998) also employed the DESS to record symptoms experienced following treatment discontinuation and recorded significantly higher numbers of patients reporting ‘trouble sleeping’ after 5-8 days of paroxetine withdrawal compared with fluoxetine or sertraline. In the same study sertraline treated patients reported more symptoms than fluoxetine treated patients.

5.6.3.3. Effect of treatment on MADRS and HAMD sleep items

The MADRS has a sleep item component similar to HAMD but it is not divided into different aspects of sleep problems, it is merely summarised as ‘reduced sleep’ (Lader et al., 2005). ‘Reduced sleep’ is a reduction in depth and/or duration of sleep time compared with the normal time when patients are well. With respect to MADRS sleep in the present study, patients’ sleep duration or depth of sleep was significantly improved by over 50% by week 8 and continued to improve significantly for all treatments by week 12. This improvement was also significant for paroxetine indicating that patients felt that their sleep duration had improved more than the other treatments.

The HAMD sleep item results in the current study indicated that, for the 12 weeks of treatment, although all patients felt that their sleep overall was improved in terms of getting more sleep and overall sleep duration, this was statistically significant only for paroxetine. A similar significant improvement in the sleep component of HAMD in ‘early insomnia’ associated with SOL or difficulty falling asleep was seen in the current study for all treatments overall. Post-hoc analysis revealed that this effect was significant for paroxetine.
The mean HAMD baseline scores of > 3 for the 3 combined sleep components were significantly reduced overall for all treatments with a > 50% response reduction to a mean of 1.5 for the overall sleep component by week 8. The early insomnia component was similarly improved with a reduction in scores from the mean baseline ≥ 0.9 to > 50% to ≤ 0.4 by week 8. Furthermore, results showed that for fluoxetine there was a significant improvement in ‘early insomnia’ over the full 14 weeks with patients experiencing less difficulty and taking a shorter time getting to sleep even during discontinuation of treatment.

As previously discussed Section 1.6.2 the SSRIs are not prescribed for aiding sleep, but by improving depression, as a consequence perception of sleep may improve. It is therefore perhaps not surprising that patients reported improvements in the sleep components of the depression scales. According to the physician rated scales patients in the current study reported overall significant improvements in MADRS and MADRS ‘sleep’, and HAMD, HAMD sleep and HAMD early insomnia. Significant improvements were also reported for the individual treatments for the patients treated with paroxetine or sertraline in MADRS ‘sleep’; with paroxetine in HAMD ‘sleep’ whilst patients treated with paroxetine also reported a significant improvement in HAMD early insomnia for the 12 weeks of treatment. These results indicate that patients took less time to get to sleep, and had better quality of sleep if they were in the paroxetine treated group.

All patients in the present study were included in the current analysis and not differentiated into subgroups between high and low insomnia scores, which contrasted with the Fava et al. (2002) study whereby patients were divided into subgroups between patients having high or low insomnia at baseline. The HAMD was recorded to assess whether there was any difference in the sleep items of the 284 depressed patients treated with the SSRIs for between 10 and 16 weeks (Fava et al., 2002). The findings in the current study substantiate the improvements reported in the Fava et al. (2002) study into the effects of treatment with paroxetine 37 mg/day, fluoxetine 42 mg/day or sertraline 108 mg/day. There was a significant improvement in sleep items for early, middle or late insomnia from baseline to endpoint, although there was no difference between treatments or between subgroups within treatment. The doses quoted differ to the current study for the patient mean dose being higher and almost double those of the current study, and were further increased if patients required up-titration.

Other studies have also reported on the use of the HAMD to show improvements in sleep following antidepressant treatment. Patients reported significant improvement in the
physician rated HAMD sleep component score with reduced sleep disturbance, of early, middle and late insomnia following 8 weeks of treatment with fluoxetine compared with baseline (Gillin et al., 1997). This significant improvement in HAMD sleep disturbance was also reported at endpoint week 8 by Armitage et al. (1997b). Similar significant improvements in the sleep items for HAMD on patients treated with fluoxetine or sertraline were found after 56 days compared with baseline (Aguglia et al., 1993).

5.6.3.4. Effect of treatment discontinuation on MADRS and HAMD sleep items

During the abrupt discontinuation week 13 compared with week 12, as previously discussed in the overall depression ratings (Section 5.6.3.2), scores were significantly increased for the MADRS sleep component for paroxetine and sertraline showing a worsening of symptoms with patients feeling that their sleep duration or depth was reduced.

A similar pattern was seen in the raw data for the HAMD perception of overall sleep and early insomnia components for both paroxetine and sertraline during the discontinuation week, with a rebound effect and an increase in scores, indicating that symptoms worsened. This did not reach statistical significance, however. Conversely the scores for fluoxetine for MADRS sleep and HAMD sleep and early insomnia continued to decline showing that even during discontinuation sleep continued to improve and had no adverse impact on the sleep components. This direction is similar to the overall MADRS and HAMD and likely to be due to the longer half-life of fluoxetine of up to 4 days.

5.6.3.5. Treatment and ZUNG questionnaire

In the current study patients were required to rate their own depression severity compared with that of the physician using the ZUNG questionnaire. Patient-reported depression gave similar reductions in scores to HAMD and MADRS, although not as dramatic, with a significant subjective improvement in depression symptoms compared with baseline scores. The ZUNG improvement was therefore similar to MADRS and HAMD and showed a similar ≥20% reduction by week 2, from mild depression >50 (50-59 mild depression) to <50 (normal), and with further reductions at weeks 8 and 12 ≥35%. There was no significant difference between treatments on the ZUNG and all 3 treatments appeared to be efficacious. These data show that the physician rated scales of HAMD and MADRS were corroborated by the patient’s own rating and patients did not feel depressed at week 12. A study that used both the ZUNG and MADRS to compare the effect of the SSRI antidepressants fluoxetine and sertraline, reported similar improvements when comparing their outcomes so this self-completion ZUNG questionnaire is comparable to MADRS (Aguglia et al., 1993).
5.6.3.6. Effect of treatment discontinuation on ZUNG

Although not statistically significant there appeared to be a worsening of depression with an increase in the level of depression at week 13 following abrupt discontinuation of paroxetine. This confirmed what was seen with the physician rating scales of MADRS although in HAMD sertraline also showed a slight worsening of scores. This worsening of self-rated depression following paroxetine withdrawal confirms the results obtained by Hindmarch et al. (2000a) whereby a significant discontinuation effect was observed. However, the scores for the treatments in the current study at week 13 were marginally lower than the Visit 3 post-discontinuation in the Hindmarch et al. (2000a) study and there was also a marked increase in the level of depression from paroxetine withdrawal. The scores for paroxetine, fluoxetine and sertraline before discontinuation were 37.2, 39.1 and 40.6, and after 1 week discontinuation in the study reported here were 38.7, 38.6 and 39.4 respectively. In comparison the scores reported in the Hindmarch et al. (2000a) study were similar at 38.3, 40.9 and 38.3 before discontinuation but 48.6, 42.8 and 40.6 after 5-7 days of discontinuation for paroxetine, fluoxetine and sertraline, respectively, showing that paroxetine had caused a significant effect (Figure 5.33) although not clinically significant.

![Figure 5.33: Effect of treatment discontinuation on ZUNG questionnaire (Hindmarch et al., 2000a)](image)

5.6.4. Subjective sleep and Leeds Sleep Evaluation Questionnaire (LSEQ)

Using the validated sleep visual analogue scale LSEQ in the current study it was possible to obtain a more refined overview of subjective change in sleep behaviour with antidepressant treatment compared with the crude items in MADRS and HAMD. The LSEQ was utilised in order to capture and quantify subjective ratings data on the actual quality of sleep and the
various aspects of ‘getting to sleep’ GTS, ‘quality of sleep’ QOS, ‘awakening from sleep’ AFS and ‘behaviour following wakening’ BFW were determined.

5.6.4.1. Effect of treatment on LSEQ

In the present study post-hoc analysis for the 12 weeks of treatment showed that GTS ‘getting to sleep’ was significantly improved overall, however, there was no difference between treatments, which suggested that patients all felt that the time taken to fall asleep was reduced as shown in Figure 5.23. The reduction in scores following sertraline treatment was not as prominent as paroxetin or fluoxetine where scores dropped by week 2 and then appeared to plateau. The delay in the improvement with sertraline in GTS was also observed by Kasper et al. (2010) and it was found that patients did not find it as easy to get to sleep when treated with sertraline compared with agomelatine. The improvement in GTS during the first weeks of treatment with fluoxetine also confirms the data by Stephenson et al. (2000) whereby patients felt that it was easier to get to sleep by week 4; therefore verifying that fluoxetine did not impair patients’ sleep but instead improved efforts to get to sleep.

Paroxetine also showed a greater trend to improve GTS at weeks 1 and 2; this effect was also reported by Alexander et al. (1997). In contrast according to Bennie et al. (1995) patients treated with sertraline tended to have less trouble getting to sleep than those treated with fluoxetine. However this was not the case in the current study. Moreover none of the treatments impaired or adversely affected the patients’ ability to get to sleep and improvements were consistent with the depression scale evidence of MADRS and HAMD that symptoms of depression were alleviated.

For ‘quality of sleep’ QOS scores were significantly improved overall in the present study for the 12 week data, with a significant improvement and reduction of scores for paroxetine for the 12 week data set. This result indicates that patients treated with paroxetine felt that their sleep quality during the night had improved more than the other treatments, although in general all treatments improved subjective sleep quality. In fact by week 1 scores had dropped dramatically from baseline for paroxetine so that the effect on QOS was almost immediate. Most of the other studies reported compare the SSRIIs with sedating antidepressants so it is difficult to draw distinct conclusions with regards to differences between the treatments. Improvements in QOS, however, were shown in the study from Stephenson et al. (2000) whereby QOS was improved with fluoxetine for the 6 weeks of treatment.
According to Bennie et al. (1995) patients treated with fluoxetine or sertraline showed similar significant improvement in QOS over the 6 week study. Fairweather et al. (1993) also showed that depressed elderly patients also reported improvements in QOS over the 6 weeks of the study in those patients on fluoxetine treatment. Kerr et al. (1997) reported that over six weeks of treatment the ‘quality of sleep’ of depressed patients improved in the paroxetine treated group, in comparison to dothiepin, with a similar marked improvement to the current study at week 2. The current study in which patients treated with paroxetine showed a significant improvement in QOS was also consistent with the study by Alexander et al. (1997). Although statistical analysis of the current study shows that there was a limited difference between treatments, from the charts of the raw data there were different effects. Although there was a difference in the time profile of the treatments, as with GTS, no treatment adversely affected patients’ improvement in QOS.

There was no effect of treatment or between treatments for ‘awakening from sleep’ AFS, on the current study. None of the treatments affected the patients’ ability to wake up during the 12 week treatment although there was a trend for improvement following paroxetine treatment. The studies by Alexander et al. (1997) and Kerr et al. (1997) showed that AFS was improved with depressed patients following paroxetine treatment, whereas other studies (Fairweather et al., 1993; Aguglia et al., 1993 and Kasper et al., 2010) have shown similar, even though not significant, improvements in depressed patients treated with fluoxetine or sertraline.

There was a significant reduction in scores for ‘behaviour following wakening’ BFW for all patients overall, with a trend for those patients treated with paroxetine. Patients on paroxetine felt more alert and less clumsy, by the end of the 12-week treatment. In addition, Alexander et al. (1997) and Kerr et al. (1997) both reported that paroxetine had no ‘hangover’ effect the following day compared with dothiepin. A ‘marginal but not significant’ difference was recorded in fluoxetine treated-patients compared with patients treated with dothiepin in ‘hangover’ effects, which are related to BFW. Stephenson et al. (2000) and Aguglia et al. (1993) reported improvement in BFW following both sertraline and fluoxetine treatment. In the current study, however, although scores improved from baseline the change was not significant.

In general all baseline LSEQ scores were higher for the paroxetine treated patients compared with either fluoxetine or sertraline. As sleep appeared worse in the paroxetine group as opposed to patients in the fluoxetine and sertraline groups at the start of treatment this
difference could account for the significant effects seen in those patients even though the trend for all treatments was improving. Moreover this was the case in the Alexander et al. (1997) study where patients assigned to paroxetine had significantly more sleep problems than the participants assigned to dothiepin. General improvements for all treatments seen in all aspects of sleep from the LSEQ, however, could be the effect of the respective drugs or signs of their antidepressant action. If, in the current study, depression was relieved as was shown in the MADRS, HAMD and ZUNG this might have led to better general well-being and mood which in turn encouraged a positive attitude and increased activity leading to promoting better sleep.

The LSEQ data in the current study were calculated only from those patients that wore the Actiwatch as the purpose of the study was to review the subjective and objective data. This is in contrast to the Kasper et al. (2010) study in which data for all patients including those not wearing the Actiwatch were analysed for the LSEQ as shown in Figure 5.34. Nevertheless both studies indicated improvements in the LSEQ subjective ratings for sleep following sertraline treatment.

![Graphs showing LSEQ variables GTS and QOS](Kasper et al., 2010)

5.6.4.2. Effect of treatment discontinuation on LSEQ

As previously discussed in Section 1.6.10 discontinuation symptoms are troublesome and can lead to a recurrence or increase in depression symptoms, therefore it might be expected that discontinuation would also affect subjective sleep.

The results of the current study show that although there was no significant difference in GTS between the treatments, scores for paroxetine increased which indicated that it was more difficult to get to sleep following paroxetine withdrawal. In contrast the scores from patients discontinued from fluoxetine or sertraline treatment continued to decrease indicating
that discontinuation did not affect them getting to sleep. Only one other study by Hindmarch and colleagues (2000a) has reported on the effect on LSEQ items following withdrawal of treatment. The direction of impairment following paroxetine withdrawal in the Hindmarch et al. (2000a) study was also seen in the current study, with an increase, although not significant, in scores. Interestingly in contrast to the current study this impairment was also seen following fluoxetine and sertraline withdrawal in the Hindmarch et al. (2000a) study.

The direction of change in QOS was similar to GTS in the current study following withdrawal. Paroxetine scores increased showing a worsening of effect, whereas fluoxetine and sertraline scores significantly decreased indicating that patients felt that their QOS was improved. These findings contrasted with the Hindmarch et al. (2000a) study following discontinuation. The direction of change agreed with scores for paroxetine significantly increasing with worsening QOS and with sertraline scores reducing and improving in QOS. In contrast, however, the QOS was adversely affected by fluoxetine withdrawal as scores increased in the study by Hindmarch et al. (2000a). This could be due to the end of the half-life of fluoxetine (up to 4 days) in the Hindmarch et al. (2000a) study as treatment was disrupted for 4-7 days compared to 7 days in the current study therefore allowing the active metabolite (7-15 days) to continue to have an improving effect.

Discontinuation from treatment on AFS variables was not statistically significant. The direction of the scores, however, showed that in the current study paroxetine withdrawal led to an increase in scores for AFS with a worsening of effect leaving patients feeling less refreshed. Scores following both fluoxetine and sertraline withdrawal reduced, indicating that there was little effect on AFS. This direction of effect was different to the Hindmarch et al. (2000a) study in which both paroxetine and sertraline scores increased and worsened, whereas fluoxetine scores similarly decreased. As with QOS this effect could be due to the half-lives of the antidepressants.

The effect of discontinuation on BFW in the current study only showed an improvement, but not significant, with sertraline treatment. Scores for both paroxetine and fluoxetine showed an increase in scores indicating that patients felt worse upon awakening and that their behaviour and functioning was impaired. Similarly, in the Hindmarch et al. (2000a) study, there was also an increase in paroxetine and fluoxetine scores but discontinuation from sertraline showed no change.
In the current study there was no overall statistical difference between treatments during discontinuation. However in comparing both studies there is a suggestion from the scores that although not significant, withdrawal from paroxetine caused disruption in GTS, QOS, AFS and BFW, whereas discontinuation from fluoxetine or sertraline did not affect patients to the same degree. Indeed there was a significant improvement in QOS scores in the current study during fluoxetine or sertraline withdrawal compared with a significant impairment in the Hindmarch et al. (2000) following paroxetine withdrawal. Perhaps fluoxetine and sertraline were having some negative effects which were alleviated when medication was stopped or that the half-life of the medication meant that both treatments continued to exert a therapeutic effect. It would be advisable to conduct further discontinuation studies with greater numbers of patients and maybe with a subset of poor sleepers to tease out the actual improvement or worsening of treatment in the subjective sleep profile. Only the Hindmarch et al. (2000a) study showed any statistical difference between treatments after discontinuation in LSEQ, with the QOS component being poorer following paroxetine withdrawal.

5.6.5. Actigraphy

Actigraphy was used in Chapters 3 and 4 to assess short term changes and effects on activity and actigraphic derived sleep variables of psychoactive compounds in highly controlled laboratory conditions over 1 or 2 nights. In the present study described here the objective was to assess whether actigraphy would provide a suitable objective tool to measure drug induced changes in activity and actigraphic sleep over the time course of long-term treatment ‘in the field, real-life’ situations with antidepressants, with patients in their own home environments over 14 weeks which included one week of abrupt discontinuation. Changes in the ‘sleep’ and activity profile and hence the time-course during treatment for depression was measured continuously with actigraphy. At the same time actigraphy provided a means of assessing the long term 24 h circadian patterns of rest and activity and thereby any dose response in changes of behaviour patterns. As previously discussed changes in mood and depression rating symptoms as well as subjective ratings of sleep were also measured simultaneously.

5.6.5.1. Actigraphic sleep variables

Few long term patient studies have been conducted with the same SSRIs used to treat patients in the current study on sleep and PSG variables, in fact most compare the sleep factors from LSEQ or HAMD. PSG variables have been reported in the literature and those which could be correlated with actigraphy are TST, sleep latency, sleep efficiency, and
number of wake/sleep bouts. It has been established that in major depressive disorder (MDD) paroxetine increases PSG SOL and NAW (Hicks et al., 2002) reduces TST and SE (Staner et al., 1995; Sharpley et al., 1996); fluoxetine increases number of awakenings and reduces sleep efficiency (Gillin et al., 1997) and sertraline increases sleep latency, reduces sleep efficiency and decreases total sleep time (Jindal et al., 2003). The SSRIs in the present study, as shown in reviews (Fava, 2004; Mendlewicz, 2009), ‘disrupted sleep maintenance with increased sleep latency, reduced sleep efficiency and increasing WASO’ in MDD, so this effect might be replicated in the actigraphic sleep variables in the current study. Furthermore, as depression is associated with a reduction in SWS, reduced REM latency and increased REM, that if sleep was abnormal to start with, with treatment this might be reflected in an increase in actigraphic activity levels, which could suggest that SSRIs were normalising sleep architecture.

The current study was the first to report on a 14 week actigraphy study comprising 12 weeks of antidepressant treatment, 1 week of abrupt discontinuation followed by 1 week reintroduction (Dawson et al., 2010). Machado-Vieira et al. (2008) stated that standard antidepressants usually require approximately one month or more for antidepressant effects to manifest, and commonly, patients remain symptomatic and functionally impaired during this initial period of treatment. So it would be interesting to see what the data showed during the treatment and whether actigraphy was able to track the course of treatment in comparison to the cognitive and psychometric data. In general, in the current study, following 12 weeks of treatment with SSRIs, depressed patients subjectively rated their depression significantly improved in MADRS, HAMD and ZUNG. In addition they rated their sleep better, according to improved LSEQ scores for ‘quality of sleep’ as well as improvements in the sleep components and overall depressive symptoms in line with the outcomes of the MADRS, HAMD and ZUNG questionnaires. It was therefore interesting to assess whether these changes could be replicated in the objective actigraphic data. In contrast to the subjective sleep improvements reported earlier in the MADRS, HAMD (Section 5.6.3.3 and 5.6.4.6) and LSEQ (Section 5.6.4.1) data, actigraphy sleep variables in the current study worsened and indicated that objective actigraphic sleep was actually poorer. These results were consistent with published reports of other studies from Hicks et al. (2002) and Argyropoulos et al. (2003) and reviewed in Wilson and Argyropoulos, (2005).

Actigraphy data were first analysed for sleep variables from Day 1 to week 14 (Day 98 approximately) continuously. As there was no placebo run in or baseline period, day 1/night 1 was treated as the baseline for analysis purposes of the tests and
questionnaires. However, medication commenced after the first visit to the GP surgery and it may be the case that some patients commenced on the day of the GP visit and therefore took the medication that first evening, whereas others may have started treatment the next morning. So for actigraphy, Day 1 cannot therefore be considered as a true baseline. Day 1 however is a true baseline of depression symptoms using the MADRS and HAMD and the psychometric tests which were conducted prior to treatment commencing. Patients received medication for 12 weeks after which there was a 1 week abrupt discontinuation followed by reinstatement of treatment for 1 week. Therefore whilst an analysis of the 14 weeks of data were performed post-hoc analysis of the data were also conducted from week 1 to week 12 inclusive but with removal of night 1 to investigate the effect of treatment. Week 12 to 13 was used to investigate the effect of discontinuation. This discussion, of the actigraphic sleep variables, will therefore focus on the overall 12 weeks of treatment. As the 14 week analysis also includes the discontinuation this adds no value to the interpretation of tracking treatment progress and may impact on the significance. In addition in order to aid interpretation of the results non-significant results are also discussed as they reveal trends in the direction of change throughout the course of treatment and similarities to other reported studies. The raw data for the actigraphic sleep variables for the full 14 weeks is presented in results.

The chart of the raw data for sleep latency suggests a trend that SOL increased during treatment with paroxetine and sertraline demonstrating that patients took longer to get to sleep. Although not significant for the 12 week study, there was a trend for an increase in time taken to get to sleep increasing during the first 4 weeks from 23 minutes at week 1 to 25 min at week 12 with a peak of 37 min for paroxetine at week 4. This compared with a change from 18 to 24 min for fluoxetine (week 1 to week 12) and 22 to 27 min (week 1 to week 12) following sertraline treatment. Furthermore this supports clinical PSG findings of increased sleep latency as one of the effects of SSRIs on depressed patients as they are activating compounds (Ables and Baughman, 2003; Hicks et al., 2002; Trivedi et al., 1999; Oswald and Adam, 1986; Vasar et al., 1994; Jindal et al., 2003). Paradoxically, as previously alluded to, this was again in contradiction to the HAMD early insomnia whereby patients in the current study did not complain of problems getting to sleep but instead reported that this was in fact improved. Additionally in accord with the HAMD and opposed to the actigraphy, patients felt no impact of medication on the ‘getting to sleep’ component of the LSEQ in the current study. It was reported that night-time dosing with paroxetine does not increase sleep latency as the medication is not fully absorbed (Gursky and Krahn, 2000), and since there was an increase in sleep latency during the first 4 weeks it could suggest that patients in the current study had administered in the morning.
The current study was in agreement with Staner et al. (1995) who reported that whilst patients subjective rating of quality of sleep was improved with a reduction in the HAMD sleep items, they experienced increased SOL and ‘increased awakenings’ during the sub-chronic phase at days 34 and 35 observed from PSG following paroxetine (30 mg/day) compared with baseline. This factor was also supported by the report on paroxetine, which showed that SOL was positively correlated with subjective SOL from the St Mary’s Hospital Sleep Questionnaire (SMHSQ) and objective SOL from EEG on nights 3 and 10 (Argyropoulos et al., 2003) in a patient study.

The 12 week treatment analysis, using week 1 as the baseline and with change from week 1 over time, showed a deterioration in sleep quality in all treatments overall with significant reductions in sleep efficiency overall (P < 0.05) and increased number of sleep bouts overall (P < 0.0001). These effects showed significant trends following both paroxetine and fluoxetine treatment for sleep efficiency. There was a rapid decline in SE for patients taking paroxetine to the nadir at week 5 of 77.2% which did not recover substantially over the 12 weeks from the baseline week of 81.9%. When considering that patients treated with paroxetine also showed a significant reduction in TST, this indicated that paroxetine in particular had a detrimental effect on sleep. Although there was also a trend towards reduced sleep efficiency for fluoxetine the effect was much more gradual with a higher value in the first week of 83.6% reducing to 80.5%, and with only week 11 below 80%. The higher value for week 1 indicated that fluoxetine actually improved sleep efficiency during the first week compared with the first night. Sertraline did not show any overall deterioration in actigraphic sleep efficiency with values remaining fairly constant between 80% to 82 % in comparison to the Kasper et al. (2010) study where SE for sertraline decreased from baseline 76.5% to 75.7% at week 6. The higher SE values in the current study compared to the Kasper et al. (2010) study also show that sleep was not as poor.

The number of sleep bouts and conversely number of wake bouts significantly increased from week 1 to week 12 for all treatments, which indicated more disrupted sleep with more transitions from sleep into wake. For patients treated with paroxetine the number of sleep bouts increased more rapidly than patients treated with either fluoxetine or sertraline with an increase from 16 at week 1 to 19 at week 12 with a peak of 21 bouts at week 5. Sleep bout numbers for fluoxetine treated patients rose gradually from 14 at week 1 to 18 at week 12, whereas although sleep bouts for sertraline treated patients at week 1 was 14 they rose more gradually to a peak at week 12 of 16. This data clearly shows that paroxetine induced more
sleep disruption during the early weeks of treatment than fluoxetine or sertraline and that this
trend did not recover. It is expected that as patients develop tolerance to the effects of
medication their sleep profile should normalise but this was not the case for paroxetine.

Although not significant, sleep bout times, the mean length of the sleep bout, for paroxetine
treated patients reduced from 35 min at week 1 to 29 min at week 12, with a nadir at weeks 5
and 10 of just 24 min showing more transitions from sleep to wake. Sleep bout times for
fluoxetine treated patients reduced from 38 min at week 1 to 31 min at week 12, with a nadir
at week 11 of 29 min, similarly sleep bout times for sertraline treated patients reduced from
41 min at week 1 to 33 min at week 12, with a nadir at weeks 2 and 7 of 32 min. The
increase in sleep/wake bouts correlates with the increase in total activity counts in sleep,
which whilst not significant, the data showed a considerable trend towards increased number
of total activity counts in sleep for all SSRIs but in particular for paroxetine.

The data suggests a trend towards an increase in number of sleep bouts, and an increase in
the total activity counts in sleep demonstrating that sleep was more disrupted. Moreover
although not significant the increase in WASO, appears to show an effect following
treatment with paroxetine. Although this substantiates clinical PSG findings from other
studies of sleep impairment, patients in this study subjectively felt that their sleep improved
as shown by significant improvement in LSEQ ‘quality of sleep’ as well as the MADRS and
HAMD sleep items. The reason for this discord is unclear but it may be that the impression
that sleep was improved is likely to be due to the effect of the antidepressants on patients’
perception or the improvement in mood on patients’ perception than on actual improvement
or that the additional movement did not actually impair their sleep or cause them to wake,
they just moved more. Or as suggested by Winokur et al. (2001) do SSRIs have a calming
anxiolytic effect which encourages the perception of improved sleep coupled with an
activating effect reported by Wichniak et al. (2012). Although the detrimental effects of
actigraphic reduced sleep efficiency, increased sleep latency, increased sleep fragmentation
are contrary to the subjective ratings of improved sleep they are in agreement with the
findings of the (Mendlewicz, 2009; Fava, 2004) reviews on whether the sleep disturbances
seen in depression are core symptoms of the underlying MDD, or a co-existing problem, or
moreover the result of movement disorders, agitation or akathisia brought on by the
antidepressant medication as suggested by Volkers et al. (2002).

The only other reported comparable study to the present one, with continuous actigraphy,
was conducted by Kasper et al. (2010) which was a 6 week double-blind parallel design
efficacy study of the effects of agomelatine and sertraline treatment in MDD patients (n = 313) using actigraphy and other measures including LSEQ and HAMD. In contrast to the present study where there was no baseline or washout, the Kasper et al. (2010) study started with 2 weeks placebo washout following which patients were randomised to receive agomelatine (n = 154) (25-50 mg/day) or sertraline (n = 159) (50-100 mg/day). As with the present study actigraphy was measured continuously with a 2 min epoch in conjunction with sleep diaries. The LSEQ and HAMD were completed at baseline plus weeks 2, 4 and 6 in contrast to the current study of baseline plus weeks 2, 4, 8, 10, 11, 12, 13 and 14. Patients were recruited with HAMD scores of ≥ 22 in addition to a score of ≥ 3 for items 5 and 6 relating to insomnia. At the end of 6 weeks the HAMD scores improved to 10.3 ± 7.0 and 12.1 ± 8.3 for agomelatine and sertraline, respectively. In comparison the current study recorded the HAMD scores of 7.8 ± 1.3 and 5.9 ± 1.4 (SEM) at weeks 4 and 8, respectively. Subjective sleep scores for LSEQ GTS and QOS also showed a similar but not significant trend for improvement following sertraline treatment which agreed with the Kasper et al. (2010) 6 weeks study.

With regards to the Kasper et al. (2010) study few variables were reported, but those that were showed that sertraline had a negative effect on actigraphic sleep variables. SE decreased from baseline 76.5% to 75.7% at week 6 in comparison to the current study with baseline at 81.9% and 81.3% at week 6. Sleep latency increased from ~ 24 min at baseline to ~ 28 min at week 6, in comparison to the current study of 17 min at baseline to 26 min at week 6 confirming that patients treated with sertraline took longer to get to sleep as treatment progressed. A factor which did not improve for the 12 week data. The mean length of wake bouts increased following sertraline treatment in the Kasper et al. (2010) study which compares with the current study which showed a significant increase in the number of sleep bouts with a reduction in the sleep bout time. However these variables show similar

![Figure 5.35: Actigraphy charts for SE and SOL (Kasper et al., 2010)](image-url)
traits and are indicative of a disrupted sleep pattern with more transitions from sleep and wake. For ease of reference the figures from the (Kasper et al., 2010) study for SE and SOL are shown in Figure 5.35.

The average wake movement, which is the daytime activity following sleep offset to the following sleep onset, even with poorer sleep showed that there was an indication of an increase in activity levels from week 1 for all treatments. However the values for paroxetine were much lower than either of the other treatments indicating that patients treated with paroxetine were less active during the day. This reduced daytime activity could be related to daytime tiredness due to the loss of sleep, particularly so for the first 4 weeks of treatment, whilst patients were becoming tolerant to the medication or that paroxetine tends to be more sedating compared with other SSRIs (Ables and Baughman, 2003).

Interestingly, for all treatments in the current study, there was a trend towards a significant improvement in ‘behaviour following wake’ from the LSEQ which indicated a correlation with the increase in average wake movement from the actigraphic variables. Lemke et al. (1997), showed that paroxetine treated depressed patients (n = 16) were more active in the morning in an actigraphic study whereby the pooled mean of 72 h of activity was measured with an Actometer (Zak, Germany). Data showed that depressed patients were more active in the morning compared with the evening which negatively correlated with subjective symptoms from the Multiple Affective Adjective Checklist (MACCL) being worse in the morning. This might therefore signify increased daytime activity levels and improved daytime functioning and mood which will be discussed more fully with the circadian analysis data and cognitive performance. This is also in agreement with studies previously alluded to whereby antidepressants increased daytime activity as shown in actigraphic studies (Raoux et al., 1994; Royant-Parola et al., 1986; Benoit et al., 1985). Even if sleep variables are not improved, if patients actually felt that they slept better, they might be in a more productive mood the following day with increased activity which is shown in Figure 5.36 from Raoux et al. (1994).

5.6.5.2. Actigraphic variables during discontinuation

Following the 12 weeks of stable dosing in the current study, medication was abruptly discontinued for a mean of 7 ± 2 days on matching placebo. With regards to actigraphic sleep variables there was a statistically significant reduction in sleep timing overall for TIB, SPT and TST which from post-hoc analysis was significant for sertraline. Caution should be taken however with these effects of reduced sleep period time, as it is not necessarily
inevitably comparable to better or worse sleep, indeed it may be that patients actually want or need less sleep.

Figure 5.36: Actigraphic 24h activity profile (Raoux et al., 1994)
Difference between 24 h profile mean of 3 days before treatment compared with 3 days at discharge showing increased daytime activity.

Statistically, although there was no significant change for any treatment in actigraphic sleep latency, there was a reduction in SOL, indicating that patients took less time to get to sleep following withdrawal of fluoxetine or sertraline, but there was little change in SOL after withdrawal of paroxetine. Whilst this did not reach significance, it confirmed the trend towards an improvement in the perceived ease of getting to sleep with LSEQ GTS for patients following discontinuation of sertraline and fluoxetine, whereby lower scores showed an improvement. Conversely in the current study, the GTS for paroxetine indicated a worsening effect with patients feeling that it was harder for them to get to sleep. Furthermore this is confirmed by the HAMD early insomnia whereby patients reported more difficulty getting to sleep following withdrawal of paroxetine treatment.

The direction of LSEQ GTS scores for both fluoxetine and sertraline in the current study disagreed with the Hindmarch et al. (2000a) study which showed that scores increased following withdrawal from any of the treatments in their study, indicating that it took longer to get to sleep. It must be stated that in the current study no direction of change for SOL or GTS was statistically significant, and therefore no direct conclusions can be made from the data. These observed changes, however, are worthy of further investigation. In both studies patients reported that GTS was worst following paroxetine withdrawal. Further, the HAMD
early insomnia score in the present study was also shown to worsen following both paroxetine and sertraline disruption, whereas with fluoxetine there was a hint of improvement.

With reference to actigraphic sleep quality in the current study, sleep efficiency failed to show any trend of direction for any treatment, remaining fairly constant throughout the discontinuation week although it appeared to decline following reintroduction of paroxetine treatment. The number of sleep bouts remained fairly stable throughout discontinuation for all SSRIs, although the number increased for paroxetine following reintroduction. The sleep bout time was reduced in both paroxetine and sertraline during discontinuation and further reduced during reintroduction. Interestingly WASO appeared to decrease for paroxetine during discontinuation as did the total activity counts in sleep indicating that sleep was less disturbed, but increased for fluoxetine during discontinuation.

It might be considered that these factors are indicative of poorer sleep, a pharmacological effect or patients normalising to their sleep pattern during discontinuation as the medication wears off. Paradoxically patients LSEQ QOS scores improved significantly following both fluoxetine and sertraline withdrawal. Whilst for paroxetine LSEQ QOS scores in the current study failed to show a statistically significant effect of withdrawal of treatment, the increase in scores would suggest a worsening of sleep quality. This is in agreement with the Hindmarch and colleagues study (Hindmarch et al., 2000a) which reported a significant impairment of QOS during the abrupt discontinuation of paroxetine. Additionally according to the MADRS sleep component patients, in the current study, felt that their sleep had worsened following paroxetine and sertraline withdrawal with scores increasing. This effect was replicated with increased early insomnia and poorer sleep on the HAMD sleep components following paroxetine and sertraline withdrawal. In contrast, patients treated with fluoxetine did not report a worsening of their sleep during discontinuation on the depression scales.

With regards to actigraphy in the current study, this pattern of subjective poorer sleep on abrupt discontinuation from the antidepressants paroxetine or sertraline was not reflected in the actigraphic sleep variables, nevertheless small changes were observed. Actigraphic sleep variables in combination indicated that discontinuation of treatment did not greatly affect actigraphic sleep variables by either improving or adversely affecting the sleep. Some trends however are worthy of further investigation as they suggest that discontinuation had a clinical effect. This fact may be due to the differences between the drugs whereby paroxetine
has a short $T_{1/2}$ and therefore likely to show a faster response following removal of treatment. For fluoxetine, with the longer $T_{1/2}$ this indicates that the applicable discontinuation emergent symptoms of sleep-disturbances and fatigue are less likely to occur if patients miss a few doses.

Interestingly following abrupt discontinuation daytime AWM significantly increased, particularly in favour of fluoxetine and sertraline, indicating that the patients were more active during the day. This might suggest that throughout treatment the antidepressants were having a calming effect by reducing daytime activity but on discontinuation patients were more active, or maybe removal of medication led to hyper-arousal and activation. In terms of the LSEQ, patients did not report a worsening of either AFS or BFW although there was a worsening trend towards these variables following paroxetine withdrawal in both the current and the Hindmarch study (Hindmarch et al., 2000a). Additionally patients discontinued from paroxetine treatment felt more sedated according to the LARS sedation component compared with fluoxetine or sertraline, in both the Hindmarch et al. (2000a) and the current study, which might help to explain the differences in the LSEQ and actigraphic variables.

Without obvious directions in the actigraphic variables it may be that there are different conclusions to be drawn on what the results of discontinuation indicate. It could be that patients in the current study had insufficient time on the medication to normalise their sleep wake pattern. Other discontinuation studies (Hindmarch et al., 2000a; Rosenbaum et al., 1998; Michelson et al., 2000) have been conducted on patients who were receiving maintenance therapy for longer than the 12 weeks in the current study. It could also be related to the length of the discontinuation with a longer period in the current study, as indicated by (Michelson et al., 2000) Section 1.6.10 whereby discontinuation symptoms emerged within 2 days of discontinuation following paroxetine withdrawal. More movement in sleep may indicate more disrupted sleep, less sedated sleep or even the reverse as has been discussed with fluoxetine which appears to have an effect of agitation. Alternatively the changes in activity could be related to changes in sleep architecture and REM in particular.

There appears to be more activity in the sleep of patients when fluoxetine is withdrawn and yet they did not report worsening. On the other hand patients whose paroxetine treatment was withdrawn reported worsening of sleep but their activity appears to fall causing less disruption. Perhaps fluoxetine and sertraline were having some negative effects when patients were on maintenance therapy which was alleviated when medication was stopped or that the half-life of the medication or its active metabolite meant the therapeutic effect
continued to have an effect. A PSG study by (Staner et al., 1995) showed that following withdrawal of paroxetine treatment there was an increase in REM showing a rebound effect which might have shown as a reduction in actigraphic activity, as was observed in the current study in the total activity counts in sleep. Paroxetine has a short half-life which could account for the opposite direction and rebound effect with a worsening of REM, SOL and GTS. These effects are worthy of further investigation possibly with a subset of sleep diagnosed poor sleepers to tease out the actual improvement or worsening of treatment in the subjective sleep profile.

5.6.5.3. Circadian analysis
In order to reduce day-to-day variability approximately seven days of continuous activity data, including weekends was combined to provide the arithmetic means on a week by week basis. The dates were adjusted to account for the allowable visit windows but were synchronised with the actual visit dates for the purpose of comparison with the other measures recorded at the visits. These means were then compared with subsequent weeks and relative changes were computed. For both cosinor analysis and NPCRA the weekly data were adjusted according to the visit dates in order to ensure that the means reflected the corresponding visit dates so that they could be compared with the other cognitive and psychometric variables. The start and end of the discontinuation period was also aligned with the visit dates; to ensure that an accurate assessment during discontinuation could be obtained.

5.6.5.4. Cosinor (parametric) analysis and treatment
To the author’s knowledge no other study has investigated the impact of SSRI antidepressant treatment on the cosinor rhythms of depressed patients. Analysis of the current study revealed that there was an overall significant improvement of the percentage rhythm over time for all treatments for the 12 week data, with the percentage rhythm increasing. This indicates that the sleep wake rhythm, which is a measure of the percentage of data points that can be accounted for by the cosine curve, was increasing and stabilising with treatment and becoming less fragmented and more organised. This might be beneficial for the patient, with their sleep wake pattern being more regulated.

Although there were increases in the mean activity for amplitude and mesor, with patients being more active overall, these did not reach significance for any treatment during the 12 week analysis but the data did suggest that patients were becoming more active as treatment
progressed. Moreover this confirms the trend in increasing data seen in the actigraphic variable AWM which focuses on daytime activity and not the 24 h mean.

A trend for a delay in timing occurring in the cosinor acrophase time was observed overall for the 12 weeks study with the acrophase time occurring slightly later in the biological day. This trend appeared to occur after 4 weeks of fluoxetine treatment but almost from the start of treatment with paroxetine. After an initial delay in time as treatment progressed, the data suggests that this then began to advance from week 4 onwards for paroxetine. These aspects are however very small in time, being less than 30 minutes, but could be an indication that as treatment took effect patients felt better and were more active later in the day as treatment initially took effect and then earlier with a phase advancement as treatment with paroxetine progressed.

To compare data from the current study a study in patients suffering from Seasonal Affective Disorder (SAD) showed a circadian misalignment to healthy controls with a phase delay and lower amplitude (Teicher et al., 1997). A further study of SAD patients showed that at baseline their amplitude was reduced and phase delayed compared to healthy controls (Winkler et al., 2005). Following 4 weeks of Bright Light Therapy (BLT), as depression improved, patients’ amplitude increased and normalised to almost healthy control levels, in addition BLT led to a phase advance in acrophase time occurring earlier in the biological day. With regards to actigraphic variables after 4 weeks of treatment AWM and SE had improved to healthy control levels. In an inpatient study of MDD patients (n = 26) 6 shifted their acrophase time by more than 1 h, following treatment with TCAs (Raoux et al., 1994). Interestingly in that study the 2 patients who had the earliest phase delayed, and the patient with the latest phase advanced, the direction of the others was not reported.

5.6.5.5. Cosinor (parametric) analysis during discontinuation

The trait of the clock advancing occurring earlier in the day in the current study was reversed during the discontinuation week for all treatments, with an abrupt delay of approximately 30 min in the acrophase time. This was statistically significant following fluoxetine withdrawal. In addition during this week there was also an increase in amplitude and mesor activity overall, which was again significant for fluoxetine. There was also a significant increase in percentage rhythm which was also statistically improved following fluoxetine withdrawal. Why this happened is unclear but worthy of further examination as to the true meaning of fluoxetine abrupt discontinuation on cosinor variables. These effects are positive effects and
are associated with the improvement in subjective outcomes of MADRS and HAMD depression scales as well as the direction of change in psychomotor function.

One theory could be that as REM sleep in depression is increased, activity would be reduced, then as depression improves REM sleep is reduced and activity during the other stages is therefore increased. This appears to be happening with all treatments during the 12 week chronic phase in the current study with an increase in total activity counts in sleep and an increase in sleep bouts indicating more movement. With discontinuation the reverse occurs with possibly the recurrence of more REM associated with less activity as seen following paroxetine withdrawal. This was also linked to a worsening effect with an increase in MADRS and MADRS sleep scores and an increase in HAMD early insomnia showing a possible rebound effect. However, during withdrawal from fluoxetine more activity is recorded in total activity counts in sleep and MADRS score is improved although the L5 (NPCRA) activity was reduced. The reason for this might indicate that the effect of fluoxetine continued or that withdrawal of the drug was having a true effect and depression had been alleviated with a further reduction in REM. This theory assumes that although the depressed patients in the current study complained of sleep problems according to MADRS sleep what is not known is whether they actually had the altered sleep architecture associated with depression as they were not formally diagnosed with a PSG recording.

5.6.5.6. NPCRA variables

For the purpose of this study the data were grouped into weeks which were aligned with the visit dates to allow for visit windows. Overall for the 12 week analysis in the present study, the NPCRA data analysis failed to show any significant differences between the treatment groups or treatment by time for any variable. In terms of activity levels throughout the 12 weeks of chronic treatment there was no significant difference between treatments or over time recorded for average activity, amplitude, M10 or L5.

The activity levels for paroxetine, however, were much lower than either fluoxetine or sertraline treatment throughout except for L5 activity where the levels were similar to fluoxetine treated patients. Patients treated with paroxetine or fluoxetine also increased their activity levels in M10 and 24 h average whereas activity levels for patients treated with sertraline showed a slight decline throughout the 12 week period. The increase in average activity and the M10 activity, however, do agree with increases in the actigraphic sleep variable ‘average wake movement’.
One other antidepressant and actigraphy study has reported on NPCRA variables (Kasper et al., 2010). Mean M10 activity increased in patients treated with agomelatine (a melatonergic antidepressant) but decreased in those treated with sertraline between week 1 and week 6 which confirms the effect of sertraline in the current study. L5 activity showed a similar decline for sertraline in both studies although individual weekly results were not presented in the Kasper et al. (2010) study so cannot be directly compared with the current study.

A mechanism for evaluating the resumption to normality is calculated as the RA where values close to 1 are indicative of a healthy non-depressed circadian cycle. The baseline RA of patients in the current study was higher compared with the Kasper et al. (2010) study. At baseline the RA was 0.90, 0.94 and 0.93 for paroxetine, fluoxetine and sertraline respectively, which compared with 0.87 and 0.85 for agomelatine and sertraline respectively. This suggests that patients in the current study had a higher initial baseline amplitude than the Kasper et al. (2010) study and a less disrupted rhythm. The patients in the Kasper et al. (2010) study had an inclusion HAMD score mean of 26.3 (HAMD moderate 16 - 27) which was more severe in comparison to the current study mean of 26.5 (MADRS moderate 18 – 34) (Müller et al., 2000; Müller, 2003).

It is theorised that the RA would rise as daytime activity levels increase and night-time activity levels decrease with the improvement in depression. In the current study the RA remained fairly constant throughout, albeit that for patients on paroxetine RA levels were consistently lower, this could indicate that overall patients were sleeping better and more active during the day with the stable ratios seen in RA levels. Compared to the current study the mean RA was lower in the Kasper et al. (2010) study so it could be feasible that these were more severely depressed patients. The RA was stable over the 6 weeks of treatment with agomelatine whereas it decreased in the first week of sertraline treatment and was then comparable to agomelatine.

A delay in timing was observed in the current study. There was a trend towards a significant delay in the M10 onset time for all treatments occurring later in the day by a mean of approximately 30 minutes, with a trend towards a significant delay for the sertraline group. The M10 onset time appears to follow and confirm the same effect of a trend in delay as the acrophase time in the Cosinor analysis. These outcomes suggest that patients were more active during the day as treatment took effect but that the onset occurred later, and compared favourably with improvements in the depression scales, as depression lifted activity increased.
Interestingly activity levels were similar for all patients during L5 time; with paroxetine a little higher in the current study indicating that paroxetine had a disrupting influence on activity during sleep. In comparison to the (Kasper et al., 2010) study patient numbers in the current study were much smaller but nevertheless similar trends are reported with increasing daytime activity as treatment progressed and decreasing night-time activity. Even though these results are not significant the current data trends are worthy of further investigation as suggested in line with differences in the types of depression and the differences between anxious agitated and melancholic retarded depression.

Although these results differ from the Kasper et al. (2010) study which found that, following 6 weeks of treatment sertraline decreased M10 and L5 activity compared with agomelatine, no onset time for these variables was reported. There were similarities in that sleep latency was increased, yet quality of sleep was improved as were HAMD scores, following sertraline administration over 6 weeks, compared with agomelatine.

The reason for the improvement in mood and alertness in the current study could be connected to a delay of the circadian clock as shown by the delays observed in the onset times, and increased M10 activity levels. Toddler et al. (2009) studied daytime (08:00 to 20:00 h) and night-time (00.00 to 06.00h) activity levels in depressed patients on a 4 week course of quetiapine, and found that responders increased daytime activity levels in relation to improvements in HAMD. It is unclear what comes first, whether depression affects the activity and sleep and wake timing mechanisms due to its adverse effect on sleep; that depression leads to desynchrony or whether the irregularity causes the depression.

The Interdaily Stability (IS) (Van Someren et al., 1999) which ranges from 0-1 and the closer the value is to 1, or shows an increase in value, is indicative of an improvement to a more stable rhythm and is a measure of the connection with external environmental cues. There was no significant improvement in the IS over the 12 weeks of chronic treatment overall or for any individual treatment in the current study. Comparing values presented from other studies indicated that even at baseline the current data showed that patients’ rhythms were reasonably stable with the mean values of 0.57, 0.64 and 0.65 for paroxetine, fluoxetine and sertraline respectively. These values compare favourably with other studies who have reported values of 0.62 (Baune et al., 2006) for depressed participants, 0.65 (Van Someren et al., 1999) during bright light treatment of demented patients and 0.62 (Berle et al., 2010) for schizophrenic patients treated with clozapine. However there was a trend
between treatments with paroxetine exhibiting lower values during early treatment than either fluoxetine or sertraline but which was comparable by week 12.

Intradaily Variability (IV) (Van Someren et al., 1999) indicates how fragmented the circadian rhythm is, ranging from 0 to 2 whereby a value of 0 represents a perfect fit to a sine wave, it represents the frequency of transitions between rest and activity. The higher the value the more fragmented the rhythm. In the current study the mean baseline values were 0.81, 0.65 and 0.70 for paroxetine, fluoxetine and sertraline respectively, which indicated that the IV for the paroxetine group was more fragmented and agreed with the IS. Values for both fluoxetine group and sertraline group were fairly stable throughout the 12 weeks and values for paroxetine treated patients fell to comparable levels which indicated a trend for an improvement with treatment. In comparison with other studies the baseline values here are reasonably normal. A comparable study reported values of 1.06 for depressed patients (Baune et al., 2006).

5.6.5.7. NPCRA during discontinuation

For the NPCRA variables during discontinuation there was an overall significant effect with increases in average activity, amplitude and M10 activity coupled with an advance of the L5 onset time, occurring earlier in the night. These factors were also significant for fluoxetine and might indicate that circadian de-synchronisation was normalising on withdrawal and that patients were no longer depressed as the MADR and HAMD scores did not rise significantly.

IS values decreased with a significant trend P = 0.08 overall during the abrupt discontinuation week showing a possible disruption of the stability. Although IV values decreased in the current study during the abrupt discontinuation week this was not significant.

5.6.5.8. Circadian summary

To recap circadian rhythm analysis allows for a mechanism of observing whether the 24 h cycle has improved following treatment for depression to a more robust rhythm. Not only for higher activity levels during the day and lower activity during sleep but also the timing of these events and the strength of the rhythm. The NPCRA analysis produces an average day for 7 days and changes in timing and activity levels can be observed. It has been shown in the current study that daytime activity increased over the course of treatment as well as improvements in subjective ratings of depression and yet sleep variables were not improved.
Therefore recording circadian rhythms could provide a tool to aid diagnosis, record the time course of recovery and further stabilisation of the 24 h rhythm.

As has been previously shown, from the actigraphic data, the impact of changes in sleep patterns was correlated with changes in increased daytime activity overall during the progress of 12 weeks of treatment. Therefore to explore whether 24 h rest-activity patterns were affected the activity data were further analysed using the cosinor program developed by Minors et al. (1986) and the NPCRA analysis program developed by Van Someren et al. (1999).

Changes can best be understood and described as differences in subsequent 24 h 7 day rhythms which show whether variables have changed, to what degree and whether those changes indicate an improvement. Patients with weak rhythms might exhibit changed onset times for M10 and L5 activity, improved higher IS, lower IV and a higher RA value with improvement in depression. Lower values for IS indicate a less stable rhythm and higher IV values indicate a more fragmented rhythm. Changes in these rhythm values including the timing of these events can show improvement in the 24 h cycle over a period of weeks. Although daytime activity levels increased over the course of treatment, which were associated with significant improvements in subjective ratings of depression, they were not significant for any treatment in the current study. Furthermore sleep variables were not improved. However recording circadian rhythms could provide a tool to aid diagnosis, record the time course of recovery and further stabilisation of the 24 h rhythm. It is likely that most of the patients in the current study had regular lifestyles either by being employed or having children with school runs and timetables etc., with key triggers or zeitgebers in their biological day, that their activity was to some extent controlled therefore it would be difficult to see obvious changes in circadian NPCRA compared with in-patients or Alzheimer's patients whose activity is not so controlled. Raoux et al. (1994) showed that different patients delayed or advanced their 24 h rhythms in response to antidepressant therapy so to review the circadian cycle outcomes in conjunction with whether patients were responders or not and what types of depression they had is worthy of further investigation.

5.6.6. Line Analogue Rating Scale (LARS)

5.6.6.1. Effect of treatment on LARS

At baseline, Visit 1, the mean score for the three treatment groups was in the range 59 – 68 mm, 9 – 18 mm above the mid-line or ‘normal’ point i.e. as depressed patients they felt more tired and sedated or lethargic than before they were depressed. Analysis of the change in
LARS score from Visit 1 to Visit 12, i.e. after 12 weeks of treatment, showed no significant difference between the three treatment groups. The scores were all significantly improved overall for the 12 weeks analysis which indicated that all patients felt more alert as treatment progressed. *Post-hoc* analysis showed that feelings of alertness were significantly improved for both paroxetine and fluoxetine during the 12 weeks of treatment. Interestingly in contrast to expected outcomes of the sedating reports of paroxetine, patients in the current study rated their sedation less and more improved than either fluoxetine or sertraline.

5.6.6.2. LARS during discontinuation

Treatment discontinuation from fluoxetine or sertraline showed little change whilst discontinuation from paroxetine showed a substantial increase in LARS sedation scores. Subjective sedation worsened after paroxetine withdrawal showing that patients felt more tired and lethargic during the 1 week discontinuation phase. This was, however, still much lower than their baseline. The subjective feelings of sedation after treatment withdrawal from paroxetine were not reflected in actigraphy variables as there was no reduction in daytime activity. Instead activity counts increased, perhaps an increase in activity made the patients feel more tired or their disrupted sleep increased fatigue, the worsening of LARS is also associated with the worsening of QOS in LSEQ.

This worsening trend during withdrawal confirmed the findings of Hindmarch et al. (2000a) who also reported an increase in sedation scores following paroxetine withdrawal. Rosenbaum et al. (1998) similarly reported that paroxetine caused more ‘fatigue’ than either sertraline or fluoxetine during placebo substitution. Interestingly, although not analysed in the current study, both Hindmarch et al. (2000a) and Rosenbaum et al. (1998) report worse effects of anxiety, agitation and irritability from the DESS from both sertraline and paroxetine withdrawal compared with fluoxetine. Perhaps an increase in anxiety and agitation had a negative impact on sleep and therefore increased daytime sedation levels.

5.6.7. CFQ

5.6.7.1. Effect of treatment on CFQ

The baseline CFQ values in the current study of 59, 58 and 66 for paroxetine, fluoxetine and sertraline, respectively, were comparable to the baselines of other patient studies (Fairweather et al., 1999; Preiss et al., 2013; Farrin et al., 2003) indicating that patients had similar cognitive impairment. Results from the current study showed that the mean percentage improvement in CFQ scores was 35% with scores reducing to 34, 41 and 43 by week 12 for paroxetine, fluoxetine and sertraline respectively, with a statistically significant
improvement. The scores at week 12 are comparable to the scores recorded by control participants from other patient studies (Fairweather et al., 1999; Preiss et al., 2013; Farrin et al., 2003) which indicate that patients improved in the current study.

These results again showed significant improvements for all treatments over time from baseline with similar improvement to the self-completion ZUNG. Patients felt more coordinated and alert with an increased ability to concentrate and think straight, were less clumsy, and more able to perform simple everyday tasks without impairment in memory, attention and motor function.

5.6.7.2. CFQ during discontinuation

During the discontinuation week although scores increased following paroxetine withdrawal this was not significant in the current study. In fact further reductions in scores were recorded during the discontinuation week for both fluoxetine and sertraline compared with week 12 following chronic dosing. This could indicate that patients were not adversely affected in their ability to maintain normal functioning as there was no significant impact on the CFQ scores during the period of discontinuation of treatment. These outcomes compare favourably with the increase in daytime activity. In contrast, the study by Hindmarch et al. (2000a), showed a significant increase in the CFQ scores during the week following abrupt discontinuation from paroxetine. There was also a trend for impairment following sertraline withdrawal.

5.6.8. Psychometric assessments

5.6.8.1. Critical Flicker Fusion (CFF) and Choice Reaction Time (CRT)

The present study showed that both CFF and CRT were improved significantly for all treatments from baseline with most of the effect occurring in the first 8 weeks of treatment after which the effect plateaued. These findings are in agreement with those of Fairweather et al. (1993), and Kerr et al. (1993) who showed that fluoxetine (20 mg/day), improved CFF performance compared with tricyclic antidepressants (TCAs) in depressed patients over 6 weeks. A study by Alexander et al. (1997) demonstrated that paroxetine significantly improved CFF threshold compared with dothiepin and this improvement was maintained over 6 weeks. There is limited evidence of the effects of long term use of sertraline in depressed patients on CFF or CRT. A review from Amado-Boccara et al. (1995) reported that sertraline ‘significantly increased CFF threshold compared with placebo’ and also improved CRT however the study referred to was by Hindmarch and Bhatti. (1988) was conducted on healthy participants over 8 h. This study therefore addresses this gap in
knowledge and shows that sertraline had a statistically significantly positive effect on CFF with an elevation in threshold and a reduction in reaction time.

5.6.8.2. CFF and CRT during discontinuation

Only one other study by Hindmarch et al. (2000a) has investigated the effect of brief discontinuation of paroxetine, fluoxetine, sertraline treatment on cognitive functioning of depressed patients and the effect of time on CRT and CFF. The brief treatment discontinuation of 4-7 days by Hindmarch et al. (2000a) had no overall effect on CFF for any treatment, although a slight non-significant decrease in threshold was observed following paroxetine withdrawal. This was in contrast to the current study, where although a similar trend and decrease in CFF was observed following paroxetine disruption, there was also a significant decrease in CFF threshold for sertraline also suggesting that cognitive processing was reduced during the discontinuation period. In addition in the Hindmarch et al. (2000a) study discontinuation of all 4 treatments increased reaction time, with a greater increase in the patients when they were not being given paroxetine. In contrast, in the current study reaction times were only increased in the paroxetine treated patients which were significantly increased in the within group analysis, whereas the reaction times for both fluoxetine and sertraline treated patients improved.

The results from both studies suggest that the consequence of abrupt paroxetine withdrawal causes a worsening of cognitive performance and mood symptoms. This may be related to the shorter half-life of paroxetine. Results of the current study add to the limited information available of the cognitive and psychomotor data outcome aspects of SSRI discontinuation.

5.6.9. Limitations

This study is the first to compare the SSRIIs, and to show the effect of paroxetine in activity and sleep variables compared with fluoxetine and sertraline over 12 weeks of continuous monitoring combined with 1 week abrupt discontinuation. In addition the use of actigraphy has provided additional information of the circadian behaviour of patients following treatment and during abrupt discontinuation. There are many limitations to the study, which will be discussed in this section, to consider and improve future studies and to facilitate better data collection. The data collected provides insights into the positive direction of action of the medication as seen in the improvements in the depression scales and subjective assessments.
The effect of SSRIs is well documented as previously discussed but there is little data on the use of actigraphy in long-term studies of depression. For future studies amendments to the study design are advised, to ensure that the effects seen are actual, more robust and not just by chance. The main limitations to the study were the small sample size, no placebo or non-treatment baseline and no placebo comparator. Sample size was restricted to the number of compliant patients who wore the actiwatch throughout the study, which was approximately 33% of the patients recruited. In addition of the original 99 recruited 26 withdrew before Visit 12 prior to abrupt discontinuation. Although fewer patients may have withdrawn from the study compared with standard GP treatment due to regular and routine contact with the GP surgery having an effect similar to cognitive behavioural effect CBT Lejoyeux and Adès. (1997).

Although baseline data were not available for actigraphic variables it was for available for the cognitive and psychometric assessments as well as the subjective scales, as they were recorded at the very first visit. Therefore changes in these variables could be accurately calculated. Even though there was no baseline data for actigraphy, as SSRIs supposedly have a delayed onset and may take at least 2 weeks to take effect, it was possible to calculate weekly changes from the start of medication, although adverse side effects might have occurred sooner (Mackay et al., 1999; Ferguson, 2001; Taylor et al., 2006). To have actigraphy data from placebo controls in depressed patients would have been valuable but would not have been considered ethical (Wilson et al., 2000).

5.6.9.1. Patients

The inclusion criteria stated that patients would be recruited into the study provided that in the opinion of the investigator they required antidepressant medication. However in order to ensure that there were no medication conflicts they were excluded if they had received any drug treatment for depression in the previous 3 months. Patients diagnosed as moderate to severely depressed, defined as requiring treatment with a score ≥ 20 from the MADRS at screening Visit 1 were recruited. The mean MADRS score was 26.5 (18 - 34), which was on the lower side of the moderate depression spectrum. As suggested by Fava et al. (2002) it could be considered more difficult to ascertain differences in treatment effects in patients with milder symptoms. In fact by Week 1 the mean MADRS value showed that patients were in the mild range of 9 - 17. There were more females than males at approximately 78.6%, which could have biased the outcome. In the Kasper et al. (2010) study, there were 70.6% females, and although more females are treated for depression it is likely that they
seek treatment more often than males as well as there being more hormonal differences (Grigoriadis and Roblockson, 2007).

The question of severity might be worth review as the significant improvements in the MADRS and HAMD scores occurred within the first 2 weeks for any of the treatments. Maybe the patients were not sufficiently depressed as has been shown in the MADRS scores at inclusion. Perhaps the sleep of patients was not severely disrupted at the start to show improvements in their sleep variables. The changes seen in actigraphy are very subtle compared with the objective assessments but do offer suggestions in the direction of improvement in increased daytime activity. Nevertheless all patients who fulfilled the criteria of wearing the activwatch and completed the abrupt discontinuation were included in the analysis. All patients were included in the analysis as no account was taken regarding the individual improvement by patient, so this aspect might be worthy of further investigation to expose the effects of treatment in those patients that responded more to treatment than others. Various studies have adopted this approach for example Baune et al. (2006) conducted a study of rest-activity rhythm. As only half the patients (n = 5) showed clinical improvement of ≥ 30% on the HAMD after 4 weeks of treatment with quetiapine, data were presented in 2 groups, clinical improvement and non-improvement (Baune et al., 2006). However this would defeat the object if the actigraph is to be used in general practice as it assumes a pre-selection process to show significance.

There was no placebo arm, neither was there a comparator or verum medication with known effect, so only comparisons between the three SSRIs could be made. It might have been useful to include a sedating antidepressant such as one of the TCAs e.g. dothiepin or amitriptyline which are often used as verum in studies and produce known sedating effects. It is worthy to note that, in the present study, even without a drug free baseline or placebo run in (7 day) improvements in patients from their own depressed baselines were observed.

Current treatment for depressed patients includes Cognitive Behaviour Therapy (CBT) and Mindfulness Therapy so there may have been an effect of this with the visits to the doctor which could be considered similar to CBT thereby improving patient’s feelings of self-worth. It has been shown that depressed patients, (n = 31) without medication, but given a personalized cognitive training program, exhibited statistically significant improvements in the CFQ which were correlated with improvements in the Becks Depression Inventory (BDI) (Preiss et al., 2013). The use of CBT is an interesting aspect since although this was not part of the treatment patients were assessed regularly, and their symptoms discussed with their
GP with 1:1 support, so the fact that they were in a clinical trial and receiving more attention might have affected the outcomes.

There are many types of depression, but it is assumed that no allowance for the type of depression was made. Patients may suffer from different types of depression which can be retarded and melancholic with reduced activity or anxious and agitated, or even bi-polar and exhibit different profiles (Haynes et al., 2006; Salvatore et al., 2008). The aspect of retardation in depression was discussed in a review of studies by Dantchev and Widlöcher, (1998) which disclosed that depressed anxious agitated patients improved more than those with retarded depression following fluoxetine treatment. No allowance was made for these different types of depression, so the effects that might otherwise have been seen with actigraphy, which uses activity levels, might have been cancelled out.

Another factor to consider is timing, as the present study was conducted in the winter and spring months when the amount of daylight was limited but gradually increasing, so it is unclear whether timing of the study affected patients who may have been suffering with SAD. The first patient first visit occurred in November and 22 patients completed in the months with a GMT clock, before the clocks changed to BST and when there was less sunlight ranging from 8 hours in January to 11 hours in March. Moreover more than half the patients completed their discontinuation in BST around May when there was 15 h of daylight so the extra daylight could have confounded the discontinuation outcomes.

The age range of the patients varied from the youngest at 21 years to the oldest at 84 years with nearly a third of the patients over 50. Given that depression is associated with cognitive impairment and deficits are worse when the first onset of depression is in later life it would have been prudent to limit the age range studied according to Variend and Gopal. (2008). Further, as suggested by Fairweather et al. (1993) depression often accompanies aging and the pharmacodynamic and pharmacokinetic effects of drugs are often exaggerated in older adults, and maybe the patients should have been stratified by age.

5.6.9.2. Design

As the patients were newly diagnosed and provided with medication shortly after informed consent, the study failed to allow for the collection of actigraphic data in the weeks prior to administration as either a drug-free baseline or placebo run-in. This is an important factor which would have resulted in comparative baseline data. Although actigraphy data were captured for depressed patients, in the Kasper et al. (2010) actigraphy study there was a short
washed period prior to treatment. As previously discussed, future studies should consider ensuring that a pre-treatment baseline of at least 7 days is obtained.

The actigraphic sleep variables at baseline e.g. sleep efficiency and number of sleep bouts, are similar to healthy volunteers so the chance of seeing any relative improvement was low. Moreover many of the cosinor and npcr variables i.e. IV, IS and RA are relatively close to the normal range. Paradoxically although actigraphic sleep worsened with antidepressant treatment, which supported previous findings of the effects of SSRIs on sleep, this could be due to REM being normalised. Conducting a PSG assessment therefore, before, during and after treatment would have provided valuable information as to the actual sleep architecture. The patients were the lower end of the MADRS spectrum, therefore to show actigraphic improvements it would be advisable to study patients with more severe depression.

Recruitment of patients was conducted at 12 GP centres, Investigators were trained how to conduct the cognitive and psychomotor tests and capture the data for the assessments, at the study initiation and start up. The testing was conducted at these centres which ranged from single practices in converted houses to health centres so it might be better to maybe reduce the number of centres and standardise the test facilities.

5.6.9.3. Actigraphy
The actiwatches had a finite recording period of 45 days at 1 min epoch and 90 days at 2 min epoch so in order to capture the critical periods during the start of treatment and discontinuation 3 separate periods were recorded. Recording period 1 covered the first 4 weeks and 1 min epoch was used; period 2 covered the maintenance of medication from week 4 to week 12 at 2 min epoch; and period 3 at 1 min epoch covered weeks 13 and 14 over the discontinuation period. Prior to analysis it was necessary to normalise all the data files to 2 min epoch to enable the data from the 3 files with different epochs to be comparable and then the actiwatch Sleepwatch data analysis was carried out. Some actiwatch variables, such as fragmentation index, rely on 1 min epoch data. Analysis for these variables could not be calculated, and therefore sleep disruption was determined through the number sleep/wake bouts being the number of transitions from sleep to wake and their subsequent length.

Each actiwatch contained a unique sensor with a slightly different sensitivity and unless data were derived from the same actiwatch for multiple recordings of the same patient there was a possibility that the data obtained was slightly different from each watch and might not map
exactly. According to the later Actiwatch Manual ‘inherent variation in application of Actiwatch units means that no two Actiwatches will produce exactly the same output’. By treating all the data the same and creating weekly means it might be accepted that any variation would be minimised.

A factor that cannot be changed is that when the clock changes from GMT to BST, the diurnal rhythm of the internal body clock can take over a week to adjust and affect the sleep wake pattern (Kantermann et al., 2007), so this change in the ‘body clock’ might have affected the patients sleep/wake actigraphy variables and rhythm.

One other aspect of environmental time was to take account of holidays, since many patients were treated over Christmas and the New Year. In these cases if actograms indicated that there was an unusual late bedtime with subsequent late wake time the data for the full 24h was removed so as not to impact on the weekly means. In addition for one record it was obvious from the actogram and the diary that a holiday to USA had taken place during the recording. In this instance the activity data for the holiday period was treated as an outlier and removed from the analysis as it might have skewed or influenced the data if included in the analysis.

It was previously presumed that all actiwatches retain time efficiently but by comparing marker times at download with the actual time it was possible to determine any drift in the internal timer. Prior to download the computer clock was synchronised to a radio clock, the marker on the actiwatch was then pressed to act as a reference point and to confirm the actual time of download from the computer clock. The process of checking the internal clock of the actiwatch was necessary to ensure that its timing and that of the internal sensor had not drifted. It was ascertained at this point that the internal computer clock at the GP set-up centres were not synchronised with real time. By a process of deduction it was determined that at one centre the computer clock was out of sync by approximately 1.5 h and at the other 1 h. To ensure parity across the data sets the *.awd files were adjusted with the mean of each respective centre.

Some data files when downloaded showed a reduction in activity levels which when compared with the other actiwatches for the patient indicated that the internal sensor could be faulty. Standard practice now includes calibration of the actiwatch, by running the actiwatch on a calibration jig and obtaining a certificate of validation, when a new battery is inserted to ensure that the actiwatch sensor is within the sensitivity range. If the actiwatch is
returned with a suspected sensor fault, it should be re-calibrated to confirm accuracy, prior to the data being used in any analysis.

The Actiwatch markers were used to determine bedtimes, and the patient diaries were used to confirm the bedtime and wakeup time information if the marker had not been pressed. The diaries gave an insight into the patient’s daily activities and aided interpretation of the data but they were very basic and better diaries used in clinical trials are now available. Current diaries now also include subjective scales, to monitor daily changes in perceived sleep quality, sleep timing and how long patients took to get to sleep, and whether there was any disruption in sleep continuity for toilet visits. They are also now used to record dietary information especially regarding caffeine intake and other aspects which might impact on sleep such as late exercise. An example of a simple diary is shown in Appendix XIV.

For future studies over the same timescale of 12 to 14 weeks the logistics, organisation and management of the actiwatches must be carefully planned, to ensure that the same actiwatch can be dispensed to a specific patient to maintain continuity. Actiwatches are now available which record up to 180 days, but attention to detail and accurate recording of events should be standard practice with checking clocks prior to setup and download.

There was a reduced analysis set for the current study compared with the full study data set as only patients who were compliant with wearing the actiwatch and completed all 14 weeks of the study were included in analysis. Approximately one third of patients were lost due to early withdrawal or non-compliance by not wearing the actiwatch. The mean MADRS for the included patients was lower than the full data set therefore the final study patients may have been less representative or less depressed compared with those of the total study, this may have contributed to the patients being more compliant.

It is likely that if depressed out-patient groups have a structured lifestyle with a regular sleep wake rhythm and social zeitgebers, changes in timing and circadian outcomes might be small, although increased activity levels might reflect a positive change, therefore a combination of actigraphic variables would be desirable to any single outcome (Monteleone et al., 2011; Calogiuri et al., 2013).

5.6.9.4. Discontinuation
Discontinuation studies suggest that a staggered withdrawal may be preferable to abrupt withdrawal in order to minimise and reduce the effect of discontinuation symptoms.
However the purpose of the study described here was to determine whether discontinuation symptoms would emerge if a patient missed doses, therefore abrupt discontinuation was also used in this study. The study did indeed provide evidence of a worsening of symptoms upon discontinuation although this was not entirely in agreement with the study by Hindmarch et al. (2000).

### 5.6.10. Conclusions

Actigraphy remains a relatively cheap non-invasive research instrument to study circadian rhythms and sleep wake activity patterns (Morgenthaler et al., 2007b) and has been suggested as an alternative to PSG although with some limitations (Morgenthaler et al., 2007a; McCall and McCall, 2012). The actigraphy results from the study reported here, are associated with improvements in depression and cognitive and psychomotor performance, and are thus a useful adjunct to the effect of SSRIs on depressed patients as a continuous objective indicator of the outcome of treatment on sleep and activity where PSG would be impracticable.

The main effects found in the study were that the SSRIs did not improve actigraphic sleep variables indeed the change in variables showed that overall sleep efficiency reduced and the number of sleep bouts increased. This is in agreement with PSG findings as it is known that SSRIs reduce REM and increase REM latency as reported in reviews by Wilson and Argyropoulos. (2005) and Wichniak et al. (2012). Changes in SE and number of sleep bouts, which are measured from activity counts, could be due to a reduction in REM, so theoretically a reduction in REM would increase activity.

There was no significant difference between treatments for any of the actigraphic sleep variables; neither did any treatment improve actigraphic sleep variables during the 12 weeks of chronic administration. Slight differences in the actigraphic profiles of each SSRI were however recorded; the actigraphic sleep of patients on paroxetine and fluoxetine treatment was disrupted more than those treated with sertraline. There was also a significant increase in number of sleep bouts for all treatments and a trend for reduced sleep efficiency following paroxetine and fluoxetine treatment.

Circadian rhythm NPCRA and cosinor variables for the 12 week analysis similarly failed to show any significant differences between the treatment groups. Although activity levels for paroxetine were lower than either fluoxetine or sertraline treatment, patients treated with paroxetine or fluoxetine also increased their activity levels in M10 and 24 h average. There
was a significant improvement of the percentage rhythm over time for all treatments for the 12 week data which indicates that the sleep/wake rhythm was less fragmented. A trend for a circadian delay in timing was also reported with the acrophase time occurring slightly later in the biological day which suggests that as depression was alleviated patients became more active and that this occurred later in the day.

The depression questionnaires MADRS, HAMD and ZUNG all signified that depression was significantly relieved for all treatments. Furthermore, in contrast to the actigraphic sleep variables the sleep items from MADRS and HAMD showed that patients felt that their sleep was improved which was also reflected in significant improvement in the LSEQ items, GTS, QOS and BFW. In addition LARS sedation was significantly relieved with all patients feeling more alert and less fatigued, which was also significant following paroxetine and fluoxetine treatment. The improvement in LARS although not reflected in improved sleep was reflected in increased daytime activity and improved circadian profile.

Patients’ cognitive skills were also improved for all treatments with significant reductions in CRT overall reaction times and significant improvement in CFF. Although no significant differences between treatments in CFF or CRT were found, significant improvements were recorded following treatment with sertraline in reaction times. All patients felt significantly less clumsy and more in control from the CFQ questionnaire, but there was no significant difference between treatments, each treatment significantly improved patients’ perception.

With regards to discontinuation from treatment, there was no significant difference between treatments. Only the MADRS sleep item was adversely affected and significantly worsened, patients felt that they had less sleep. This was confirmed with the actigraphic sleep variables where there was a significant reduction in timing with reduced TIB, SPT and TST and yet a trend for improved QOS was suggested with LSEQ. However, for any treatment, the daytime activity variables, AWM, amplitude, mesor, average activity and M10 activity all significantly increased following discontinuation.
CHAPTER 6 GENERAL DISCUSSION

6.1. Introduction

Treatment of disease with psychoactive medication may impact on a patient’s well-being to a greater or lesser degree, either acutely following administration or chronically when continuously administered over longer periods of time or both. These effects may be manifested in a variety of different ways depending on the disease, whether it is chronic or acute, how severe the condition is and its impact on everyday functions. Combined with the symptoms of the disease the medication may, in addition, cause unwanted side effects which may prevent the patient continuing with the recommended treatment.

Chronic long term mental diseases such as anxiety, depression, insomnia, schizophrenia, SAD and bipolar depression, are all likely to have an impact on sleep and daytime functioning and may also cause circadian desynchrony (Section 1.6.1). Psychoactive drugs, which are prescribed to treat these conditions, are designed to improve the symptoms, improve daytime functioning and may also be given to alleviate the problems of poor sleep which can have a negative impact on recovery. In addition disease such as fibromyalgia, arthritis rheumatism and painful diabetic neuropathy cause pain which may affect patients sleep and therefore daytime functioning.

Psychoactive compounds including pain relief may impart positive or negative side effects, they may cause sedation, impair everyday functioning, reduce activity or they may be alerting and improve mood and increase activity (Section 1.6.2). In addition, they may impact on sleep by increasing or reducing the amount of sleep, or affecting the sleep profile and architecture all of which may influence patients’ daytime functioning, well-being and long term outcome of recovery. To study the effect of these psychoactive compounds on a patient’s or participant’s 24 h activity profiles is a useful adjunct to the set of cognitive and psychometric assessments usually employed for monitoring the effects of CNS drugs in Phase 1 clinical trials.

In summary the main findings of the studies conducted for this thesis were that:

- Actigraphy was able to follow the acute time-course of psychoactive compounds in healthy participants.
• The impairing effects of the psychoactive compounds on cognitive and psychomotor function in acute studies were mirrored in reductions in actigraphic activity and increases in 'sleep-like' activity.

• Following acute dosing actigraphy was able to show changes in actigraphic sleep variables in healthy participants.

• The significant improvement in patients depression scores in the chronic antidepressant study was reflected in their perception of subjective improvement in sleep quality.

• The subjective improvement in patients sleep was inversely reflected in actigraphic sleep variables, manifested as an increase in movement during sleep.

• The trend for a rise in daytime activity levels suggested a link in line with the improvement in depression scores.

• Changes in actigraphic activity were observed during the abrupt discontinuation of antidepressant treatment.

6.2. Actigraphic activity

By definition a psychoactive compound is one that crosses the blood brain barrier and therefore impacts on functioning whether that manifests itself in mood changes, alerting effects or causes drowsiness and lack of co-ordination. Any drug effect that impacts on motor skills can be measured by actigraphy. By employing algorithms to calculate an assortment of variables the outcome of these psychoactive compounds on activity profiles can be measured and by dividing the 24 h day into the sleep and wake periods the effect on actigraphic sleep and daytime activity may be determined. In addition the effect and impact on the 24 h circadian rest-activity rhythm can also be measured.

Whether the effect to be measured is acute as in the case of a potent psychoactive compound in a single dose healthy participant controlled clinical trials Chapters 3 and 4, or chronic as in long term studies with patients in their own environment (Chapter 5), actigraphy may provide valuable additional information on the impact of medication on activity. There are various methods with which activity can be measured and evaluated, for example in raw activity counts over time or conversion of those activity counts to 'sleep-like' activity when the counts are below the sleep/wake threshold (Section 1.2.6). Time periods can be set to minimise or avoid the influence of alerting periods when tests are being performed to determine the real effect of the psychoactive compound on the activity profile (Section 3.5.2 and Section 4.5.2).
6.3. **Actigraphic sleep**

Traditionally sleep has been recorded with PSG and although this may provide an indication of the impact of medication on sleep architecture it is out of context with everyday life. Medications used to treat sleep complaints or those that affect sleep are first tested on healthy participants in controlled surroundings with the gold standard PSG sleep assessment and this may give an indication of the impact on sleep architecture. On the other hand, it is the effect of medication on patient’s sleep and activity in their own home environments that are important to define and might determine whether a patient would remain on or stop medication. Although not actual sleep, actigraphy provides an alternative method of unobtrusively examining the sleep wake profile, in both laboratory and home settings, and for determining effects which can be correlated with sleep architecture. The overall aim of the thesis was to investigate whether it was possible to identify and measure drug-induced changes in activity, actigraphic sleep and the rest-activity profile following acute and chronic administration of different classes of psychoactive drugs using actigraphy.

6.4. **Comparison with cognitive and psychomotor tests**

When conducted in combination with cognitive and psychomotor performance, changes in activity recorded by actigraphy can be correlated. By comparing the positive or negative effects whether in the acute phase of treatment or, during chronic dosing, the likely impact of the treatment medication on cognition as well as activity and actigraphic sleep can be determined.

Cognitive and psychomotor tests have long been established as mechanisms for assessing the impairment of psychoactive compounds (Section 1.3.1). Tests however, are snapshots of time usually employed to cover the time of maximum impact on a participant or patient as in acute dose studies. In addition they can be used to measure hangover effects and for chronic studies to assess the long term effects of treatment and whether that treatment is effective. By comparison with subjective rating questionnaires for quality of sleep, mood, sedation and cognitive impairment the associated effects on actigraphic activity levels can also be determined.

6.5. **Acute studies**

6.5.1. Chapter 3

To study the acute effects of psychoactive medication on the activity and sleep profile of healthy participants, the benzodiazepine LZP was compared with placebo, in Chapter 3. The
controlled study showed that there were significant differences in the actigraphy data between placebo and LZP. There was a statistically significant reduction in activity during the acute phase after dosing with LZP compared with placebo, which correlated with a significant performance impairment of the cognitive and psychomotor tests. In addition participants felt sedated according the LARS sedation rating.

Other authors (Kiang et al., 2003; Takahashi et al., 2003) have also reported significant reductions in activity after dosing with psychoactive medication. These studies, however, have used larger time episodes than the LZP study and ranged from 6 to 24 post dose. The use of bigger time episodes may not allow for direct comparison and correlation with frequent testing of cognitive and psychomotor performance, although they do provide an indication of the overall effect on activity. Neither are they able to map the subtle time course of the medication in relation to the pharmacokinetics, pharmacodynamics or changes in behavioural activity following medication.

In Chapter 3, actigraphy was used to assess the impact on activity caused by the benzodiazepine LZP (2.5 mg) compared with placebo, in comparison with impairment in psychometric tests. The tests used were the choice reaction time (CRT) and continuous tracking task (CTT) which were performed at specific time points across the acute post dosing period. Actigraphic activity in the study in Chapter 3 was recorded in 1 min epochs. Data therefore, could be accumulated and separated into ‘controlled’ activity during the 30 min test points and ‘spontaneous’ uncontrolled activity, between the test points, and therefore map the direct effect of treatment on activity. This finer analysis also allowed for enhanced correlation with the cognitive subjective assessment of LARS and thereby any feelings of sedation.

Reductions in ‘spontaneous’ activity levels during the 5 h acute post dose period closely followed the significant impairment in performance and suggested that actigraphy was able to detect the drug-induced effect seen in cognitive performance (Section 3.5.2). In addition, reductions in activity were also mirrored with the participants’ subjective feeling of ‘sedation’ at 4.5 h post dose.

Allen et al. (1993) also showed that LZP (2 mg) impaired psychomotor performance in healthy participants up to 5 h post dose and similarly O’Neill et al. (2000) showed that LZP 0.5 mg/day significantly impaired psychometric performance at 4 h post. The study in
Chapter 3 therefore confirms these findings and that LZP (2.5 mg single dose) significantly impaired psychometric and cognitive effects at 4.5 h post dose.

Furthermore, the morning after dosing, actigraphy was able to detect a significant reduction in activity and therefore indicate a residual impairment. Although the participants did not feel sedated according to the LARS, the psychometric tests for CRT and CTT revealed that they were still significantly impaired (Section 3.5.3). Hangover effects are usually detected by reductions in performance or using tests such as Karolinska Drowsiness Test (KDT) or the Multiple Sleep Latency Test MSLT (Takahashi et al., 2003). This study has therefore shown that hangover effects and daytime sedation can be detected as reduced levels of activity. Moreover, it is important to establish the maximum duration of impairment for patient safety to ensure that a hypnotic taken to aid sleep has no residual or hangover effects the following morning.

In addition to activity counts, the data scored as ‘sleep-like’ increased, and correlated with the time of greatest impairment in performance on the psychometric tests when participants on LZP treatment actually felt more sedated and drowsy, according to the LARS (Section 3.5.2.2). This phenomenon was also referred to as ‘inactivity’ by Roehrs et al. (2000). The finding confirms other researchers (Roehrs et al., 2000; Kawahara et al., 2002; Kiang et al., 2003) who have used similar methods to examine reductions in daytime activity.

Thus such data analysis procedures could be used to determine ‘daytime sleepiness’ as an overall reduction in activity levels not associated with actual sleep but in relation to feelings of ‘sedation’. This concept was previously described by Stanley and Hindmarch. (1997), and shown in studies conducted into the effects of antihistamines and sedating antidepressants.

A significant reduction of activity at the beginning of the sleep period during the first half-hour of the time in bed, in the LZP study, was also detected with actigraphy. These data confirm that of Mattmann et al. (1982) (Sections 1.4.3 and 1.4.4) who also showed that nocturnal motor activity was reduced and reductions in daytime activity were verified by subjective sleepiness and impaired performance following benzodiazepine administration. Borbély et al. (1983) similarly reported that night-time activity was significantly reduced compared with placebo showing the hypnotic and residual effects of triazolam and midazolam.
During the sleep period actigraphy was able to detect the sedative effects of the anxiolytic-hypnotic drug LZP on changes in sleep variables, with increased sleep efficiency, a sleep variable common to PSG (Section 3.5.2.4). Actigraphy was also able to demonstrate a reduction in movement during sleep, caused by the action of the LZP, resulting in a significant reduction in the number of sleep bouts and increase in sleep bout time. Therefore actigraphy was able to provide an indication of the clinical effects of medication on sleep.

Studies have shown that LZP alters PSG sleep architecture (Section 1.4.4.1) (Grözing et al., 1998; Saletu et al., 1990) as determined by reducing sleep latency, number of awakenings, Stage 1 and REM sleep, whilst increasing TST and Stage 2 sleep. Although actigraphy is not able to identify changes in sleep stages or architecture the study in Chapter 3 did show an increase in actual sleep percent, longer sleep bout times, and reductions in the number of wake bouts (Section 3.5.2.4). This study clearly indicates actigraphy can provide a less expensive, non-invasive alternative for detecting changes in sleep due to the effect of a drug.

6.5.2. Chapter 4

Actigraphy was further used in Chapter 4 to assess the impact on activity associated with the impairment caused by the psychoactive antihistamine promethazine in psychometric tests in comparison with placebo. As in Chapter 3 the tests performed were the choice reaction time (CRT) (Hindmarch, 1980) and continuous tracking task (CTT) (Hindmarch et al., 1983) which were performed at specific time points across the 12 h day together with LARS (Hindmarch and Gudgeon, 1980) to measure subjective sedation. These tests have been shown to be sensitive to the CNS impairing effects of the antihistamine promethazine (Hindmarch et al., 2001a, 1999).

Actigraphic data were treated in the same way as the methods described in Chapter 3. Data were accumulated and separated into ‘controlled’ activity during the test points and ‘spontaneous’ uncontrolled activity, between the test points, to map the direct effect of treatment on activity. There was evidence of a significant impairment in cognitive and psychomotor performance up to 9 h following a single dose of promethazine (25 mg) compared with placebo (Section 4.5.5). Activity levels, however, although lower than placebo, were not statistically significantly reduced (Section 4.5.1). The performance of the tests coupled with the wheal and flare assessments, when activity was restricted and controlled, covered a large part of the time, which could therefore account for the lack of
available spontaneous time when activity was not restricted. Moreover the alerting effects of the performance of the tests might have impacted on the activity levels.

To limit the effects of the tests, activity data were separated into periods when the tests were not being performed, and activity was not controlled. This ‘spontaneous activity’ data accounted for the last 15 minutes of each hour. Post-hoc analysis revealed a significant reduction in activity levels between 5-8 h post dose (Section 4.5.2). This supports the evidence that promethazine 25 mg reduced daytime activity measured by actigraphy at 6 h post dose and impaired psychomotor performance (Stanley, 1997; Hindmarch et al., 1999). This reduction was also associated with significant subjective sedation, as measured by LARS. The participants in the Chapter 4 study similarly reported feeling sedated with a significant effect of LARS sedation overall and up to 9 h after dosing.

Psychometric tests, conducted at +1, +3, +6, +9, and +12 post dose, were more spread out to cover the pharmacokinetic effect of promethazine, than the LZP study when tests were conducted hourly. This regime of tests meant that participants had theoretically more ‘spontaneous’ time. The time taken for each test point however, was greater, which restricted the opportunity for actigraphic assessment of spontaneous time. Nevertheless, the activity counts in the epochs were reduced to very low levels which were calculated as being ‘sleep-like’ being under 40 counts per 1 min epoch.

It was also established that this ‘sleep-like’ activity during the 12 h post dose period was significantly increased following promethazine administration compared with placebo with significant effects at 5 h and 6 h post dose. This timing coincided with the $T_{max}$ (2–8 h) (Strenkoski-Nix et al., 2000) of the drug and when the impairment of the psychometric tests was greatest. From these data it was clear that promethazine increased the amount of ‘sleep-like’ behaviour and that this persisted for up to 6 h after dosing.

Actigraphy was therefore able to demonstrate that there was a significant increase in ‘sleep-like’ behaviour in the acute phase of treatment immediately following day-time dosing and that this effect, as with the LZP study, was mirrored in the impairment of the psychometric tests and in LARS participant reported sedation.

When given 1 h prior to sleep at night promethazine is known to increase TST and reduce the number of awakenings (Adam and Oswald, 1986). Promethazine, in the Chapter 4 study, was administered in the morning to allow the psychometric tests and wheal and flare
assessments to be conducted during the day. Thus it is likely that the bedtime sedating effects had diminished and therefore no difference in the actigraphic sleep variables was reported compared with placebo. It is also interesting to note that although there was no effect on actigraphic sleep variables, there were significant reductions in activity observed at 11 h post dose, which could indicate that if taken at night there might be a hangover effect of medication the following morning.

Although actigraphy was unable to detect overall significant impairment in activity levels associated with promethazine, significant impairment in cognitive and psychomotor tests was recorded. Greater reductions in spontaneous activity and increases in sleep-like activity may have been masked by the test regime, although an effect was detected with actigraphy following post-hoc analysis. The study therefore supports the evidence from Stanley. (1997) who measured actigraphic ‘sedation’ following promethazine administration with significant reductions in activity up to 6 h post dose. The study in Chapter 4 therefore provides additional evidence of the usefulness of actigraphy in studying the subtle and unobtrusive effects of sedating compounds.

6.6. Chronic study

The studies in Chapters 3 and 4 were performed under strictly controlled conditions, on healthy participants with standardised validated tests and procedures. LZP and promethazine were used as comparator drugs for the study drugs because of their known effect on the tests and actigraphy was able to show the continuous profile of the medication in association with the time limited tests. Participants adhered to the strict protocol sleep restrictions which confirmed that they were not sleep deprived so that any changes to their sleep and activity could be ascribed to the medication.

The psychoactive medications used in Chapters 3 and 4 are however, generally prescribed to patients to treat chronic conditions. LZP is prescribed to treat anxiety and promethazine for allergic rhinitis. Furthermore, as these compounds have known sedating and impairing properties they are often used as study comparators to test the effect of new medications. They afforded therefore ideal opportunity and conditions in which to test the theoretical aspect of using actigraphy to record changes in the activity profile in association with psychometric tests.

To study the effect of the medication on the activity profile of the patients with these conditions in their own environments would be beneficial, since the sedative effects of
medication could be hazardous and potentially lead to accidents and it is important to rigorously assess long term effects rather than base conclusions on a narrow time frame. Studying the effect of medication over longer periods of time on patients is more problematic than acute studies.

Changes in sleep can be recorded in the patient population by PSG but it is expensive and time consuming. Even if the recording is conducted in the patient’s home it provides only a portion of the 24 h picture. Whilst PSG is useful for determining the night-time effect of a drug it does not provide information on the effects of medication on daytime functioning and on the 24 h circadian sleep wake activity profile. Actigraphy may therefore provide a less expensive real-life alternative to PSG.

As a continuous measure actigraphy can be conducted over an extended period of time, to acquire activity data in the patient’s natural environment. It can provide objective information on sleep quality, daytime activity or inactivity and an indication of circadian rhythmicity. In association with subjective questionnaires and cognitive and psychomotor tests it is able to add to the information and evidence to deliver the complete picture of the effects of medication in patient groups.

Actigraphy requires little effort from patients or participants which may be particularly important when studying certain population groups. For example depressed patients might find participating in a long antidepressant sleep study with PSG onerous, and may be more likely to withdraw or not comply with study restrictions. Actigraphy therefore provides a means of continuously recording the sleep and wake activity, whereby subtle changes can be observed.

The present study detailed in Chapter 5 investigated whether the use of actigraphs would provide an objective measure of the ‘in the field’ long term chronic effects of medication. In order to determine whether actigraphy would be able to contribute to the measurement of the long term chronic effect of medication it was necessary to compare the outcomes of the other diagnostic assessments of depression and sleep with questionnaires, as well as cognitive and psychomotor assessments. It was important to assess whether the outcomes described above showed changes with the depression status of the patients, and if any changes correlated with the actigraphy data.
The benefit of actigraphy in long-term studies was particularly evidenced in Chapter 5, the 14 week randomised, double-blind study of the effects of paroxetine 20 mg/day, fluoxetine 20 mg/day or sertraline 50 mg/day on depressed patients with actigraphy. This was the first study to investigate the effect of SSRI antidepressant treatment on the time course and duration of action on activity in depressed patients with actigraphy in conjunction with subjective questionnaires and cognitive and psychomotor performance. Patients diagnosed with depression with a MADRS score ≥ 20 were recruited to the study. Assessments were conducted at regular defined interviews and actigraphic activity was continuously monitored. In addition during week 13 medication was abruptly discontinued and replaced by placebo, for a week, to mimic the effect of patients missing doses, followed by a further final week on SSRI treatment. The detailed findings and comparisons with other authors are discussed in full in Section 5.6.

6.6.1. Actigraphy

6.6.1.1. Actigraphic sleep variables for the 12 week actigraphy study

The current study in Chapter 5 was the first to report on a 14 week actigraphy study comprising 12 weeks of antidepressant treatment, 1 week of abrupt discontinuation followed by 1 week reintroduction (Dawson et al., 2010). Actigraphy data were analysed for sleep variables from Day 1 to week 14 (Day 98 approximately) continuously, week 1 to week 12 and weeks 12 and 13 to cover the discontinuation period (Section 5.4.3). Weekly means for the data were then calculated and analysed.

Given that the 14 week data included night 1 when it was not known whether patients had administered medication and the confounding discontinuation period only the results for the 12 week chronic study and the separate discontinuation period will be discussed in this section. Concise details of the 14 week findings and comparisons with other authors are discussed in full in Section 5.6.

There was no overall significant effect of time or treatment for sleep latency although the data suggests that there was a trend for SOL to increase during treatment with paroxetine and sertraline. This interestingly conflicts with patient’s perception from HAMD and LSEQ that insomnia early and GTS were improved, but supports clinical PSG findings that SSRIs increase sleep latency as they are activating compounds (Trivedi et al., 1999; Hicks et al., 2002; Jindal et al., 2003).
Furthermore, there was a significant deterioration in actigraphic sleep quality during the 12 week treatment analysis, for all treatments overall with significant reductions in sleep efficiency and increased number of sleep bouts across time. In addition patients treated with paroxetine also showed a significant reduction in TST. The reason for this discord is unclear but Winokur et al. (2001) suggested that SSRI s have a calming anxiolytic effect which encourages the perception of improved sleep, coupled with an activating effect, and additionally Wichniak et al. (2012) reported that hypnotics are often co-prescribed with SSRIs to aid sleep.

Daytime activity as average wake movement (AWM) although not significant appeared to increase from week 1 for all treatments. The values for paroxetine were lower which, could reflect that paroxetine has a more sedating effect compared with other SSRIs (Ables and Baughman, 2003). This increase in AWM was positively linked to a trend for improvement in LSEQ ‘behaviour following wake’. If patients actually felt that they slept better they might be in a more productive mood and more active the following day.

During discontinuation daytime actigraphic activity as average wake movement (AWM) was significantly increased, particularly after fluoxetine and sertraline withdrawal suggesting that patients were more active during the day. This might imply that throughout treatment the antidepressants were having a calming effect by reducing daytime activity but on discontinuation patients were more active, or maybe removal of medication led to hyper-arousal and activation. Patients did not report a worsening of either awakening from sleep (AFS) or behaviour following wake (BFW) from the sleep questionnaire LSEQ, although patients discontinued from paroxetine treatment felt more sedated according to the LARS sedation component.

There may be different conclusions to be drawn regarding the changes in actigraphic sleep variables during discontinuation of treatment. Without baseline, comparison of patients’ actigraphic sleep before and after treatment cannot be made. Additionally without PSG to confirm the changes in sleep architecture, increased movement in sleep may indicate more disrupted sleep or that the changes in activity could be related to changes in sleep architecture and REM in particular. When fluoxetine is withdrawn there appears to be more activity in sleep but patients did not report sleep worsening. In contrast patients withdrawn from paroxetine reported worsening but their activity appeared to fall. It could be that patients on fluoxetine or sertraline were having some negative effects whilst on maintenance therapy which was alleviated when medication was stopped or that the half-life of the
medication continued to have an effect. Alternatively with their active metabolite it could have meant the therapeutic effect continued to have an effect thereby reducing the effect of abrupt discontinuation. Staner et al. (1995) showed that withdrawal of paroxetine increased REM. This effect might be reflected as a reduction in actigraphic activity, as was observed in the current study in the total activity counts in sleep. In addition paroxetine has a shorter half-life compared with sertraline or fluoxetine which could account for a rebound effect and worsening of REM, SOL and GTS.

6.6.1.2. Circadian analysis

Activity data were combined into seven day weekly blocks which included weekends to provide the arithmetic means on a week by week basis. Weekly means were compared with subsequent weeks and relative changes calculated. Data were analysed by both the cosinor and NPCRA analysis programs (Section 1.6.9.1 and Section 1.6.9.2, respectively).

6.6.1.3. Cosinor (parametric) analysis and treatment

No other study, to the author's knowledge, has investigated the impact of chronic SSRI antidepressant treatment on the cosinor rhythms of depressed patients. Analysis revealed that there was an overall significant improvement of the percentage rhythm over time for all treatments for the 12 week data, with the percentage rhythm increasing (Section 5.5.5.3). This indicated that the sleep wake rhythm was improving and stabilising with treatment and becoming less fragmented and more organised. This might be a beneficial outcome for the patient, with their sleep wake pattern being more regulated.

Increases in the mean activity for amplitude and mesor, suggested that patients were becoming more active as treatment progressed, although this did not reach statistical significance during the 12 week analysis for any treatment. Interestingly, this trend confirms the increase seen in the AWM actigraphic variable, which only focuses on daytime activity and not the 24 h mean.

An indication that as treatment took effect, and patients felt better according to the MADRS, they were more active later in the day, observed by a delay in the acrophase time, which occurred slightly later in the biological day. However this effect appeared to reverse from about 4 weeks onwards as treatment with paroxetine progressed. These aspects are very small in time, being less than 30 minutes, but worthy of further investigation.
There are very few studies to compare these SSRI effects and what they mean in terms of depression however a study of seasonally affective disorder (SAD) patients showed that baseline amplitude was reduced and acrophase phase delayed compared to healthy controls (Winkler et al., 2005). Following treatment with 4 weeks of Bright Light Therapy (BLT), patients' amplitude increased and almost normalised to healthy control levels, as depression improved. In addition BLT led to a phase advance in acrophase time occurring earlier in the biological day. Actigraphic variables were also reported and after 4 weeks of treatment AWM and SE had also improved. A study of major depressive disorder (MDD) inpatients (n = 26) conducted by Raoux et al. (1994), showed that 6 patients shifted their acrophase time by more than 1 h, following treatment with TCAs. Interestingly, of those patients two with the earliest phase, delayed, and the one with the latest phase, advanced.

During the discontinuation week for all treatments, the trait of the advancing clock timing was reversed, with an abrupt delay of approximately 30 min in the acrophase time. This was statistically significant following fluoxetine withdrawal and associated with significant increases in amplitude, mesor and percentage rhythm. Why this happened on fluoxetine withdrawal is unclear but worthy of further examination as to the true meaning of fluoxetine abrupt discontinuation on cosinor variables. These effects were associated with the improvement in subjective outcomes of MADRS and HAMD depression scales, as well as improvement in psychomotor function.

In depression, in theory, as REM sleep is increased, activity would be reduced, then depression improves REM sleep is reduced and activity increased. During the 12 week chronic phase in the Chapter 5 study there was an increase in total activity counts in sleep and in sleep bouts indicating more movement which appeared in all treatments. Upon discontinuation of paroxetine less activity was seen which could mean that this effect was reversed with possible recurrence of REM. A worsening of MADRS and MADRS sleep scores also showed a possible rebound effect.

More activity was recorded in total activity counts in sleep following withdrawal from fluoxetine and yet MADRS score was improved. This might indicate that there was a further reduction in REM and as fluoxetine has a longer half-life the effect of fluoxetine continued or that depression had been alleviated. This explanation assumes that although the depressed patients in the current study complained of sleep problems according to MADRS, as PSG was not conducted it is not known whether they actually had the altered sleep architecture associated with depression before treatment began.
6.6.1.4. Non-parametric circadian rhythm analysis (NPCRA) variables

The NPCRA data analysis for the 12 week analysis, failed to show any significant differences between treatments for any variable. M10 activity levels for paroxetine were again much lower than either fluoxetine or sertraline treatment throughout. Patients treated with paroxetine or fluoxetine increased their M10 and 24 h average activity levels, whereas activity levels for patients treated with sertraline showed a slight decline throughout the 12 week period. The increase in average activity and the M10 activity, however, agree with observed increases in the AWM actigraphic sleep variable. Mean M10 activity levels have been reported to increase in patients treated with agomelatine (a melatonergic antidepressant) but decrease in those treated with sertraline between week 1 and week 6 in an antidepressant study by Kasper et al. (2010). This confirms the effect of sertraline seen in the study reported in Chapter 5.

A disturbance in the sleep-wake rhythm results in a low RA as shown in Alzheimer’s patients (Van Someren et al., 1999), whereas higher values indicate a rhythm of higher amplitude (Berle et al., 2010; Calogiuri et al., 2013). The RA levels would theoretically increase with an improvement in depression, as daytime activity levels increase. In the present study however, the RA levels at inclusion were already relatively high and remained fairly constant throughout the study. This could indicate that overall patients were more active during the day. Interestingly the RA levels for the patients on paroxetine were consistently lower than patients on fluoxetine or sertraline, which might be explained by the lower activity levels during the day.

Furthermore the baseline RA values of patients in the Chapter 5 study were higher than those in the Kasper et al. (2010) study. Patients in the current study reported in this thesis had higher initial baseline amplitudes and less disrupted rhythms. In addition the inclusion HAMD scores of patients in the Kasper et al. (2010) were, by comparison, greater than the MADRS score for inclusion and suggested that their patients were more depressed.

As has been reported there was a delay in cosinor acrophase time observed in the current study (Section 5.5.5.4). There was also a trend towards a significant delay in the NPCRA M10 onset time for all treatments occurring later in the day, by a mean of approximately 30 minutes, with a trend towards a significant delay for the sertraline group. The M10 onset time delay confirms the delay in acrophase time reported in the cosinor analysis. This suggests that as treatment took effect patients were more active during the day, and that the
onset of activity occurred later, and was associated with improvements in the depression scales, activity increased as depression lifted.

During the L5 time in the study reported in Chapter 5, activity levels were similar throughout treatment for all patients. Activity levels for patients treated with paroxetine were a little higher (non-significant) than fluoxetine or sertraline indicating that perhaps paroxetine had a disrupting influence on activity during sleep. Even though these results were not significant the current data trends are worthy of further investigation in conjunction with different types of depression.

Whether depression affects activity and the sleep / wake timing mechanism, due to its adverse effect on sleep, or that depression leads to desynchrony, or whether the irregularity causes the depression is unclear. The reason for the improvement in mood and alertness in the Chapter 5 study could be connected to a delay of circadian timing as shown by the delays observed in the onset times, which is associated with an increase in M10 activity levels.

There was an overall significant effect during discontinuation with increases in average activity, amplitude and M10 activity coupled with an advance of the L5 onset time, occurring earlier in the night. These factors were also significant for fluoxetine and might indicate that circadian desynchronisation was normalising on withdrawal and that patients were no longer depressed as the MADR and HAMD scores did not rise significantly.

There was no significant change however in the IS or IV over the 12 weeks of chronic treatment overall. Values reported from other studies (Section 5.6.5.6) indicated that patients’ rhythms in the Chapter 5 study were reasonably stable even at baseline.

6.6.1.5. Circadian summary

There was evidence that daytime activity levels as M10, average activity and AWM increased in association with improvement in depression rating and sleep questionnaires. It is likely that the activity of most of the patients in the current study was to some extent controlled by external factors therefore it might be difficult to see obvious changes in circadian NPCRA compared with studies conducted in hospitalised patients whose activity is not so controlled. These analysis methods do allow for different aspects of actigraphic activity to be reviewed, and are worthy of further investigation.
6.6.2. Questionnaires

6.6.2.1. Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAMD) and ZUNG

The depression questionnaires MADRS and HAMD, administered by the local physician, were used to assess improvement in depressive symptoms and the ZUNG depression questionnaire was completed by the patient. The MADRS, HAMD and ZUNG scores (Section 5.5.7) all showed that patients responded well to treatment, with statistically significant improvement in depression scores. By week 14 patients were considered to be ‘in remission’ according to the MADRS score. There was no statistically significant difference between treatments. These findings are in agreement with similar 10 to 16 week studies with similar medications (Fava et al., 2000, 2002) (Section 5.6.3).

Discontinuation symptoms are a recognised outcome of abrupt SSRI withdrawal which can lead to a rebound and resumption of depression symptoms. Although the SSRI’s have different pharmacokinetics and half-lives, which could reflect their effect time, depression questionnaires revealed that although there was a slight increases in scores following paroxetine withdrawal on HAMD, and following paroxetine and sertraline withdrawal on MADRS, this was not statistically significant for treatment or time (Section 5.5.7). This differs to Rosenbaum et al. (1998) where both MADRS and HAMD scores of patients treated with paroxetine or sertraline, after one week treatment disruption, were significantly higher compared with fluoxetine.

Although the SSRIs are not prescribed for aiding sleep and PSG studies have shown that they have a deleterious effect on sleep, by improving depression, perception of sleep may improve. The MADRS and HAMD sleep-related questions indicated that for MADRS, patients’ sleep duration or depth of sleep was significantly improved for all treatments by week 12 with a significant effect for paroxetine. The HAMD sleep item also indicated that, patients felt that their sleep was statistically improved (again significant for paroxetine). This was also seen in the sleep component of HAMD in ‘early insomnia’ associated with SOL for all treatments overall (again significant paroxetine).

These improved sleep aspects of both questionnaires contrast with no improvement in actigraphic sleep variables, paradoxically these worsened. Perhaps the effect of the SSRIs was to normalise sleep architecture impaired by depression. The HAMD findings substantiate the improvements reported in the Fava et al. (2002) study with the same SSRIs.

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During the abrupt discontinuation week scores were significantly worsened for the MADRS sleep component for paroxetine and sertraline. A similar worsening was seen in HAMD with a rebound effect and an increase in scores for paroxetine and sertraline.

Patient-reported depression with the ZUNG provided similar improvements with reductions in scores to HAMD and MADRS. This finding supports comparable data with similar improvements in ZUNG and MADRS (Aguglia et al., 1993). During discontinuation self-rated depression following paroxetine worsened confirming the results obtained by Hindmarch et al. (2000a).

6.6.2.2. Leeds Sleep Evaluation Questionnaire (LSEQ)

In Chapter 5 the Leeds Sleep Evaluation Questionnaire (LSEQ) showed that ‘getting to sleep’ (GTS) was significantly improved overall for the 12 weeks of chronic treatment. Subjective GTS is comparable to actigraphic sleep latency but this was not improved. ‘Quality of sleep’ QOS was also significantly improved whereas actigraphic variables indicated sleep was worsened with increases in sleep bouts, activity and WASO.

No effect of ‘awakening from sleep’ AFS, was observed, none of the treatments adversely affected the patients’ ability to wake up indicating that there was no hangover effect. Reduction in ‘behaviour following wakening’ BFW indicated a trend for improvement overall, all patients feeling more alert and less clumsy.

There was no overall statistical difference between treatments during discontinuation for any of the LSEQ variables apart from QOS scores with a trend for improvement following withdrawal from fluoxetine and sertraline. Although there were indications that patients withdrawn from paroxetine experienced a worsening of GTS and AFS, this was not significant. Discontinuation of sertraline treatment on indicated a trend for improvement.

Paradoxically increased actigraphic sleep latency was not associated with ease of ‘getting to sleep’ neither were increased sleep bouts and actigraphic sleep activity with ‘quality of sleep’. The reason for the discord may be related to the patients’ perception of improved sleep following treatment with LSEQ and actigraphy, or that additional movement did not actually impair their sleep or cause them to wake. Winokur et al. (2001) suggested that SSRIs have a calming anxiolytic effect which encourages the perception of improved sleep and Wichniak et al. (2012) reported an activating effect with SSRIs.
6.6.2.3. Line Analogue Rating Scale (LARS)

At baseline, patients felt more tired and sedated or lethargic than before they were depressed. Scores were all significantly improved for the 12 weeks analysis overall which indicated that all patients felt more alert as treatment progressed and no significant difference between the three treatment groups was reported.

LARS worsened after paroxetine withdrawal, but this was still lower than baseline, whereas discontinuation from fluoxetine or sertraline showed little change. LARS feelings of sedation after paroxetine withdrawal contrasted with actigraphic variables with increased activity. Maybe the increase in activity made the patients feel more tired or their disrupted sleep increased fatigue. Worsening of LARS was associated with worsening of QOS in LSEQ. These findings confirmed those of Hindmarch et al. (2000a) who reported that paroxetine increased sedation scores.

6.6.2.4. Cognitive Failures Questionnaire (CFQ)

Baseline CFQ values indicated cognitive impairment, but by week 12 scores were significantly improved and comparable to control participants from other patient studies (Fairweather et al., 1999). Patients felt more co-ordinated and alert and more able to perform simple everyday tasks without impairment in memory, attention and motor function.

During paroxetine discontinuation scores increased, but not significantly. In contrast scores following fluoxetine and sertraline discontinuation reduced. As these effects were not significant, impact on the CFQ scores indicated that patients were not adversely affected in their ability to maintain normal functioning.

6.6.3. Critical Flicker Fusion (CFF) and Choice Reaction Time (CRT)

Patients’ cognitive function was significantly improved for all treatments in the 12 week study (Section 5.5.7). Both CFF and CRT total reaction time, were improved from baseline most of the effect occurring in the first 8 weeks of treatment, after which the effect plateaued. Fairweather et al. (1993), and Kerr et al. (1993) also showed that fluoxetine improved CFF performance in depressed patients over 6 weeks and Alexander et al. (1997) demonstrated that paroxetine significantly improved CFF threshold over 6 weeks. There is limited evidence of the effects of long term use of sertraline in depressed patients on CFF or CRT. This study therefore addresses this gap in knowledge and shows that sertraline also had a statistically significantly positive effect with a CFF elevation in threshold, and a
statistically significant reduction in total reaction time in CRT. This clearly demonstrates that the SSRI antidepressants improved cognitive function as depression was improved.

Discontinuation from paroxetine, however, significantly worsened total reaction time of CRT whereas discontinuation from sertraline significantly worsened CFF processing. A study by Hindmarch et al. (2000a) investigated the effect of brief discontinuation of the same SSRIs on CRT and CFF but no effect on CFF processing was reported for any treatment in contrast to the current study. All treatments increased reaction time, with a greater increase in time with patients discontinued from paroxetine. This was in contrast to the Chapter 5 study where reaction times significantly increased only with paroxetine withdrawal, whereas reaction times were not impaired following fluoxetine and sertraline withdrawal. The results from both studies suggest that the consequence of abrupt paroxetine withdrawal causes a worsening of cognitive performance and mood symptoms which may be related to the shorter half-life of paroxetine. Furthermore, the Chapter 5 study also adds to the limited information available of the cognitive and psychomotor performance data outcomes of long term SSRI treatment and discontinuation.

6.6.4. Conclusions

The main effects found in the study were that the SSRIs did not improve actigraphic sleep variables indeed the change in variables showed that overall sleep efficiency reduced and the number of sleep bouts increased. This is in agreement with PSG findings as it is known that SSRIs reduce REM and increase REM latency as reported in reviews by Wilson and Argyropoulos (2005) and Wichniak et al. (2012). Changes in SE and number of sleep bouts, which are measured from activity counts, could be due to a reduction in REM, so theoretically a reduction in REM would increase activity.

The study showed that there was no significant difference between treatments for any of the actigraphic sleep variables; neither did any treatment improve actigraphic sleep variables during the 12 weeks of chronic administration. Slight differences in the actigraphic profiles of each SSRI were however recorded; the actigraphic sleep of patients on paroxetine and fluoxetine treatment was disrupted more than those treated with sertraline. There was also a significant increase in the number of sleep bouts for all treatments and a trend for reduced sleep efficiency following paroxetine and fluoxetine treatment.

Circadian rhythm NPCRA and cosinor variables for the 12 week analysis similarly failed to show any significant differences between the treatment groups. Although activity levels for
paroxetine were lower than either fluoxetine or sertraline treatment, patients treated with paroxetine or fluoxetine also increased their activity levels in M10 and 24 h average. There was a significant improvement of the percentage rhythm over time for all treatments for the 12 week data which indicates that the sleep/wake rhythm was less fragmented. A trend for a circadian delay in timing was also reported with the acrophase time occurring slightly later in the biological day which suggests that as depression was alleviated patients became more active and that this occurred later in the day.

The depression questionnaires MADRS, HAMD and ZUNG all demonstrated that depression was significantly relieved for all treatments. Furthermore, in contrast to the actigraphic sleep variables the sleep items from MADRS and HAMD showed that patients felt that their sleep was improved which was also reflected in significant improvement in the LSEQ items, getting to sleep, (GTS), quality of sleep (QOS) and behaviour following wake (BFW). In addition LARS sedation was significantly relieved with all patients feeling more alert and less fatigued, which was also significant following paroxetine and fluoxetine treatment. The improvement in LARS although not reflected in improved sleep was reflected in increased daytime activity and an improved circadian amplitude.

Patients’ cognitive skills were also improved for all treatments with significant reductions in CRT overall reaction times and significant improvement in CFF. Although no significant differences between treatments in CFF or CRT were found, significant improvements in reaction times were recorded following treatment with sertraline. All patients felt significantly less clumsy and more in control from the CFQ questionnaire, there was no significant difference between treatments, each treatment significantly improved patients’ perception.

With regards to discontinuation from treatment, there was no significant difference between treatments. Only the MADRS sleep item was adversely affected and significantly worsened, patients felt that they had less sleep. This was confirmed with the actigraphic sleep variables where there was a significant reduction in timing with reduced TIB, SPT and TST and yet a trend for improved QOS was suggested with LSEQ. However, for any treatment, the daytime activity variables, AWM, amplitude, mesor, average activity and M10 activity all significantly increased following discontinuation.
6.7. Limitations

There are many issues surrounding the use of actigraphy to consider, the main limitations are described below. Recommendations to overcome some of these limitations are also listed.

6.7.1. Actigraphy limitations and recommendations

Actiwatches have sensors unique to each device; to ensure that data from one period to another is comparable the same watch should be used. The sensors on watches can degrade or break; to ensure that the sensor is accurate they should be regularly calibrated and validated. Sensors also lose time during recording; checking internal clock time markers with computer clocks ensures that real time is recorded accurately.

Actiwatches have finite lengths of recording times, when using the older versions allowance should be made to cover the study with the least number of changes. Different sensors give different activity levels therefore long term studies should ensure that, where possible, the same actiwatch is used for one patient throughout.

6.7.2. Acute studies

In the acute studies in Chapters 3 and 4 data were extracted to compartmentalise the activity data between the tests, this limited the amount of available data. The activating effects of performing the tests could also have impacted on the activity levels and reduced impairment. When using actigraphy to measure acute changes in activity and actigraphic sleep, future studies might consider including additional unrestricted time.

Actigraphy is particularly useful for ensuring participant compliance to study restrictions during the washout period, but they can be removed. Restricting removal ensures continuous record between periods.

6.7.3. Long-term studies

To cover longer studies actiwatches can be set up with larger epochs. Using larger epochs greater than 1 min, however, restricts the ability to calculate some variables which rely on the 1 min activity epoch e.g. fragmentation index. In the case of the antidepressant study different epochs of 1 min and 2 min were used (Section 5.6.9.3). To ensure parity the actiwatch files were edited to the larger 2 min epoch so that errors caused by trying to force 2 minute data into a 1 minute epochs were not introduced. This is not an issue, however, for NPCRA analysis as the data are treated in whole hours.
Actigraphy is currently unable to detect sleep from ‘quiet wake’, when the activity is set at the medium setting, which would be especially useful in clinical situations, better algorithms to detect sleep and wake would be beneficial. Chronic long term studies should in addition incorporate diaries so that bedtimes can be clarified, when markers have not been pressed.

The depression study in Chapter 5 covered all ages from 18 to 84 years, depression occurs at any age; thus dividing patients into different age bands should be considered. Patient numbers were reduced after the exclusion of those not wearing the actigraph, coupled with the confounding factors of patients in real life environments, greater sample sizes might be advised in future to smooth out any outliers. No allowance was made for the type of depression, i.e. whether patients were melancholic with psychomotor retardation, or were anxious with agitation, as these differing activity levels may also have confounded the results. Neither was allowance made for whether patients responded to treatment or not, non-responders again may have affected the outcomes. Depression severity at inclusion was moderate, perhaps in future, include patients with more severe depression and stratify for depression level. The actigraphic activity and sleep variables were not indicative of severely impaired sleep/wake schedules so changes induced by treatment were small.

Baseline activity recordings were not recorded in the depression study Chapter 5 neither was there any placebo run in; comparisons of activity and sleep prior to treatment would be advisable. There was no placebo comparator or comparable sedating antidepressant used, this would have allowed comparisons between activating and sedating antidepressants. The PSG sleep architecture and diagnosis of the patients was unknown, ideally for future studies a sleep PSG baseline should be recorded. In addition post study PSG at 12 weeks and 13 weeks would provide further evidence of changes in sleep architecture with antidepressant treatment.

The study was conducted at different times of the year with varying lengths of daylight (Section 5.6.9.1). It would be interesting to see whether the increasing amount of available sunlight effected the depression levels, as SAD patients are more depressed during the winter months (Winkler et al., 2005). During the current study patients’ recordings were conducted across the clock changes from GMT to BST, in addition holidays such as Christmas and New Year impacted on activities and bedtimes, future consideration of these events is advised. No account was made for morningness or eveningness preferences; this may have affected the circadian timing aspects.
It would be interesting to follow-up the patients after the study 12 weeks of chronic antidepressant medication could be extended after discontinuation or further recording without medication. Ensuring that circadian desynchrony does not re-emerge when pharmacological therapy has ended is important for the long term recovery from depression.

6.8. Further research

The studies presented have highlighted that for both acute and chronic drug studies actigraphy is useful and suggestive of further research. Actigraphic recordings following administration of a variety of psychoactive compounds, and their effects on actigraphic variables in relation to PSG, would be a useful database, not only in healthy participants but also of patients. This could be used as a reference point for clinicians. Studies using actigraphy to measure the ‘sleep-like’ sedative activity of other psychoactive compounds and drug groups are warranted and will be necessary to further validate this method as a useful tool in psychopharmacology.

For depression studies one factor not considered in the current study was the extent of response to treatment, and whether there were actigraphic differences between responders and non-responders. Other studies have looked at this aspect and grouped the patients accordingly (Rosenbaum et al., 1998; Todder et al., 2009).

Further research into the circadian rest-activity rhythms of a variety of mental illnesses including bi-polar and schizophrenia and moreover the different types of depression in patients would be desirable together with the subsequent acquisition of reference recordings. These could be used to not only determine if there are different rhythms in the varied forms of depression but to also build a reference database with which clinicians could compare their patients.

Variables which indicate improvement in rest-activity rhythms could be standardised with ranges of values and a program devised to interpret response and positive outcome (Maglione et al., 2012). It has been suggested that the worse the depression the more disrupted is the rhythm (Burton et al., 2013; Moraes et al., 2013) so to monitor this longer term would be useful, to ensure that not only has resynchronisation occurred but that the positive outcome has been maintained. Maintenance of the improved rhythm is important to safeguard the long term recovery from depression (Courtet and Olié, 2012). Depression is multi-factorial and so continual re-evaluation of depression is essential to determine whether
dose titrating is necessary, if relapse is occurring, whether supplementary medication is required or if psychotherapy with CBT might be useful.

It is accepted that chronobiology (Malhi and Kuiper, 2013) plays an important part in the treatment of depression and to record circadian rest-activity changes with actigraphy might be useful in recognising remission with a return to normalisation of the circadian rhythm. In a series of papers (Malhi et al., 2013a) a holistic approach is suggested which discusses a variety of aspects including diagnosis, treatment and the management of depression (Malhi et al., 2013b; Lampe et al., 2013; Berk et al., 2013). It has been suggested that although melatonin in itself does not have an antidepressant effect, altering circadian timing with melatonin might be (Boyce and Hopwood, 2013). If used in association with SSRIs, light therapy or psychotherapy the clinician may find the use of actigraphy beneficial as an adjunct to determine restoration of circadian rhythmicity (Kuiper et al., 2013).

A review of circadian rest-activity timing using actiwatches with associated delays and advances in depression in general practice would be useful to build on the limited data available. Most studies have been conducted in research groups with small numbers, and focused on patients within drug trials so that the positive outcome of the medication is reported. Other studies have been conducted in short periods of time (e.g. less than 6 weeks) when it is recognised that the depression response is longer (at least 3 months). Thus in future long term actigraphy studies, with larger numbers, to track the time course of treatment up to 6 months, irrespective of the treatment or medication would be useful. A greater understanding of the circadian rhythm and the dis-regulation of sleep might provide new strategies of behaviour or treatment or both (Germain and Kupfer, 2008).

PSG studies have shown that the SSRIs adversely affect sleep and this was supported by the actigraphy data in the current study even though patients felt that their sleep was improved. The correlation between subjective and objective actigraphic sleep is therefore worthy of further investigation.

Clinical trials of antidepressants are varied, with different classes of antidepressants, a variety of outcome variables, long-term use in patients, short-term effects in healthy participants as well as hospitalised patients and patients in their own homes to name but a few, it is difficult for the clinician to draw conclusive evidence of which ones work best. To aid the clinician with a simple non-invasive diagnostic tool such as circadian rest-activity
rhythms with actigraphy might be unrealistic but might help to unravel the interpretation of meta-data and clinical trials (Kirsch et al., 2008; Sussman, 2007).

6.9. Conclusions

The acute studies in this thesis provide evidence that actigraphy is sensitive not only to the acute sedating effects of LZP and promethazine, as measured by a reduction in behavioural activity, but also to the residual effects of the drug the morning after dosing. These studies also confirm that the actiwatch is able to detect the effects of a hypnotic on sleep and is able to provide an indication of the clinical effects of medication. Moreover these studies add further evidence that actigraphy can provide a reliable and sensitive indicator of the time course of action of psychoactive drugs. In both acute studies the data also showed that it was possible to detect changes in daytime activity due to the psychoactive effect of the medication. Actigraphy appears therefore to be a useful adjunct to clinical studies to measure the effect of sedating medication on activity even when confounding cognitive assessments are being performed.

Issues surrounding the use of actigraphy as a tool in clinical research basically centre on the validation of the actigraphy devices including standard operating procedures and methods of recording activity which can be interpreted and standardised as has been the case with PSG (Morgenthaler et al., 2007a). Algorithms to detect sleep and wake, especially during quiet wakefulness, are required as these remain an anomaly within the actigraphy community. In addition, in order to optimise the measurement of activity it is important to consider study design to capture the required variables without interference from confounding factors. Further studies are required to validate different therapeutic interventions in a variety of patient groups (Peterson et al., 2012).

It is often difficult to draw conclusive evidence when comparing different studies because of the different actigraphs used, the differences in the study protocols and methodology, time spans and epoch length, coupled with the development of the device over the last 30 years and the different algorithms to calculate the derived actigraphic variables. Often the limitations of the device, the logistics of the protocols and the patients / participants pre-decide the methods employed, therefore it would be useful to collect normative data and data for specific sub-types for comparison across studies.

Actigraphy remains a relatively cheap non-invasive research instrument to study rest-activity in longer term chronic studies (Morgenthaler et al., 2007b) and has been suggested as an
alternative to PSG although with some limitations (Morgenthaler et al., 2007a; McCall and McCall, 2012). The actigraphy results from the study reported in Chapter 5, are associated with improvements in depression and cognitive and psychomotor performance, and are thus a useful adjunct to the effect of SSRIs on depressed patients as a continuous objective indicator of the outcome of treatment on sleep and activity where PSG would be impracticable.

It is interesting to observe that, although not statistically significant, as depression was alleviated there were suggestions that circadian rest-activity rhythmicity was improved and daytime activity was increased with treatment as evidenced in the actigraphic variables of M10 activity, average wake movement and amplitude. This mirrored clinically significant improvements in MADRS and HAMD and subjective sleep quality and demonstrated a consistent improvement in depression. These findings suggest that as depression was lifted and mood improved patients became more active during the day.

Interestingly night-time actigraphy data showed that the number of sleep bouts increased particularly with paroxetine treatment. This might suggest that sleep was impaired but as there was neither baseline nor pre-dose data, and since the sleep bout values were not excessive, it cannot be deduced that actigraphic sleep was worse during the 12 week chronic phase. It may in fact mean that patients were less restricted in their sleep. Depressed patients have more REM and shorter REM latency, whereas SSRIs are known to disrupt sleep by reducing REM and increasing REM latency. If patients sleep was therefore improved with a reduction in REM, theoretically this might manifest as increased activity during sleep as sleep was normalising. Unfortunately this aspect could not be explored as the sleep architecture of the patients was unknown.

The study reported in Chapter 5 provides valuable evidence of the potential for actigraphy to continuously record and track the effect of medication on depressed patients. This study was the first to investigate the effects of chronic antidepressant treatment over 12 weeks with actigraphy followed by a period of abrupt discontinuation. A positive outcome for this study was that patients were compliant and wore the Actiwatch for 14 weeks. However one beneficial aspect for further study consideration for this group of compounds would be to define the effect of treatment on the activity profiles of responders and non-responders. Potentially these devices and standard outcomes could be used to aid clinicians as to the progress of medication. The Help4 Mood EU Consortium project which *aims to develop a system to support the treatment of people who are significantly affected but are still able to
live at home and may also be working’ is using actigraphy. However there remain six issues to address: ‘Better clinical guidelines; further field studies; longitudinal data; improved analytical methods; characterising actigraphic variation in different types of depression’ (Burton et al., 2013).

To summarise, this thesis has demonstrated that actigraphy has the potential of being a useful tool for drug research and clinical diagnosis and treatment, given the caveats outlined. Although the thesis has focused on psychoactive compounds, actigraphy has been successfully used and remains to be a useful objective tool for recording the impact on sleep and activity profiles in a multitude of situations where PSG would be unacceptable. Conditions such as chronic pain in arthritis, diabetic neuropathy, fibromyalgia, rheumatism and ME that disrupt sleep with the consequence of sleep loss and lead to reduced daytime functioning may be better understood with long-term assessment via actigraphy. In addition mental conditions which deteriorate over time in the aging population such as dementia, Alzheimer’s disease and transient ischemic attacks or disorders that can abruptly deteriorate with subtle changes in sleep and wake patterns e.g. bipolar disorder and schizophrenia may be ideal diseases for actigraphy to play a role in clinical evaluation.

The studies presented in this thesis have endorsed previous findings and shown that psychomotor performance impairment and reduced processing skills, and subjective assessment of sedation are associated with changes in actigraphy (Stanley, 1997; Stanley and Hindmarch, 1997; Stanley et al., 1999). In contrast to the psychometric tests which are a snapshot at a defined time actigraphy provides an unobtrusive continuous measurement of activity and therefore any changes in activity associated with the effects of a drug or condition may be measured in a more time-specific manner.
REFERENCES


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APPENDICES
Appendix I: CRF – MADRS

MONTGOMERY-ASBERG DEPRESSION RATING SCALE

INFORMATION NOT OBTAINED:

If this information was not obtained, place a tick (X or √) in the INFORMATION NOT OBTAINED box. No other information should appear under this module.

MADRS ITEMS:

Based on an interview by a qualified clinician, tick (X or √) the one response that best describes the patient in reference to items 1-10. The evaluator must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

TOTAL SCORE:

Add the responses to questions 1 - 10 and place in Total Score box.

PLEASE NOTE THAT THE TOTAL MADRS SCORE FOR VISIT 1 MUST BE ≥ 20 FOR PATIENT TO BE ELIGIBLE FOR EnROLLMENT

THE SAME EVALUATOR SHOULD EVALUATE THE SAME PATIENT AT ALL VISITS.
MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)

INFORMATION NOT OBTAINED □

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

Check the box which best characterizes the patient at this time

1. APPARENT SADNESS
   Representing despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.
   □ 0 No sadness.
   □ 1 Looks dispirited but does brighten up without difficulty.
   □ 2 Appears sad and unhappy most of the time.
   □ 3 Looks miserable all the time. Extremely despondent.

2. REPORTED SADNESS
   Represented by reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.
   □ 0 Occasional sadness in keeping with the circumstances.
   □ 1 Sad or low but brightens up without difficulty.
   □ 2 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   □ 3 Continuous unvarying sadness, misery or despondency.

3. INNER TENSION
   Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.
   □ 0 Placid. Only fleeting inner tension.
   □ 1 Occasional feelings of edginess and ill-defined discomfort.
   □ 2 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   □ 3 Unrelenting dread or anguish.
   □ 4 Overwhelming panic.
## Montgomery-Asberg Depression Rating Scale (MADRS)

### 4. Reduced Sleep
Representing the experience of reduced duration or depth of sleep compared to the subject's own pattern when well.

- **0**: Sleeps as usual.
- **1**: Slight difficulty dropping off to sleep or slightly reduced, fitful sleep.
- **2**: Sleep reduced or broken by at least two hours.
- **3**: Less than two or three hours sleep.

### 5. Reduced Appetite
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- **0**: Normal or increased appetite
- **1**: Slightly reduced appetite.
- **2**: No appetite. Food is tasteless.
- **3**: Needs persuasion to eat at all.

### 6. Concentration Difficulties
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

- **0**: No difficulties in concentrating.
- **1**: Occasional difficulties in collecting one's thoughts.
- **2**: Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- **3**: Unable to read or converse without great difficulty.

### 7. Lassitude
Representing a difficulty getting started or slowness initiating and performing everyday activities.

- **0**: Hardly any difficulty in getting started. No sluggishness.
- **1**: Difficulties in starting activities.
- **2**: Difficulties in starting simple routine activities which are carried out with effort.
- **3**: Complete lassitude. Unable to do anything without help.
MONTGOMERY - ASBERG DEPRESSION RATING SCALE (MADRS)

8. INABILITY TO FEEL
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

☐ 1. Normal interest in the surroundings and other people.
☐ 2. Reduced ability to enjoy usual interests.
☐ 3. Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
☐ 4. The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. PESSIMISTIC THOUGHTS
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.

☐ 1. No pessimistic thoughts.
☐ 2. Fluctuating ideas of failure, self-reproach, or self-depreciation.
☐ 3. Persistent self-accusations, or definite but still rational ideas of guilt, or sin. Increasingly pessimistic about the future.
☐ 4. Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. SUICIDAL THOUGHTS
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not influence the rating.

☐ 1. Enjoys life or takes it as it comes.
☐ 3. Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
☐ 4. Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

(DHDS)
Total Score __________
HAMILTON DEPRESSION SCALE - 17 ITEM SCALE

INFORMATION NOT OBTAINED:

If this information was not obtained, place a tick (X or √) in the INFORMATION NOT OBTAINED box. No other information should appear under this module.

HAM-D ITEMS:

Tick (X or √) one appropriate response for each of the 17 items on this scale.

TOTAL SCORE:

Enter the score for all 17 items.

THE SAME EVALUATOR SHOULD EVALUATE THE SAME PATIENT AT ALL VISITS.
HAMILTON DEPRESSION SCALE: 17-ITEM SCALE

INFORMATION NOT OBTAINED □

CHECK THE NUMERIC CODE which best describes the patient.

1. DEPRESSED MOOD: (Sadness, hopeless, helpless, worthless)
   □, Absent
   □, These feeling states indicated only on questioning
   □, These feeling states spontaneously reported verbally
   □, Communicates feeling states non-verbally — i.e., through facial expression, posture, voice, and tendency to weep
   □, Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT
   □, Absent
   □, Self-reproach, feels he has let people down
   □, Ideas of guilt or rumination over past errors or sinful deeds
   □, Present illness is a punishment. Delusions of guilt
   □, Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE
   □, Absent
   □, Feels life is not worth living
   □, Wishes he were dead or any thoughts of possible death to self
   □, Suicide ideas or gestures
   □, Attempts suicide (any serious attempt rates 4)

4. INSOMNIA EARLY
   □, No difficulty falling asleep
   □, Complains of occasional difficulty falling asleep, i.e., more than 1/2 hour
   □, Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE
   □, No difficulty
   □, Patient complains of being restless and disturbed during the night
   □, Waking during the night — any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE
   □, No difficulty
   □, Waking in early hours of the morning but goes back to sleep
   □, Unable to fall asleep again if gets out of bed

7. WORK AND ACTIVITIES
   □, No difficulty
   □, Thoughts and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies
   □, Loss of interest in activity, hobbies or work — either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or join activities)
   □, Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
   □, Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores; or if patient fails to perform ward chores unassisted

8. RETARDATION: Slowness of thought and speech; impaired ability to concentrate; decreased motor activity
   □, Normal speech and thought
   □, Slight retardation at interview
   □, Obvious retardation at interview
   □, Interview difficult
   □, Complete stupor
## HAMILTON DEPRESSION SCALE: 17-ITEM SCALE

### 9. AGITATION
- None
- Fidgetiness
- "Playing with" hands, hair, etc.
- Moving about, can't sit still
- Hand-wringing, nail-biting, hair-pulling, biting of lips

### 10. ANXIETY/PSYCHIC
- No difficulty
- Subjective tension and irritability
- Worrying about minor matters
- Apprehensive attitude apparent in face or speech
- Fears expressed without questioning

### 11. ANXIETY (SOMATIC): Physiological concomitants of anxiety, such as:
- Gastrointestinal—dry mouth, wind, indigestion, diarrhea, cramps, belching; cardiovascular—palpitations, headaches; respiratory—hyperventilation, sighing; urinary frequency; sweating.
  - Absent
  - Mild
  - Moderate
  - Severe
  - Incapacitating

### 12. SOMATIC SYMPTOMS/GASTRO-INTESTINAL
- None
- Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen
- Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for GI symptoms

### 13. SOMATIC SYMPTOMS/GENERAL
- None
- Heavyness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability
- Any clear-cut symptom rates 2

### 14. GENITAL SYMPTOMS: Loss of libido, menstrual disturbances
- Absent
- Mild
- Severe

### 15. HYPOCHONDRIASIS
- Not present
- Self-absorption (bodily)
- Medical occupation with health
- Frequent complaints, requests for help, etc.
- Hypochondriacal delusions

### ACTUAL WEIGHT CHANGE
(since the last visit)

### 16. LOSS OF WEIGHT
- No weight loss or weight loss NOT caused by present illness
- Weight loss probably caused by present illness
- Definite weight loss caused by present illness

### 17. INSIGHT
- Acknowledges being depressed and ill
- Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- Denies being ill at all

| Total Score of Questions 1-17 | 278 |
Appendix III: CRF – ZUNG

**Zung Self-Rating Depression Scale**

**INFORMATION NOT OBTAINED:**

If the information was not obtained, place a tick (X or √) in the INFORMATION NOT OBTAINED box. No other information should appear under this module.

This is a patient rated scale and should be completed by the patient.

Ask the patient to complete the questionnaire using a black ball point ink pen.

The patient should fill out the form per the instructions on the CRF.

The patient must circle the appropriate number for each of the questions.

**IF THE PATIENT LEAVES BLANKS FOR SOME ANSWERS:**

If the patient is still in the office, ask the patient to complete the questions.

If the patient has left the office, the Investigator or Study Coordinator must document (in the CRF visit comments section) that the questions were not completed by the patient.

For example: “Patient did not complete question 5 of the Zung Self-Rating Depression Scale.”
ZUNG SELF-RATING DEPRESSION SCALE

INFORMATION NOT OBTAINED □

Listed below are 20 statements. Please circle the appropriate number in each row indicating how each of the following statements has applied to you during the past week.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel downhearted and blue</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Morning is when I feel the best</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have crying spells or feel like it</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have trouble sleeping at night</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I eat as much as I used to</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I still enjoy sex</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>7. I notice that I am losing weight</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>8. I have trouble with constipation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. My heart beats faster than usual</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I get tired for no reason</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. My mind is as clear as it used to be</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. I find it easy to do the things I used to do</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I am restless and can’t keep still</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. I feel hopeful about the future</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>15. I am more irritable than usual</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>16. I find it easy to make decisions</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>17. I feel that I am useful and needed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. My life is pretty full</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>19. I feel that others would be better off if I were dead</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. I still enjoy the things I used to do</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>
Appendix IV: CFQ

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**COGNITIVE FAILURES QUESTIONNAIRE**

**INFORMATION NOT OBTAINED:**

If the information was not obtained, place a tick (X or V) in the INFORMATION NOT OBTAINED box. No other information should appear under this module.

**This is a patient rated scale and should be completed by the patient.**

Ask the patient to complete the questionnaire using a black ball point ink pen.

The patient should fill out the form per the instructions on the CRF as follows:

**Visit 1 = "In the last three months"**

**Visits 2-14 = "Since the last visit"**

The patient must circle the appropriate number for each of the questions.

**SUBSCORE:**

Add the number of the circled responses (i.e., very often, quite often, etc.) for each category questions 1-25 and place in the subscore box.

**TOTAL SCORE:**

Add the four subscores and place in the total score blank.

**IF THE PATIENT LEAVES BLANKS FOR SOME ANSWERS:**

If the patient is still in the office, ask the patient to complete the questions.

If the patient has left the office, the Investigator or Study Coordinator must document (in the CRF visit comments section) that the questions were not completed by the patient.

For example: “Patient did not complete question 5 of the Cognitive Failures Questionnaire.”
COGNITIVE FAILURES QUESTIONNAIRE

INFORMATION NOT OBTAINED □

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last three months. Please circle the appropriate number:

| Question                                                                 | 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. | 11. | 12. | 13. | 14. | 15. | 16. | 17. |
|--------------------------------------------------------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Do you read something and find you haven't been thinking about it and must read it again? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you find you forget why you went from one part of the house to the other? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you fail to notice signposts on the road?                             | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you find you confuse right and left when giving directions?           | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you bump into people?                                                 | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you find you forget whether you've turned off a light or a fire or locked the door? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you fail to listen to people's names when you are meeting them?       | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you say something and realize afterwards that it might be taken as insulting? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you fail to hear people speaking to you when you are doing something else? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you lose your temper and regret it?                                  | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you leave important letters unanswered for days?                     | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you find you forget which way to turn on a road you know well but rarely use? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you fail to see what you want in a supermarket (although it's there)? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you find yourself suddenly wondering whether you used a word correctly? | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you have trouble making up your mind?                                | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you find you forget appointments?                                    | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
| Do you forget where you put something like a newspaper or a book?       | 4  | 3  | 2  | 1  | 0  |    |    |    |    |     |     |     |     |     |     |     |     |     |
**COGNITIVE FAILURES QUESTIONNAIRE**

Please circle the appropriate number:

<table>
<thead>
<tr>
<th>Question</th>
<th>Very Often</th>
<th>Quite Often</th>
<th>Occasionally</th>
<th>Very Rare</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away? (as in the example of throwing away the matchbook and putting the match in your pocket.)</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>19. Do you daydream when you ought to be listening to something?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>20. Do you find you forget people's names?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>22. Do you find you can't quite remember something although it's on the tip of your tongue?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>23. Do you find you forget what you came to the shops to buy?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>24. Do you drop things?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>25. Do you find you can't think of anything to say?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

(DNDE) Subscore: [ ] [ ] [ ] [ ] [ ] [ ]

Total Score: ________
LEEDS SLEEP EVALUATION QUESTIONNAIRE

INFORMATION NOT OBTAINED:

If the information was not obtained, place a tick (X or √) in the INFORMATION NOT OBTAINED box. No other information should appear this module.

This is a patient rated scale and should be completed by the patient.

Ask the patient to complete the questionnaire using a black ball point ink pen.

The patient should fill out the form per the instructions on the CRF as follows:

Visit 1 = “Compare getting to sleep last night with getting to sleep in the past week”

Visits 2-14 = “Compare getting to sleep using the medication with getting to sleep normally, i.e., without the medication”

IF THE PATIENT LEAVES BLANKS FOR SOME ANSWERS:

If the patient is still in the office, ask the patient to complete the questions.

If the patient has left the office, the Investigator or Study Coordinator must document (in the CRF visit comments section) that the questions were not completed by the patient.

For example: “Patient did not complete question 4 of the Leeds Sleep Evaluation Questionnaire.”
INFORMATION NOT OBTAINED □

Each question is answered by placing a vertical mark on the line. If no change was experienced then place a mark in the middle of the line. If a change was experienced then position your mark according to the nature and extent of the change.

1. How would you compare getting to sleep last night with getting to sleep in the past week?
   a. Easier than usual
   b. Quicker than usual
   c. Felt more drowsy than usual
   d. Harder than usual
   e. Slower than usual
   f. Felt less drowsy than usual

2. How would you compare the quality of sleep last night with the quality of sleep in the past week?
   a. More restful than usual
   b. Fewer periods of wakefulness than usual
   c. Less restful than usual
   d. More periods of wakefulness than usual

3. How did your awakening this morning compare with your pattern of awakening in the past week?
   a. Easier than usual
   b. Took shorter than usual
   c. More difficult than usual
   d. Took longer than usual

4. How did you feel on waking?
   a. Alert
   b. Tired

5. How was your sense of balance and coordination upon getting up?
   a. Less clumsy than usual
   b. More clumsy than usual
**LINE ANALOGUE RATING SCALES**

**INFORMATION NOT OBTAINED:**

If the information was not obtained, place a tick (X or √) in the INFORMATION NOT OBTAINED box. No other information should appear under this module.

This is a patient rated scale and should be completed by the patient.

Ask the patient to complete the questionnaire using a black ball point ink pen.

The patient should fill out the form per the instructions on the CRF.

**IF THE PATIENT LEAVES BLANKS FOR SOME ANSWERS:**

If the patient is still in the office, ask the patient to complete the questions. If the patient has left the office, the Investigator or Study Coordinator must document (in the CRF visit comments section) that the questions were not completed by the patient.

For example: “Patient did not complete a line of the Line Analogue Rating Scales.”
These scales are designed to allow you to assess how you feel now compared to how you usually feel. For each of the eleven lines you should place a vertical mark somewhere along the line to indicate how you feel. The closer you mark towards either end of the line, the greater the change in your feelings. If you are feeling no different from usual then place the mark in the middle of the line. If you make a mistake, score out the error with a single line and initial and date the error. Remember the marks are to show how you are feeling now.

| More anxious | Less anxious |
| Less tired | More tired |
| Less happy | More happy |
| More relaxed | Less relaxed |
| More drowsy | Less drowsy |
| Less dizzy | More dizzy |
| Less clumsy | More clumsy |
| More alert | Less alert |
| Less energetic | More energetic |
| More sad | Less sad |
| More depressed | Less depressed |
CRT RESULTS

INFORMATION NOT OBTAINED

MRT (ms) _______ _______ _______ Time (24-hour clock) _______ _______ _______ _______

RRT (ms) _______ _______ _______ _______ _______ _______ _______ _______

TRT (ms) _______ _______ _______ _______ _______ _______ _______ _______

CRITICAL FLICKER FUSION RESULTS

INFORMATION NOT OBTAINED

CFF (Hz) _______ _______ _______ Time (24-hour clock) _______ _______ _______ _______
Appendix VIII: Diary over clock change patient A10
### AM ACTIVITIES
- Dog a green art
- Made up need know
- Dinner - Church
- Washing in line
- Frisbee
- Aysen
- Collected eggs
- Prepped a "K"
- Prepping
- Repaired band

### PM ACTIVITIES
- Prepped for tomorrow
- Washed clothes
-前三季度
- finished
- Post surgery
- Prepped mind

Please ensure that you are wearing your actigraph while you sleep.

### AM ACTIVITIES
- Day a green art
- Drives for restaurants
- Cooking - Across the Aisles
- Evening - 30 min
- Driving - children watch
- Drinks
- Driving - collect prices
- Prepared lunch

### PM ACTIVITIES

Please ensure that you are wearing your actigraph while you sleep.
Appendix IX: Actiwatch actogram for patient A10 AW1

AW start time reset for incorrect computer clock, matches diary
Appendix X: AW file for patient A10 AW2

Last 2 days after clock changed, 2 min epoch. AW set up before clock change, downloaded after clock change
Close up view of GMT to BST patient A10
Appendix XI: Sleep analysis during clock change from GMT to BST patient A10

- Start date: 01-Feb-1999 (Mon)
- Start Time: 19:00
- Age: 42
- Sex: F
- Interval: 2.00

Day Scale

Analysis start: 21:00
Bedtime: 22:36
Sleep end: 06:50
Assumed sleep: 07:38
Actual awake time: 01:18 (15.4%)
Actual sleep time: 07:10 (18.4%)

- Sleep efficiency (%): 78.2%
- Sleep latency: 00:36
- Mean length of sleep bouts: 00:48:53
- Mean length of wake bouts: 00:03:43
- Number of wake bouts: 21
- Number of immobile phases: 37
- Total activity score: 5683

- Wake movement:
  - No of minutes moving: 108
  - Mean length of immobility: 10.8
  - Immobility of 1 min (%): 78.4
  - Fragmentation index: 21.3

- Immobility phases of 1 min (%):
  - Total activity score: 5683
  - Mean activity score: 12.9
  - Mean score in active periods: 149.70

- Mean length of sleep bouts: 00:20:29
- Mean length of wake bouts: 00:03:43
- No of minutes immobile: 206.2 (17.4 %)
- No of minutes moving: 210.0 (17.4 %)
- Mean length of immobility: 9.6
- Immobility of 1 min (%): 69.1

- Fragmentation index:
  - Mean score in active periods: 149.70

- Total activity score: 5683
  - Mean activity score: 12.9
  - Mean score in active periods: 149.70
Appendix XII: Actogram for patient A10, AW3 during discontinuation week 13 and resumption of treatment week 14
## Appendix XIII: Visit Dates

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patient Number</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Visit 11</th>
<th>Visit 12</th>
<th>Visit 13</th>
<th>Visit 14</th>
</tr>
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<tbody>
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20 patients included in analysis
FFV = 25/11/98 LPD = 06/7/99
7 patients completed in GMT
13 patients discontinuation occurred during BST longer daylight
0/18 patients started after clocks changed
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18 patients included in analysis
FFPV = 16/11/98 LPLV = 20/7/99
8 patients completed in GMT
10 patients discontinuation occurred during BST longer daylight
2/18 patients started after clocks changed
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</tbody>
</table>

18 patients included in analysis  
FFPV = 11/11/98 LPV = 01/7/99  
7 patients completed in GMT  
11 patients discontinuation occurred during BST longer daylight  
0/10 patients started after clocks changed
## Daily Habits and Sleep Questionnaire

**Please complete this section in the evening, before going to bed.**

**Today's Date**

<table>
<thead>
<tr>
<th>Start Time</th>
<th>End Time</th>
</tr>
</thead>
</table>

| 11pm | 12am | 1am | 2am | 3am | 4am | 5am | 6am | 7am | 8am | 9am | 10am | 11am | 12pm | 1pm | 2pm | 3pm | 4pm | 5pm | 6pm | 7pm | 8pm | 9pm | 10pm | 11pm |
|---------|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|         |       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

Enter: C = Caffeine; Tea, Coffee, Cola, Chocolate; E = Exercise; A = Alcohol; M = Meditation; N = Nap; F = Food

**Any additional comments:**

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**Please complete this section in the morning, within 15-25 mins of waking.**

**Today's Date**

<table>
<thead>
<tr>
<th>Start Time</th>
<th>End Time</th>
</tr>
</thead>
</table>

1. How refreshed did you feel upon waking up? (place a vertical mark on the line below)
   - Not at all
   - Very refreshed

2. How was the quality of your sleep last night? (place a vertical mark on the line below)
   - Very good
   - Very bad

3. When did you go to bed last night (lights out)?
   - __ : __ (24 hour clock)

4. How long did it take you to fall asleep?
   - __ Hours __ Mins

5. How many times did you wake up?
   - __ Times

6. What was the total duration of these night awakenings?
   - __ Hours __ Mins

7. How many times did you get up to use the bathroom?
   - __ Times

8. When did you finally wake up this morning?
   - __ : __ (24 hour clock)

9. Did you wake up earlier than intended?
   - Y  N
   - If answer is Yes: By how much earlier?
   - __ Hours __ Mins

10. When did you get up this morning?
    - __ : __ (24 hour clock)

11. How did you awaken this morning?
    - e.g. alarm/disturbance/naturally?

12. How long did you sleep last night (time from falling asleep to waking in the morning, excluding all waking periods)?
    - __ Hours __ Mins

13. Did you take any naps yesterday?
    - Y  N
    - If Yes, how many naps and for how long in total?
    - __ Naps __ Hours __ Mins

**Any additional comments:**
Refereed journal articles


Conference Abstracts / Presentations


Stanley, N., Dorling M.C., Dawson, J. and Hindmarch, I. (2000) The accuracy of Mini-Motionlogger and Actiwatch in the identification of sleep as compared to sleep EEG, Sleep, 23 (S2), 386.