

**THE USE OF MELATONIN FOR SLEEP DISTURBANCE
IN DEPRESSION AND DEMENTIA.**

by

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THESIS ABSTRACT:

Background: Sleep disturbance is a characteristic symptom of both depression and dementia. Melatonin has been shown to be helpful in disorders of the sleep wake cycle. There is also some evidence to suggest that it may have antidepressant properties. We conducted two separate pragmatic randomised controlled trials investigating the use of melatonin in depression and dementia respectively to see whether there was an effect on sleep.

Methods: All patients included in both trials were in a primary care setting. Patients were randomised double blind to exogenous slow release 6 mg or placebo adopting parallel and crossover designs in the depression and dementia trials respectively. Objective measures of sleep were made using wrist actigraphy for the main outcome, although subjective measures of sleep were also taken using sleep diaries and the Leeds Sleep Evaluation Questionnaire. Subsidiary measures also included the Beck Depression Inventory in the depression study and the Mini Mental State Examination in the dementia study.

Results: There was no effect of melatonin on sleep for treating either depression or dementia, although a trend towards improvement in mood was seen in the depression trial. There was difficulty in recruiting people to both trials possibly because of ethical concerns by referrers associated with involving people with mental health problems in research.

Conclusions: Despite widespread claims made about the beneficial properties of melatonin, its use is probably best suited to people with disorders of circadian rhythms. Nevertheless, there is some evidence to suggest that melatonin may have some mood elevating properties and this warrants further investigation.

SUMMARY FOR EXPERIMENT I :

Randomised controlled trial to determine whether melatonin acts as a natural sleep-promoter and antidepressant

Objectives: The hypnotic and circadian-rhythm-synchronizing properties of exogenous melatonin suggest a role in treating the sleep disturbance associated with major depressive disorder (MDD). We explored this further in a randomised controlled trial (RCT).

Methods: Thirty three participants with DSM-IV diagnoses of MDD and self reported early morning awaking were recruited from a general practice (GP) setting and were randomised, double-blind, to slow release melatonin 6 mg vs. placebo for 4 weeks.

Outcomes: The Beck Depression Inventory (BDI), sleep diaries, the Leeds Sleep Evaluation Questionnaire (LSEQ) and wrist actigraphy.

Results: Thirty one of 33 patients completed the trial. There was greater impaired sleep efficiency in the melatonin group at baseline, but otherwise no significant between group differences. General Linear Modelling compared outcomes after 4 weeks of treatment. Both groups showed significant improvement in: (1) BDI scores ($F_{1,30}=29.1, p<.0001$); (2) behavior following wakefulness on the LSEQ ($F_{1,30}=8.9, p<0.006$); (3) total time asleep ($F_{1,28}=44.5, p<0.0001$) and (4) sleep efficiency ($F_{1,28}=14.6, p<.001$) using wrist actigraphy, possibly because of spontaneous remission, or from a benefit of over 4 weeks of concomitant antidepressant treatment. However, the melatonin group had significantly greater improvement in awaking from sleep ($F_{1,30}=4.8, p=0.04$) on the LSEQ and getting to sleep approached significance ($F_{1,30}=3.8, p=0.06$). A trend to improvement in mood on the BDI was also observed with melatonin.

Conclusions: This is the largest RCT to date that examines the effect of exogenous melatonin in Major Depressive Disorder. Results suggest an effect of melatonin on mood as well as sleep and further large-scale trials are merited.

SUMMARY FOR EXPERIMENT II:

Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia.

Background: Disturbance of sleep is common in individuals with dementia where there may be reversal of the sleep-wake cycle. People with dementia of the Alzheimer's type have melatonin secretion rhythm disorders. There is some evidence that treatment with exogenous melatonin may be an effective treatment for sleep disturbance associated with dementia. A randomised double-blind placebo-controlled crossover trial was undertaken to test the hypothesis that slow-release exogenous melatonin 6mg improves sleep for people with dementia.

Methods: 44 participants with DSM IV diagnoses of dementia with sleep disturbance were selected for a 7 week randomised double-blind crossover trial of slow-release melatonin 6mg versus placebo. Sleep parameters were objectively measured using wrist actigraphy.

Results: 25 out of 44 completed the trial. Sleep was significantly disturbed in the sample population. Melatonin had no effect on median total time asleep ($n = 25, z = 1.35, p = 0.18$), number of awakenings ($n = 25, z = 0.32, p = 0.75$) or sleep efficiency ($n = 25, z = 0.17, p = 0.24$). Nor were there any carry-over effects from melatonin.

Conclusions: Contrary to previous findings, we found no evidence that 2 weeks of exogenous melatonin is effective in improving sleep in people with dementia, although possible benefits of melatonin following longer periods of administration cannot be discounted.

PREFACE:

This thesis was undertaken by the author between April 2002 and April 2004. The idea for this research was prompted by the author's brother (Paul Serfaty), who wanted to know what the evidence base was for the use of melatonin in jet lag. As a result of this conversation and ensuing literature search it became apparent that the sleep promoting properties and potential rhythm entraining effects of melatonin had not been properly tested in dementia or depression and that further research was timely. At the same time the author was aware that one of his patients was suffering from dementia was wandering and causing distress to relatives and the author was curious to know whether this had been tried in dementia? Consultation of the literature revealed that very little information was available on the use of melatonin in either dementia or depression, but that further research was warranted. The author devised and planned two studies examining the use of melatonin in sleep disturbance in dementia and depression, with applications for funding being successful. Two research fellows were employed to recruit participants and liaise with GPs and nursing homes.

In conclusion the author of this thesis devised and designed the projects, was involved in some of the data collection and most of the data entry. The author was involved in all the data analysis (with advice from the in house statistician). The author prepared the papers for publication in peer reviewed journals with input from Dr Raven (supervisor) and Bob Blizzard (in house statistician) who are co-authors on the publications. The thesis presented here is entirely the work of the author.

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PART I: BACKGROUND TO THESIS

Chapter 1 MELATONIN: AN OVERVIEW

1.1. Background to thesis

Since time immemorial, organisms have been exposed to changes in environmental lighting associated with the solar cycle. Evolution has optimised functioning by allowing organisms to develop circadian rhythms in order to regulate biological functions according to the day-night cycle. The circadian rhythm controls such things as the timing of hormone production, sleep and body temperature. Although the neurohormone melatonin (N-acetyl-5-methoxytryptamine) is integrally involved in circadian processes in photoperiodic animals, its importance in the human is only currently being elucidated.

In the late 1980s, it was suggested that melatonin may be of benefit in a number of psychiatric disorders and its potential use as therapeutic agent for the treatment of mild depression and insomnia was raised (Arendt, 1989). With the burgeoning interest in complementary therapies in the last decade, there has been a melatonin “craze” in the media, advocating its widespread use with claims of the beneficial effects of melatonin being commonplace. Sales of melatonin have soared, initially in the United States, but now increasingly so in the UK and Europe. Wide-ranging claims of the beneficial properties include melatonin’s use in anti-ageing, cancer, reduction of high blood pressure, AIDS, coronary heart disease, epilepsy and sexual vitality. However, despite this, examination of research evidence suggests that many of the claims made about the beneficial effects of melatonin are unsupported. Although melatonin may act as a chemical “Zeitgeber” (from the German, meaning “time giver”) and thus entrain biological rhythms, including the sleep wake cycle, the use of this ‘naturally occurring’ compound for treating psychiatric disorders and disorders of the sleep-wake cycle, has yet to be fully evaluated. Of particular interest, and a focus of this thesis, is research into the use of

melatonin as a hypnotic, anti-depressant and in the treatment of sleep rhythm disorders associated with depression and dementia

This thesis is presented in four parts. The first part's principal focus will be a brief overview of melatonin, a review of the use of exogenous melatonin in disorders of the sleep wake cycle and its use in psychiatric disorders, paying particular attention to affective disorders and dementia. The second and third part are two randomised controlled trials using melatonin for the treatment of disorder of sleep in depression and dementia respectively. The fourth part will provide overall conclusions with recommendations for further research.

1.2. History

In 1729, Jean Jacques d'Ortois de Mairan demonstrated an endogenous circadian rhythm in the heliotrope plant that continued after the removal of external light stimulus (Moore-Ede et al, 1982; Dement et al, 1994). This discovery laid the foundation for the theory that an internal rhythm exists in living organisms which may be independent of extrinsic factors such as a light-dark cycle. In 1907, Legendre & Pieron (1910) (see Dement et al 1994) performed a series of experiments whereby the plasma of sleep-deprived dogs was injected into non-sleep-deprived dogs; the latter group subsequently fell asleep. Thus, Legendre & Pieron proposed the hypnotoxin theory: that there is a build of sleep promoting substances or toxins produced by wakefulness which then induces sleep. One such putative somnogen has now been identified as melatonin (Reppert and Weaver, 1995; Reppert, 1997).

Melatonin was first isolated from pineal glands of cattle by the dermatologist Aaron Lerner at Yale University in 1958 (Lerner et al, 1958). The next year, Lerner found that melatonin

was a hormone created in the pineal gland through the action of certain enzymes on a precursor chemical, which he found to be serotonin (5-hydroxy tryptamine). In the 1960s (Reiter, 1992), melatonin's responsiveness to light in animals was identified (e.g. Wurtman et al, 1963; Axelrod et al, 1964; 1965). The importance of the pineal in seasonal and circadian rhythms was highlighted in the 1970's (Herbert , 1972; Hoffman; 1973; Reiter, 1980). In the 1980s, melatonin became increasingly studied and was identified as factor contributing to the synchronisation of rest-activity in birds (Menaker et al, 1981) and in rats (Redman et al, 1983). Indeed, it was suggested by Arendt (1983) that it may be used hasten the resynchronisation of human 24 hour rhythms. In the 1990s melatonin has been identified as being important in circadian rhythms in sheep (Woodfill et al, 1994), in sighted humans (Middleton et al, 1997) and even in plants (Poggeler et al, 1991). By the 1990s, the popular media adopted melatonin as a wonder drug (Fig 1.1) with "Melatonin" appearing on the cover of Newsweek. However, Arendt (1996) points out that the claims made in the popular media are mostly nonsense.



Figure 1-1 Melatonin, wonder drug?

1.3. Site of synthesis

Melatonin occurs in a variety of plants (Murch et al, 1997). There is evidence that organs exist with circadian pacemaker properties in invertebrates (e.g. arthropods and molluscs). For example, in cockroaches, the optic lobes are sites of circadian pacemakers (Edmunds, 1988). The pineal gland (epiphysis cerebri), however, is first thought to have appeared in primitive vertebrates known as lampreys. The pineal further developed in fish, amphibians and lacertilian reptiles as a photoreceptor organ (Ralph, 1975) and is accompanied by accessory pineal organs which are directly photosensitive. In mammals, the pineal's most important innervation is through post ganglionic sympathetic pathways arising from the superior cervical ganglion.

The history of our understanding of the human pineal is well described by Arendt (1995). The first surviving written description of the pineal gland was by Galen (130-200 AD), although he refers to work by Herophilus (325-280BC). More detailed descriptions did not develop until later. In 1662, Descartes suggested that pineal function was influenced by light through the retina. He is also quoted as suggesting it is the seat of the human soul, where mind, body and soul came together. The human pineal was originally thought to be a vestigial structure, it has now been shown to be the principal site of synthesis and release of melatonin, although negligible amounts may be produced from the retina, gut and blood platelets. Melatonin levels in some organs may surpass plasma levels by 10 to 100 times (Reiter et al, 2000; Bubenik, 2001; Messner, et al, 2001)

1.4. Anatomy of the pineal

Most anatomical studies on the human pineal rely on post mortem examination, although the anatomical structure of the pineal has been widely studied in a range of other species. The gross anatomy of the pineal reveals that it is part of the epithalamus. Its name is derived from its adult shape, a pine-cone structure of variable weight and dimension which becomes apparent by the fourth year of life. It is bounded superiorly by the splenium of the corpus callosum and inferiorly by the superior colliculi. Its embryological origin is the ependymal lining of the third ventricle and it is attached to the roof of this by a pedunculated base and projects into the superior subarachnoid cistern. Although the pineal body is located near the centre of the brain, there is a lack of a blood brain barrier. The nerves contained therein are typically post ganglionic. The arterial supply is through branches of the posterior cerebral arteries and posterolateral central arteries and its venous return through the Great Cerebral Vein (of Galen). Melatonin is quickly released into the circulation once it is produced and blood levels are thought to reflect accurately the synthetic activity of the pineal gland.

Functional neuroanatomical models of the pineal in humans have been derived from a combination of animal models, using comparative anatomy (Collin, 1972), and post mortem examination of human brain (Wehr et al, 2001). Light falls on the retina and produces electrical impulses which are relayed by the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), where there is a circadian pacemaker (Moore, 1996). Efferent fibres from the SCN inhibit the firing of neurones in the paraventricular nucleus in the hypothalamus (Moore et al, 1996). The paraventricular nucleus acts through sympathetic fibres in the anteromedial cell column of the spinal cord and is relayed to the pineal through multisynaptic pathways. Falling light levels result in an abrupt decrease in

firing of the inhibitory neurones in the SCN near dusk and, conversely, their firing rate increases near dawn (Mrugala et al, 2000). Blind people have the same amount of melatonin as sighted people and low light levels are associated with increased pineal stimulation and melatonin synthesis (Moore, 1996). It has been suggested that the circadian pacemaker region consists of two component oscillators. One is entrained to dusk and controls the onset of melatonin secretion and the other is entrained to dawn and controls the offset. A schematic diagram of the neuroanatomical pathways associated with the pineal gland is shown below:

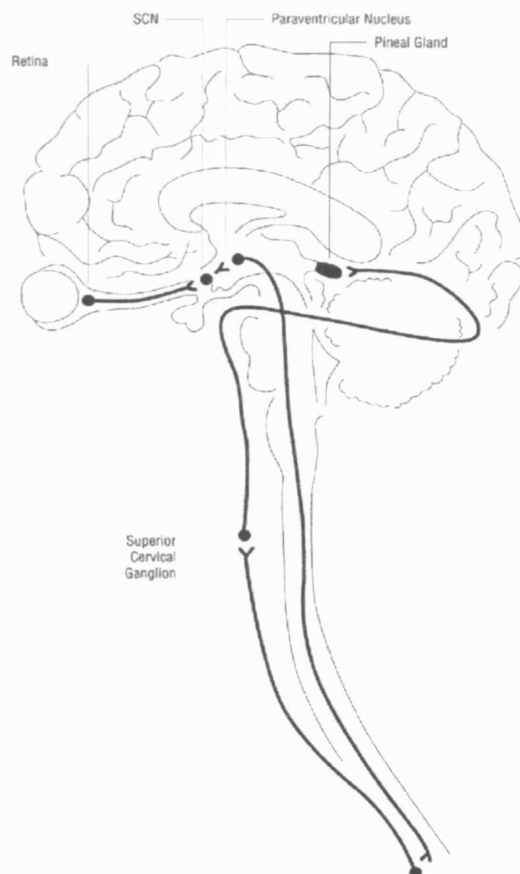


Figure 1-2 Schematic diagram of neuroanatomical pathways associated with the pineal gland.

Reproduced from Wehr et al, (2001) Archives of General Psychiatry, 58, fig 1, page 1110. In patients with damage to the pathways involved in melatonin production (described above), chronic absence of endogenous melatonin secretion is associated with impaired sleep quality (Scheer et al, 2004).

At a microscopic level, pinealocytes form the parenchyma of the pineal gland. Other constituents include glial cells and neurones, blood vessels and connective tissue. There are also melanocytes and other parenchymal elements, including calcareous concretions which may fill the pineal so extensively as to nearly destroy it. This may play an important role in the loss of function seen with increasing age, with particular reference to those with dementia. In humans, although calcification probably starts in early life, it is not obvious on radiological examination until post puberty. For a detailed description refer to Shafii and Shafii (1988) and Arendt (1995).

1.5. Biosynthesis of melatonin

The biosynthesis and metabolism of melatonin is described by Arendt (1995). Tryptophan, an amino acid, is taken up from the circulation by the pinealocytes. Tryptophan is then converted to 5-hydroxytryptophan by the enzyme tryptophan-5-hydroxylase. The enzyme L-amino acid decarboxylase then facilitates the conversion of 5-hydroxytryptophan to 5-hydroxytryptamine (serotonin). The concentration of serotonin in the pineal is about 100-fold greater than in the brain as a whole. Serotonin N-acetyltransferase, the rate-limiting enzyme in the production of melatonin, then converts serotonin to N-acetylserotonin. This latter compound is methylated by hydroxyindole-O-methyltransferase to melatonin (N-acetyl-5-methoxytryptamine).

Serotonin N-acetyltransferase increases 30-70 fold at night, at least in rodents, and indeed melatonin production occurs essentially at night (scotoperiod) in all species, whether nocturnal or diurnal and has therefore been given a variety of labels including the “darkness hormone” or “the Dracula Hormone”. As it also exerts influences on circadian rhythms it has also been called “time in a bottle” or “circadian glue”. A summary of the synthesis of melatonin is shown in Fig 1.3:

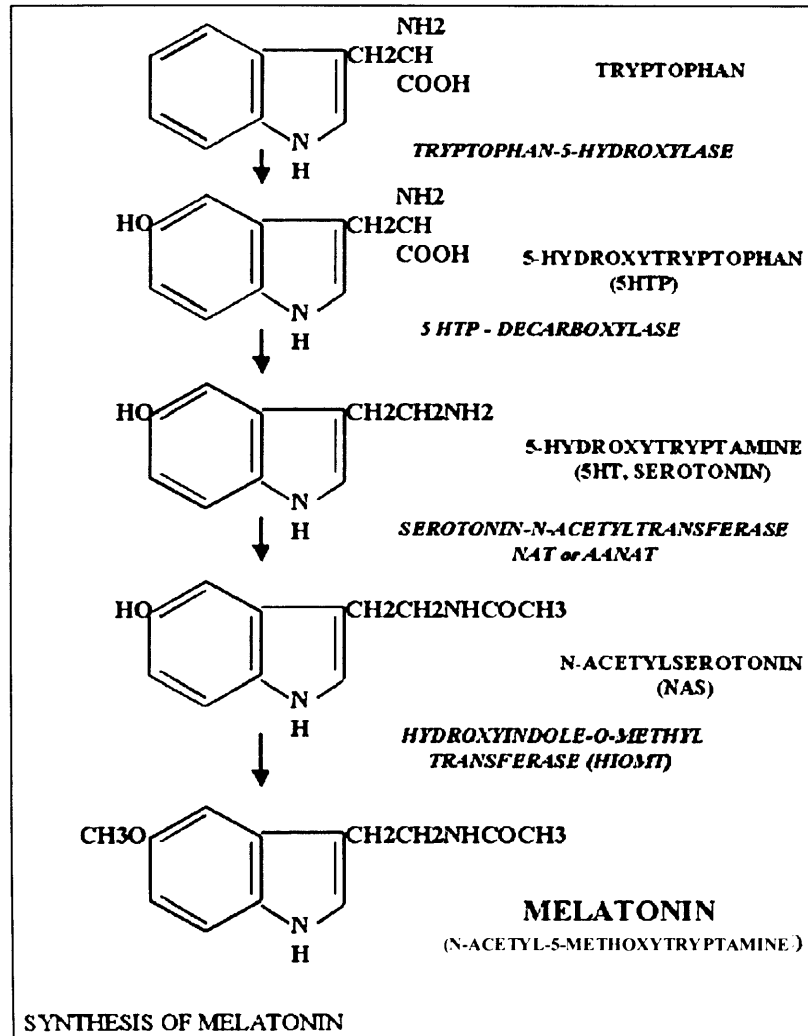


Figure 1-3 Biochemical Pathway for Melatonin synthesis.

1.6. Catabolism of melatonin

Melatonin is mainly broken down in the liver, but also to a lesser extent the kidney. This is done through 6-hydroxylation followed by sulphate or glucuronide conjugation. In humans 90% of a dose of melatonin is accounted for by sulphate conjugation with 6-sulphatoxy-melatonin being detectable in the plasma, saliva (Voultsios et al, 1997) and urine (Aldhous and Arendt, 1988). As an alternative pathway to 6-hydroxylation, some melatonin is also converted to 5-methoxyindoleacetic acid (Vanecek, 1998).

A number of drugs may affect melatonin synthesis, secretion or metabolism. First, melatonin levels may be reduced. Benzodiazepines, commonly used in the treatment of sleep disturbance, activate gamma-aminobutyric acid (GABA) receptors. GABA inhibits melatonin synthesis and secretion (McIntyre et al, 1993), although the effects of benzodiazepines on melatonin secretion is variable (Table 1.1). A number of other routinely prescribed drugs may also reduce melatonin levels. These include stimulants, beta-blockers, or drugs that activate hepatic melatonin metabolism. Indeed, afternoon doses of beta blockers used for treating hypertension completely abolish the melatonin rhythm the next night, as do α_2 blockers such as clonidine and α -methyl-*para*-tyrosine which reduces presynaptic catecholamine synthesis.

Secondly, melatonin levels may be raised through increased production or decreased catabolism. Melatonin is produced from N-acetyl-serotonin, a product of serotonin. Drugs that increase serotonin levels, such as SSRIs, may also increase melatonin levels. The catabolism of melatonin is inhibited by drugs such as chlorpromazine and psoralens (used to treat psoriasis), which therefore boost the amplitude of melatonin levels. Although a number of commonly used drugs such as dihydropyridine calcium antagonists or prostaglandin inhibitors probably alter melatonin secretion (Claustrat et al 2005), their effect on melatonin secretion in humans remains to be elucidated. Other commonly used psychotropic drugs which have an effect on dopamine neurotransmission, such as dopaminergic agonists and antagonists and opioid receptor blocking agents, are not capable of any marked modification of melatonin levels (Claustrat et al, 2005).

Finally, phase changes may also be affected by drugs which act on noradrenaline reuptake inhibition, e.g. antidepressants acting on the noradrenaline pathways, by phase advancing melatonin secretion.

A summary of the regulation of melatonin synthesis is shown in Fig 1.4:

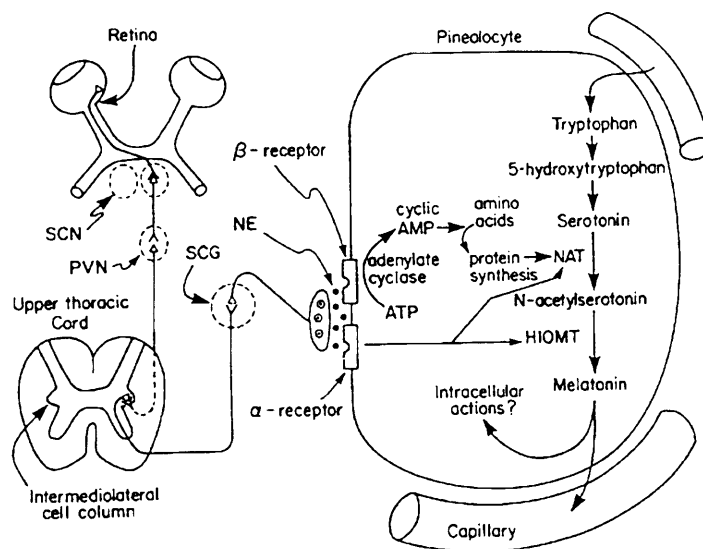


Figure 1-4 Summary of the regulation of melatonin synthesis.

SCN= Supra Chiasmatic Nucleus, PVN= Paraventricular Nucleus, CCG= Superior Cervical Ganglion, NE= Norepinephrine (Noradrenaline), AMP= Adenosine Mono Phosphate, ATP= Adenosine Tri Phosphate, NAT N-Acetyl Transferase, HIOMT= Hydroxy Indole Methyl Transferase.

1.7. Physiological actions melatonin

At the simplest level, melatonin and serotonin are present in unicellular algae and their concentrations exhibit circadian rhythmicity (Poggeler et al, 1991). The role of melatonin in regulating circadian rhythms in humans is becoming increasingly recognised. Most of our knowledge of the neurophysiology of melatonin is derived from rodent studies. In all mammals the central endogenous oscillator of the circadian system is located in the bilaterally arranged suprachiasmatic nucleus of the hypothalamus. Various molecular mechanisms of rhythm generation have been identified and these are associated with “clock genes” (Korf et al, 2003). Studies in mice and rats suggest that melatonin may be of more

importance in entraining circadian rhythms when there is impairment of the retinohypothalamic tracts and that the neurotransmitter glutamate plays a role in this process through pituitary adenylate cyclase-activating peptide (PACAP) (Korf et al, 2003).

1.8. Melatonin receptors

Two main melatonin receptors have been identified in mice and other species. The classification of these has now been approved by the nomenclature committee of the international union of basic and clinical pharmacology (IUPHAR; Dubocovich et al, 1998) into MT₁ and MT₂ receptors (previously known as Mel_{1a} and Mel_{1b} respectively). The MT₃ receptor described in hamsters has now been shown to be the enzyme quinine reductase 2 (Nosjean et al, 2000). Neuronal firing of the mammalian suprachiasmatic nucleus (SCN) is inhibited by SCN MT₁ receptor specific binding and the MT₂ receptor is implicated in a phase shifting response (Liu et al, 1997), though the mechanism in humans remains to be elucidated.

1.9. Melatonin secretion and age

In the human, the consensus of opinion is that rhythmic secretion of melatonin starts at about the age of 2 months, reaches a peak at ages 3-5 years and, following a slowly declining plateau, decreases substantially following puberty and in old age. A schematic diagram of peak melatonin secretion with age is shown (Fig 1.5). The notion that melatonin levels fall with age has been challenged (Zeitzer et al, 1999; Fourtillan et al, 2001) and the use of melatonin-suppressing medications and, uncontrolled environmental lighting have been proposed as a possible explanations for the different findings.

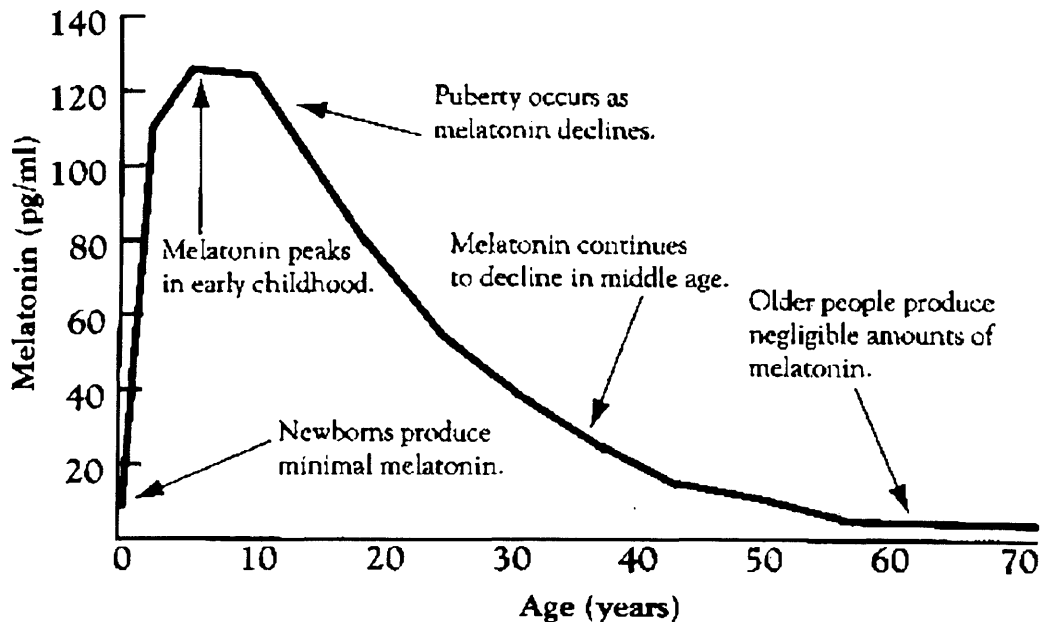


Figure 1-5 Change in melatonin secretion with age

1.10. Human melatonin cycle and phase response curve to zeitgebers

Biological rhythms have a repetitive pattern or periodicity. Time when most diurnal animals wake and become active is designated as Circadian Time 0 (CT 0). The animal, if diurnal, is usually active during the day and then settles around sunset. Similar rhythms are seen with respect to hormonal changes. Rhythms with a periodicity of more than a day are referred to as ultradian and less than a day, infradian. When they are endogenously generated and approximate to a 24 hour cycle they are referred to as “circadian”. Although rhythms may, in theory be internally generated or externally imposed, it is more commonly a combination of these two factors. Internally generated rhythms are thought to be controlled largely from the suprachiasmatic nucleus (Arendt, 1995). Although the endogenous rhythm of melatonin secretion appears to be driven by a pacemaker in the suprachiasmatic nucleus (SCN), this pattern may be affected by exogenous factors known

as zeitgebers or “time givers”. A number of zeitgebers have been described (Arendt, 1995). These include light/ dark, level of activity, posture (standing from the supine position may increase plasma melatonin by 20-30%), social cues (such as meal times), temperature, knowledge of clock time and drugs, as well as melatonin itself (Table 1-1). Light is the most important zeitgeber, but in situations where people are subjected to environments where there are consistently low levels of light, such as in Antarctica or in the case of retinal blindness, social and other zeitgebers are more important (Arendt, 1995).

The biological rhythm, when internally generated by the SCN and not influenced by external factors, cycles over a period known as “Tau” or “ τ ”. In humans, melatonin demonstrates a tau of about 24.2 hours and may be genetically determined (Korf, 2003). In sighted people, light suppresses melatonin and this is dependent on the intensity of light. A plot of melatonin secretion with time shows a typical pattern as shown in Figure 1.6 below.

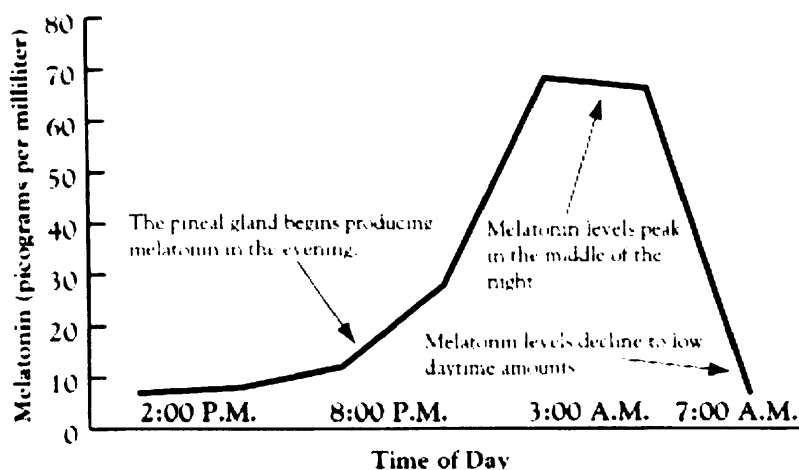


Figure 1-6 Schematic diagram to show the pattern of secretion of melatonin in humans.

One definition of dim light melatonin onset time (DLMO) is the point at which melatonin levels reach 10pg/ml. In humans DLMO time is usually 14 hours after sleep offset or CTO. Melatonin secretion rises in the early evening (sunset) in animals and about 1-2 hours before bedtime in humans. Melatonin levels then reach a plateau during the middle of the night and starts declining in the early hours of the morning. The start of this decline is known as the synthesis offset time (SynOff) and the Dim Light Melatonin Offset time reached when melatonin levels fall below 10pg/ml. Because there may be considerable variation between individuals in melatonin levels (amplitude) it has been suggested that the SynOff provides a more accurate measure of the melatonin cycle, particularly given that this is highly reproducible within individuals (Lewy et al, 1999).

1.11. The effects of light on the melatonin cycle

Light intensity varies inversely with the square of the distance from the source. The closer the light, the brighter it is. Exposure to low intensity (200-300 lux or lower) light at night, in the blue band range (460-480 nm) in particular, suppresses melatonin production (Zeitzer et al, 2000 and Thapan et al, 2001). In normal people, although evening light delays the melatonin onset by suppression, the primary zeitgeber appears to be morning light (Arendt, 1995). Phase delays occur in normal individuals when they are exposed to light in the late subjective day/early night and phase advances occur when the person is exposed to light in the middle to late subjective night (Arendt, 1995). A dead zone is also present when no shifts occur. As discussed in the next section, there may be a differential response to zeitgebers, depending on which phase they occur in the melatonin cycle (Lewy et al, 2001a). There is also some evidence to suggest that sensitivity to light is both environmentally and genetically determined.

1.12. Summary of factors influencing melatonin secretion

As previously highlighted a number of factors including light, posture, drugs and hormones will influence melatonin secretion. Although it is beyond the scope of this thesis to list all studies, a summary of the important factors, the effect(s) on melatonin and authors (Health Protection Agency, 2006) are given in Table 1-1 below.

Table 1-1 Various factors influencing melatonin secretion

Factor	Model	Effect(s) on melatonin	Comment	References
Light	Humans	Suppression (>30 lux broad spectrum white in controlled studies) intensity required depends on previous light exposure	Maximum effective wavelength 460-480 nm	Zeitzer et al, 2000; Thapan et al, 2001; Brainard et al, 2001; Owen and Arendt, 1992, Hebert et al., 2002
Light	Animals	Suppression (intensity depends on species and environment)	Maximum effective wavelength 480 nm in mice	Foster and Hankins, 2002
Light	Humans	Entrainment: with scheduled sleep-darkness <200lux Without other time cues >200 & <1000 lux	Short wavelengths more effective than white	Zeitzer et al, 2000; Wright et al, 2001; Middleton et al, 2002, Warman et al, 2003, Lockley et al. 2003
Light	Animals	Entrainment (intensity depends on species and environment)		Elliot, 1981
Timing of sleep or rest-activity cycle	Humans Animals	Changes in timing (and sometimes amplitude after abrupt phase shift) e.g. shift work, jet lag in humans	Partly a secondary effect, sleep modifies light-dark exposure	(Barnes et al., 1998, Rajaratnam and Arendt, 2001, Turek and Van Reeth, 1988, Feve-Montange et al., 1981)
Timing of light-dark cycle	Humans Animals	Changes in timing (and sometimes amplitude after abrupt phase shift) e.g. shift work, jet lag in humans		(Deacon and Arendt, 1996, Illnerova and Sumova, 1997)
Posture	Humans	Increase on standing up after a period of recumbency at night	20 min required to stabilize, may not affect timing	(Deacon and Arendt, 1994) Voultsios et al, 1997
Exercise	Humans	Increase at night, induces phase shifts	Very hard exercise	(Buxton <i>et al.</i> , 2003)
Adrenergic β -receptor antagonists	Humans Animals In vitro	Decreased synthesis, can be almost completely suppressed overnight	Anti-hypertensives	Arendt et al, 1985; Simmoneaux and Ribelayga, 2003 Klein et al, 1997
Some serotonin (5HT) uptake inhibitors	Humans	Increase with fluvoxamine	Antidepressant (probably metabolic effect)	(Hartert et al., 2001, Skene et al., 1994)
Noradrenalin uptake inhibitors	Humans	Increase/change in timing	Antidepressants	(Checkley <i>et al.</i> , 1986)

Factor	Model	Effect(s) on melatonin	Comment	References
MAO a inhibitors	Humans Animals	Increase, may change phase	Antidepressants	(Arendt, 1989)
Alpha- adrenoceptor antagonists	Humans	Decrease with alpha-1, increase with alpha-2	Probably via GABA related mechanisms	(Palazidou et al., 1989b, Palazidou et al., 1989a)
Benzodiazepines	Humans Animals In vitro	Varied, e.g. decrease with diazepam, alprazolam, not triazolam, temazepam, zopiclone In vitro and in vivo results not necessarily similar		(McIntyre et al., 1993, Monteleone et al., 1989, Niles, 1991, Copinschi et al., 1990, Mann et al., 1996, Cardinali and Golombek, 1998)
Vasopressin	In vitro	Increase	Potentiates noradrenergic stimulation	Simoneaux and Ribelayga, 2003
Dopamine	In vitro	Possible effects both inhibitory and stimulatory		Simoneaux and Ribelayga, 2003
Acetylcholine	Animals (<i>in vivo</i> microdialysis) & In vitro	Inhibition of synthesis		Simoneaux and Ribelayga, 2003
Glutamate	In vitro	Inhibition of synthesis	Inhibits noradrenalin stimulation	Simoneaux and Ribelayga, 2003
GABA	In vitro	Inhibition of synthesis	Inhibits noradrenalin stimulation	Simoneaux and Ribelayga, 2003
Nitric oxide	In vitro	Inhibition of synthesis		Simoneaux and Ribelayga, 2003
Testosterone	Animals Humans	Stimulation	Castration reduces melatonin synthesis. Treatment of male hypogonadism decreases melatonin, hyperandrogenic women have increased melatonin	Simoneaux and Ribelayga, 2003 (Puig-Domingo et al., 1992, Luboshitzky et al., 1997)
Oral contraceptives	Humans	Increase	Possible metabolic effect	Wright and Badia, 1999; Simoneaux and Ribelayga, 2003; (Kostoglou-Athanassiou <i>et al.</i> , 1998)
Progesterone		Controversial		
Oestradiol	In vitro	Inhibition of synthesis		Simoneaux and Ribelayga, 2003
Oestradiol	Animals	Decrease (inconsistent)	Ovariectomy increases melatonin in rats and sheep (transient) but inconsistent between species. Possible metabolic effect by competition for the CYP1A2 metabolic pathway?	Simoneaux and Ribelayga, 2003 (Cheng Z.N., 2001)

Oestradiol	Humans	Decrease (inconsistent, insufficient data)	Oestradiol treatment for delayed puberty lowered aMT6s in a case report. No effect of ovarian suppression in precocious puberty Menopause may be associated with increased melatonin	(Arendt et al., 1989, Berga et al., 1989, Okatani et al., 2000)
Oestrous cycle	Animals In vivo microdialysis	Inconsistent in whole animals No differences	Pro-oestrous decline in rodents	Simoneaux and Ribelayga, 2003
Menstrual cycle	Humans	Inconsistent and conflicting reports	Never properly assessed in constant routine conditions in humans.	Arendt, 1995
Oestradiol, Progesterone	DMBA treated rats	Decrease		Simoneaux and Ribelayga, 2003
Smoking nicotine	Humans	Possible change, insufficient data		(Tarquini <i>et al.</i> , 1994)
Alcohol	Humans	Decrease, dose dependent		(Ekman <i>et al.</i> , 1993)
Caffeine	Humans	May delay clearance, i.e. increase		(Shilo et al., 2002, Hartter et al., 2003)
Some non-steroidal anti-inflammatory drugs	Humans	Decrease		(Murphy <i>et al.</i> , 1996)
Chlorpromazine	Humans	Increase	Antipsychotic. Metabolic effect	(Ozaki et al., 1976, Smith et al., 1977, Beedham et al., 1987)
Luteinising hormone	In vitro	Increased production	Few data	Simoneaux and Ribelayga, 2003
Benserazide	Animals Humans	Decrease No amplitude change in Parkinson patients, possible phase change	Aromatic amino-acid decarboxylase inhibitor	(Arendt et al., 1981, Fertl et al., 1991, Ho and Smith, 1982)
Calcium channel blockers	Humans	Possible effects		(Escames <i>et al.</i> , 2004)

1.13. Effects of melatonin in peripheral tissues

Melatonin may also control the regulatory mechanisms for rhythmic clock gene expression in peripheral tissues (Abraham et al, 2003). It has been suggested that desynchronisation between the rhythms in the central pacemaker, the suprachiasmatic nucleus, and the

peripheral target tissues of the clock causes pathologies associated with shift work and jet-lag (Arendt, 1997) and this desynchronisation may also be present in depressive disorders and may explain dysphoric symptoms.

1.14. Effects of exogenous melatonin

Melatonin is given as a tablet allowing fast release into the circulation. Its estimated half life is between 35 and 50 minutes and it is therefore rapidly eliminated (Waldhauser et al, 1984). When given by the oral route it is therefore quickly released into the body and does not mimic the endogenous profile, but leads to supraphysiological (pharmacological) levels over a short time (Claustrat et al, 2005). Slow release preparations enable the pharmacokinetics of melatonin to be extended to 5-7 hours (Aldous et al, 1985) and may be more likely to mimic the natural endogenous rhythm of melatonin secretion.

Two main effects of exogenous melatonin have been identified. First, melatonin has mild hypnotic effects (Zhdanova, 2005) and three to four hours after melatonin is given is associated with lowered alertness, performance and body temperature (Dollins et al 1994; Deacon and Arendt, 1995). Indeed, it appears to induce sleepiness via thermoregulatory changes by increasing distal vasodilatation and hence heat loss with consequent hypothermia (Cagnacci et al, 1997). Secondly, it acts as a zeitgeber by shifting the circadian rhythm of sleep and endogenous melatonin (Arendt et al, 1984; 1985). Exogenous melatonin has also been shown to act as a zeitgeber (Sack et al, 1991, 2000; Herxheimer and Petrie, 2005; Arendt and Skene, 2005).

There may be considerable individual variations in the response to exogenous melatonin depending on the phase of circadian endogenous melatonin levels (Lewy and Sack, 1993). The direction and magnitude of the change in timing (phase shift) in response to exogenous melatonin is described as the phase response curve (PRC) and knowledge of the optimal time of administration is useful. An example of the phase response curve is described by Lewy et al (2001b) and shown in Fig1.7 below.

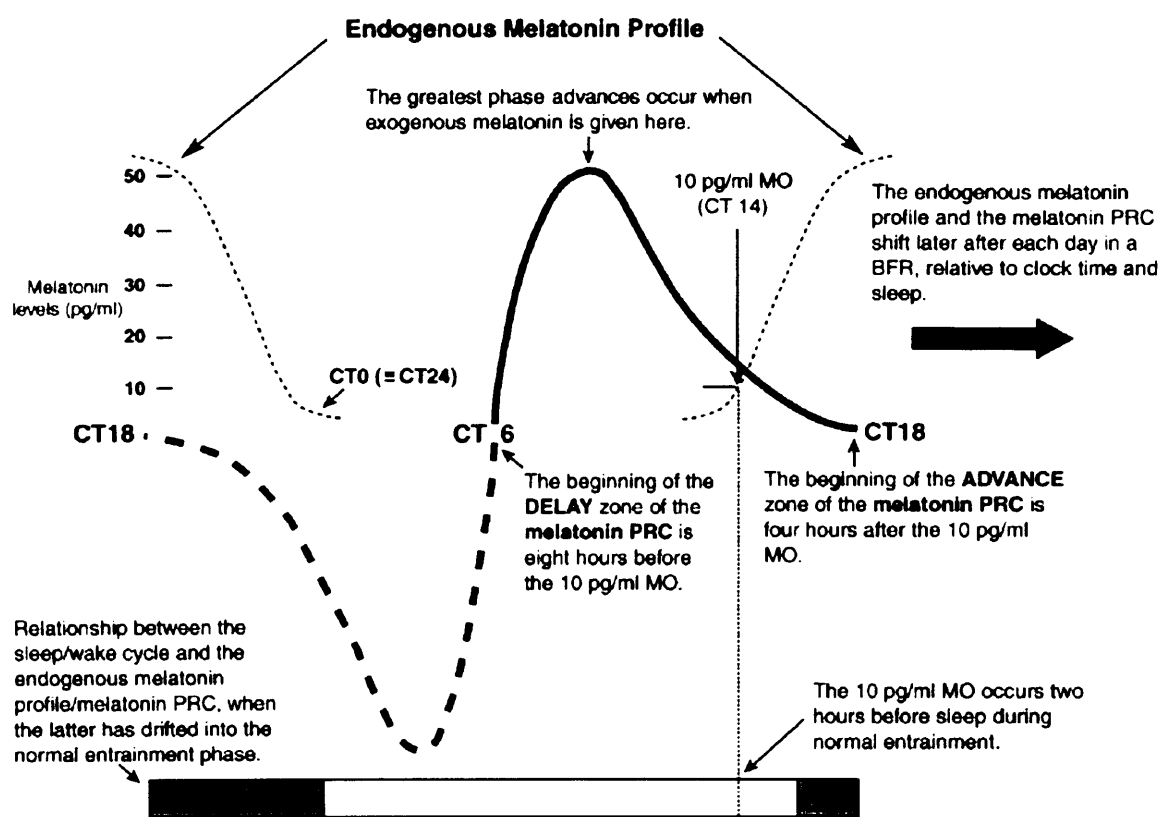


Figure 1-7 Phase response curve

Relationship between the endogenous melatonin profile and the melatonin phase response curve (PRC) in humans. Also shown is the phase relationship between the entrained circadian system and the sleep/wake cycle in normal (sighted) people. MO=Melatonin Onset; BFR = Blind Free runners; CT = Circadian Time; (Reprinted from Lewy et al, 2001, Brain Research, 899, 96-100 with permission from Elsevier).

The endogenous melatonin profile is shown by the thin dotted line. Superimposed is a thicker line which demonstrates that the greatest phase advance (uninterrupted line) or phase delay (interrupted line) depends on when exogenous melatonin is given.

The convention in describing circadian phase disorders is to refer to circadian time (CT). CT 0 is the sleep “off-set time” at which the person wakes and when melatonin secretion is suppressed. Administration of melatonin during the phase-advance portion of the curve results in a shift in the cycle to an earlier time of day; administration during the phase delay portion of the curve shifts the cycle to a later time. This is summarised in Table 1.1 below:

Table 1-2 Variation in response to melatonin depending on time of administration

Circadian Time (CT)	Type of response
20- 4	Delay responses or No advance responses
4 – 5	Crossover point
6 – 13	Advance responses or No delay responses
14 – 19	Reduced responses

(NB CT 0 = wake up time).

The dose of melatonin is also important. For a hypnotic effect, doses of melatonin of 3-10 mg taken 30- 60 minutes prior to sleep are used, although doses as low as 0.1- 0.3 mg may

be sufficient (Zhdanova, 2005). To act as a zeitgeber, it has been suggested that plasma melatonin levels need to be elevated to nighttime levels of between 60-200 pg/ml as opposed to daytime levels of less than 3-10 pg/ml (Dollins et al, 1994). Although doses of 3-10 mg have been used, more recently it has been shown that lower doses of 0.5 mg can augment entrainment of the endogenous circadian pacemaker by the light/dark cycle (Deacon and Arendt, 1995; Lewy et al, 2001a; Zhdanova et al, 2001; Arendt and Skene 2005). It is striking that there can be a thousand fold increase in plasma melatonin after ingestion of a 10mg dose when compared to peak levels normally occurring at night in a young healthy adult (Zhdanova, 2005).

A number of complicating factors need to be considered when determining the chronobiotic properties of melatonin (Arendt and Skene, 2005). First, because melatonin acts as a hypnotic (Zhdanova, 2005) the subsequent phase shifting properties of melatonin may be in part a result of changes in timing of light exposure. Secondly, a high dose of melatonin may spill over into the phase delay portion of the phase response curve and delay onset of melatonin secretion, or if in the phase advance portion may result in a less marked effect. Thirdly, repeated exogenous administration of melatonin may result in a down-regulation of receptors and less effect (Zhdanova, 2005). Fourthly, melatonin may result in transient phase shifts and a sleep wake pattern that returns to normal once melatonin is stopped. Finally, since melatonin can have acute sleep promoting influences the sleep wake cycle cannot be used as a reliable circadian phase marker.

1.15. Adverse effects of exogenous melatonin

There is evidence to suggest that in humans, the adverse effects from low doses of melatonin are probably minimal (Arendt, 1997; Seabra, 2000; Shamir 2000;

Andrade 2001; Singer et al, 2003; Herxheimer and Petrie, 2005), although a number of earlier studies and animal data suggests that melatonin is associated with a variety of possible adverse effects, there is a danger of extrapolating these findings to humans.

Exogenous melatonin is probably safe (Buscemi et al, 2006), most trials report adverse events in a cursory and uninformative way (Ioannidis and Lau, 2001) and few reports describe at what time points adverse events are detected or elicited (Herxheimer, 2006).

Psychiatric symptoms have been associated with the use of melatonin. Carmen et al (1976) suggested that there was a worsening of depressive symptoms, with lower mood, sleep disturbance, weight loss. However, in this study enormous doses (> than 1 gm) of melatonin were used and patients had comorbid diagnoses. Evening melatonin may also produce a circadian phase advance and may worsen early morning awakening in depression. Exogenous melatonin (or its withdrawal) may trigger or exacerbate manic episodes in people who are so predisposed (Leibenluft, 1997), although this finding is contradictory in that it has also been suggested that melatonin may improve sleep and decrease the severity of manic symptoms. (Robertson et al, 1997; Bersani et al, 2000). Nevertheless, in the light of these findings careful monitoring is advisable when undertaking studies using melatonin for the treatment of sleep disturbance in people with bipolar disorder or bipolar disorder, depressed.

The majority of physiological and pharmacological effects of melatonin described is from studies in animals, but there is also some information from studies in humans (Arendt, 1995); the physiological function of melatonin in animals as a photoperiodic signal and its possible photoperiodic function in humans is described in chapters 5 and 7 respectively. Pharmacologically it has been observed to cause vasoconstriction (Mahle et al, 1997; Viswanathan et al, 1997) or vasorelaxation (Weekley et al, 1995; Cagnacci et al, 2001a) in animal tissues. Physiologically in rats, it lowers blood pressure (Chuang et al, 1993; Tom et al, 2001), but has also been observed to constrict cerebral and coronary arteries and reduce cerebral blood flow (Capsoni et al, 1995). Because of these cardiovascular effects of melatonin in animal models, caution is probably wise when investigating the effects of melatonin in humans who have significant vascular disease. Nevertheless, it is worth noting that in humans, at low doses, there have not been significantly raised reports of adverse events with melatonin (e.g Singer et al, 2003). Indeed it may even have a protective effect. In rats Regrigny et al, (1998) suggests that melatonin diminishes the risk of hypoperfusion-induced cerebral ischaemia by shifting the lower limit of cerebral blood flow autoregulation to a lower pressure level and thus improve the cerebrovascular dilatatory reserve. This arterial effect is consistent with reports of melatonin suggesting that melatonin may relieve headaches (Gagnier et al, 2001; Claustrat et al 1997).

Melatonin may also affect endocrine function. In many mammals, melatonin affects prolactin and gonadotropins (Griffiths et al, 1987; Smith et al, 1987) and delays sexual maturation in experimental animals (Lang et al, 1985; Rivest et al,

1985). In humans high melatonin levels have been found in women with hypothalamic amenorrhea (Berga et al, 1988; Laughlin et al, 1991) and in men with hypogonadism (Karasek 1990; Puig-Domingo 1992). Exogenous high doses of melatonin 300 mg have been used in humans as a female contraceptive (inhibiting ovulation) in combination with progesterone (Voordouw et al, 1992). It follows that caution should be used in women who are pregnant or planning pregnancy. Other endocrine effects of melatonin have been observed in mammals. Melatonin may suppress insulin (Rasmussen et al, 1999), though this effect is not invariably found (Bizot-Espiard, 1998). As exogenous melatonin reduces glucose tolerance and insulin sensitivity in post-menopausal women (Cagnacci et al, 2001) caution may be advisable where there are known problems with glucose control.

Various other reports have suggested that melatonin has been found to increase retinal susceptibility to light-induced damage in rats (Leino et al, 1984; Wiechmann et al, 1992) or protect the retina from oxidative damage (Siu et al, 1999), but the effect in humans is not known.

There has been one study which reported increased seizures when melatonin was given to neurologically compromised children (Sheldon, 1998), but once again these findings are contradictory with an anti-convulsant and neuro-protective effect also being reported (Munoz-Hoyos et al, 1998).

It has been suggested that melatonin has anticancer properties, and may enhance immune function (Maestroni, 1993; Reiter et al, 2000), but once again these

findings are confusing. Melatonin may exacerbate autoimmune conditions such as arthritis (Maestroni et al, 2001) and for this reason people with autoimmune conditions were excluded by Singer et al, (2003). There is also a suggestion that melatonin may potentiate warfarin (Herxheimer and Petrie, 2005) and therefore caution may be advisable for people taking warfarin.

A number of pharmacological and physiological effects associated with the use of exogenous melatonin have been observed. A systematic review of melatonin has reported it to be safe (Buscemi et al, 2006). However, concern about the quality of the data has been raised (Herxheimer, 2006), suggesting that adverse events are reported in a cursory and uninformative way (Ionnidis et al, 2001). Despite adverse events being rare, much of the concern raised reflects findings from the use of melatonin in animal models and such findings may not necessarily be extrapolated to humans. Similarly, although melatonin has been used in humans at very high doses in people with significant comorbidity (Carmen et al, 1976) one cannot conclude it is unsafe in lower doses. Caution may be advisable in people with bipolar disorder, a history of vascular disease, diabetes mellitus, rheumatoid arthritis or those taking warfarin, but the evidence is too weak to warrant excluding such people for safety reasons. Nevertheless careful monitoring of patients' relevant factors is recommended. At present, the only absolute contraindication should be in the use of melatonin in those who are pregnant or planning pregnancy, given that little is known about the effects of melatonin on the fetus.

1.16. Licensing of the use of melatonin

Melatonin in both the UK and USA is not classed as a drug. Its use in the UK was subject to exemption as a special case (private correspondence, ref MF 8000/7701) by the Medicines Control Agency (Department of Health London)

Chapter 2 AN OVERVIEW OF SLEEP

“No small art is it to sleep: it is necessary for that purpose to keep awake all day.”

Friedrick Nietzsche (Thus Spake Zarathrustra).

2.1. History and definition

Sleep and dreams have always been the source of much speculation and have figured widely in art, religion and literature throughout the ages. In Greek mythology Nyxt (Night) had two sons, Thamus (Death) and Hypnos (Sleep). The juxtaposition of these two states resulted in the longstanding belief that sleep was a passive vegetative state. At the beginning of the 20th century when Freud published works examining the nature of dreams, scientific interest in sleep and dreams emerged (Freud, 1900). The lay notion that sleep serves a restorative function has increasingly gained support (Oswald, 1980).

Sleep is defined as a condition of body and mind which normally recurs for several hours every night, in which the nervous system is inactive, the eyes closed, the postural muscles relaxed and the consciousness practically suspended (Concise Oxford Dictionary). In this state there is a reversible perceptual disengagement from, and a decreased responsiveness to, the environment.

The variety of physiological and behavioural processes that accompany sleep are well described (Carskadon and Dement, 2000). Behaviourally, there is usually recumbency, quietening and closed eyes, although less common behaviours such as sleep walking and bruxism may occur. Physiologically, there are changes in the

respiratory, cardiovascular, gastrointestinal, neurological, reproductive and musculoskeletal systems.

2.2. Stages of sleep

As long ago as the 1920s two separate states in sleep were known; non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (MacWilliams, 1923). However, it was not until the development of the sleep encephalogram that there was a burgeoning of sleep research, with more precise and detailed descriptions of sleep and the characterisation of its different phases (Arensky and Kleitman, 1953; Dement and Kleitman, 1957).

NREM sleep is somewhat arbitrarily divided into 4 stages, with increasing depth and decreased arousal with each phase (1-4). In NREM sleep, although there is fragmented mental activity, the brain actively regulates the body. REM sleep by contrast, is characterised by a highly activated brain in a paralysed body with EEG activation, muscle atonia and with episodic bursts of eye movement occurring during this phase. Mental activity during REM is also associated with dreaming (Dement and Kleitman, 1957), as 80% of people woken during this phase have vivid dream recall.

2.3. Neurophysiological findings in different stages of sleep

It is generally accepted that in normal circumstances adult humans enter into sleep via NREM sleep, proceed into REM sleep and then alternate between the two throughout the night. During sleep onset, electromyographic investigation reveals muscle relaxation, electro-oculographic measurements suggest asynchronous eye

movements and the EEG pattern shows changes from clear alpha rhythms (8-13 cycles per second) in wakefulness to a low voltage mixed frequency pattern. This pattern is characteristic of stage 1. Although the person reports losing their train of thought and experiences vague imagery at this stage, this may not coincide with perceived sleep onset. During this stage, patients may also experience localised muscle contractions (hypnic myoclonia) along with visual imagery and also respond to stimuli. For the normal young adult it takes about 1 to 7 minutes to pass through stage one sleep.

Stage 2 follows stage 1 sleep with the appearance of K-complexes or sleep spindles in the EEG. Indeed, it has been suggested that a characteristic of sleep onset is the appearance of these changes. Even at this stage, the individual may respond to meaningful stimuli, such as his or her name being called. This stage lasts about 10-25 minutes.

Stage 3 and 4 sleep (also called deep sleep or slow wave sleep, SWS) are identified when slow (2 hertz) high voltage waves (≥ 75 microvolts) appear in 20-50% or $>50\%$ of the EEG record respectively. NREM sleep lasts about 20-40 mins for the first cycle. Body movements then signal a lightening of sleep once more for a few minutes followed usually by REM sleep.

The first NREM-REM cycle lasts 70-100 minutes and then the cycle lengthens to 90-120 minutes. During the later stages of sleep the REM stages become more pronounced and the lighter stages of sleep dominate the NREM portion. Brief episodes of wakefulness also intrude near the transitions into REM sleep. Body

temperature regulation is also lost during REM sleep and may be used as a marker of sleep.

2.4. Normal characteristics of sleep and changes with age

The total length of the sleep period in people 16-93 years of age in a UK population is 7.04 (SD 1.55) hours per night in the week and an hour longer at week ends (Groeger et al, 2004). In the normal individual, NREM sleep constitutes about 75-80% and REM about 20-25% of total sleep, with wakefulness accounting for less than 5%. There may be a significant variability both within and between individuals in sleep length and pattern. Age is one of the strongest factors affecting sleep stages across the night. Unlike the adult, in the new born, transition to sleep is via REM and the REM-NREM cycle period is shorter (90mins). As any parent may experience, the sleep pattern of the human infant is consolidated in the first 3-6 months of life when there is increasingly developed slow wave sleep (stage 3 and 4). Slow wave sleep gradually decreases with age and is said to parallel the loss of cortical density (Feinberg, 1983). By the age of 60, there is loss of SWS particularly in men, although REM sleep is maintained in old age unless there is organic brain dysfunction (Prinz,1982). This effect may be important as changes in transitions between the stages of sleep are associated with differences in movement and the latter may be used as a measure of sleep. There is also a profound increase in inter-individual variability in sleep with age (Williams et al, 1974).

Sleep recovery tends to favour a preferential rebound of the stage in which loss of sleep has occurred. This is an important consideration as disrupted sleep may be experienced in the first night of a sleep laboratory and characteristically occurs with

delayed onset of the REM period (Agnew et al, 1966). Indeed, the first REM period may even be missed.

2.5. Biases which may effect sleep and its evaluation.

There may be characteristic changes in sleep which occur, peculiar to depression and dementia respectively. These are described in chapters 12 and 18 in this thesis. There also exists a number of factors which may cause problems when evaluating sleep which are common to both depression and dementia and some factors which apply specifically to each condition. For convenience the general problems are described below to avoid repetition and the the specific problems which apply to evaluation of sleep in depression and dementia are described within parts II and III of this thesis respectively.

Memory is significantly affected by sleep. In particular memory is lost in the three minutes prior to sleep onset (Wyatt et al 1994) and also recall of awaking depends on the stage of the sleep cycle. This may be of particular relevance when collecting self report data about sleep; for example information about the number of awakenings. There are also cognitive deficits commonly associated with depression, which may introduce further problems when using rating scales, described in section 8.3, which rely on self report for quantitative information about sleep. In dementia sleep itself will further impair memory problems which are already present. Thus, using self report as a main outcome measure for sleep is likely to be unreliable at best for depression and useless in dementia.

Sleep may be differentially affected by drug ingestion. Benzodiazepines tend to suppress slow wave sleep, whereas tricyclic antidepressants and monoamine oxidase inhibitors suppress REM sleep, with a decrease or increase in motor activity respectively. Withdrawal is associated with a rebound of that sleep stage and associated motor activity. Wrist actigraphy, described in section 8.2 relies on movement as a proxy measure of sleep. It follows that administering drugs which may differentially effect the stages of sleep, and thus movement, may also interfere with evaluation of sleep using actigraphy.

2.6. Conclusions

The characteristics that define sleep and wakefulness are subject to debate. Sleep onset is characterised by EEG changes observed in stage 2 sleep. Cognitive changes in sleep include disengagement from the environment and memory impairment. The physiological changes that take place during the different phases of sleep, include periods of movement which can then be used as proxy measures of sleep in wrist actigraphy. However, there is significant variability both between and within individuals and gender and age difference in sleep. The different stages of sleep are also affected by psychotropic drugs. Memory problems are likely to bias information using self report measures of sleep and drug effects may interfere with the stages of sleep measured using wrist actigraphy.

Chapter 3 TREATMENTS OF PSYCHIATRIC DISORDERS VIA MODULATION OF ENDOGENOUS MELATONIN

3.1. Control of endogenous melatonin secretion in psychiatric disorders

A number of factors have been identified which control circadian rhythms and are known as zeitgebers (time givers). Zeitgebers interfere with the timing of endogenous melatonin secretion. Experiments which aim to manipulate endogenous melatonin secretion (described in this thesis) using exogenously administered preparations therefore need to consider the influence these zeitgebers may have on this endogenous cycle. Light is the main zeitgeber in the normal setting. A number of weaker zeitgebers have also been described, including knowledge of clock time, behavioural regimens associated with work and social activity, feeding times, temperature and drugs, as well as melatonin itself (Arendt, 1995). It has been suggested that modulating endogenous melatonin secretion may also provide a mechanism through which to influence sleep and mood. Attempts have been made to treat sleep disturbance in affective disorders or dementia by manipulating endogenous melatonin using light. However, the use of non light zeitgebers is also beneficial in for example personnel working in low light level such as in the Antarctic (Arendt, 1995), although their role in depression and dementia remains to be explored. Indeed, there is a dearth of information about the mechanism that controls the sleep wake cycle in depression and dementia. Nevertheless, good sleep hygiene is often advocated, although it is unclear whether the beneficial effects are working through entraining the endogenous melatonin cycle.

3.2. The use of light in the modulation of endogenous melatonin and psychiatric disorders

A theoretical rationale underpinning the use of light in the treatment of psychiatric disorders where there is a chronobiological dysfunction is that light acts as a zeitgeber and may be

working through endogenous melatonin. Although melatonin is strongly associated with the control of the sleep-wake cycle, its mechanism of action remains uncertain (Enns, et al 1999). Artificial bright light has been used in the treatment of sleep disorders (Campbell et al, 1998; Chesson et al, 1999), adaptation to time zones (Herxheimer and Petrie, 2005), shift work changes (Eastman, 1999), seasonal lethargy (Partonen et al, 2000), premenstrual depression (Parry et al, 1998) and bulimia nervosa (Lam et al, 1998). Only the use of light treatment in affective disorders and dementia will be briefly described.

The strongest evidence that light might help in the treatment of affective disorders applies to seasonal affective disorder (SAD), but in non-seasonal depression the evidence is less clear (Tuunainen et al, 2005). There have also been some case reports to suggest that light therapy may trigger manic episodes. The first controlled clinical trial of bright light in SAD was conducted in 1984 by Rosenthal et al. Lewy et al (1987; 1988) and Sack et al (1990a) suggested that morning light would correct phase delays in circadian rhythms in winter depression. Although a shift to an earlier phase position is associated with the antidepressant effect of morning light (Lewy et al, 1987, 1988; Sack et al 1990a, Dahl et al, 1993; Avery et al 1997) or morning plus evening light (Terman et al, 1988), there is no clear correlation between the size of the phase shift and clinical improvement, which weakens an argument for a causal effect (Eastman et al, 1993; Thalen et al, 1995; Wirz-Justice et al, 1995; Yamada et al, 1995; Thompson et al, 1997). A review of the efficacy of light treatment (Terman et al 1989) and a more recent Cochrane review (O'Grady et al, 2003; Tuunainen et al, 2005) suggests that there may be an advantage of morning over evening light. Furthermore, there appears to be a benefit of light over non-photic placebo (Terman et al 1998; Eastman 1998). However, as described in section 3.3, light therapy may not be acting through melatonin alone.

In dementia the modulation of endogenous melatonin is even more complex. There is a loss of circadian rhythmicity in melatonin secretion in people with Alzheimer's disease. There is also disruption of endocrine secretion (Prinz et al 1982; Touitou et al, 1982; Ancoli-Isreal et al, 1997), which may also contribute to disruption of melatonin secretion, a principal zeitgeber. There appears to be some evidence that light therapy improves nocturnal sleep in dementia (Van Someren et al, 1999; Forbes et al, 2003). Although the precise mechanism mediating these processes is unclear. Possibly older people have a reduction in sensory input, because they are less active and less exposed to daylight, and this also affects endogenous melatonin. Furthermore, barriers such as spectacles and cataracts may make the eyes less sensitive to bright light. Finally, there may be fewer social zeitgebers (van Someren et al, 1993).

Neuropathological investigation in dementia has also revealed a loss of vasopressin-secreting neurones in the SCN area pertinent to the neural pathways supplying the pineal gland (Liu et al, 2000; Swaab et al, 1985). Liu et al (2000) nevertheless point out it would be premature to assume that these neurones have died, as they could simply be inactive. Nevertheless, disruption of this system may explain disruption of the sleep-wake cycle. In rats it is possible to demonstrate that exposure to bright light may reactivate these cells and reverse the disturbance of the sleep wake cycle associated with increasing age (Witting et al, 1993). In rats light prevents the decrease in SCN neurones with age (Lucassen et al, 1995), but it is unclear whether stimulation by light reactivates SCN neurones. Several studies have investigated the use of light therapy in managing sleep and behavioural disturbance and its effect on mood and cognition in people with Alzheimer's disease. For further information the reader is referred to the Cochrane review by Forbes et al, (2003).

3.3. Synergistic effect between light and exogenous melatonin

Manipulation of the human circadian system may be brought about by bright light and melatonin (Deacon, 1994). Several other issues arise when considering light in the treatment of psychiatric disorders. The use of light in combination with other treatments is of interest, as it may be that there exists a synergistic effect. In the case of depression, light has been used with antidepressant medication (Beachemin et al, 1997) and sleep deprivation (Neumeister et al 1996). Only one trial has investigated the use of light in combination with melatonin. Haffmans et al, (1998) conducted a trial (see section 7.4) in dementia investigating differently timed light and melatonin. The authors suggested that “*research on the effects of a treatment with only melatonin on motor restlessness is recommended*”.

3.4. Conclusions

Light studies demonstrate that it is possible to influence endogenous melatonin secretion, although it is unclear whether melatonin is the therapeutic ingredient mediating the response.

Chapter 4 METHODS OF SEARCHING THE LITERATURE

In this thesis, a review of the use of exogenous melatonin in psychiatric and other disorders of the sleep wake cycle will now be presented. Part II and III of this will describe two experiments using exogenous melatonin. The first involves the its use in depression and the second its use in dementia. The theoretical background which applies specifically to the experiments will described in Parts II and III respectively.

Systematic reviews have already been conducted into the use of melatonin in jet-lag (Herxheimer and Petrie, 2005) and cognitive impairment in dementia (Jansen et al, 2006). Meta-analyses have also been conducted into the use of exogenous melatonin in sleep disorders (Brzezinski et al, 2005; Buscemi et al, 2006). Extensive reading was undertaken when planning the studies described in this thesis, but the literature review presented specifically focuses on the use of melatonin for sleep problems in depression and dementia respectively, using search strategies described in section 4.2. As will be seen, very few RCTs have been published. A systematic review is not only beyond the scope of this thesis, but in the authors opinion, because of the wide variation in conditions, would be inappropriate. Indeed, combining all studies which use melatonin for a variety of conditions using methods similar to Buscemi et al (2006) may lead to inconsistent results (Arendt, 2006).

4.1. Search methods for literature review

There were 6 stages of searching which ran concurrently.

1. Key primary electronic databases.
2. Grey literature – Conference proceedings and dissertations
3. Hand searching of key journals

4. References within bibliographies e.g. books
5. Direct contact with selected suppliers melatonin.
6. Direct contact of selected authors by email.

Although the overview and background of the thesis was prepared using the above, the search strategy employed was designed to generate a very high sensitivity for identifying papers where exogenous melatonin was used for treating patients with dementia or depressed mood.

1. Electronic searching:

(i). **Electronic databases** were used and accessed through the Royal Free and University College Medical School, Royal Free Campus Library Server:

- a) *MEDLINE*, Dialog 1951- current: Compiled by the U.S. National Library of Medicine (NLM) and published on the Web by Community of Science, MEDLINE[®] is a comprehensive source of life sciences and biomedical bibliographic information. This is a similar database to PubMed and consultation with an experienced librarian suggested that this would not add anything to the search.
- b) *EMBASE*, Dialog 1980- current: The Excerpta Medica database, is a comprehensive bibliographic database covering the worldwide literature on biomedical and pharmaceutical fields.
- c) *PsycInfo*, Dialog 1887- current:PsycInfo is an electronic bibliographic database that provides abstracts and citations to the scholarly literature in the behavioural sciences and mental health. The database includes material of relevance to psychologists and professionals in related fields such as psychiatry, management, business, education, social science, neuroscience, law, medicine, and social work.

- d) *PASCAL*, 1973 – Current: *PASCAL* is a multilingual, multidisciplinary database that covers the core scientific literature in Science, Technology and Medicine with special emphasis on European literature (45% of the indexed documents).
- e) *CINAHL* 1982 - current: Citation Index for Nursing and Allied Health was searched using the Dialog interface. This database covers the nursing and allied health literature.

(ii) Cochrane data bases

The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews. These databases include:

- a) Cochrane database for systematic reviews.
- b) Database of Abstracts of Reviews of Effectiveness.
- c) The Cochrane Central Register for Controlled Trials (CENTRAL).
- d) The Cochrane Database for Methodology of Reviews
- e) The Cochrane Methodology Register (CMR)

(iii) Grey literature

- a) Using Medical Research Council Index to theses and www.controlled-trials.com
- b) Dissertation abstract 1861 – current: This is a database of dissertation abstracts listing research undertaken for PhDs, Masters thesis submitted to over 1,000 universities.
- c) Index to thesis outline 1970 – current: This provides a comprehensive listing of all theses with abstracts accepted for higher degrees by Universities in Great Britain and Ireland since 1716.

- d) Index to scientific and technical proceedings 1990 – current: Fields cover agriculture and environmental sciences, biochemistry and molecular biology, biotechnology, medicine, engineering, computer science, chemistry, and physics.
- e) The metaRegister of controlled trials (mRCT): This is an international database of ongoing randomised controlled trials in all areas of healthcare, built by combining registers held by public, charitable and commercial sponsors of trials.
- f) National Research Register (NRR): This is a register of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service.
- g) Research Findings Register (ReFeR): This is a register of quality assured information that emerge from completed projects funded by the Department of Health, including the NHS executive.
- h) SIGLE- Grey literature in Europe and the Index of the Pharmaceutical Association. 1980- Current: SIGLE (System for Information on Grey Literature in Europe) is a bibliographic database covering European non-conventional (so-called grey) literature in the fields of pure and applied natural sciences and technology, economics, social sciences, and humanities.

4.2. Developing a search strategy

In order to achieve a high sensitivity for identifying papers, thesaurus terms were included as well as searching on key text words. To increase sensitivity, the use of 'OR' was used to combine data sets, moreover no language or publication type filters were used. The search strategy was used for the period from 1951 for Medline as a pilot and the results generated a search strategy translated into other databases. The search strategy was reduced to two concepts: melatonin (the independent variable) and mental disorders (e.g. dementia,

affective disorders or manic depression (the dependent variable). For each concept, a list of words were generated and these were combined, using the logical operator 'OR', with their respective thesaurus terms. To increase sensitivity no language or methodology filters were employed. The search strategy (see below) was developed and refined initially in the Medline database before being translated for use in the other databases. An example of the strategy is given below.

Table 4-1 Example of a search strategy

Advanced Search: MEDLINE - 1951 to date (MEZZ)

Search history:

No.	Database	Search term	Info added since	Results	
1	MEDLINE - 1996 to date	Melatonin	Unrestricted	5762	Save title
2	MEDLINE - 1951 to date	Melatonin	Unrestricted	11069	Save title
3	MEDLINE - 1951 to date	Melatonin.W..DE.	Unrestricted	9306	Save title
4	MEDLINE - 1951 to date	2 OR 3	Unrestricted	11069	Save title
5	MEDLINE - 1951 to date	2 OR 3	Unrestricted	11069	Save title
6	MEDLINE - 1951 to date	affective ADJ disorders	Unrestricted	12334	Save title
7	MEDLINE - 1951 to date	Mood-Disorders.DE. OR Depressive-Disorder.DE.	Unrestricted	42849	Save title
8	MEDLINE - 1951 to date	Mania	Unrestricted	3970	Save title
9	MEDLINE - 1951 to date	Bipolar ADJ disorder	Unrestricted	18262	Save title
10	MEDLINE - 1951 to date	Bipolar-Disorder.DE. OR Cyclothymic-Disorder.DE.	Unrestricted	17328	Save title
11	MEDLINE -	mood ADJ disorders	Unrestricted	8139	Save title

	1951 to date				
12	MEDLINE - 1951 to date	Affective-Disorders-Psychotic.DE.	Unrestricted	1743	Save title
13	MEDLINE - 1951 to date	Depression	Unrestricted	155110	Save title
14	MEDLINE - 1951 to date	depressed OR depressive	Unrestricted	100277	Save title
15	MEDLINE - 1951 to date	6 OR 7 OR 10 OR 11 OR 12 OR 13 OR 14	Unrestricted	225663	Save title
16	MEDLINE - 1951 to date	8 OR 9	Unrestricted	19316	Save title
17	MEDLINE - 1951 to date	4 AND 15	Unrestricted	808	Save title
18	MEDLINE - 1951 to date	16 AND 4	Unrestricted	75	Save title
19	MEDLINE - 1951 to date	Dementia	Unrestricted	48039	Save title
20	MEDLINE - 1951 to date	Dementia.W..DE. OR Aids-Dementia-Complex.DE. OR Alzheimer-Disease.DE. OR Aphasia-Primary-Progressive.DE. OR Creutzfeldt-Jakob-Syndrome.DE. OR Dementia-Vascular.DE. OR Kluver-Bucy-Syndrome.DE. OR Lewy-Body-Disease.DE. OR Pick-Disease-Of-The-Brain.DE.	Unrestricted	55558	Save title
21	MEDLINE - 1951 to date	4 AND 20	Unrestricted	85	Save title
22	MEDLINE - 1951 to date	exogenous ADJ melatonin	Unrestricted	364	Save title
23	MEDLINE - 1951 to date	exogenous ADJ melatonin	Unrestricted	364	Save title
24	MEDLINE - 1951 to date	23 AND 15	Unrestricted	18	Save title
25	MEDLINE - 1951 to date	23 AND 16	Unrestricted	1	Save title
26	MEDLINE - 1951 to date	19 OR 20	Unrestricted	72024	Save title
27	MEDLINE -	26 AND 23	Unrestricted	4	Save title

	1951 to date				
28	MEDLINE – 1951 to date	26 AND 4	Unrestricted	107	Save title
29	MEDLINE – 1951 to date	limit set 17 H=Y	Unrestricted	530	Save title
30	MEDLINE – 1951 to date	limit set 18 H=Y	Unrestricted	75	Save title
31	MEDLINE – 1951 to date	limit set 28 H=Y	Unrestricted	87	Save title
32	MEDLINE – 1951 to date	29 OR 30 OR 31	Unrestricted	604	Save title

As can be seen from the above, for the 11,069 articles published on melatonin, although 692 (530 + 75 + 87) were identified for each dependent variable dementia, affective disorders and dementia), because there was some overlap in articles cited in each group 604 articles were scrutinised with the full details of relevant papers obtained and any additional papers reviewed using cross referencing. Very few trials RCTs were published and most trials comprised of case reports and open label studies.

The table 4.2 below shows a summary for the search strategies for melatonin in affective disorders and dementia for the different electronic databases and demonstrates that Medline, EMBASE and PASCAL, which are biased towards medical research, generated significantly more references than Psycinfo and CINAHL which are orientated to towards psychologically and nursing literature respectively.

Table 4-2 Summary for search strategy using different electronic data bases

Electronic database searched	Total relevant articles
MEDLINE (1951-Current)	604
EMBASE (Dialog 1980-Current)	219
PsycInfo (Dialog 1887-Current)	67
PASCAL (1973- Current)	191
CINAHL (1982-Current)	37

(ii) Cochrane Data Bases

- a) Cochrane database for systematic reviews: a systematic review for the use of melatonin for the prevention and treatment of jet leg was identified (Herxheimer and Petrie, 2002)
- b) Database of Abstracts of Reviews of Effectiveness: There exists one protocol for melatonin in cognitive impairment (Forbes et al, 2005).
- c) The Cochrane Central Register for Controlled Trials (CENTRAL) was searched using terms melatonin and Exploded MeSH for mood disorders, bipolar disorder and dementia respectively. Forty nine, 4 and 6 articles were identified respectively.
- d) The Cochrane Database for Methodology of Reviews did not generate any articles.
- e) The Cochrane Methodology Register (CMR) did not generate any trials.

(iii) The Grey literature

The “Grey” literature was surveyed. However, what is striking is that most of the research published is undertaken in vitro or using animals. Because of the slightly different search terms findings for each data base is given separately.

- a) Medical Research Council Index to theses and www.controlled-trials.com/mrct.

This database allows access to e) described below.

- b) Dissertation abstract 1861 – current

Fifty nine theses were published citing mood disorders or dementia melatonin. However only one PhD (The effects of melatonin on sleep and cognition in cognitively impaired elderly individuals, Jean-Louis (1997)) was relevant. It is worth noting however that two PhD investigated the effects of exogenous melatonin in humans (Yang, 1999; Sharkey, 2001)

- c) Index to thesis outline 1970 – current: Melatonin used as a search term. 111 theses made reference to melatonin, which included all species. There were no studies identified which investigated the use of exogenous melatonin for treating either affective disorders or dementia.
- d) Index to scientific and technical proceedings 1990 – current: None of the 35 and 45 studies identified from searching melatonin and mood and melatonin in dementia respectively were relevant.
- e) MetaRegister of Controlled Trials: Melatonin was entered as a search term 12 trials, including the trial of melatonin for sleep disturbance in dementia described in this thesis, were identified.
- f) National research Register (NRR): No records found
- g) Research Findings Register (ReFeR): No trials identified.
- f) SIGLE- Grey literature in Europe and the Index of the Pharmaceutical Association. Search term entered using melatonin only. 55 records identified. Non applied to the use of exogenous melatonin in affective disorders or dementia.

2. Direct suppliers of melatonin

A number of suppliers of melatonin were identified world wide using google.com. These were all commercial organisations. An email was sent out asking if they had conducted any

research evaluating the effects of melatonin in depression or dementia. Manufacturers of melatonin provided information about the cost and form of melatonin (capsules or tablets, slow release). Non reported conducting research in the field. However one company - Vitapure Ltd (formerly Genzyme Pharmaceuticals), 37 Hollands Road, Haverhill, Suffolk CB9 8PU, England- indicated that they would be interested in further research in the area and were prepared to supply slow release melatonin free of charge.

3. Hand reviews of key journals and conference proceedings.

Articles.

Review of the abstracts from the electronic search generated the most commonly used papers for melatonin. Information about current research in the field was also identified through the Society for Light Treatment and Biological Rhythms (SLTBR).

4. Handsearching references in papers identified from electronic searching

All articles cited in papers relevant to the use of exogenous melatonin in humans were reviewed. Any paper, published in English, which was not identified from electronic searches was ordered through the interlibrary loan system and the full length article reviewed.

5. Reference to books published on melatonin.

Books published on melatonin were identified using Psychlit and commercial websites (e.g. amazon.com). Direct contact of selected authors by email. Identifying books on melatonin was also made using commercial websites such as www.amazon.co.uk.

7. Direct contact of selected authors by email

Authors who had published in both the field of melatonin and also specifically had published RCT in melatonin in depression and melatonin in dementia were contacted to see whether they were aware of any unpublished RCTs evaluating the use of melatonin in this patient group.

Findings

Randomised Controlled trials (RCTs) are considered the “Gold standard” in research. Given the dearth of papers, published material, RCTs, open label trials and case reports , all published trials are presented in chronological order.

An overview of studies published between 1976 and 2005 describing the use of exogenous melatonin is presented in chapters 5 and 7. Chapter 5 outlines the use of exogenous melatonin in sleep disorders, blind people and jet lag. A detailed review describing the use of melatonin in affective disorders and dementia is presented in chapter 7. A descriptive summary of these trials is also presented in tables 5.1 for RCTs in sleep disorders , blind people and jet lag and tables 7.1. and 7.2 presents a summary of all studies published for affective disorders and dementia respectively. For a detailed description of the studies the reader should consult the text.

Chapter 5 THERAPEUTIC USES OF EXOGENOUS MELATONIN IN NON-PSYCHIATRIC DISORDERS

5.1. Melatonin and sleep disorders

The modulatory effects of the pineal appear to be controlled by the secretion of melatonin. It has been hypothesised to have two functions in the treatment of sleep disorders. First it has a direct soporific effect (Zhdanova and Wurtman, 1997; Lavie, 1997) and secondly it helps entrain circadian rhythms (Sack, Lewy and Hoban, 1987). There is evidence to suggest that melatonin might be useful in the treatment of (i) free running circadian rhythms, (ii) shift work, (iii) jet lag, and (iv) sleep disorders in older people without dementia. Each of these fields is discussed below.

5.2. Melatonin in people with free running circadian rhythms

In most people, the endogenous circadian pacemaker oscillates with a period of just over 24 hours (Sack and Lewy, 1997). This therefore requires synchronisation or entrainment to hold back the rhythms to the 24 hour day. Such adjustments rely on environmental cues, particularly the light-dark cycle (Moore-Ede et al, 1982). In totally blind people, light cues are unavailable and disturbance of the circadian rhythm commonly occurs (Miles et al 1977; Orth et al, 1979; Lewy and Newsome 1983; Sack, Lewy and Hoban, 1987; Sack, Stevenson and Lewy, 1990; Nakawaga, Sack and Lewy 1992; Sack et al, 1991; Sack et al, 1992; Sack and Lewy, 1997; Lockley, 1997). This is associated with daytime sleepiness and night time insomnia. The ideal therapy would entrain the 24 hour cycle so that the endogenous rhythm parallels the circadian process of day and night. A pharmacological zeitgeber would be the most practical way for the light dark cycle to be entrained.

In 1983 Redman et al were the first to demonstrate that exogenous melatonin could entrain rhythms in rats. Building on this work, Sack, Lewy and Hoban (1987) were the first to report phase shifts with melatonin and triazolam administration. A number of reports of satisfactory entrainment, though not proven conclusively, were then published. Initially a single case report (Arendt et al, 1988) and then further reports suggested that synchronisation of the sleep-wake cycle can occur in blind men (Sack et al 1990; Sack et al, 1999) and blind children with learning difficulties (Palm, 1991; Lapiere and Dumont 1995) using melatonin. Then RCTs on small groups of cases were published (Sack et al, 1991, Lockley et al, 2000; Sack et al, 2000; Hack et al, 2003, 2004).

Sack et al (1991) conducted a double-blind, placebo-controlled trial on five totally blind men with free-running endogenous melatonin rhythms. They were given exogenous melatonin (5 mg) at bedtime (22.00 hr) for 3 weeks. This phase-advanced the circadian rhythm in 4 out of 5 blind people with free running melatonin cycles.

Lockley et al (2000) undertook a single-blind design on seven blind participants who had free running urinary 6-sulphatoxymelatonin (aMT6s) and cortisol rhythms. Five participants were given placebo or 5 mg melatonin orally daily at 21.00 hours and two melatonin only. Urinary aMT6s and cortisol (n=7) and core body temperature (n=1) were used as phase marker. The efficacy of melatonin in entraining the free-running cortisol rhythms was dependent on the circadian phase at which the melatonin treatment started. Four of the seven free-running subjects who received melatonin exhibited a shortening of their cortisol circadian period (τ) and in three of these four the τ was statistically indistinguishable from entrainment. The three other subjects continued to free-run during the melatonin treatment at a similar τ as prior to and following treatment. Using reliable physiological markers, the

efficacy of melatonin in entraining the free-running cortisol rhythms can be assessed.

Entrainment appears to be dependent on the circadian phase at which the melatonin treatment commenced. Daily melatonin administration can entrain free-running circadian rhythms.

Sack et al (2000) performed a crossover study in which seven totally blind participants were given an exogenous dose of melatonin 10mg or placebo one hour before their preferred bedtime for three to nine weeks. The timing of the production of endogenous melatonin was measured as a marker of the circadian time (phase) and sleep was monitored using polysomnography. All subjects had lengthened free running rhythms of a mean of 24.5 hours. In six out of 7 participants, melatonin entrained the rhythm to a 24.0 hour cycle. They concluded that melatonin can entrain the rhythm in most blind people. It was later shown that the one individual who could not be entrained with 10mg or 20 mg, did respond to 5mg of melatonin. This is important as it suggests that too much melatonin may spill over into the wrong zone of the melatonin phase response curve (Lewy et al, 2002). Lewy et al(2001) have continued to accumulate evidence of entrainment, building on their cohort of people previously described (Sack et al, 2000).

Hack et al, (2003) Conducted a placebo single blind controlled trial in which 10 participants were randomised to 0.5 mg melatonin or placebo, at 21.00, for 26-81 days depending on the individuals circadian period. Subjective sleep was assessed using daily sleep and nap diaries and urinary cortisol and MT6s were assessed. Findings suggest that melatonin is effective at entraining the free-running circadian system in most blind subjects studied.

5.3. Shift Work

Shift workers, especially those who work night shifts, suffer from the effects of circadian desynchrony in that their endogenous rhythms are often out of time with the desired sleep time. This results in symptoms of insomnia such as delayed sleep onset, a persisting fatigue that does not disappear after sleep, and irritability. Shift workers can also experience more serious symptoms such as epigastric pain, indigestion, peptic ulcer, and even cardiovascular complaints (Morre-Ede and Richardson 1985). Research carried out in this area has been limited, but the few studies that have attempted to treat the condition with melatonin have had some success.

Folkard et al (1993) conducted a double blind randomised trial in 17 police officers, following a 4 weeks baseline period of data collection. A crossover design was used so that 5mg melatonin or placebo was given for 14 days and then vice versa. Melatonin/placebo was given at bedtime. A number of measures were used: sleep diaries, mood checklists, work load ratings, ratings of alertness and memory tasks. Findings from the data analysed should be treated with caution as only 7 participants completed the trial. Findings suggested that melatonin improved sleep and alertness, but may have impaired mental processing and resulted in an increased rating of mental load.

Dawson et al (1995) conducted a study on simulated shift work comparing bright light, placebo or melatonin (4mg in three divided doses across the sleep wake period). Similarly to the study described above they measured melatonin levels and sleep using wrist actigraphy as an objective measure of sleep. Melatonin did show an improvement in the quality of sleep which they suggested was due to the hypothermic effects of melatonin, although they failed to show a phase shifting effect. It is worth noting that the timing of melatonin may account for

this because it may not have been given at the right time in the phase response curve (Lewy et al, 1992).

One of the most rigorous studies to date was undertaken by Sack and Lewy (1997) who used exogenous melatonin 0.5mg in a group of 24 healthcare workers. They took blood and salivary samples to estimate DLMO time and showed considerable variability in phase shifting of night workers. Outcome measures included melatonin levels and objective measures of sleep using wrist actigraphy. Melatonin seems to significantly augment the phase shifts in a subgroup of workers who did not shift with placebo alone. They however point out that many questions about factors which shift phases remain; individual factors (age, sex, morning-eveningness), optimal parameters for melatonin administration and clinical applicability of melatonin. They also raise the issue of safety of melatonin in the long term, although no deleterious side effects have been reported, except at extremely high doses (240mg) (Arendt et al 1987).

Jorgensen and Witting (1998) conducted a double blind, placebo controlled crossover trial. Physicians were given 10 mg of sublingual melatonin/placebo after a string of nights/days. Sleep was assessed using the Stanford Sleepiness Scale (Hoddes et al, 1973). Although the authors suggest melatonin improved sleep and alertness during sleep and wake periods respectively, this was not statistically significant and therefore the authors suggestion that there were modest improvements with melatonin needs to be treated with caution.

Wright et al (1998) conducted a randomised placebo double blind crossover trial of melatonin 5mg for 3 consecutive nights after night shift duty in fifteen emergency physicians. Global assessment of recovery was measured on a visual analogue scale. Secondary outcomes

included the Profile of Mood States (McNair et al, 1981). They concluded that there were no differences in sleep quality, duration or tiredness scores, sleep latency, hours of sleep obtained. However, no objective measures of sleep were taken.

Jockovich et al (2000) recruited emergency residents for a prospective randomised double blind crossover trial. Residents worked a string of at least three nights and each period of nights was separated by at least one week of days. Nineteen volunteers were then randomised to receive either melatonin 1mg or placebo 30 minutes prior to sleep. Objective measures were made using actigraphy and subjective measures taken using the Stanford Sleepiness Scale (Hoddes et al, 1973) and Profile of Mood states (McNair et al, 1981). No differences in sleep or mood were observed between melatonin and placebo. However, numbers were small and it may be that residents did not have time to adjust to the new sleep-wake cycle.

In conclusion, there is some evidence that melatonin may be of benefit in a subgroup of melatonin responders, but most studies have been poorly designed, with small numbers, few objective measures taken and there is also a concern that wrongly timed melatonin could lead to sleepiness at work.

5.4. Jet lag

Until Wiley Post made the first flight around the world 60 years ago, the condition now known as jet lag was unheard of (Kayumov et al 2000). Nowadays it is a common, albeit transient complaint, of travellers who fly across a number of different time zones (Winget et al, 1984). Jet lag results in a desynchronisation of circadian rhythms of the sleep-wake cycle with local time. This can be troublesome as there is daytime fatigue and sleep disturbance and also a detrimental effect on mental efficiency weakness and irritability (Comperatore and Krueger,

1990). A number of both real and simulated studies have now emerged that have examined the efficacy of exogenous melatonin as a treatment for the symptoms of jet lag (Arendt, 1995) and recently a systematic review was published, examining the evidence for melatonin in the prevention and treatment of jet lag (Herxheimer and Petrie, 2005).

Arendt and Marks (1983) first suggested that melatonin might hasten the resynchronisation of human 24-hour rhythms after time zone changes. In 1987, she and colleagues were the first to test melatonin for the treatment of jet lag (Arendt et al 1986; 1987). They conducted a double blind RCT in which 17 participants who flew Eastward (from London to San Francisco) over 8 time zones used melatonin 5mg (n=8) or placebo (n=9). They took the preparation prior to their departure from the USA and upon return to the UK 14 days later. Biochemical measures included urinary samples and oral temperature. Measures of sleep were made using a visual analogue scale and wrist monitors. Six out of nine participants allocated to the placebo group reported symptoms of jet lag. None of those allocated to the melatonin group reported such symptoms, the main difference between the groups being a reduction in sleep latency (time taken to get to sleep) associated with melatonin. There was also a significant improvement in mood, although melatonin did cause drowsiness if taken in the late afternoon. Although activity recordings suggested there was disturbed sleep in jet lagged subjects, the findings were not clear cut.

Skene et al (1989) undertook a double-blind randomised trial in which 61 participants flew East (from UK) to West (to Australia and New Zealand) and back. Two days prior to the outward journey melatonin was taken at equivalent to 02.00 at the local destination time and at bedtime 4 days after flying. On the return journey melatonin was taken at the local bedtime for four days after arrival. Evening tiredness was significantly increased in the melatonin

group 4 days after administration, suggesting a timing effect instead of the pharmacological hypnotic effect.

Petrie et al (1989) conducted a double blind, placebo controlled crossover trial in participants travelling Eastward from New Zealand to London (over 12 time zones) and Westward 3 weeks later on the return flight. Twenty participants were given melatonin 5 mg (or placebo) three days before flight, during flight, and once a day for three days after arrival.

Melatonin/placebo was given on either the outward or the return flight. Outcome measures included: visual analogue scales to measure feelings of jet lag and tiredness, the POMS (McNair, 1981) and retrospective ratings 10 days after arrival of sleep pattern, energy, and daytime tiredness. Feelings of jet lag were less for subjects taking melatonin with fewer days required to establish a normal sleep pattern (2.85 v 4.15), to not feel tired during the day (3.0 v 4.6), and to reach normal energy levels (3.25 v 4.7). For all participants, jet lag was more severe on the return (westward) than the outward (eastward) journey. They concluded that melatonin could alleviate jet lag and tiredness after long haul flights.

Nickelsen et al (1991) conducted a double blind RCT of melatonin (5mg) versus placebo on 36 volunteers flying from Frankfurt to the USA and 2 weeks later in the reverse direction. After the Westbound flight, participants took melatonin or placebo at bedtime for 7 days. On the Eastbound flight they took it at bed time for 5 days. Sleepiness was assessed on self rating using the Stanford Sleepiness Scale (Hoddes et al, 1973), a visual analogue scale using ratings 1-10. They also included measures of cortisol and melatonin. Results showed an advantage of melatonin over placebo.

Claustrat et al (1992) selected 30 volunteers for their sensitivity to Eastward jet lag and then randomised double blind to melatonin (8mg) or placebo. Participants took 8 mg of melatonin (or placebo) at 22.00 hours on the day of their nocturnal flight from the USA to France and for 3 days thereafter at between 22.00 and 23.00. Thirty seven self rated questionnaires using visual analogue scales were completed on day 7. Median sleep efficiency scores were improved in the melatonin group with reports by one participant of a tachycardia and the other of a “heavy head” Indeed, support for this simplified protocol was obtained from a less formal study by Lino et al (1993) who suggested that a single dose of melatonin 5 mg on the evening of arrival is sufficient to prevent classical symptoms of jet lag.

Petrie et al (1993) undertook an RCT in 52 international aircrew who were given early or late melatonin (5mg) or placebo returning to New Zealand from London via Los Angeles. Subjective measures of jet lag (visual analogue scales,) sleep (Stanford Sleepiness Scale; Hoddes et al, 1973) and, mood (Profile of Mood States; POMS, McNair et al, 1981) were made. Timing was important, with melatonin being associated with significantly less jet lag and sleep disturbance when given during the phase delay period, but sleep problems were exacerbated if given in the phase advance stage of the phase response curve. However, the results need to be interpreted with caution as the participants in this study travelled over 12 time zones.

Comperatore et al (1996) conducted a double blind randomised controlled trial of melatonin 10mg versus placebo on the sleep-wake cycle of 29 army aviation personnel flown from the USA to the Middle East. Activity monitors were used to estimate rest cycle activity according to methods described by Comperatore et al (1993). A computerised battery also tested dual task vigilance, simple reaction time, choice reaction time, Profile of Mood States (McNair et

al, 1981) and the Stanford Sleepiness Scale (Hoddes et al, 1973). Data was available on 23 of 29 subjects. The melatonin (10mg) group made significantly fewer errors in a cognitive test compared to the placebo group and experienced less sleep disruption. However this trial tested the adaptation of US soldiers to night operations at the destination in the Middle East and therefore strictly speaking, is not an adaptation to the new time zone.

The above findings therefore suggested that appropriately timed doses (administration should coincide with evening time at destination) of melatonin are associated with a reduction of self-rated symptoms. For further reviews also see (Herxheimer, 2005; Arendt 1995; Sanders et al, 1998; Buscemi et al, 2006). However, two recent studies shed doubt on earlier conclusions.

In 1997 Spitzer et al published their findings from a study of a group of 257 physicians flying from Oslo to New York and back again five days later. This is one of the largest studies to date. This double blind RCT was directed at examining the treatment of jet lag with melatonin (either 0.5mg or 5mg taken at bedtime, or 0.5mg taken on a shifting schedule). They also developed a new, syndrome-specific instrument (Columbia Jet Lag Scale), that could identify prominent day-time symptoms of jet lag distress. The authors found no significant differences between the groups in overall jet lag scores for the six days after travel and concluded that there was no benefit of melatonin for the treatment of jet lag. They did not examine post travel symptoms of sleep onset and only four days were given at the outbound destination which is unlikely to give participants time to adjust to the new time zone. Furthermore, because of the design it is possible that there was a large placebo effect as 3 out of four participants would have received melatonin which would have

diluted the treatment effect. They did however identify the limitations of the study, indication that there was a need for further research.

Suhner et al (1998a) conducted a double blind randomised controlled trial on 320 volunteers from the University of Zurich travel clinic, flying eastwards through 6 to 8 time zones. Participants were given either melatonin 0.5mg, melatonin 5mg, melatonin 2mg slow release, or placebo at bedtime for the first 4 days after the flight. Sleep was evaluated using the sleep logs and the Karolinska Sleepiness Scale, the POMS and a symptoms questionnaire. Only completers were analysed. Fatigue scores on the POMS were similar for 5mg and 0.5mg and both less than for placebo. Self rated sleep quality, sleep latency and fatigue and daytime sleepiness were all better on melatonin. The 2mg slow release form was less effective than either of the fast release tablets.

Suhner et al (1998b) conducted a double blind trial in which 160 volunteers travelled from North America to Switzerland across 6-9 time zones. 137 completed the study. People were randomised to melatonin 5mg, zolpidem 10mg (a hypnotic), zolpidem 10mg plus melatonin 5mg or placebo. This was taken between 5-9pm at the local time on the day of the flight and for 4 days at bedtime thereafter. Assessments were made of sleep quality and mood using the POMS (McNair, 1992). Wrist actigraphy monitoring was used in 80 participants. Those who missed more than one dose were excluded from the analysis. Sleep quality was significantly improved by zolpidem and was reported as the most effective jet lag medication. The melatonin group alone felt least sleepy and the combined melatonin plus zolpidem the most sleepy the day after the flight, presumably because of the side effects of zolpidem.

In a further study by Edwards et al (2000), 31 volunteers were recruited to a study using a matched pairs, double-blind design, to examine the effects of oral melatonin (5mg) or placebo in people travelling from London to Eastern Australia. Data were analysed on 26 of the 31 volunteers. Those taking the melatonin showed no significant differences from the placebo group in perceived irritability, concentration, meal satisfaction, or ease in getting to sleep and staying asleep, as measured using a questionnaire incorporating items for tiredness, sleep, meal satisfaction and ability to concentrate. However, melatonin was given at the wrong time of the phase response curve.

Beaumont et al (2004) undertook a study of 27 healthy air force volunteers 19-47 years of age, (18 men, 9 women) equally randomised to slow release caffeine 300 mg on day 1-5, or melatonin 5 mg on the pre-flight day at 16.00 and at 23.00 for 3 days, or placebo at the same times after they had flown eastward over 7 time zones. They were prohibited from sleeping during the overnight flight. Outcome measures included EEG polysomnography, wrist actigraphy and sleep log questions and oral temperature. The authors concluded that daytime caffeine alleviated daytime sleepiness but exerted unwanted effects on sleep. Although melatonin improved subjective sleep, this was not apparent on objective measures. This was a well designed trial, although the sample size is small and the dose of melatonin such that it is more likely to be acting as a hypnotic than a chronobiotic at this dose. Further studies are required to evaluate the use of slow release caffeine or melatonin for people who have not had previous sleep deprivation.

Thus, although earlier work suggests melatonin may play a positive role in the reduction of symptoms associated with jet lag, with up to one out of every two people benefiting from taking melatonin (Herxheimer and Petrie, 2005), there is not sufficient evidence to

demonstrate that people benefit from taking melatonin prior to the day of travel (Petrie et al, 1993; Revell and Eastan, 2005). Although low doses seem as effective as high doses, slow release preparations are possibly less effective (Suhner et al, 1998a). There is also evidence to suggest that it is easier to lengthen the circadian rhythm. RCT should control variables which may predict outcome and although some of the trials tried to control for these, little is known about the interaction between factors such as the hypnotic effects of alcohol. General linear modelling may help to determine predictors of the treatment effect. As can be seen from these studies a variety of subjective measures are used to measure sleep. Objective measures including biochemical salivary melatonin and wrist actigraphy was used in but a few studies (Arendt and Marks, 1983; Sunher et al, 1998b) and may provide more objective criteria to examine any melatonin treatment effects.

5.5. Sleep disturbance in older people without dementia

Sleep disturbance is a frequent complaint amongst the older population (65 and over) and typically is associated with a decline in melatonin production with age (Touitou 1982; Iguchi et al, 1982; Sack et al, 1986; Zhdanova, 1998) and variable melatonin onset time (Haimov et al, 1994). It was suggested that age-related insomnia might be related to a potentially correctable melatonin deficiency (Haimov et al, 1994; Wurtman and Zhdanova 1995, 2001).

Initial reports by Haimov et al (1993) suggested that fast release melatonin increased sleep initiation in elderly people with insomnia. They then conducted a double blind RCT (Haimov et al, 1995) in which 51 melatonin deficient elderly insomniacs were given slow release, or fast release melatonin (2mg) or identical looking placebo given 2 hours before bedtime. Sleep was measured using wrist actigraphy. Results found that sleep initiation

was improved by the slow release preparation and that it further improved with the slow release preparation suggesting that tolerance had not developed.

Garfinkel et al (1995) reported a small RCT with a crossover design, on 12 elderly participants (aged 68 to 93) who had long term insomnia and were receiving treatment for various chronic non-psychiatric illnesses. In addition, all participants had low melatonin levels when compared to age-matched individuals without sleep disturbance. Garfinkel et al (1995) gave participants controlled-release melatonin 2mg or placebo two hours before desired bedtime every night for three weeks. Wrist actigraphy- an established method, based on wrist movements, that can distinguish between sleep and wakefulness and thus produce an objective measure of sleep duration (Cole et al 1992)- was used to collect the data. Analysis of the data showed that although total sleep time was not significantly affected, melatonin was associated with significant improvements in both sleep efficiency (SE; total time asleep as a percentage of total time in bed) and wake after sleep onset (WAO; which is the time awake accumulated after sleep onset). However a pilot study by Wurtman and Zhdanova (1995) suggested that much lower doses of melatonin (0.3mg)/placebo given before bedtime to people with insomnia, aged 51-78 years, improved objective and subjective measures of sleep quality. The authors concluded that melatonin can promote and sustain sleep in elderly insomniacs.

Further support for the use of melatonin in the treatment of insomnia in the healthy elderly comes from an open label study by Fainstein et al (1997). Exogenous melatonin 3mg was administered 30 minutes before expected sleep time for 21 days to 22 healthy elderly participants with sleep disturbance alone. Melatonin was associated with significantly increased subjective evaluations of sleep quality and a significantly diminished number of

sleep interruptions. The authors conclude that melatonin may be useful in the treatment of primary insomnia in elderly patients, as well as having a potential in reducing the use of benzodiazepine medication, since many of the participants either reduced or stopped their benzodiazepine intake.

Building on the results of their pilot study (Wurtman and Zhdanova 1995), Zhdanova et al (2001) reported an RCT on 30 healthy elderly participants, 15 of whom had impaired sleep efficiency. All participants received placebo or melatonin 0.1mg, 0.3mg and 3mg for a week in a randomised order half an hour before bedtime, with one week washout between treatments. Outcome measures included sleep reports, wrist actigraphy and polysomnography in the last three nights of each treatment period. Unfortunately, the genders and ages of participants are not specified, other than being over 50. All doses of melatonin were effective in restoring sleep efficiency. The 0.3mg dose of melatonin was reported as being more physiological and the higher dose not only induced hypothermia, but also caused the plasma melatonin to be elevated into the daylight hours.

In a double blind randomised placebo controlled crossover trial by Baskett et al (2003), healthy people over 65 years with sleep maintenance problems were screened using Pittsburgh Sleep Quality Index and excluded if on hypnotics or had comorbidity. Forty people (20 normal sleepers and 20 people with sleep maintenance problems) were equally randomised to 4 weeks 5 mg melatonin or placebo and then given placebo/melatonin with each phase being separated by a 4 weeks washout period. Sleep quality was assessed using sleep diaries, the LSEQ and actigraphy. There were baseline differences, but melatonin did not improve quality of sleep.

Overall, the limited number of studies published to date most support a beneficial effect of melatonin for sleep disturbance in the healthy elderly. There is also a suggestion that very low doses of melatonin (0.1 to 0.3mg) are at least as effective as pharmacological doses (3mg to 6mg) (Zhdanova et al 2001) .

A summary of the RCTs of melatonin in non psychiatric disorders is given in table 5.1-2.

Table 5-1 Summary of RCTs of melatonin for sleep disorders in blind people and shift work.

For more details see text.

Studies in Sleep Disorders	n	Study Design	Measure of interest	Main outcome	Result
(i) Totally blind					
Sack et al, 1991	5	RCT	Circadian rhythm	Melatonin onset time	Melatonin synchronises free running melatonin in blind people
Lockley et al, 2000	5	Single blind design	Circadian Rhythm	Cortisol and MT6	Melatonin administration can entrain free-running circadian rhythm
Sack et al 2000	7	Randomised Crossover trial	Endogenous melatonin and sleep-wake activity	Blood samples and polysomnography	Entrainment of circadian rhythms
Hack et al 2003	10	Single blind RCT	Biochemical markers and sleep and nap diaries	Cortisol and MT6	Melatonin effective at entrainment of circadian rhythms
(ii) Shift Work					
Folkard et al 1993	15	Double-blind crossover	Sleep duration and quality	Sleep diaries	Improved daytime sleep and night time alertness
Dawson et al 1995	36	RCT	Sleep	Wrist actigraphy	Improvement in quality of sleep with melatonin over placebo
Sack and Lewy, 1997	9	Double blind crossover trial	Sleep	Wrist actigraphy DLMO	Melatonin augmented the phase shift in a subgroup of workers who did not shift on placebo alone
Jorgensen and Witting, 1998.	18	Double blind crossover trial	Sleep	Stanford Sleepiness Scale	There was a trend towards improvement in sleep with melatonin with 10mg melatonin.
Wright et al, 1998	15	Double blind crossover trial	Sleep	Global assessment of recovery using a VAS POMS	No beneficial effect of melatonin.
Jockovich et al, 2000	19	Double blind crossover trial	Sleep	Wristy actigraphy POMS Stanford Sleepiness Scale	No beneficial effects of melatonin 1 mg compared to placebo.

Table 5-2 Summary of RCTs of melatonin for sleep disorders in jet lag and older people without dementia.

(iii) Jet Lag	n	Study Design	Measure of interest	Main outcome	Result
Arendt et al 1987	17	RCT	Jet lag symptoms	Visual Analogue Scale for Jet Lag Wrist Actigraphy	Reduction in sleep latency
Nickelsen et al, 1991	36	RCT	Jet lag symptoms	Stanford Sleepiness scale	Advantage of melatonin on sleep over placebo
Claustrat et al, 1992	30	RCT	Jet lag symptoms	Visual Analogue scale for sleep	Improved median sleep efficiency
Petrie et al 1993	52	RCT	Jet lag symptoms	Visual Analogue Scale for Jet Lag and Stanford Sleepiness Scale	Significantly less jet lag and sleep disturbance
Comperatore et al 1996	29	RCT	Sleep-wake activity	Wrist actigraphy	Less sleep disruption and performed better on cognitive test
Spitzer et al 1997	257	RCT	Jet lag symptoms	Columbia Jet Lag Scale	No difference between groups in jet lag scores
Suhner et al, 1998a	320	RCT	Jet lag symptoms	Karolinska Sleepiness Scale POMS	Self rated sleep quality, sleep latency, fatigue and daytime sleepiness were better on melatonin.
Suhner et al, 1998b	160	RCT	Jet lag symptoms	Sleep quality , wrist actigraphy, POMS	Zolpidem better than placebo or melatonin, but melatonin alone better than combined melatonin and zolpidem.
Edwards et al 2000	26	Matched pairs; double blind	Jet lag symptoms	Jet Lag Questionnaire	No difference between groups in jet lag scores
Beaumont et al, 2003	27	RCT	Sleep	EEG polysomnography Actigraphy	Slow release caffeine reduced sleepiness and melatonin improved subjective measures of sleep.
(iv) Older people without dementia	n	Study Design	Measure of interest	Main outcome	Result
Haimov et al 1995	51	Double-blind crossover	Sleep-wake activity	Wrist actigraphy	Improvement in sleep maintenance and initiation
Garfinkel et al 1995	12	Crossover RCT	Sleep-wake activity	Wrist actigraphy	Significant improvements in sleep efficiency and wake after sleep onset
Wurtman and Zhdanova, 1995	9	RCT	Sleep	Questionnaire and motor activity	Low dose melatonin improves subjective and objective measures of sleep
Zhdanova et al 2001	30	RCT	Sleep-wake activity	Polysomnography	Improvement in sleep efficiency
Baskett et al, 2003	40	RCT	Sleep	LSEQ and actigraphy	Melatonin did not improve the quality of sleep

Chapter 6 THE THEORETICAL BASIS FOR THE ROLE OF MELATONIN IN DEPRESSION AND DEMENTIA

6.1. Introduction

Melatonin secretion is disrupted in both depression and dementia. Evidence suggests that melatonin plays an essential role in entraining biological rhythms. An understanding of how melatonin secretion is disturbed will help inform research investigating its exogenous use for the treatment of disorders of mood and disorders of the sleep-wake cycle. This chapter will focus on how melatonin may be implicated in the aetiology of affective disorders and dementia. This will help clarify the theoretical rationale underpinning the two clinical trials investigating the use of exogenous melatonin in depression and dementia described in this thesis.

Most of the hypotheses linking melatonin to mood disorders and disruption of the sleep-wake cycle have been described for Seasonal Affective Disorder SAD (Rosenthal et al, 1984), although melatonin may also play a role in non-seasonal depression, bipolar disorder, mania, dementia, eating and panic disorders (Shafii and Shafii, 1998). For convenience, the theoretical basis implicating melatonin in the aetiology of sleep disturbance in affective disorders and dementia will be addressed using a similar approach.

6.2. Melatonin and SAD

In the case of SAD four main hypotheses have been proposed: (i) The melatonin hypothesis. (ii) the circadian phase hypothesis. (iii) the amplitude hypothesis and (iv) the serotonergic hypothesis.

(i) The melatonin hypothesis:

As bright light of sufficient intensity suppresses melatonin secretion in humans, it has been suggested that abnormally high levels of melatonin account for depression in the winter months in the case of SAD (Lewy et al, 1980) and that antidepressant effects are due to suppression of melatonin. Indeed, there are differences in melatonin levels in untreated depressed SAD patients compared to normal controls (Danilenko et al, 1994), but this finding is not universal (Partonen et al, 1996, 1997).

However, attempts to manipulate endogenous melatonin using light treatment reveal some interesting results. The antidepressant effects of light treatment are not dependent on melatonin suppression (Rosenthal et al 1986) which argues against the melatonin hypothesis. Furthermore, in an RCT where melatonin secretion was blocked, using the beta-adrenergic blocker atenolol, there was no therapeutic effect of atenolol (Rosenthal et al, 1988). If SAD is due to abnormal melatonin secretion, one might expect atenolol to have a therapeutic effect. This theory has been refined with a suggestion that the timing of administration of the beta blocker may be important, as truncating the delayed phase of melatonin secretion in SAD patients with propranolol resulted in a response and patients relapsed when switched to placebo (Schlager, 1994). Manipulating melatonin through exogenous administration is no more consistent with this theory. If SAD is due to abnormally high levels of melatonin in winter, then administering melatonin should cause patients to relapse. However, this has not been observed to be the case (Rosenthal et al, 1986).

(ii) The circadian phase hypothesis and SAD:

Circadian rhythms may be phase delayed in SAD. Lewy et al (1987) first suggested that there was a subgroup of depressed patients with Seasonal Affective Disorder (SAD) in whom

melatonin secretion was exceptionally delayed. Although this circadian phase hypothesis is disputed (Checkley et al, 1993) there is increasing evidence to support a phase delay.

There is some evidence that manipulating the endogenous melatonin cycle using light therapy in the morning improves symptoms of SAD by causing a phase advance in melatonin secretion (Lewy et al, 1989; Dahl et al, 1993; Danilenko et al, 1994) and that the timing of light predicts whether there is a response to treatment (Wirz-Justice et al, 1993). However, this theory does not wholly hold water as there may not be a difference between light given in the morning or evening (Tuunainen et al, 2005). It may be that a more careful assessment of DLMO to predict the antidepressant response to differently phased light is important (Terman et al, 2001; Lewy et al, 2003; 2006). Furthermore, abolishing melatonin secretion with beta blockers still results in a therapeutic effect from light treatment.

Manipulation of the melatonin cycle using exogenous melatonin is another possibility. Lewy et al (1988) found that if melatonin was given in the early afternoon, it provides a corrective phase advance. Nevertheless, as the above evidence suggests, it remains unclear whether melatonin is causal in SAD or whether melatonin is merely one mechanism with which to manipulate the patients' sleep and mood.

(iii) Amplitude hypothesis and SAD:

The amplitude hypothesis suggests that it is the amplitude of melatonin that is reduced rather than the timing of the circadian rhythm which is abnormal. Beck-Friis (1983) originally described a subgroup of depressed patients (non-seasonal depression) with a "low melatonin syndrome". Indeed, it has been confirmed that people with non-seasonal depression have a significantly lower concentration of serum melatonin than control subjects suggesting the possibility that the functioning of the pineal gland is altered in these patients (Brown et al,

1985; McIntyre et al 1986; Souetre et al, 1989). Caution is always required when investigating melatonin levels as a marker for depression. A low level of melatonin at a single time point can result from either a phase shift or a change in amplitude and psychoactive drugs or environmental conditions may cause changes in melatonin secretion.

It has been suggested that manipulation of endogenous melatonin through light therapy in SAD works through melatonin by increasing the β -adrenergic receptor sensitivity activity and increasing production of melatonin in the pinealocytes. However such attempts at manipulation have produced some interesting results. Thalen et al (1995) found lowered melatonin following light treatment, which argues against the amplitude hypothesis. The precise role of the melatonin changes that are associated with light therapy remain unclear. It has been established that melatonin levels rebound after dim light (300 lux) (Salinas et al, 1992). If low melatonin levels were implicated in the aetiology of SAD, then boosting melatonin using dim light should be an effective treatment in SAD; it is not. Using exogenous melatonin at night (to boost melatonin levels and increase zeitgeber strength) or in the morning (to elongate melatonin secretion or induce a phase delay) did not have any better effect (Wirz-Justice et al, 1990). As suggested previously by Shafii and Shafii, (1998), there is insufficient evidence to convincingly refute low melatonin as an explanation for SAD.

(iv) The serotonin hypothesis and SAD:

The serotonergic hypothesis considers that serotonin dysfunction causes SAD and that melatonin dysfunction is an epiphenomenon (Childs et al, 1995). Carbohydrate craving may also reflect a functional serotonin deficiency, which would be consistent with the serotonin theory of SAD, given the prominent symptom of carbohydrate cravings in winter

depression (Rosenthal et al, 1984). It has also been suggested that melatonin and serotonin are freely interconvertible (Panzer, 1998). Thus, as melatonin is a product of serotonin, it would hardly be surprising to find that low serotonin levels result in low melatonin levels in depression. Similarly, drugs which affect serotonin levels would result in changes in melatonin levels. It is also well established that decreased serotonergic neurotransmission is implicated in the aetiology of non-seasonal depression (Delgado et al, 1990). Mills and Faunce (1991) found that melatonin inhibits monoamine oxidase (MAO) activity and increases brain levels of serotonin, dopamine, and noradrenaline. Therefore melatonin may indirectly enhance mood acting through other neurotransmitter systems, but it is serotonin rather than melatonin levels per se that are important. This hypothesis remains largely untested.

6.3. Melatonin and non seasonal depression

The information about the role of melatonin in non-seasonal depression remains limited. However, for convenience this will be presented in a similar format to the theories underpinning depression in SAD.

(i) Melatonin hypothesis

The evidence if anything suggests that in depression, melatonin levels are reduced (Shafii and Shafii, 1998; Beck-Friis, 1985), although there are some gender differences, with females having higher melatonin levels in depression (Sekula et al, 1997). Overall, the evidence to date does not support raised melatonin levels in non-seasonal depression.

(ii) The circadian phase hypothesis and non-seasonal depression

Early morning waking is a characteristic feature of non-seasonal depression. It has been postulated that this is due to a phase advance in melatonin secretion. However, as pointed out originally by Checkley (1989) there is little evidence supporting a phase advance in non-seasonal depression and indeed there has been some suggestion that the fundamental rhythm disturbance in depression may be a weakening of the coupling processes between internal pacemakers and an abnormal sensitivity to environmental information (Daimon et al, 1992).

(iii) Amplitude hypothesis:

Differences in amplitude of melatonin in people with and non-seasonal depression are not always present (Thalen et al, 1995). Although low melatonin levels have not been universally reported (Voderholzer et al, 1997), the overall consensus of opinion suggests that the amplitude of melatonin is low in patients with depression (Beck-Friis et al, 1985; Shafii and Shafii, 1998). These findings would be consistent with the amplitude hypothesis for non-seasonal depression.

(iv) The serotonin hypothesis and non seasonal depression:

It is well established that serotonin dysfunction is associated with non-seasonal depression (Delgado et al, 1990). According to the serotonin hypothesis, early morning waking influences the melatonin amplitude and phasing through other zeitgebers (for example, exposure to morning light). Thus, alterations in melatonin secretion would be seen as epiphenomena of depression. Also, Mills and Faunce (1991) found that melatonin inhibits MAO activity and increases brain levels of serotonin, dopamine, and noradrenaline.

6.4. Melatonin and bipolar disorder

(i) Melatonin hypothesis:

There is some evidence of low melatonin levels in depressed bipolar patients (Numberger et al, 2000; Beck-Friis et al, 1985). This would mitigate against the melatonin hypothesis in depressed bipolar patients.

(ii) Circadian phase hypothesis:

Depressed bipolar patients were found to differ from unipolar depressed patients and normal controls with a phase delay in melatonin secretion observed (Numberger et al, 2000). It has been suggested that there may be a phase advance in melatonin in mania (Maurizi 2000; Shafii and Shafii, 1998). However, the significance of these phase shifts is yet to be determined.

(iii) Amplitude hypothesis:

There is some evidence that manic or depressed people have higher or lower melatonin respectively and it has been suggested that the amplitude of melatonin secretion is associated with the mood state (Lewy et al 1979). It has been noted in bipolar disorder, though not in all studies (Numberger 2000, Whalley et al, 1991; Lam et al, 1990), that patients may be more sensitive than controls to light's melatonin suppressant effects (Lewy et al 1981, 1985; Numberger et al, 1988).

(iv) The serotonin hypothesis:

There have been no studies specifically addressing this question.

6.5. Melatonin and Dementia

(i) Melatonin hypothesis in dementia:

The secretion of melatonin is determined by signals originating in the suprachiasmatic nucleus (Reppert et al 1988) and the cell numbers decrease with age. In the case of dementia neurodegenerative processes appear to disrupt these cells (Swaab et al, 1985; 1987).

Melatonin levels are reduced in dementia and therefore disruption in the sleep wake cycle in dementia cannot be accounted for by raised melatonin levels.

(ii) Circadian phase hypothesis:

In dementia the circadian rhythm of melatonin secretion is lost (Satlin et al, 1991) and sleep disturbance is a characteristic symptom. There is evidence to suggest that melatonin may act as a zeitgeber. It is possible that loss of the circadian rhythm of melatonin accounts for disruption of the sleep wake cycle and that exogenous melatonin may be helpful in entraining the circadian rhythm.

(iii) The amplitude hypothesis:

The amplitude of endogenous melatonin secretion in Alzheimer's disease is significantly lower (Satlin et al, 1991; Uchida et al, 1996; Ohashi et al 1999) and related to severity of impairment of mental function (Mishima et al, 1999). Thus a potential for the sleep disturbance in dementia may be offered through replacement of endogenous by exogenous melatonin and by melatonin acting as a zeitgeber. However, the relationship between the amplitude of melatonin and disruption of the sleep-wake cycle remains to be elucidated.

(iv) The serotonin hypothesis:

In dementia the neurodegenerative process is so marked that a variety of neurotransmitters and hormones are disrupted. Diminution of pineal melatonin has been related to degeneration of serotonergic and noradrenergic innervation of the SCN rather than the pineal gland per se (Ruzsas and Mess 2000). Serotonin influences sleep. It may be that serotonin dysfunction rather than melatonin dysfunction is the cause of sleep disturbance. The precise mechanism of sleep disturbance in dementia is unknown and the serotonin hypothesis cannot be discounted.

6.6. Theoretical rationale for investigating the use of exogenous melatonin

In conclusion, the strongest evidence supports a phase delay in melatonin secretion in SAD. A phase advance in biological rhythms has been proposed in depression, but the evidence for this is weak (Checkley, 1989). Although the melatonin hypothesis has been largely discounted the amplitude hypothesis and serotonergic hypotheses in affective disorders cannot be wholly discounted. There also exists the possibility that in depression, it is changes in receptor sensitivity to melatonin, rather than the absolute level of melatonin which are important.

Imputing causality is always difficult. It remains unclear whether symptoms such as early morning waking cause a phase advance in melatonin secretion or whether the phase advance in melatonin secretion causes early morning waking, or whether these are circular systems. In Alzheimer's disease there is both a reduction in the amplitude of melatonin and a delay in melatonin secretion (Satlin et al, 1991; Dijk et al, 2000; Wu and Swaab, 2005).

The manipulation of endogenous melatonin through the use of light continues to be researched. Light treatments are now being used in patients with SAD, depression, mania, and dementia and are described elsewhere in this thesis. Although light treatment appears to be of some benefit, it may not work through melatonin.

Exogenous melatonin has been shown to be a zeitgeber for disorders of the sleep wake cycle. There is great interest in complementary medicines and given some theoretical rationale underpinning the use of melatonin as a treatment for sleep disturbance, its use in affective disorders and dementia is of considerable interest. Indeed, Arendt (1995) suggested that *“melatonin has possible therapeutic potential in the treatment of mild depression and insomnia using time, low-dose oral treatment...although no substantial clinical trials have yet been reported”*. In this thesis, two trials will be presented examining the use of exogenous melatonin in the treatment sleep disturbance in depression and dementia respectively.

Chapter 7 THERAPEUTIC USE OF EXOGENOUS MELATONIN IN AFFECTIVE DISORDERS AND DEMENTIA

7.1. Exogenous Melatonin in Depressive disorders

Sleep disturbance is a major cause of morbidity in depression, to the extent that it is increasingly viewed as part of the pathophysiological process underlying this disorder (van Bommel 1997). In addition, disruption to circadian rhythms other than the sleep wake cycle is known to occur in affective disorders (Lewy et al 1995). The hypnotic properties of melatonin as well as its ability to synchronise circadian rhythms (Lockely et al, 2000; Sack et al 2000) provide a strong theoretical basis to support the hypothesis that exogenous melatonin may have a beneficial effect in the treatment of depression. This hypothesis is strengthened by the finding that the amplitude of the melatonin secretion rhythm is reduced in depression (Wetterberg 1978; Claustrat et al 1984; Frazer et al 1986) and findings from animal models that melatonin increases brain serotonin (Anton-Tay, 1968; Coztias et al, 1971).

Following a number of case reports suggesting that there were improvements in mood in patients with Parkinsonism (Shaw et al, 1973) and normal human subjects (Anton-Tay et al, 1971; Cramer, 1974), Carman et al (1976) published the first trial into the efficacy of melatonin as a treatment for patients satisfying criteria for major depressive illness (Spitzer et al, 1975). This was a double-blind crossover trial of melatonin versus placebo in the treatment of depression in inpatients. Melatonin was given either orally divided into four equal doses daily, or intravenously once or twice daily. The melatonin was either followed or preceded by a placebo. Behavioural ratings were obtained by a nurse using a modification of the Bunney-Hamburg Mood and Behavior Rating Scale (Bunney and Hamburg, 1963). However, the study was discontinued as findings suggested the

melatonin was making patients worse. The authors argued that melatonin was ineffective in the treatment of depression and also that it was associated with an increase in the number of psychotic symptoms. However, this study contained serious flaws, some of which are evident in hindsight since new information has become available, which makes interpretation of the results impossible. Firstly, patients selected for the study comprised only eight inpatients with different diagnoses in a different setting; six moderately to severely depressed in patients and two patients with Huntington's chorea and there is no information about the profile of melatonin secretion in this latter group. Secondly, the dose of melatonin (150 to 1600mg) was not just in varying amounts, but also in some cases, over five thousand times higher than the low dose melatonin (0.3 mg) now thought to be effective (Lewy et al, 2001a); plasma melatonin levels only need to be elevated to 60-200pg/ml at night and 3-10pcg/ml in the day (Dollins et al, 1994). With such enormous doses, even with the short half life of melatonin, it is unlikely that levels would fall below 10pcg/ml associated with DLMOff. Thirdly, the timing of melatonin is important (Reppert and Weaver, 1995) and the response depends on the time melatonin is given in the phase of endogenous melatonin secretion. The melatonin was three times daily melatonin and with such massive doses that it is likely that the melatonin cycle will be swamped by the exogenous product. Indeed, this point was raised by Zhdanova et al, (2001), who suggested there is an optimum response to melatonin in sleep disturbance in older people with insomnia. Fourthly, the authors give no estimate of a pre-study power analysis. Given the small number of people in the trial it is likely that both type 1 and type 2 errors are probable. In type 1 errors, their authors may conclude that melatonin has a detrimental effect on mood, when indeed it has no effect. In a type 2 error, the authors may conclude that melatonin has no beneficial effect on mood when indeed there is an effect.

Nevertheless, the authors concluded at that melatonin should not be used in the treatment of

depression. For over two decades very little research was published in the use of melatonin in depression, possibly because of the negative results reported in the Carman et al (1976) study. However, in the light of more recent data, this issue clearly needs reconsidering.

The next report in the literature was in 1997 by DeVries and Peeters. They published the case of a 44-year-old woman with a first major depressive episode. The patient's sleep had been very disturbed (2 to 3 hours per night), she had not responded to psychotherapy and she was reluctant to take standard sleep medication or anti-depressants. Melatonin (5mg) was given as a first line treatment for seven days, during which time the patient's sleep improved greatly (to 6 to 8 hours per night) and she also experienced an improvement in her mood rated by the Zung self rating depression scale (Zung, 1965). Subsequently the patient was prescribed fluoxetine, after which her clinical condition improved further. This led the authors to hypothesise that adjunctive melatonin could contribute to reducing the insomnia associated with major depression, as well as helping with the clinical symptoms of depression, either before anti-depressant treatment is started or during the initial delay in its anti-depressant effect.

Fainstein et al (1997) conducted an open-label study of melatonin 3mg administered 30 minutes before bedtime to 41 older people patients separated into three groups; patients with sleep disturbance alone (n=22), patients with sleep disturbance and depression (n=9) and patients with sleep disturbance and dementia of Alzheimer's or vascular type (n= 10).

Melatonin was given for 21 days 30 minutes before the expected bedtime. Assessment of the quality of sleep and daytime alertness was done using structured clinical interviews as well as by collecting data from sleep logs conducted by the patients or their caregivers. Four of the nine older adults with depression and sleep disturbance were reported as having improved

subjective sleep quality, although there was not a subjective improvement in mood. It is important to note that neither patients nor the assessors were blind to the treatment and therefore caution is advised when interpreting these findings.

The first RCT was reported by Dolberg et al (1998) and involved 19 outpatient volunteers. Sleep difficulty was not specified as an inclusion criterion, but all patients met DSM-IV criteria for major depression (American Psychiatric Association, 1994). All were given fluoxetine 20mg as the sole antidepressant and, additionally, ten received slow-release melatonin and nine received placebo treatment. Initial dosage of melatonin was 5mg and this was increased to 10mg in 2.5mg increments if no improvement in sleep was observed after week two. Treatment was administered daily at 9pm and was maintained over a four week period. Patients' mood and sleep quality were measured using the Hamilton Depression Rating Scale (Hamilton, 1960) the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) and the Pittsburgh Sleep Quality Index (Buysee, 1989). The authors report no differences in mean rate of mood improvement between the two groups after four weeks, although the melatonin group did show a statistically significant improvement in sleep quality. However, analysis was conducted on completers only, and they did not perform an intention to treat analysis or provide information on which groups (melatonin or placebo) dropouts came from. Therefore, reports of the beneficial effects of melatonin may have been accounted for by differential drop out.

A cohort study by Dalton et al (2000) was conducted on a group of nine outpatients with treatment-resistant depression (defined as failure to respond to two or more trials of medication for at least eight weeks). Major Depression was diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994) using the Structured Clinical

Interview for DSM-IV (SCID; First et al, 1995), and each patient scored 18 or more on the 17-item Hamilton Depression Rating Scale (HAM – D; Hamilton 1960). All participants took slow-release melatonin 5mg half an hour before bedtime daily for four weeks in addition to their antidepressant medication. Doses were increased to 10mg if a 50% reduction in HAM - D score was not evident by week two (this was the case for all participants). Participants' mood and sleep were assessed using standardised rating scales and they also completed daily ratings of sleep duration and quality. Of the eight patients who completed the trial, six reported a significant decrease in insomnia. The authors also report that melatonin had a minimal effect on mood, replicating the findings of the previous study. However, this study did not have a control group and the possibility that the improvement in sleep is accounted for factors other than melatonin (e.g. by spontaneous remission) nevertheless needs to be born in mind.

The largest trial published to date, by Serfaty et al (2003), examining the use of melatonin in non-seasonal depression is described in Section II of this thesis. It is therefore not described here. Nevertheless a summary of this trial is shown in table 7.1 for completeness.

Thus, until the trial by Serfaty et al (2003) it is inappropriate to draw general conclusions from the above studies, particularly as these have used small numbers of participants, sometimes with a range of diagnoses. The same outcome measures have not been used across studies, making comparison difficult. Furthermore, the participants involved have varied both in the severity of their symptoms and in their prescribed medication. However, the results so far do indicate a possible role for melatonin in the treatment of insomnia associated with Major Depression, although its role as a potential anti-depressant is less supported in the literature.

7.2. Melatonin and Seasonal Affective Disorder

In humans, the suppression of melatonin secretion by light results in a circadian rhythm where endogenous melatonin levels are minimal during the daytime, begin to rise in the evening, and peak at around 2 - 4am before decreasing again throughout the early morning as light levels increase (Arendt 1995). The dark mornings during winter mean that the decrease in melatonin production is naturally delayed, and vice versa during the summer months. There is some speculation that this underlies the pathophysiological mechanisms of Seasonal Affective Disorder (SAD), leading to the testable hypothesis that inducing an earlier secretion in melatonin levels through increasing light levels in the early morning may alleviate the depressive symptoms of SAD. This hypothesis is the basis for treating SAD through light exposure, with enough success for this method to become accepted practice (Terman et al, 1989; Enns et al, 1999).

Melatonin secretion is suppressed by sunlight and the longer nights during the winter months mean that its secretion occurs for longer during this time. This suggests that high melatonin levels are associated with SAD and that treatment of SAD with melatonin might lead to exacerbation of the depressive symptoms. Indeed, Rosenthal et al (1985) noted that administration of melatonin led to a relapse in SAD in 8 patients experiencing a remission after phototherapy. However, Wirz-Justice et al (1990) observed that melatonin 5 mg had no effect when it was administered to 17 patients with winter depression either early in the morning or late at night and they suggested that light therapy remains the treatment of choice.

However, melatonin does have chronobiotic (time-setting) properties, and a small dose given at the appropriate time will lead to an advance in the melatonin phase (Lewy et al

1992). This means that melatonin secretion will begin earlier. With this hypothesis in mind, Lewy et al, (1998) conducted a trial of melatonin for the treatment of SAD. In this pilot study ten participants meeting DSM-IV criteria for SAD were given either very low dose melatonin (0.25mg) or placebo during the afternoon (so as to cause an advance in the natural melatonin phase) for a period of three weeks. Only the participants were blind to the assigned treatment condition. Using a significant decrease in score on the SIGH-SAD (Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version; Williams et al 1988) as an indicator of response to treatment, all five of those participants taking melatonin were categorised as responders, as well as one out of five of those taking placebo. The authors attribute the success of this pilot study to the phase-advancing properties of melatonin, which means that when exogenous melatonin is given during the afternoon, endogenous secretion of melatonin begins earlier in the evening. It also tails off at an earlier time the following morning. Administering melatonin at a time when it would be expected to lead to a phase advance could lead to re-entrainment of the circadian rhythm, and a subsequent clinical improvement.

Leppamaki et al (2003) examined the effect of controlled release melatonin 2 mg or placebo on sleep quality, sleepiness after waking and atypical depressive symptoms in 58 people with subsyndromal SAD. Ratings of mood were undertaken using a revised version of the Hamilton Depression rating scale-Seasonal Affective Disorders Version Self-rating format (Williams et al, 1991). Sleep was evaluated using the Groningen List of Sleep Complaints (GLSC, Department of Biological Psychiatry, University Hospital of Groningen, The Netherlands; unpublished). At three weeks they suggested that people had significant improvement in quality of sleep and mood, but not sleepiness after waking. However, there were no objective ratings of sleep and the questionnaire used and the

psychometric properties of the GLSC remain to be evaluated. Furthermore, positive changes in atypical depressive symptoms were seen in the placebo group.

Lewy et al (2003) conducted a randomised double blind controlled trial of melatonin (0.225-0.3mg; given either in the morning or evening) or placebo. Following a baseline period of data collection, 100 people with winter depression were given the intervention for 3 weeks. People were asked to keep constant sleeping times and record them in diaries. Assessments were made of DLMO time and mood using the Structured Interview Guide for the Hamilton Depression Scale-Seasonal Affective Disorder Version (SIGH-SAD; Williams et al, 1988). Patients whose DLMO was phase delayed responded to a corrective advance, with the best response in the evening melatonin group, but there was no antidepressant effect.

Lewy et al (2006) conducted a study over 4 years to test the phase shift hypothesis; they suggested that, for people with seasonal depression, low dose melatonin administration in the morning or afternoon/evening induces phase delays or advances respectively. Eighty one patients with a history of SAD were randomised to placebo, morning or afternoon/evening melatonin (in 0.225 or 0.3 mg daily melatonin taken in divided doses). Data were collected during a 3 weeks baseline period and during a following 3 weeks intervention period. Sixty eight completers were analysed. DLMO time was the main outcome measure. Ratings of mood were also taken using the Hamilton Depression Rating Scale: Seasonal Affective Disorder Version (SIGH-SAD; Williams et al, 1991). The sample population was typically phase delayed. Correlations between depression ratings and circadian phase revealed a therapeutic window for optimal alignment of circadian rhythms. There were no significant pre and post treatment difference scores in SIGH-SAD.

It may be that the sample size was insufficiently powered to detect significant differences in SIGH-SAD scores. Also the results need to be interpreted with caution because almost 20% ((13/81) x 100) of their sample did not complete the study.

To date these studies are unique in their use of melatonin as a treatment for SAD. Work so far has focused on phototherapy, which although fairly successful is inconvenient, since light exposure needs to take place in the early morning or evening for several hours. Although only one small pilot study has shown positive results, melatonin's potential role in this field is one that certainly justifies future research

7.3. Melatonin in mania

Robertson and Tanguay (1997) published a case report of the use of melatonin in a 10 year old boy with bipolar disorder refractory to lithium, carbamazepine and valproic acid which suggested that melatonin aborted a manic episode and restored the normal sleep-wake cycle. However, the boy described in this case had a long history of relapses and remissions and even relapsed on melatonin and therefore it is likely that the temporary improvement may have been spontaneous remission. Furthermore, no objective measures of mood or sleep were made.

Leibenluft et al (1997) studied five patients with rapid cycling DSM-III R bipolar disorder who were treated with melatonin 10 mg q.i.d. for 12 weeks in a double blind placebo controlled fashion with concomitant medication. The authors found no positive effects of melatonin. However, this dosing regimen would not mimic the natural melatonin cycle and blood levels of melatonin remained consistently elevated throughout the 24 hour cycle. Although the authors did try to obtain objective measures of mood, depression and mania,

using structured interviews (Williams et al, 1998; Kasper et al, 1989), no objective of sleep were made. The authors did however suggest that exogenous melatonin (or its withdrawal) may trigger or worsen manic episodes in susceptible individuals, as one person was seen to worsen on withdrawal of melatonin. However, numbers in this study are small and this conclusion needs to be treated with extreme caution.

There has been one open label pilot study, resulting in two publications from the same data, describing the use of melatonin in mania (Bersani, 1997; Bersani and Garavini 2000). Eleven patients with a diagnosis of bipolar disorder, manic episode were treated with melatonin 3mg at night for one month. Patients were selected for lack of response to hypnotic medication, but melatonin was given in addition to standard anti-manic (lithium salts, carbamazepine, valproate and neuroleptics) and hypnotic treatment (benzodiazepines). A sleep questionnaire and the Brief Psychiatric Rating Scale (BPRS; Overall, 1974) were used. Although all patients were described as responding, with increased duration of sleep, the absence of a control group questions the validity of these findings (Bersani and Garavini 2000). Speculation has been made about the role of melatonin in mania, with abnormal levels/rhythms thought to be involved (Maurizi, 2000), but there is a lack of evidence to support the use of exogenous melatonin in the treatment of bipolar disorder.

7.4. Melatonin in people *with* dementia

The dampening of the melatonin rhythm that is associated with ageing is more pronounced in individuals with Alzheimer's disease. This, as well as the observation that exogenous melatonin can be of use in improving sleep quality in the healthy elderly, gives rise to the hypothesis that it could provide a valuable tool in the treatment of sleep disturbance in Alzheimer's disease. Perhaps surprisingly it is only recently that a handful of studies has

emerged seeking to examine this hypothesis. Because of the limited number of studies available investigating the use of exogenous melatonin in dementia, studies are reported in chronological order.

In the open-label trial by Fainstein et al (1997) previously described (section 5.5), patients with sleep disturbances and dementia of the degenerative or vascular type were also studied (n=10). Exogenous melatonin 3mg was administered 30 minutes before expected sleep time for 21 days. Although patients with sleep disturbance and depression reported improved sleep and decreased awakenings, participants with dementia did not exhibit significant changes in these variables. However, an amelioration of “sundowning” behaviour (signs of agitation displayed in the evening by individuals with dementia) was reported in 7 out of 10 patients. It is important to note that patients with dementia are likely to suffer from poor recall and insufficient information is given on how caregivers assessed quality of sleep in another person.

Two case studies (Jean-Louis et al, 1998; Brusco et al, 1998b) provided impetus for further work. The Jean-Louis study (1998a) reports on the use of exogenous melatonin in two community-residing elderly women with Alzheimer’s disease. Each was given melatonin 6mg or placebo two hours before bedtime for a period of ten days in a double-blind crossover trial. Whilst the first volunteer did not show any improvement in sleep, wakefulness or mood associated with melatonin intake, the second participant did show some improvements. Her rest activity cycle became more organised when taking melatonin. Additionally, a reduction in delusional states and depressed moods was observed in this participant. Other neurological variables did not show meaningful variations.

Brusco et al (1998a) reported on two male monozygotic twins both with a diagnosis of Alzheimer's disease. Both twins had been diagnosed eight years previously and received similar care and medication, including thioridazine 50mg/day due to behavioural and sleep disorders. Prior to the study they had exhibited similar progressions of the disease. One twin (NN) received melatonin 6mg at bedtime daily for 36 months. After three months this twin discontinued thioridazine treatment. The other twin (ZZ) did not receive melatonin. At the time of reporting, the twins displayed very different clinical pictures. Overall, NN exhibited a lack of progression of the cognitive and behavioural signs of the disease during the time he received melatonin, whilst ZZ displayed a significant deterioration of the clinical conditions of the disease.

An open label study was also reported by Brusco et al, (1998b, republished using different analyses of the same data 1999, 2000). In this retrospective study, 14 patients with Alzheimer's disease were given melatonin to investigate its effects on sleep and cognitive function. All patients received 9 mg gelatin melatonin capsules at bed time for 22 to 35 months. Overall quality of sleep was assessed from sleep logs filled by the patients or their carers. Neuropsychological functioning was assessed using the Functional Assessment Tool for Alzheimer's Disease (FAST; Auer and Reisberg, 1997), the Mini-Mental, Alzheimer's Disease Assessment Scale (ADAS; Mohs and Cohen, 1988) and Mattis' and Blessed's scales (Blessed et al 1988). Sundowning was no longer detectable in 12 patients and was attenuated in 2 patients suggesting a significant improvement of sleep quality in all cases (Brusco et al, 199b). They also found no significant changes in initial and present evaluation in scores of FAST, MMSE, ADAS and Mattis' and Blessed's scales (Brusco et al, 1999; 2000) and suggesting that clinically, patients exhibited a lack of progression of the cognitive and behavioural signs of the disease during the time they received melatonin.

However, this was not a randomised controlled trial, assessors were not blind to the intervention and subjective ratings of sleep by observers in dementia are notoriously unreliable.

In the first RCT, Jean-Louis et al (1998b) reported a number of positive effects of exogenous melatonin in ten elderly patients residing at home. Patients were selected for the study on the basis of self-reported sleep-wake disturbances, irrespective of their level of cognitive impairment. Ten people entered the trial. A diagnosis of Alzheimer's disease was made in two individuals, and an observation of a mild cognitive impairment in the remaining participants. Volunteers received placebo or immediate release melatonin 6mg for 2 hours before usual bedtime for two ten-day periods in a placebo-controlled double-blind crossover trial. Analysis of actigraphic variables indicated a significant reduction in sleep onset latency associated with melatonin administration. The sleep efficiency index also showed a trend toward improvement, although there was no increase in the total sleep time. In addition, melatonin had significant effects on a number of neuropsychological variables. Notably, it was associated with significantly reduced depressed mood and enhanced delayed recall. The ability to concentrate also showed a marginal increase with melatonin. No significant effects were noted on the ability to perform other cognitive tasks, although melatonin was not associated with any deterioration in cognition, leading the authors to conclude that melatonin can improve some aspects of sleep, memory and mood in the elderly. However, the number of people in this trial was small and the degree of cognitive impairment mild in most of the participants.

Subsequent studies have reported melatonin to have a therapeutic effect on the rest-activity cycle in individuals with dementia of the Alzheimer's type. In a small (n=7) double blind

crossover trial Tozawa et al (1998) reported that melatonin 6mg for four weeks had a considerable therapeutic effect on the rest-activity cycle when administered to patients with degenerative dementia of the Alzheimer's type. Melatonin or placebo was given for 4 weeks after a 2 weeks run in period. A 2 week washout was then given and placebo or melatonin was then given. Wrist actigraphy was used as the main outcome measure and the authors noted that melatonin significantly reduced night time activity after the second week of treatment. They measured serum melatonin levels 2 hourly on the 29th day of the treatment period confirmed that serum melatonin rose following oral administration. This report has however never been published in a peer reviewed journal and it is difficult to know how much authority these results should carry.

Haffmans et al, (1998) conducted a 5 week randomised double blind placebo controlled trial to examine the effects of melatonin and light in six patients with DSMIV diagnoses of (senile) dementia recruited from a medium stay ward. All were given 10,000 lux of light for 30 minutes twice a day for 5 days and then given 7 days of melatonin 2.5 mg or placebo at night-time. Outcomes used were the Clinical Global Impression (CGI), the Dutch version of the geriatric behavioural observation scale (GIP) and the Social Dysfunction and Aggression Scale (SDAS) Although the authors suggest that the placebo group showed a significant reduction in motor restlessness judged by the Clinical Global Impressions Scale and were more able to sit down or continue their activities on the GIP, a large number of measures were taken and the number of patients was very small with only 6 out of 10 people completing the study. Although they suggest light therapy, but not combined light and melatonin is effective for motor restlessness, caution is necessary when interpreting the results because of the small numbers involved in the trial.

In a further open label trial Cohen-Mansfield et al (2000) reported similar results in a small elderly institutionalised population (n=10) suffering from dementia. Residents were given exogenous melatonin 3mg (on average) one hour before expected bedtime. Sleep and agitation were recorded by nursing staff and overall a decrease in agitation scores was noted, as well as a decrease in daytime sleepiness. Changes in sleep behaviour at night were not significant. As above, this study indicates that melatonin may have a role in the improvement of sleep and the reduction of “sundowning” behaviour in this population.

The first large RCT was conducted by Serfaty et al (2002) and is described in this thesis. In this trial, 25 patients with a DSM-IV diagnosis of dementia and sleep disturbance were treated with exogenous slow release melatonin. Of these, eighteen had diagnoses of dementia of the Alzheimer’s type, four had vascular dementia, and three had mixed Alzheimer’s / vascular dementia. Data was collected through the use of wrist actigraphy as well as subjective assessments of sleep quality and quantity from both the patients and their carers. However, contrary to previous findings, this study does not report any therapeutic effects of exogenous melatonin in this population.

There have been three further trials published, *since* the trial undertaken by Serfaty et al (2002) and described in this thesis. For convenience the details are included in this section.

The first was an open label study by Cardinali et al (2002b) who treated 45 Alzheimer’s disease patients with 6-9 mg of melatonin. The authors used a global assessment of sleep which recorded: time to bed, number of awakening episodes, length of average wake interval, external disruption of sleep, as well as morning freshness and daily alertness. They suggest that there were significant differences between initial and final assessment at 120 days and

also report no significant side effects from melatonin. However, this study has no more information on methodology than provided above and neither the assessors, nor the patients could have been blind to the intervention. Nor was there a control group. The claims by the authors that melatonin improves sleep and suppresses sundowning has to be treated with caution.

The second trial was by Asayama et al (2003) who conducted a double blind study in the use of 4 weeks' melatonin (n=11) or placebo (n=9) on the sleep-wake rhythm, cognitive function and non cognitive function in people with dementia of the Alzheimer type. Sleep time and activity was checked using wrist actigraphy and cognitive function rated using the clinical dementia rating scale (Hughes et al, 1982), the Mini Mental State Examination (Folstein et al, 1975) and the Alzheimer's disease assessment scale (Rosen et al, 1984). Records were analysed using Cole's algorithm (1992) by analysing differences between melatonin and placebo groups after 4 weeks of melatonin/placebo, having made adjustments for baseline sleep. Asayama et al (2003) found that melatonin significantly ($p=0.017$) prolonged sleep time and decreased night activity ($p = 0.014$), but did not affect daytime sleep or activity. It was also found that cognition on the ADAS improved in the melatonin group ($p=0.017$), as did non-cognitive functions ($p=0.002$). They suggested that melatonin was useful in the care of patients with dementia of the Alzheimer's type.

Finally, the third and largest RCT published was by Singer et al (2003). The methodology used was similar to that described in this thesis. The aims were to determine the safety and efficacy of melatonin in the treatment of sleep disturbance in people with Alzheimer's disease. This was a multicentre randomised placebo controlled trial of three interventions; 10mg melatonin, 2.5mg slow release melatonin and placebo. The study was undertaken in private

homes and long-term care facilities. 157 people with Alzheimer's disease were recruited through 36 centres and data for 151 participants were analysed using an intention to treat analysis. People were entered into the trial proving they satisfied diagnostic criteria of the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association; McKhann et al, 1984) for probable AD, slept an average of less than 7 hours per night (as documented by wrist actigraphy) and had two or more episodes per week of night time activity reported by the caregiver. Sleep was defined by an automated algorithmic analysis of wrist actigraphy data. Each of the three interventions was given one hour prior to the habitual bedtime. This assumed that the melatonin onset time was two hours prior to sleep onset. Objective measures of sleep were made using wrist actigraphy. Caregivers were also asked to complete a sleep diary. Secondary outcomes included ratings of dementia (MMSE: Folstein et al, 1975 ; the Alzheimer's Disease Assessment Subscale: Rosen et al, 1984), as well as function in activities of daily living (Galasko et al, 1997). They also assessed mood using the Hamilton Rating Scale for Depression (Hamilton, 1960) and took measures for neuro-psychiatric symptoms. No statistically significant differences were observed using objective measures of sleep judged by wrist actigraphy, although there was a trend towards 30 minutes greater sleep in the melatonin groups relative to placebo. Nor was there an excess of adverse side effects in the melatonin group. Although caregiver ratings of participants' sleep showed improvement in the 2.5mg melatonin group, generally the compliance with sleep diaries was poor and therefore it is unclear how much authority these results should carry. The authors did however describe one "free running" patient who appeared to be a responder to melatonin. Nevertheless, the authors concluded that melatonin was not an effective soporific for the treatment of sleep disturbance in Alzheimer's disease.

To summarise, work with the elderly population has supported the hypothesis that melatonin may be of use in the treatment of the sleep difficulties associated with healthy aging. Although these hypnotic properties may not be so effective when administered to dementia patients, there are indications that melatonin is associated with a reduction in “sundowning” behaviour. Early case studies and small RCTs examining the use of melatonin for the treatment of sleep disorders associated with Alzheimer’s disease yielded positive results. At the time of the study described in this thesis, no large RCTs had been undertaken to investigate the use of melatonin in dementia. Subsequently, the large scale trial described by Singer (2003) found the same negative effect of melatonin as the study described in this thesis.

7.5. Summary of the effects of exogenous melatonin in depression and dementia.

This literature review shows that initially trials investigating the use of exogenous melatonin in mood disorders and dementia consisted of case reports. This was followed by open label studies and then mostly RCTs involving small numbers.

Generally studies which show positive findings are more likely to be published (Song et al, 2001). Meta-analyses based on a literature search will thus include such studies differentially, and the resulting bias may invalidate the conclusions. Small studies that are less precise will tend to have a larger standard error. The effect of an intervention can be measured and expressed as an odds ratio (OR). If all studies are published, then the larger the sample size, the smaller the standard error and the greater the likelihood of the findings being representative of the intervention. A plot of each trial's effect size against some measure of its size, such as the precision ($1/\text{Standard Error}$), the overall sample size, or the standard error shows a funnel shape which is balanced (Sutton et al, 2000); this is referred

to as a funnel plot and an example of standard error against the log odds ratio is shown (Figure 7-1).

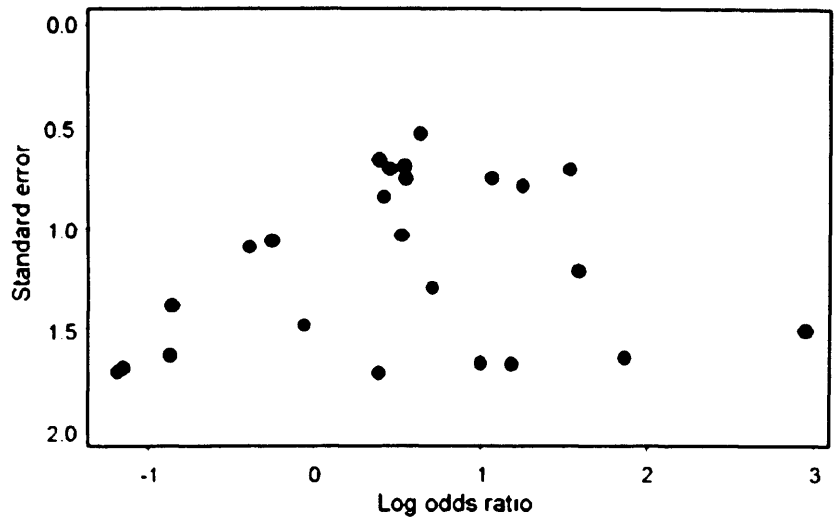


Figure 7-1 Funnel Plot showing no evidence of publication bias.

However, generally publication bias will favour studies with a positive result (large odds ratio). A plot of the standard error against the log of the odds ratio will then give a asymmetrical plot as shown in shown below (Fig 7-2).

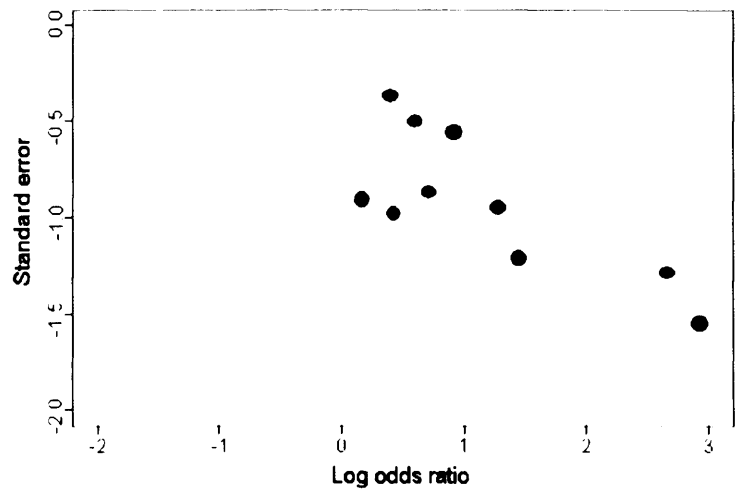


Figure 7-2 Funnel Plot showing evidence of publication bias.

A summary of these trials which have used exogenous melatonin in affective disorders and dementia respectively is given in tables 7.1 and 7.2 respectively. For practicality only the main outcome measures are presented, although more detailed information is provided in the body of this thesis. Although a funnel plot of the findings from the studies described in tables 7.1 and 7.2 respectively is beyond the scope of this thesis, we may expect to see the following pattern; one trial (Carman et al, 1976) which suggested a negative result would be represented by an outlying point at the bottom left hand side of a funnel plot, a number of points represented by small trials and showing a similar pattern to that shown in Fig 7.2 would be presented by a collection of points on the bottom right hand side of the plot and the top of the funnel would be represented by the larger trial by Singer et al, (2003) and would show a minimal treatment effect.

Table 7-1 Summary of all trials melatonin for sleep disorders in affective disorders.

Affective Disorders					
Depressive disorders	n	Study Design	Measure of interest	Main outcome	Result
Carman et al 1976	8	Double-blind crossover	Clinical Condition	Bunney-Hamburg Mood and Behaviour Rating Scale	Melatonin ineffective and increased number of psychotic symptoms
Vries & Peeters 1997	1	Case study	Clinical Condition	Zung Self-Rating Depression Scale	Improvement in sleep and mood
Fainstein et al 1997	9	Open label	Sleep-wake activity	Sleep diaries	Improved sleep quality
Dolberg et al 1998	19	RCT	Sleep Quality	Pittsburgh Sleep Quality Index	Improvement in sleep quality but not mood
Dalton et al 2000	9	Open label	Clinical Condition	Hamilton Rating Scale for Depression	Improvement in sleep quality but not mood
Serfaty et al, 2002	33	Double-blind RCT	Sleep Clinical condition	Wrist actigraphy Beck Depression Inventory	No improvement in sleep with melatonin, non-statistically significant trend towards and improvement in mood.
SAD	n	Study Design	Measure of interest	Main outcome	Result
Rosenthal et al 1985	8	Double blind cross over trial	Clinical condition	Clinical condition	Melatonin worsened symptoms of depression.
Wirz-Justice et al, 1990	17	RCT	Clinical condition and biochemical measures	Hamilton Depression Rating Scale	No therapeutic action of melatonin was found
Lewy et al 1998	10	Parallel groups; placebo controlled (pilot)	Clinical Condition	Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder	Improvement in clinical symptoms
Leppamaki et al, 2003	58	RCT	Sleep and mood	Groningen List of Sleep Complaints Rating Scale-Seasonal Affective Disorder	Subjective improvement in sleep with melatonin and mood with placebo
Lewy et al, 2003	100	Blind RCT	Sleep and mood	DLMO Hamilton Depression Rating Scale-Seasonal Affective Disorder	Phase delayed patients had a corrective phase advance with melatonin at the correct time. No effect on mood.
Lewy et al, 2006	81	Double blind RCT	Biochemical measures and mood	DLMO Hamilton Depression Rating Scale-Seasonal Affective Disorder	Evening melatonin caused a phase advance but morning melatonin did not cause a phase delay. No effect on mood.
Mania/bipolar illness	n	Study Design	Measure of interest	Main outcome	Result
Perston and Tanguay 1977	1	Case report	Clinical Condition	No ratings made	Suggested melatonin led to the relief of insomnia
Benlutf et al, 1997	5	Double blind RCT	Sleep and mood	Sleep Questionnaire Hamilton Depression Rating Scale	No effect of melatonin on sleep or mood
Ansani and Garavini 1977; 2000	11	Open label (pilot)	Sleep-wake activity	Sleep questionnaire	Increased duration of sleep

Table 7-2 Summary of all trials of melatonin for sleep disorders in dementia

Older People with Dementia	n	Study Design	Measure of interest	Main outcome	Result
Fainstein et al 1997	10	Open label	Sleep-wake activity	Sleep diaries	Reduction in sundowning behaviours
Jean-Louis et al 1998a	2	Case study	Sleep-wake activity	Wrist actigraphy	First participant showed improvement in sleep and mood. Second showed no improvement
Brusco et al 1998a	2	Twin study	Neuropsychological evaluation	Functional Assessment Tool For Alzheimer's Disease	Twin taking melatonin showed significant clinical improvement
Jean-Louis et al 1998	10	Double-blind crossover	Sleep-wake activity	Wrist actigraphy	Improvement in sleep and some cognitive tasks
Brusco et al 1998b; 1999;2000	14	Open label	Subjective report	Sleep diary	Improvement in sleep quality and arrest of cognitive decline.
Haffmans et al, 1998	6	Light ± melatonin or placebo	Behaviour	Dutch version of Geriatric Behavioural Observation Scale	Light therapy, but not with melatonin is effective at improving motor restlessness
Tozawa et al 1998	7	Double blind crossover	Sleep-wake activity	Wrist actigraphy	Improvement in rest-activity cycle
Cohen-Mansfield et al 2000	10	Open label	Sleep-wake activity	Nurses' observations	Improvement in sundowning behaviour
Serfaty et al 2002	25	RCT	Sleep-wake activity	Wrist actigraphy Leeds Sleep Evaluation Questionnaire	No therapeutic effects of melatonin
Cardinali et al, 2002	45	Open Label	Subjective report	Global assessment of sleep	Improvement in Global Assessment of Sleep.
Asayama et al, 2003	18	RCT	Sleep-wake activity	Wrist actigraphy Alzheimer's Disease Assessment Scale.	Melatonin prolonged sleep and decreased night time activity.
Singer et al, 2003	151	RCT (Crossover)	Sleep-wake activity	Wrist actigraphy Sleep diary	No therapeutic effects of melatonin

Chapter 8 MEASURES OF SLEEP AND MOOD

8.1. Brief overview of measuring sleep

The precise definition of sleep and its accompanying psychological and behavioural manifestations have been refined over the years (Chapter 2). A number of methods have been used for its measurement in humans using both qualitative and quantitative methods. Sleep may be measured by self report, observer report, or by using more objective methods involving the use of technology. Objective measures are particularly useful in that they minimise the risk of systematic biases. Measures of sleep quality are also clinically important as complaints about sleep are common and they may be a symptom of many sleep and medical disorders (Buysse et al, 1989). Although subjective sleep quality may be related to sleep efficiency, it is not related to the different stages of sleep measured by sleep polysomnography (Akerstedt et al, 1994).

EEG polysomnography is considered to be a Gold Standard for measuring sleep, but it is not without problems, especially in the naturalistic setting. An alternative and almost as robust method involves the use of wrist actigraphy, also an objective measure of sleep. Subjective methods include observer or self report. Although qualitative methods may be of interest, this chapter will focus on the use of wrist actigraphy (section 8.2) and how sleep may be evaluated through self or observer report (section 8.3), as these methods were used in the experiments described in Parts II and III of this thesis.

Electrical (EEG) rhythms in animal brains were demonstrated in 1875 by Richard Cayton. Characteristic differences between asleep and awake EEG in humans were subsequently identified by Hans Berger in 1928. Following this Harvey, Hobart and Davis (1937-39) (see

Dement (1994) at Chicago University described differing EEG patterns during sleep, indicating different sleep states. Episodes of sleep where the eyes moved in a rapid fashion were identified (Aserinsky and Kleitman, 1957). This type of sleep has since been termed Rapid Eye Movement (REM) sleep, also known as paradoxical sleep. Dement and Kleitman (1957) examined the pattern of sleep describing different stages of sleep that occur in a cyclical nature across the course of the sleep period. For a more extensive description of sleep polysomnography the reader is referred to a systematic review by Bloch (1997).

Samuels (1964) was one of the pioneers to examine the use of objective and subjective measures in evaluating sleep disturbance in depressed patients. In this study, he demonstrated the benefit of using subjective measures of sleep in hospitalised depressed patients. He showed that the patients own rating of sleep discriminated between drug and placebo nights, whereas nurses' ratings did not. In order to determine the validity of subjective estimates of sleep, these were compared with objective measures using EEG. There was a correlation between subjective and objective measures (Lewis 1969). However, patients tended to overestimate the delay in getting to sleep and underestimate the total sleep time. Similarly, a correlation was also found in the case of self reported sleep and EEG changes following drug administration (Adam, 1976). Different methods of assessing sleep have since been used and it has been suggested that subjective self reports are sensitive to changes in sleep (Johns, 1971), especially when evaluating psychopharmacological interventions in particular. However, it was not until the advent of a technological revolution in the mid 1980s that a practical way of measuring sleep became possible using wrist actigraphy.

8.2. Wrist actigraphy in sleep disorders

Background to wrist actigraphy:

Organisms demonstrate a rhythmicity in biological function which is expressed in behaviour. It is evident that organisms behave differently when asleep than in a state of wakefulness. To say that an organism behaves is to say that it moves (Tyron, 1985). Obtaining a measure of movement (or lack thereof) may thus provide a measure of sleep. However, it cannot be assumed that measures of movement provide a reliable measure of sleep. In order to establish the validity of movement as an accurate measure of sleep, it needs to be compared against other measures. Other measures of sleep include objective measures such as polysomnography and subjective measures using rating scales such as the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975; Parrot and Hindmarch 1980). The technique which enables measurement of movement is the use of wrist actigraphs. Actigraphy allows us to measure the motor component of behaviour and a change in overt behaviour will be reflected in these actigraphy readings during sleep. It is also possible to examine the effects of various psychoactive drugs on motor behaviour (Stanley, 1997). Wrist actigraphy also provides a relatively unobtrusive way to measure a person's circadian activity in a naturalistic setting. The role of wrist actigraphy in the study of sleep and circadian rhythms is thoroughly reviewed by Ancoli-Israel et al (2003).

History of actigraphs

In the late 1950s mechanical measurement of human activity was first made in children by using a modified self-winding wrist watch (Schulman and Reisman, 1959). By the 1970s the first solid state wrist worn actigraph was developed (Colburn, 1976). Advances in technology have enabled these devices to become increasingly sophisticated with a reduction in size of the device, increased memory and prolonged battery life (Kripke et al, 1978; Borbely, 1984;

Redmond and Hegge, 1985). A number of actigraphs are available commercially. The four main commercially available actigraphs include the mini motion logger, the Gaewiler monitor, the Actiwatch (Stanley, 1997) and the device used in the studies described in this thesis which is piezo-electric electronic sensor device (Somnitor[®]).

Piezo-electric electronic sensor devices rely on an observation by Pierre and Jacques Curie in the 1880's who noticed that applying pressure or mechanical stress to certain natural nonsymmetrical crystals produced an electrical charge in direct proportion to the pressure. When those same crystals were subjected to an electric field, they expanded or contracted in direct proportion to this. These collective properties go by the term "Piezoelectric effect". These "Piezos" can serve as durable electromechanical transducers converting mechanical energy into electrical energy (and similarly converting electrical energy into mechanical energy). Such novel transducer mechanisms were used in the Somnitors described in the two studies in the RCTs in this thesis. They are highly reliable and user friendly and provide a rapid and sensitive measure of movement. A typical Somnitor images is shown in Figure 8.1.

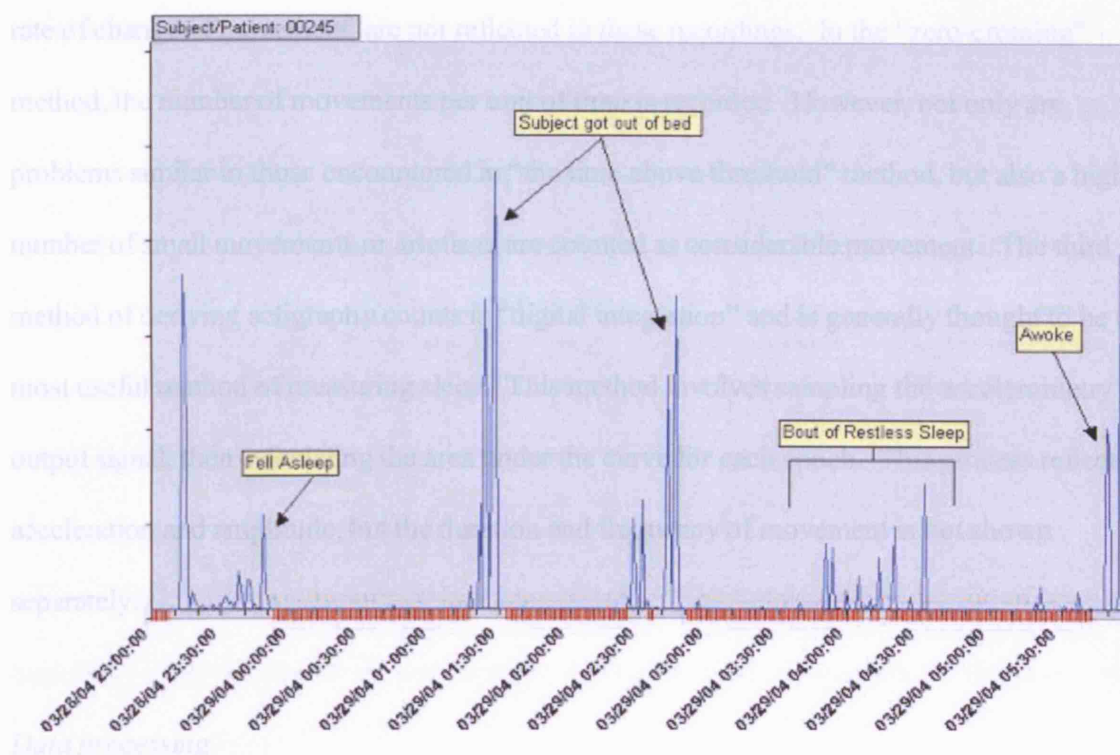


Figure 8-1 Typical actigraph printout

Although data from such a wrist movement detector could be manually scored to distinguish sleep from wakefulness with a high degree of accuracy (Mullaney et al, 1980), the painstaking nature of this scoring makes it an impractical method for everyday use. Webster et al (1982) took the next step by developing methods to generate an automatic scoring system using a computable set of algorithms.

Data acquisition

Three different methods have been used to derive activity counts in actigraphy; time above threshold, zero-crossing method and digital integration. In the “time above threshold” strategy, cumulative counts are made for the amount of time that the level of the signal is above a defined threshold. However, the degree to which the threshold is exceeded and the

rate of change of movement, are not reflected in these recordings. In the “zero-crossing” method, the number of movements per unit of time is recorded. However, not only are problems similar to those encountered in “the time above threshold” method, but also a high number of small movements or artefacts are counted as considerable movement. The third method of deriving actigraphy counts is “digital integration” and is generally thought to be the most useful method of measuring sleep. This method involves sampling the accelerometry output signal, then calculating the area under the curve for each epoch. This process reflects acceleration and amplitude, but the duration and frequency of movement is not shown separately.

Data processing

Algorithms are used to interpret the data generated from wrist actigraphy and a number of these have been developed to help discriminate between sleep and wakefulness (Webster, 1982; Cole et al, 1988, Cole et al, 1992; Sadeh et al. 1989). In Webster et al’s (1982) original algorithm movements of more than 30 seconds are interpreted as a wake period. However, this algorithm is liable to produce a significant number of false positives, for even when people are asleep, they may move for more than 30 seconds. Cole and Kripke (1988) published data on the use of wrist actigraphy in a small number of individuals with sleep problems, resulting in further developments on how to acquire and analyse the data. These changes resulted in a higher proportion of correct classifications and a more accurate estimation of sleep efficiency. In the Sadeh et al (1989) algorithm they demonstrated that actigraphy was a useful way of measuring sleep efficiency and could distinguish between clinical groups.

Cole et al (1992) then further developed and validated automatic scoring methods to distinguish sleep from wakefulness (during the sleep period) based on wrist actigraphy from the non-dominant wrist. The final algorithm correctly distinguished sleep from wakefulness approximately 88% of the time. Actigraph sleep percentage and sleep latency estimates correlated 0.82 and 0.90 respectively with corresponding parameters scored from the polysomnogram ($p < 0.0001$). This algorithm (Cole et al, 1992) is one of the most commonly used in commercially available wrist actigraphs. With the development of new technology, Neurim (personal communication) developed their own software for use with the more accurate Piezo electric sensor devices ("Somnitors"). It is also possible to analyse data from Somnitors using the algorithms developed by Cole et al (1992) or Sadeh et al (1989) as previously described.

Actigraphy correlates well with polysomnography for sleep efficiency, but less well for sleep latency and sleep onset which needs to be born in mind when interpreting results.

Nevertheless, actigraphy is particularly useful in assessing treatment effects, or night to night variations in a subjects sleep. Unfortunately, it is not known how the algorithms compare to each other as each has only been compared individually to polysomnography (Ancoli Israel et al, 2003). Data published to date suggests that the algorithm developed by Cole et al (1992) is the most widely used and has also been applied to people with depression (Cole et al, 1992) and an elderly population (Garfinkel et al, 1995). Data presented in this thesis using actigraphy is therefore generated using the Cole et al (1992) algorithm.

Reliability and validity of actigraphy:

There is evidence to suggest that actigraphy devices are both reliable and provide a valid measure of sleep. Correlation is high between two devices won by the same person (same or

different wrist) with agreement rates of 93 to 99%, suggesting that actigraphs provide a reliable measure (Sadeh et al, 1994). Most tests for the validity of actigraphy compare this with EEG polysomnography. Correlations between wrist actigraphy and polysomnography depend on which aspect of the sleep wake cycle one is measuring, the diagnosis of the population under study and the setting. During the sleep period, actigraphy is more accurate at detecting sleep (sensitivity), but less reliable at detecting wake (specificity) (Pollak et al, 2001; Kushida et al, 2001); People may move considerably during the period of non rapid eye movement sleep, particularly during stages 3 and 4 (see section 2.2) and therefore it may be difficult to distinguish this from periods of wakefulness in sleep.

In nursing home populations, which is a population of study in this thesis, correlations between sleep recorded by wrist actigraphy and EEG polysomnography were 0.81-0.91 for total sleep time (TST) and 0.61- 0.78 for percent sleep (Sleep Efficiency; SE) (Ancoli-Israel et al, 1997). In summary although actigraphy has been shown to produce a reliable and valid measure of sleep, validity may be reduced in populations where sleep is more disturbed (Ancoli-Israel et al, 2003).

Calculation of sleep parameters using wrist actigraphy:

The time at which the individual goes to bed and gets up is recorded by pressing a button on the wrist actigraph. The time in bed (TIB) is the length of time between going to bed and getting up. The sleep latency (SL) is the time duration between bedtime and sleep onset (SO). The wake after sleep onset (WSO) are the midsleep arousals, i.e. the time spent awake after sleep onset. The total sleep time (TST) is the time spent asleep after sleep onset. The movement index (MI) is a record of the (number of zero crossings/TIB) x 100 and is a measure of the number of movements during the TIB. The number of awakenings (NWA) are

the total number of awakenings during the sleep period based on algorithm's criteria. The sleep efficiency (SE) is the $(TST/TIB) \times 100$. Data collection intervals, epoch length, can be set between 1sec-1hour. In the studies presented, using the Cole et al (1992) algorithm, the epoch length was set at 30 seconds. In the studies described in this thesis the time and date on the wrist actigraphs was set just prior to each visit using software supplied by Neurim Pharmaceuticals.

Comparisons of sleep using wrist actigraphy, sleep logs and diaries:

It has been suggested that sleep logs and data for sleep generated by wrist actigraphy yielded similar results for sleep timing, sleep duration, sleep onset and sleep offset, but not for sleep latency, number and duration of night awakenings or number of naps (Lockely et al, 1999). This has face validity as the latter measures are less likely to be subject to accurate recall. Comparison of actigraphy and diary recordings of sleep during space flight found that actigraphy is more reliable (Monk et al, 1999). Adherence to recording of sleep using observer rating also seems to decline over time (Sadeh 1994) and in children and adolescents a period of at least 7 nights is recommended to get five nights of useful data (Sadeh 1996).

Actigraph placement as a potential sources of error:

Different locations of actigraph placement have been used such as dominant versus non dominant wrist, ankle or trunk. Wrist placement is superior to ankle and trunk placement. Also there is evidence to suggest that the actigraph should be placed on the dominant wrist (Middlekoop et al, 1995). Most sources of error may come from people not wearing the actigraphs, or where in the case of daytime measurement of movement, there may be artefacts from for example riding in a vehicle. There have also been a number of factors that have been shown to affect actigraph recordings. Subjects with sleeping partners have a greater number

of movements than those who sleep alone (Pankhurst et al, 1994), there is a decline in movement with age and men have more night-time movement than women (Reyner and Horne, 1995).

Use of actigraphy in affective disorders and dementia

Actigraphy has been used in one bipolar patient and showed severe disturbance of rest activity rhythms (Wirz-Justice et al, 1999). Two studies undertaken in depression reported that specific depressive syndromes were characterised by distinctive circadian activity rhythms. In children with seasonal affective disorder, compared to controls, there was a blunted amplitude of the circadian rhythm, but a normal phase of activity (Glod et al, 1997). Depressed adults had significantly greater motor activity in the morning than the evening and those who indicated poor sleep on the Pittsburgh Sleep Quality Index (Buysee et al, 1989) also had higher night-time motor activity (Lemke et al, 1997). Activity and circadian rhythms have been studied in ageing and dementia. Overall activity levels decline with age (Pollak et al, 1997; Sakurai et al, 1998; Jean-Louis et al, 1999) and there is an increase in overall activity both in the day and night in dementia (Mishima et al, 1997), although actigraphic measures may not correlate accurately with behavioural measures (Friedman et al, 1997), with little evidence of sundowning (Martin et al, 2000).

Summary:

Although actigraphy may not be 100% accurate when compared to polysomnography, reliable and valid information can still be obtained about sleep. Actigraphy is particularly useful for home recording where an evaluation of the person's sleep is required in their natural sleeping environment where the effects of laboratory conditions may alter the individual's typical

sleeping patterns. Actigraphy is best at estimating total sleep time (TST). However as sleep becomes more fragmented, data generated from actigraphs become less accurate.

8.3. Subjective measures to evaluate sleep

A number of methods have been used to make subjective measures of sleep. The important factors in this process will be addressed with examples given to illustrate why the measures used in the experiments described in this thesis were chosen. Subjective ways of measuring sleep may use both quantitative and qualitative methods. Qualitative methods may be particularly useful to assist in the development of a questionnaire so that quantitative estimations of sleep may be made. Qualitative methods may also be of benefit because they may elicit information which may have been missed using a rigid questionnaire. For example, a questionnaire may ask specifically about an aspect of sleep (e.g. time of awakening) following the use of a drug, but fail to provide the investigator with important information about its side effects. The patient may feel anxious all day following a particular hypnotic (eg triazolam), but this information may not be elicited using a structured questionnaire. Questionnaires used to measure sleep need to be examined carefully to ensure that they have been carefully developed and evaluated or a number of pitfalls may arise. For example in a study by Grandner et al (2004) participants were asked to describe their total sleep time as follows “On a workday, how many hours, not including naps, do you usually sleep during the one day?” Responses were recorded in whole numbers. Additionally participants were asked about five sleep complaints, “You had difficulty in falling asleep”, “You were awake a lot during the night”, “You woke up too early and could not get back to sleep”, “You woke up feeling un-refreshed”, and “sleepiness interferes with functioning”. The sleep problems were then recorded on a Likert scale (1= Never, 2=Rarely, 3=A few nights a month, 4=A few nights a week,

5=Every night or almost every night). Although this study was conducted on a large sample (n= 1,004), the questions may be regarded as leading. However, the questionnaire was conducted over the phone and is therefore less likely to be subject to a Halo effect whereby a bias is created by an observer's tendency to rate, perhaps unintentionally, certain items on the questionnaire in a manner that reflects those which were previously anticipated. Another criticism of such semi structured interview techniques is that it is also possible that the interviewer presented verbal cues and a response bias due to expectations by the interviewer cannot be excluded. An alternative method would be to use similarly semi structured interview techniques, but to use non leading open questioning styles and then to focus on precise information such as "Tell me about your sleep?" and then to follow this up with "Are you waking at the same time, earlier, or later than usual?" . Then depending on the response ask for example "How much earlier are you waking?", "On average how many nights a week?". In this thesis we will describe two intervention studies to investigate the therapeutic effects of exogenous melatonin in depression and dementia respectively. Sleep diaries were used to collect both quantitative and qualitative data on sleep (see item A-11 in the appendix). Such diaries are a useful way to collect information about sleep by allowing the individual to make comments on that night's sleep. It also enables comparison to be made with data collected using other methods.

In the development of a questionnaire to measure sleep, it will be important to ensure that it is both valid and reliable (in other words it measures what we think sleep is, and one can repeat the measure and obtain a similar result). The use of such methods has been described by Samuels (1964), and since then a number of measures developed. Visual analogue scales are one of the most commonly used ways to measure sleep (Aitken et al,

1969; Lader and Norris, 1969; Herbert et al, 1976). These usually consist of a 10 cm line with two extremes at either end.

A number of rating scales, have been used to collect information about sleep (Johns, 1971; McDonald and King, 1975). One of the most frequently used rating scale is the Leeds Sleep Evaluation Questionnaire (LSEQ; Parrot and Hindmarch, 1978) (see item A-10 in appendix). This measure uses visual analogue scales to assess four aspects of sleep: Getting to Sleep (GTS), Quality of Sleep (QOS) Awakening from sleep (AFS) and Behaviour Following Wakefulness (BFW). Although other measures of sleep exist (Webb et al, 1976; Frankel et al 1973), the reliability and validity of the LSEQ has been well established (Parrot and Hindmarch, 1978).

Another questionnaire commonly cited, particularly in the North American Literature is the Pittsburgh Sleep Quality Index (PSQI; Buysse et al, 1989). Buysse and coworkers advocate the use of the PSQI over other subjective measures of sleep, such as the LSEQ, as they argue that it provides qualitative as well as quantitative information. However, the PSQI measures change in the last month and therefore may not be appropriate for studies which aim at evaluating the effects of interventions which are brief (i.e. less than a month).

8.4. Questionnaires used to evaluate mood

Many rating scales for depression are currently in use, including the Beck Depression Inventory (BDI; Beck et al, 1961) (item A-7 in appendix), the Hamilton Depression Rating Scale (HRSD; Hamilton 1960) (see item A-8 in appendix), the Zung Self-rating Depression Scale (Zung, 1965) and the Center for Epidemiological Studies Depression Scale (Radloff, 1977). The BDI and the HDRS are the most popular.

The most widely used self-report instrument in both research and clinical settings for measuring depressive symptom severity is the 21 item Beck Depression Inventory (BDI; Beck et al, 1961). Each item represents a symptom characteristic of depression ranging on a 4 point Likert Scale (0-3). A cut off of 14 or more is considered to be at least moderate depression in a primary care setting (Beck and Steer, 1987). The BDI has been extensively evaluated in a variety of settings and has been demonstrated to have high reliability and validity (Beck et al, 1988).

The Hamilton Depression Rating Scale (HDRS) is a more objective measure of depression severity (Hamilton, 1960) which takes about 10-30 minutes to administer and complete. The HDRS is a 21 item clinician rated instrument that is completed following a thorough clinical interview. Each item presents a symptom of depression (e.g. depressed mood, guilt, insomnia) and is rated according to its severity as experienced by the patient during the past few days or week. There is also an observer rated component. The scale represents ascending levels of severity. Of 21 items whose scores are considered, 10 items include 5 point scales ranging from 0-4 and the remaining 11 items include a 3 point scales ranging from 0 to 2 . Detailed factor analysis support its validity (Hamilton, 1967) and a comprehensive review of the HDRS is available (Hedlund and Vieweg, 1979).

8.5. Questionnaire used to evaluate cognitive impairment

The Mini-Mental State Examination (MMSE; Folstein et al, 1975) (item A-9 in appendix) is one of the most widely used instruments to screen and measure cognitive impairment, although a number of amendments have been suggested, such as in the Standardized Mini-

Mental State Examination (SMMSE; Molloy et al, 1991) or Modified Mini-Mental State Examination (MMMSE; Teng et al, 1987).

The maximum score on the MMSE is 30, with different domains assessed; orientation to time and place (10 points), registration of three words (3 points) attention and calculation (5 points), recall of three words (3 points), language (8 points) and visual construction (1 point). The recommended cut off score for cognitive impairment is 23 or 24. Detailed information about the test/retest reliability and internal consistency is well described (Tombaugh and McIntyre, 1992). It has a correlation of 0.78 with the Weschler adult intelligence scale for verbal IQ and 0.66 for performance IQ. Test/retest reliability is 0.89 and a combination of test/retest reliability and inter-rater reliability 0.83. However, age, socioeconomic status and educational level all influence the score. The scale takes 5-10 minutes to administer and has good participant acceptability. The MMSE is therefore a very useful screening tool (Anthony et al, 1982), particularly for cognitive impairment in a community setting (Illifee et al, 1991). Although MMSE was created to differentiate organic from functional organic disorders, and could be used as a quantitative measure of cognitive impairment in an attempt to measure change (Folstein et al, 1975), it is rather insensitive to subtle changes in cognitive ability (Riley-MCarten et al, 2002). The Alzheimer's Disease Assessment Scale (ADAS; Rosen et al, 1984), has been suggested for measuring change in cognitive function. However, it takes around 40 minutes to administer and is specifically for use in people with Alzheimer's Disease.

Chapter 9 DIAGNOSIS OF DEPRESSION AND DEMENTIA

9.1. Background to diagnosis

In psychiatry, diagnostic categories are concepts which are predominantly based on the clinical picture. Ideally, diagnosis should be based on aetiology. Historically, in the case of “functional” illnesses such as depression, the diagnosis is based predominantly on a constellation of symptoms, whereas in psychiatric conditions regarded as “organic” in nature, such as Alzheimer’s disease, diagnosis is informed by pathological or causal mechanisms which are only slowly being elucidated and are multifactorial. Thus, current classificatory systems are based on phenomenology, response to treatment and prognosis until aetiology is elucidated.

9.2. Diagnosis of depression

Depression may be harder to diagnose than dementia for a number of reasons. Feeling sad is virtually a universal phenomenon and most people experience mild to moderate depressive symptoms from time to time, for example as a normal reaction to negative events such as loss of a partner or job. These symptoms may vary in severity and time course and if lasting more than a few days or weeks, may be considered to represent illness. The simplest form of classification is severity, taking depression as a continuum, constructing a list of symptoms and then assigning a score according to the number of symptoms present. One might then arbitrarily use a cut off score to define caseness; i.e. if a defined number of criteria are reached, then the individual is defined as a case of depression. It is then possible to measure this against a gold-standard e.g. psychiatrist’s opinion. Over the years there has been a proliferation of assessment instruments (Nezu et al, 2000) to measure depression and depression related constructs.

A number of diagnostic systems for classifying depression have been developed since the early work of Kraepelin, which separated psychosis into the two broad syndromes of dementia praecox (schizophrenia) and manic-depressive illness (affective disorders). For depression, Leonard (1959) proposed the now widely accepted differentiation between bipolar depression (with manic episodes) and unipolar depression (in the absence of manic episodes). Since then, there have been a number of ways of diagnosing depression. The diagnostic criteria of Feighner et al (1972) were developed so that categories were grouped together on the basis of clinical features without making assumptions about aetiology. These criteria contain operational definitions for sixteen psychiatric diagnoses, stating both the symptoms required for a diagnosis and those which exclude it. For a diagnosis of depression there is the requirement of a specific depressed mood of at least one month duration, plus five out of a list of eight other depressive symptoms (four indicating “probable” depression). The depression is classified as secondary only if there is a pre-existing non-affective psychiatric disorder or serious medical illness. The Feighner system was then developed into the Research Diagnostic Criteria (RDC; Spitzer et al, 1975) but with symptoms only lasting one week. In RDC, depression is classified as major or minor. A diagnosis of major depression may be subtyped into primary, secondary, recurrent, psychotic, incapacitating, endogenous, agitated, retarded, situational or simple. Minor depressive disorder requires depressed mood plus at least two of a list of symptoms. “Intermittent” is classified as a depression of a similar intensity to minor depression but of an intermittent nature and lasting at least two years. It is these criteria from which are derived the Diagnostic Statistical Manual (DSM) criteria.

A number of classification systems have thus been developed, with the International Classification of Diseases (ICD) being used in Europe and DSMIV in North America for the diagnosis of mental disorders. In the ICD10, the letter F denotes the category for mental,

behavioural and developmental disorders and the following digits (F00-F99) provide the broad diagnostic group. Thus F00-F09 classifies diagnoses of dementia and F30-39 the affective disorders. Another number following these principle categories codes for subtype of illness.

The American Psychiatric Association Diagnostic and Statistical Manual for the Mental Disorders version 4 (DSM-IV; American Psychiatric Association, 1994) uses a similar system, although differences exist and are well described in standard textbooks of psychiatry (e.g Johnstone, 1998). The fourth digit indicates whether it is a single episode or recurrent. The fifth digit indicates the current state of disturbance.

In order to diagnose a major depressive episode (DSMIV) or a mood (affective) disorder, depressive episode (ICD10) the symptoms should be present for at least 2 weeks. In both the DSMIV and ICD10 classificatory systems these diagnoses are excluded if hypomanic or manic symptoms (including symptoms for mixed episode in DSMIV) sufficient to meet the criteria for hypomanic or manic episode in the individuals life are present. The episode must also be not attributable to psychoactive substance use or any organic mental disorder. In addition to affective symptoms of either depressed mood or loss of interest described in DSMIV or two affective symptoms, the depressed mood and loss of interest or decreased energy/increased fatigability described in ICD10, there must also be a number of biological and cognitive symptoms. The diagnostic criteria are shown in item A-2 in the appendix.

Although it needs to be acknowledged that newer versions of ICD and DSM have attempted to resolve some of the problems with classification, a number of difficulties remain. For example, although it is generally accepted that based on aetiology represents a gold standard in classification, even where the causes of psychiatric disorders are known their aetiology may be

multifactorial. Furthermore, people may suffer from co-morbid illness and belong to both diagnostic groups (e.g dementia and co-morbid depression).

In the ICD-10 classification of depression, under other recurrent mood disorders, there exists a diagnosis of Recurrent brief depressive disorder, ICD-10 code 38.10. Although the disorder meets symptomatic criteria for depression and occur about once a month over the past year, the individual episodes last less than 2 weeks (typically 2-3 days) (c.f. depressive episodes) and do not occur solely in relation to the menstrual cycle.

Although classificatory systems may provide operational definitions for typical patterns of symptoms they do not advise professionals on how to go about gathering the information necessary to make diagnoses. Psychiatric diagnosis relies predominantly on eliciting symptoms and signs and the reliability and validity of the information may be questionable. Many factors contribute to low reliability: the setting, the way the questions are asked, the interaction between the interviewer and interviewee, the expectations of both the patient and interviewer. In an attempt to standardise diagnosis, structured interviews are often used. In the study of melatonin in depression it was felt that it would be reasonable to use a structured interview to diagnose depression, but in the study of melatonin for dementia, it was not felt ethical to subject older people to similar procedures and therefore reliance on the consultant psychiatrist's DSMIV diagnosis was made.

The Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer, 1978) is designed to yield a diagnosis according to the New York Research Diagnostic Criteria and is based on the Feighner criteria. It uses a hierarchical system to make a diagnosis so that the investigator can omit lower order questions if the criteria for a higher order diagnosis have

been met. It has high reliability and inter-rater reliability. However, although it has been adapted to meet a variety of clinical and research needs the main drawback is that it can take anything between 1 ½ and 2 hours to complete. This may deter people from participating in studies and also may not be considered ethical in vulnerable patients and therefore the section for mood disorders only was used to diagnose depression in the sample population for study 1.

9.3. Diagnosis of dementia

Dementia is characterised by the development of deficits in a variety of areas of cognition. In order to diagnose the syndrome, it needs to be demonstrated that there is first, a global mental impairment compared to the individual's normal performance. Secondly, that the impairment has been gradually progressive over a period of some months and thirdly that other causes have been ruled out which cause a similar clinical picture.

Although the Mini Mental State Examination (Folstein et al, 1975) (item A9 in appendix) may be used as a simple screening instrument (Illiffe et al, 1991), the diagnosis of dementia has to be made using more specific diagnostic criteria. The DSM-IV provides a concise definition of dementia. (See items A3-5 in the appendix). In this system, Dementia is classified as being of the Alzheimer's type (item A3 in appendix), Vascular Dementia (item A4 in appendix), Dementia due to general Medical Conditions, Substance-induced Persisting Dementia, Dementia due to multiple aetiologies or Dementia not otherwise specified (item A5 in appendix). The borderland between dementia of the Alzheimer's type and vascular dementia is complicated, and in vivo diagnosis may not distinguish these categories as clearly as a post mortem diagnosis.

The DSM-IV criteria for a diagnosis of Alzheimer's disease are given in the appendix (item A-3 in the appendix) The patient is required to have developed deficits in multiple domains of cognitive function and these should be significant enough to impair social or occupational functioning. The course should be progressive and not associated with other CNS disease, systemic disorders, or substance abuse. Also, deficits should not be due to acute organic or functional illness. ICD10 criteria suggest at least 6 months illness, but are less specific in the domains of impairment required. A diagnosis of Alzheimer's disease may be made using structured interview schedules published by the National Institute of Neurological Communication Disorders and Stroke/Alzheimer's Disease and Associated Disorders Association (NINCDS/ADRDA) research diagnostic criteria (McKhann et al, 1984). When diligently applied, 80% specificity is possible (Blacker et al, 1994). However, this can be a lengthy assessment process and is not routinely used in the clinical setting.

Vascular dementia results from repeated ischaemic damage to the brain and diagnostic criteria are given in item A4 in the appendix. Diagnostic criteria for Vascular Dementia are less well developed (Verhey et al, 1996) than for Alzheimer's disease and there is no firm consensus on the most appropriate criteria for clinical trials. DSM-IV criteria are similar to criteria for diagnosing Senile Dementia of the Alzheimer's Type (SDAT), but require the presence of focal neurological symptoms or neuroimaging evidence of infarction. The ICD10 criteria require a history of strokes or transient ischaemic attacks, together with neuropathological or neuroimaging evidence of vascular lesions.

There is also a clinically recognised dementia, confirmed through post mortem examination, of Dementia of the Lewy Body (DLB) type which is not in DSMIV or ICD10.

DLB type is defined by eosinophilic inclusions (Lewy Bodies) in the cortical neurones and diagnostic criteria given in item A6 in the appendix. In vivo diagnosis, and in particular the distinction from Alzheimer's disease, can be difficult. Although dementia presents in a similar way to SDAT, frontal lobe and visuo-spatial impairments occur early in the disease. There may also be Parkinsonian motor features, visual hallucinations and systematised delusions (McKeith et al, 1996). Symptoms characteristically fluctuate and there may be falls and syncopal episodes.

Finally, there are a number of rarer diagnostic categories of dementia which include frontotemporal dementia, alcohol related dementia, degenerative dementias and acquired causes of cognitive impairment. These types of dementia are rare and represent a heterogeneous group.

In conclusion, although the definitive diagnosis of dementia is made on the basis of histopathological evidence on post mortem examination, it is possible to come to a clinical diagnosis using defined criteria based on symptoms and signs. For the purpose of research, diagnostic criteria of the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association; McKhann et al, 1984) may be used to predict the subtype of dementia. However, in the study of melatonin in dementia described in this thesis, we relied on a DSM-IV clinical diagnosis given by an experienced consultant. All patients entered into the study had been investigated thoroughly and we did not think it was necessary or ethical to subject participants to lengthy diagnostic procedures. Although clinical diagnosis is less specific for distinguishing subtypes of dementia, it is extremely good at distinguishing between health and dementia.

Chapter 10 TRIAL DESIGN

10.1. History

The concept of causality developed in medicine over the nineteenth century as it became increasingly apparent that a specific cause could lead to a specific disease (e.g. cholera). However, this approach is simplistic and does not fit many diseases which are multifactorial in nature (e.g. ischaemic heart disease). Hill (1965) suggested that there are a number of factors that strengthen an association and suggest a causal relationship. However, as Hill (1965) points out, there may be a number of spurious reasons for an association; an event may occur by chance or random error, there may be a reverse causality, the existence of confounders, or there may be selection bias or information bias. Evidence for causality is supported by the time sequence of a cause and effect, strength of the association, consistency with the existing knowledge and a dose-response relationship. Because of the difficulties in establishing cause and effect, research methodology has used designs which enable the scientist to refute a hypothesis. Sir Karl Popper (1902-1994) was generally regarded as one of the most influential philosophers of the 20th Century. The core of Popper's philosophy depends on the refutability of possible hypotheses (Popper, 1959). Popper points out that although there may be strong evidence for cause and effect, it is impossible to prove causality as there may be a number of unknown factors that cause an effect. However, if a factor which is thought to be causal turns out to be false, then one counter-instance falsifies the whole theory.

Comparative clinical trials, which are planned experiments on human beings, were virtually unknown before the 1940s; the history of these is described by Pocock (1983). The principles behind the design of clinical trials are very important. One of the most established texts

describing their design is Altman (1991), while Jadad (1998) provides a particularly good basic summary of the issues pertaining to randomised controlled trials.

10.2. The double blind randomised controlled trial

When designing a trial it would ideally be preferable to have an intervention group and a comparison group which is identical in every respect and where the only difference is the treatment which they receive. However, it is also recognised that an outcome may be biased by patient and trialist factors; for example expectations in the treatment. Therefore, ideally, the trial should incorporate a blinding process of both patient and trialist to the intervention. This type of trial is a double blind controlled trial. In conducting such a trial, it is also important that participants are allocated to the different arms (intervention groups) in an unbiased way. This is done through a process of random allocation, although it cannot be guaranteed that this process will lead to the groups being very similar. Although some adjustment may be made to a potentially unequal randomisation process, it may be advantageous to control for factors which we know may predict outcome prior to randomisation. For example, outcome from depression may be predicted by baseline depression scores. It follows that if patients with severe depression were allocated to a particular group, then we might expect the outcome to be poorer in that group. One way of overcoming these problems is to “stratify” the sample randomised so that the characteristics of the participants are as similar as possible across the study. So, for example, in a trial in which we are studying the response of people with depression to melatonin or placebo, we may choose to group patients by severity and then randomise them to one of the two interventions. In reality, there are often a number of factors which may predict outcome and, in small trials in particular, it is not feasible to stratify for all of these. Indeed the benefits of stratification are not universally accepted (Peto et al, 1976; Meier, 1981). It is often preferable to keep a trial

simple as the increased complexity of a trial allows for greater chance of errors in its execution and therefore stratification was not used in the two experiments described in this thesis.

The simplest design for a clinical trial is called a parallel group design. In this design, two groups of patients (A or B) are studied concurrently and one may be given an active or new treatment and the other group no treatment, placebo or an established comparison. In trials where it may be difficult to recruit participants, but it is necessary to obtain a relatively precise treatment effect, alternative designs need to be considered.

10.3. Crossover trials

The most popular alternative is the crossover design in which each participant receives a pair of treatments in a sequence (such as A-B or B-A). The time during which each of the interventions is administered and evaluated is called a period. In the typical crossover design, following a baseline period of data collection, participants are randomly allocated to one of two alternative treatments (A or B) for a specified time and then switched to the other treatment (B or A respectively). In drug trials there may be a washout period between each intervention (Woods et al, 1989).

There are two main advantages of a crossover design. The first is economy in numbers, since each participant provides two observations in response to treatment. The second is that comparisons can be made within participants and this reduces the effect of inter-individual variability as patients act as their own controls.

There are however some basic rules that need to be observed when conducting a crossover trial. The first consideration is that there may be changes in level of morbidity irrespective

of any intervention. For example, patients suffering from fever associated with influenza may recover irrespective of an intervention. Thus the outcome may be a reflection of *when* the outcome measure is taken. This is usually referred to as a *period effect*. Crossover studies should not be used in conditions where spontaneous recovery is likely to occur before the end of the trial. In trials investigating changes in sleep patterns, seasonal effects may be observed in both sleep and melatonin secretion. However, this is unlikely to be an important effect in this trial as the period of intervention was relatively brief a cross over design used and randomisation process makes it likely that seasonal biases introduced because of seasonal effects are controlled for.

The second consideration is that the response to treatment may be affected by the timing or sequence of the intervention; that is, there is an interaction between the treatment and the period in which it is given. This effect is referred to as a *period by treatment* interaction. There may several possible causes for such an interaction effect. One of the most important is the possibility that the treatment given during the first period carries over into the second period. For example, if we give an antibiotic or placebo to eradicate a bacterial chest infection, then we might expect the group that has received the antibiotic first to have recovered by the time they have switched to placebo, whereas those who were started on placebo may respond favourably only when they have been given the second treatment. Thus if we examine the effects of treatment at the end of period one, we might find a difference between antibiotic and placebo. However if we examine the effect only at the end of period two, we will find no difference between those allocated to the active treatment compared to placebo. Ignoring such rules can bias the results in a crossover trial, especially when comparing a curative drug with placebo (Khan et al, 1996). Thus,

crossover trials are preferred in situations where the person is suffering from a chronic or incurable condition.

Treatment by period interactions may occur in other situations. For example, the effect of the intervention may continue to improve in the second period as a result of the effects of intervention in the first period. This effect is called a “*residual*” or “*carry over*” effect. Thus, a person given a placebo in the second period may appear to continue to improve on placebo by virtue of the fact that the agent given in period 1 continues to have a “carry over” effect. This process reduces the apparent effect of the active intervention. This problem may in part be dealt with by having a washout at the end of the first intervention period.

Thirdly, differential dropout may also occur. People may drop out from a trial for a variety of reasons unrelated to the intervention group; trial fatigue, illness, death. This would cause differences in the numbers in the first period, compared to the second intervention period. This is also a period effect, but should not be too serious as it should occur randomly. Possibly a more important effect caused by differential dropout may be because the patient is unhappy about not being allocated to a particular intervention. Alternatively, differential dropout during the course of the study may be caused by the intervention itself, for example intolerable side effects associated with a drug. The introduction of such bias may require the data from the second period to be discarded, severely weakening the power of the trial.

In conclusion, crossover designs are recommended for interventions where the disease is stable, chronic or incurable and where it is possible to keep the treatment period short. This minimises dropouts and treatment effects are less likely to persist during the next period. A rapid onset treatment effect of brief duration also minimises these effects. Even if the above

rules are observed, the disadvantages of crossover trials cannot be ignored and analysis needs to examine for carry over effects. Indeed, Everitt (1994) advises testing for carry over effects following period 1 and only if absent may the data be used to test for treatment and period effects from all data. The methods used for such an analysis are described in section 20.5.

10.4. Criticism of randomised controlled trials

Although with the advent of evidence based medicine, randomised controlled trials are now regarded as the “gold standard” this study design may not always be the most appropriate depending on the research question to be addressed. Other methodologies may provide useful information prior to embarking on complex and costly research. For example, qualitative research methodology may be a useful way to formulate a question to be tested using quantitative methods. It has even been argued that for some complex interventions, such as psychotherapy for depression, RCTs may not be the most appropriate approach (Parloff, 1995). Furthermore, it has been suggested that non-randomised trials may be preferable under certain circumstances: where there is an absence of research in an area; when randomised controlled trials are regarded as unethical; when randomisation is not possible on the basis of geography; when observational data is readily available and can provide preliminary evidence of an association; or when there is a good understanding of the variables that affect outcome (Black 1996).

A well-designed randomised controlled trial aims to sample a representative population under study and through a process of randomisation, eliminate confounding variables by hoping that these occur in all arms of the intervention by chance. Although randomisation may result in participants not getting the treatment of their choice, it is the only safe way of eliminating known *and unknown* biases from treatment allocation (Jadad, 1998). However

RCTs are not a panacea to answer all clinical questions and they may also be affected by chance, measurement bias and losses to follow-up. Furthermore, selection criteria may be so tight that there may be difficulty in generalising the findings so that they may be applied to clinical situations.

10.5. Types of trials

Depending on the aspects of the interventions that investigators wish to evaluate, RCTs can be classified as: explanatory or pragmatic; as efficacy, effectiveness, or equivalence trials; and as phase I, II or III. Explanatory trials consider whether or not an intervention works and if so, then how it does so. Typically, these trials are designed in such a way that the results are likely to yield an accurate evaluation of the interventions, by setting strict inclusion criteria that will produce highly homogeneous study groups. In such trials, placebos are often used as controls and interventions are precisely defined and analysis of hard outcomes using both data for completers only and an intention to treat analysis is made. However, there may be inherent weaknesses in this design. Considerable bias may occur if there is a reason for dropouts in a particular intervention group and indeed findings may not be applicable to clinical practice. For this reason, researchers have developed the pragmatic randomised controlled trial.

The aim of pragmatic trials (also called management trials) is not only to determine whether the intervention works, but also to describe the advantages and disadvantages in clinical practice (Sackett and Gent, 1979). This is an important question, because if few people can tolerate the treatment, then it follows the likely benefit will be poor. Studies tend to use more lax criteria, to include participants with a variety of characteristics, similar to those seen by clinicians in their daily practice and often include soft outcome measures,

such as subjective measures of quality of sleep. The contrast between explanatory and pragmatic trials is described in more detail in Schwartz and Lellouch (1967) and Jadad (1998).

When conducting an RCT, it is also necessary to determine whether the treatment works or not. Two terms may be used to describe this: efficacy and effectiveness. Efficacy refers to whether the treatment works in those who receive it (Fletcher et al, 1996). Trials which aim to evaluate efficacy tend to be explanatory trials and often may be reported using analysis of completers. Effectiveness is used to describe whether the treatment works in those to whom the trial has been offered (Fletcher et al, 1996). These trials tend to be pragmatic and are often carried out in conditions in which the intervention has already been of proven efficacy. It may not always be possible to demonstrate a difference in efficacy or effectiveness between two or more interventions, but it may be possible to demonstrate that a new intervention is as effective as an established intervention (Armitage, 1994). Such a trial is called an equivalence trial.

Phase I, II and III trials are used to evaluate a new drug. Phase I trials focus primarily on safety, phase II are conducted on a small number of patients and represent a pilot stage and once a drug has been shown to be reasonably safe and efficacious, phase III trials are typically effectiveness trials. Phase IV trials may be conducted once a drug is being approved and are mainly promotional, surveying tolerability and side effects.

10.6. Assessment of pragmatic trials

There have been many complaints that, for decades, trials have been inadequately reported (Dickinson et al, 2000; Jadad et al, 2000; Thornley et al 1998; Hotopf et al, 1997). This

may then lead to biased results and therefore inappropriate practice. In the mid-1990s, an international group of clinical trialists, statisticians, epidemiologists and biomedical researchers developed the Consolidated Standards of Reporting Trials (CONSORT) statement (Begg et al, 1996). These have subsequently been revised with a view to guiding the reporting of parallel-group RCTs (Moher et al, 2001). The revised checklist consists of 22 items which are deemed to be important, so that biased treatment effects are not ignored and so that the reliability and relevance of findings can be accurately evaluated. It is recommended that the trial is reported in four stages; enrolment, intervention allocation, followup and analysis. There is also a requirement that the authors provide details of where (page and paragraph) the information is available.

In summary, RCTs seek to measure and compare the outcomes of two or more clinical interventions; a new active intervention against a standard control or placebo treatment. Randomisation aims to ensure that unknown factors which may influence outcome are minimised at baseline. Parallel or cross-over trials are most commonly used and pragmatic trials are particularly useful in a naturalistic setting. Analysis is best considered using intention to treat and reported according to clear guidelines laid out in the CONSORT statement (Begg et al, 1996).

Chapter 11 AIMS OF STUDIES

Various types of chronobiologic disorders have been identified. First, those in which the melatonin secretion occurs earlier than it should, that is, it is phase advanced. Such disorders include: advanced phase sleep syndrome, usually (though not invariably; Barnes et al, 1998) adaptation to night work and east to west jet lag. Secondly, those in which melatonin secretion is phase delayed; this includes delayed sleep phase syndrome, re-adaptation from certain night work schedules, west to east jet lag and seasonal affective disorder. Thirdly situations in which the rhythm of melatonin secretion is reduced or lost: this includes old age, depression and dementia and it is these latter two groups that are of particular interest in this thesis and aims to answer the following:

- 11.1. EXPERIMENT I: a randomised double blind placebo controlled trial to test the hypothesis that slow release melatonin 6mg given at bedtime for 4 weeks improves sleep and mood in people with depressive disorder.**

- 11.2. EXPERIMENT II: a randomised double blind placebo controlled crossover trial to test the hypothesis that slow release melatonin 6mg given at bedtime for 2 weeks improves sleep in individuals with dementia with sleep disturbance.**

PART II:

**A DOUBLE BLIND RANDOMISED CONTROLLED TRIAL TO DETERMINE WHETHER
MELATONIN IS A NATURAL SLEEP-PROMOTER AND ANTIDEPRESSANT**

Chapter 12 MELATONIN IN DEPRESSION: INTRODUCTION

Sleep disturbance is believed to be central in the morbidity of depressive disorder (Bersani, 1997) and many experience the illness as primarily a disorder of sleep (van Bommel, 1997). Sleep disturbance is seen an early indicator of depressive relapse, appearing before mood changes (Perlis et al, 1997). A meta-analysis of sleep studies reveals that the most widespread and severe disturbances of sleep are found in depression (Benca et al, 1992) and a variety of manipulations of the sleep-wake cycle have been shown to improve depressive symptoms (van Bommel, 1997).

One of the factors implicated in the control of the sleep-wake cycle is the pineal hormone melatonin. Its secretion is stimulated during darkness and suppressed by light. Disruption of circadian rhythms and the sleep wake cycle is known to occur in affective disorders (Lewy, 1995), with reports that the amplitude of melatonin secretion rhythm may be, though not always, reduced in depression (Wetterberg, 1978; Claustrat et al, 1984; Frazer et al, 1986). It is particularly reduced during the early part of the secretory period (McIntyre et al, 1989) and overall evidence suggests a generalised phase advance in biological rhythms in depression (Checkley, 1989).

In humans, there is growing evidence to suggest that melatonin has hypnotic properties and may help synchronise circadian rhythms (Dahlitz et al, 1991; Arendt, 1995; Lewy et al, 1995; Webb & Puig-Domingo, 1995), presumably acting via specific melatonin receptors found in the suprachiasmatic nucleus (Weaver et al, 1993). Therefore a number of randomised controlled trials have used exogenous melatonin to treat insomnia (Haimov et al, 1995; Garfinkel et al 1995; Zhdanova et al, 2001), free running circadian rhythms (Lockely et al, 2000; Sack at al, 2000), jet lag (Arendt et al, 1986; Arendt, 1987; Petrie et al,

1989; Claustrat et al, 1992; Petrie et al, 1993) and sleep disorders associated with shift work (Sack and Lewy, 1997; Skene et al, 1996).

In humans, there exists a diurnal variation in melatonin secretion (Arendt, 1995) which appears to be affected by light levels. There is some suggestion that abnormalities in melatonin secretion are associated with seasonal affective disorder (SAD). In SAD, patients sleep longer, have increased appetite and reverse diurnal variation of mood. It has been postulated that increased melatonin secretion may have a role in SAD. Lewy et al, (1992) conducted a pilot study where 10 participants were given “blind” either very low dose melatonin (0.25mg) or placebo during the afternoon, so as to advance the natural melatonin phase so that secretion is less delayed. This pilot on 5 participants suggested that melatonin could lead to a re-entrainment of the circadian rhythm and subsequent clinical improvement.

Melatonin occurs naturally in a variety of plants (Murch et al, 1997). A meta-analysis of randomised clinical trials has demonstrated a significant antidepressant effect of St John’s Wort (Linde et al, 1996). It has been suggested that this effect may be due to the high concentration of melatonin found in this medicinal plant (Murch et al, 1997). Thus, there is also some evidence to suggest that exogenous melatonin may be beneficial for either adjunctive treatment of depression or as a possible novel antidepressant (Anton-Tay et al, 1971; Cramer et al, 1974; Arendt, 1989; Brown, 1995). Furthermore, in all the published studies using exogenous melatonin and in a report on the effects of melatonin on healthy volunteers (Wright et al, 1986), treatment with low-dose melatonin does not appear to be associated with any significant side-effects (Buscemi et al, 2006).

There have been few trials examining the use of melatonin in depressive disorder. In the earliest published trial into the efficacy of melatonin as a treatment for depression, Carman et al (1976) found melatonin to be not only ineffective in the treatment of depression, but also that it increased the number of psychotic symptoms reported in a group of inpatients. However, this RCT had to be abandoned because of the side effects caused by the high doses of melatonin used and contained methodological flaws that question the validity of these conclusions as previously described in section 7.1. Perhaps partly due to the negative results reported in the Carman study, another study did not follow it for over two decades. Since the Carman et al (1976) study, only 4 studies have been published (excluding the one described in this thesis) using melatonin in non-seasonal depression. The first was a case report by De Vries and Peeters (1997) suggested that melatonin may have been of benefit in mood and sleep in major depression and the other 3 studies, suggested melatonin had a minimal effect on mood, but improved sleep. Two were open label studies (Fanstein et al, 1997; Dalton et al, 2000) and one an RCT examining the synergistic effect of melatonin and placebo added to fluoxetine 20 mg daily (Dolberg et al, 1998). The exact dose of melatonin for an effect on mood remains uncertain. Doses of melatonin of 3-10mg was used in the above studies, however, Zhadanova et al (2000) suggested that doses of melatonin as low as 0.3 mg were associated with improvements in self reported ratings of mood associated with the acute effects of smoking cessation in non depressed individuals.

In conclusion, sleep disturbance is a cardinal feature of depressive disorder and a disruption of the circadian rhythm of melatonin secretion is also evident. There is considerable theoretical and clinical evidence to suggest that melatonin may be beneficial in sleep disturbance in depression. However, studies to date have used small numbers of participants, with a range of diagnoses, doses of melatonin and little information about

timing. Furthermore, in the case of depressive disorder, no objective measures of sleep have been used. We conducted the largest double blind randomised controlled trial of melatonin versus placebo using wrist actigraphy as an objective measure of sleep, to test whether melatonin is a natural sleep promoter and antidepressant.

Chapter 13 MELATONIN IN DEPRESSION: HYPOTHESES

We undertook a randomised double blind placebo controlled trial to test the hypothesis that melatonin improves sleep and mood.

Null hypothesis

1. Slow release melatonin 6mg given at bedtime for 4 weeks will have no effect on sleep quality and duration in adults with Major Depressive Disorder with Early Morning Waking.
2. Slow release melatonin 6mg given at bedtime for 4 weeks will have no effect on mood in adults with Major Depressive Disorder with Early Morning Waking.

Chapter 14 MELATONIN IN DEPRESSION: METHODS

The study was undertaken in North London between October 2000 and January 2003 following approval by local ethical committees.

14.1. The study setting and referrals

The study took place through liaison with General Practices linked to the North Central Thames Primary Care Research Network (NoCTeN). Participants were recruited through General Practices from direct GP referrals, practice databases and from waiting rooms. Anyone with suspected depression between the ages of 18 to 65 was considered for the trial. Self referrals from GP waiting rooms were screened using the Centre for Epidemiological Studies Depression Scale (CES-D; Radloff 1977), with those scoring 16 or more being considered for the study. Possible recruits were provided with information about the trial and those who consented were then screened within 3 days by the research fellow for a score of 17 or more on the Beck Depression Inventory (BDI; Beck et al, 1961). Those satisfying these criteria were given a more in depth interview using the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer, 1978) to ensure that they also met diagnostic criteria for DSM-IV Major Depressive Disorder (American Psychiatric Association, 1994).

14.2. Selection criteria

Inclusion criteria: Participants 18-65 years were required to satisfy DSM-IV criteria for a diagnosis of Major Depression (unipolar or bipolar), score 17 or more on the BDI and be sleeping 1 hour less than normal on at least 3 days per week.

Exclusion criteria: People were excluded from the study if they: had another axis 1 diagnosis, were suffering from delusions or hallucinations, were actively suicidal or had received ECT within the last 6 months. It was agreed that participants would not be taking

hypnotic medication, or alternatively had been receiving the same dose of medication for at least 4 weeks prior to entry into the trial.

14.3. Design

The study was a six week double blind placebo controlled trial. All participants received usual GP care in addition to the trial medication. Although changes in medication were discouraged within the 6 weeks of the trial, any changes were recorded, as it was not felt ethical to restrict the use of antidepressants. Participants were randomly allocated to one of two groups using random numbers generated by the clinical trials co-ordinator at the Royal Free Hospital. After a week's baseline data collection, melatonin or placebo tablets were given for 4 weeks at the participant's usual bedtime. This was followed by a one week washout period. Melatonin 6 mg slow-release (synthetic origin) was provided by Genzyme Pharmaceuticals Ltd. The melatonin was a sustained release matrix for a gradual release of melatonin over 6-8 hours. The melatonin or placebo was given at bedtime. The melatonin and placebo were identical with respect to preparation and packaging. Both the pharmacist dispensing the trial medication and the researchers were blind to the treatment received. The tablets were distinguishable only by batch number held by the manufacturer. The code for treatment allocation was only broken once the trial was completed. At the end of the trial patients continued with usual GP care.

14.4. Outcomes measures

Measures of sleep: Three ways of measuring sleep were used. First, objective measures of sleep were obtained using wrist actigraphs. These provide measures of sleep onset time, wakening, rest period and sleep efficiency. Wrist actigraphy is an established method, based on wrist movements, that can distinguish sleep from wakefulness with a reliability of

88% using an algorithm described by Cole et al (1992) and is described in section 8.2. All participants were instructed to press a button on the actigraph to indicate the time at which they went to bed and also to press it again when they got up out of bed. In cases where the button was not pressed, the time the person went to bed and got up was taken from sleep diaries(Appendix item A-11). When the actigraphs . Secondly, subjective measures of sleep were collected using the Leeds Sleep Evaluation Questionnaire (LSEQ; Parrot and Hindmarch, 1978) (appendix item A-10). This measure uses visual analogue scales to assess four aspects of sleep: Getting to Sleep (GTS), Quality of Sleep (QOS) Awakening from sleep (AFS) and Behaviour Following Wakefulness (BFW). Thirdly, detailed diary information enabled collection of data to ascertain whether the participant took the melatonin, what time they went to bed, what time they fell asleep, the number of awakenings, what time they woke up and what time they got up. Participants were also asked to write comments on their sleep (Appendix item A-11).

Measures of depression: Two measures of depressive symptoms were used.

(i). First, the most widely used self-report instrument in both research and clinical settings for measurement of depressive symptom severity, the Beck Depression Inventory (BDI; Beck et al, 1961) (appendix item A-7). The BDI is a 21-item self-report measure of depressive symptoms. Each item represents a symptom characteristic of depression ranging on a 4 point Likert Scale (0-3). A cut off of over 14 is considered to be at least moderate depression in a primary care setting.

(ii). Secondly, a more objective measure of depression severity using the 21 item Hamilton Depression Rating Scale (Hamilton, 1960) (appendix item A-8). The HDRS is a 21 item observer rated instrument that is completed following a thorough clinical interview. Each

item presents a symptom of depression and is rated according to its severity as experienced by the patient.

Subsidiary measures: Measures of compliance with melatonin/placebo were made, by asking individuals to record whether they had taken the melatonin/placebo, but pill counts of the number of remaining tablets were not done. A measure of blindness was also taken from both the patients and researcher respectively using a 10 cm visual analogue scale with 0 cm indicating Melatonin and 10 cm indicating Placebo.

The objective measures of sleep, using wrist actigraphy, were collected during the last three days of the baseline data collection week (week 0), the first and fourth week of the melatonin/placebo phase (week 1 and 4) and at the end of the washout phase (week 5). Subjective measures of sleep using the LSEQ were collected at the end of each week and sleep diary entries made daily by the participants. The BDI was completed at the end of each week. The HDRS was collected at the end of weeks 0, 1, 4 and 5.

14.5. Statistical analysis

Pre-study power: Power calculations were performed using Epi Info 6 (1994) in order to estimate the numbers required to detect significant differences in sleep and mood. Total sleep time is reported as significantly diminished in depressive disorder (Gillin et al, 1979), with 67% of non depressed people sleeping between seven and a half and 8 hours. Originally we assumed that normal people sleep 8 (s.d. 1) hours and that depressed people sleep at least 1 hour less than usual (which is the ICD 10- diagnostic criteria for sleep disturbance in depression). Thus at 90% power at a $p < 0.05$ level of significance, 17 people would be

required in each group. Assuming a 20% dropout, 41 people would need to be recruited to the study in order to detect a significant improvement of melatonin on sleep. It is worth noting that more recent data since the study was undertaken suggested that a normal population, aged 16-83 years, sleeps 7.05 (s.d. 1.55) hours (Groeger et al, 2004) and using the same argument, because of the larger standard deviation in sleep, 30 people, 60 people in all would be required. In retrospect, a more appropriate approach would be to employ sleep data collected from a depressed population, similar to the sample population under study. Gillin et al (1979) found that total sleep time in 18 depressed subjects was roughly five and a half hours (s.d. 1 hour). Thus, we will assume that there will be an improvement in sleep of at least one hour from 5.5 (s.d. 1.00 hour) to 6.5 (s.d. 1.00) hours with melatonin, then at 90% power at $p < 0.05$ significance, 15 people will be required in each group, 30 in all, to demonstrate a beneficial effect of melatonin on sleep. Allowing for a 20% dropout, 36 participants would be required.

Studies of depression in populations in primary care has suggested that there is a standard deviation of 4 points in the HDRS (Mynors-Wallis et al, 1995). A 5-point change in mean HDRS score is usually taken as significant. This corresponds to an effect size of 1.2 standard deviations. Thus eleven participants would be required in each arm (a total of 22) to demonstrate an advantage of melatonin over placebo in the treatment of depression. Allowing for a 20% dropout rate over the 6 week study, we predicted we would need to recruit 26 participants in order to achieve the required number of participants completing the study to measure a significant change in mood.

Missing data: Actigraph data was collected during the last three days of four periods; the baseline period, the first and fourth week of melatonin/placebo and the washout period.

Data points were averaged for each period. In cases where baseline data were missing, average values for each group (melatonin or placebo) were entered (see section 15.3 for numbers). In the case where sets of data were missing for subsequent time period, last observation carried forward was used.

Analysis: Data were analysed using Statistical Package for Social Sciences (version 10.1.3). Data collected from actigraphs was converted into an analysable form and was analysed using software supplied by Neurim Pharmaceuticals Ltd (Tel Aviv, Israel).

Data were normally distributed and therefore the following tests were used: unpaired t-test (continuous data) and Chi Squared test (categorical data). In order to adjust for differences in baseline characteristics between the melatonin and placebo groups General Linear Modelling (GLM) was used. Average data sets for each of the periods under study were entered into the analysis. Outcome measures were considered as a “within subject factor”. Data were then analysed by “group” (melatonin or placebo), a “between subject factor” affected the outcome. Both a completers data analysis and an intention to treat analysis were undertaken. However, intention to treat data only is presented here. Completers data is given in the appendix (items A-12-15). Subsidiary analysis of sleep aimed to determine the accuracy of self report data by correlating this with objective actigraph data.

Chapter 15 MELATONIN IN DEPRESSION: RESULTS

15.1. Referral and recruitment

Period of recruitment and recruitment location: The recruitment period took place over 17 months from May 2001 to Sept 2002. Thirty percent (18/60) of general practices (a total of 50 GPs) linked to the North Central Thames Research Network (NoCTeN) agreed to participate in the study.

Referrals screened: A total of 203 people were approached for the study; 80 participants were referred directly by their GP, 68 recruited through screening questionnaires/posters in GP surgeries and 33 through a data base search of people with a previous history of depression, 22 contacted the research team after having seen an information sheet or heard about the study by word of mouth from a friend or relative.

Reason for failure to meet selection criteria: Of the 170 out of the 203 who did not then participate in the study, 84 did not satisfy inclusion criteria (10 did not have diagnostic criteria for depression and 74 did not have a disturbance of sleep). Forty four who satisfied entry criteria were excluded because they refused to participate, 31 could not be contacted/did not respond to calls and 11 did not have a sufficient command of English to be assessed.

Referral source of patients recruited: Thirty three patients were recruited to the study; 16 were referred by their GP, 13 were identified from data bases and 4 self referred.

15.2. Participant flow

Thirty three patients agreed to the trial and were randomised to melatonin/placebo. However, two people dropped out immediately after assessment. Two people completed the self report data at baseline when the researcher delivered the actigraph for baseline recording (week 0), but withdrew immediately after. A summary of the participant flow is given in the flow diagram in Figure 15.1.

15.3. Numbers analysed and management of missing data

Baseline data: Baseline self report questionnaires were completed on 31 participants and baseline actigraph data, the main outcome measure, was available in 27, because two participants had forgotten to wear the device and in two the actigraph did not function.

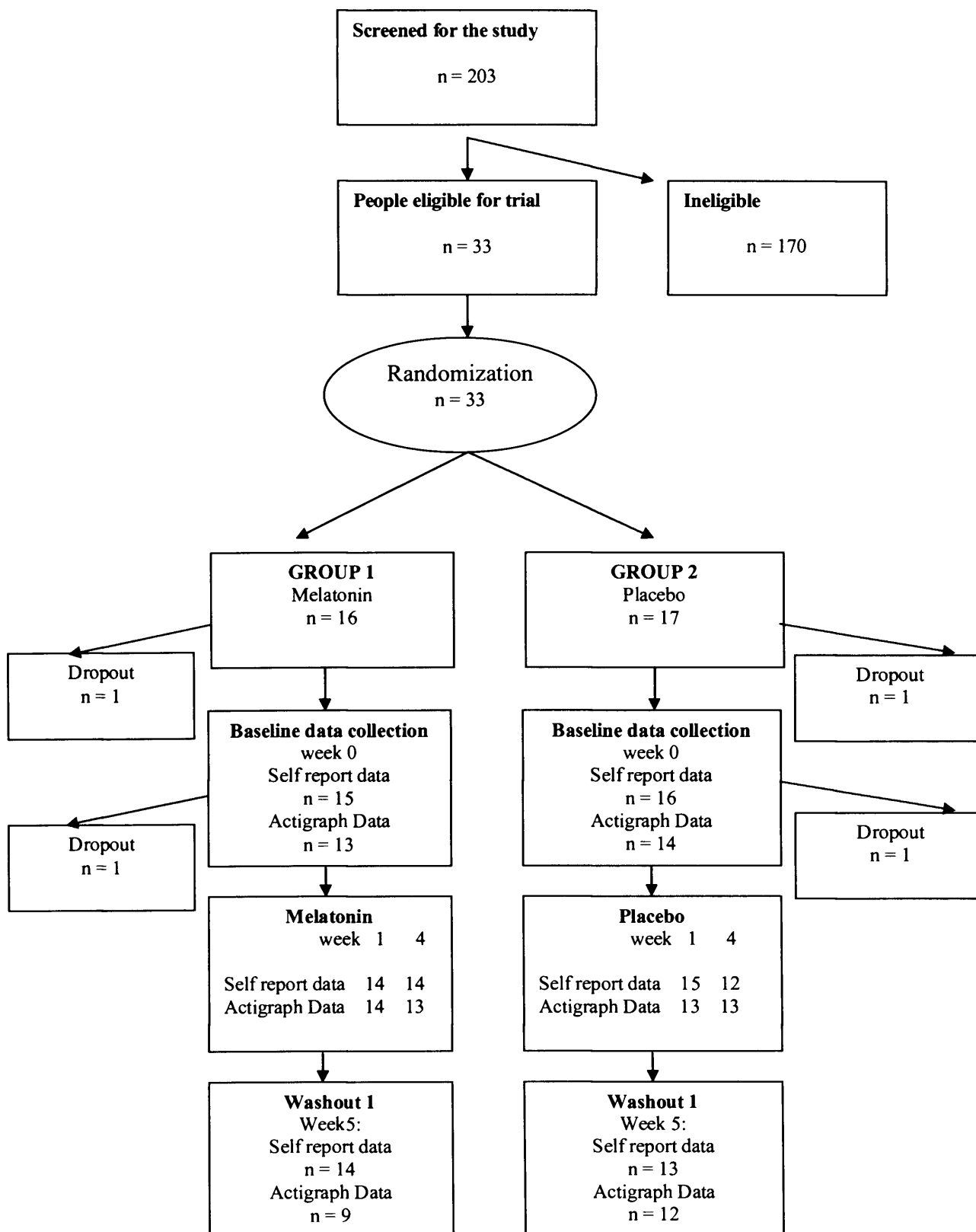
Followup data: At least 2 actigraph data readings were available in 29 patients during the course of the study. Attrition meant that fewer actigraph readings were available at the end of the study (Figure 15.1) with self report data being available in 27 and full sets of actigraph data available in 21. In cases where actigraph recordings were available, all but but two participants (one in the melatonin group and the other in the placebo group) did not press the button on the actigraph. The actigraphy data was therefore calculated using sleep diary times for the time the person went to bed and the time they got up.

Intention to treat analysis/missing data: this was undertaken on 31 using self report data and in 29 people using actigraph data (Tables 15.1-2). Last observation carried forward was used for missing self report measures. Mean baseline scores for actigraph recordings were substituted for the two participants in whom data were missing at baseline and, where

followup actigraphy data were missing, last observation carried forward was used.

Completers data were also examined and these data are given in the appendix (Table A-15).

Figure 15-1 Flow diagram of data available for RCT of melatonin in depression



15.4. Examination of baseline data:

Demographic and other information: (see Table 15.1). At baseline there were no significant differences in participants' age, use of prescribed antidepressants or use of as required hypnotic medication. The mean time the person thought they had been unwell to the time of diagnosis for the group as a whole was 28.3 (sd 67.3) weeks. This time was almost 4 times greater in the placebo group, but there was no significant difference between the groups. It should be noted that the sample size was small and the standard deviation was great. The length of time psychotropic medication had been prescribed was not recorded.

Table 15-1 Basic demographic and other information: melatonin in depression study

Basic demographic and other information of 31 participants in the melatonin in depression study.				
	Melatonin	Placebo	t or X²	Sig
Gender				
Male	3	1	Small numbers	NS
Female	<u>12</u>	<u>15</u>		
Total:	15	16		
Age	38.1 (sd 11.6)	42.0 (sd 12.6)	0.9	NS
Time of illness to diagnosis (weeks)	11.2 (sd 11.7)	43.8(sd 91.6)	1.3	NS
Antidepress. Medication:				
Yes	12	10	Small numbers	NS
No	<u>3</u>	<u>6</u>		
Total	15	16		
Number of days data collected in week or week ends:				
Collected in the week	10	7	1.3 (df 2)	NS (0.4)
One week end day	5	7		
Two week end days	1	3		

Biases associated with period of data collection:

Biases may be introduced because of a number of factors affecting sleep. These include time of the year (people sleep slightly longer in winter) and whether sleep data are collected in the week or at week ends. As participants were randomised over the year seasonal effects are likely to be minimal. Data were coded for whether data were collected in the week, on one week end day or on two week end days and a chi square analysis undertaken by group (melatonin or placebo). There were no significant differences between groups (Table 15.1).

Outcome measures (see Table 15.2)

a) Sleep measures:

(i) Actigraphy data: Findings suggest that at baseline patients spent an average of over eight hours in bed, but that sleep was poor, with patients spending, at most, a mean of 6.5 hours asleep (placebo allocated group). There were also a significant number of objective awakenings (at least 24), compared with subjective reports of 2.3 to 3.1 awakenings (placebo and melatonin allocated groups respectively) reported using sleep diaries. In both groups, sleep efficiency was under 85%. Between group comparisons for baseline actigraphy data suggests some significant differences. For those allocated to the melatonin group, prior to receiving melatonin/ placebo, the WSO was longer ($df = 27, t = 2.26, p = 0.03$) and there was poorer sleep efficiency when compared with the placebo group ($df = 27, t = 2.38, p = 0.025$). This suggested there was poorer sleep at baseline for the melatonin group.

(ii) Sleep diary: There were no significant differences in baseline measures for the time taken to get to sleep or number of awakenings for people allocated to melatonin or placebo groups. All the depressed patients reported that it took over an hour to get to sleep and

scores are strikingly similar. However it is important to note that there was a particularly large standard deviation for these scores. Patients reported waking a mean of at least three times in the night.

(iii) LSEQ: At baseline, on all 4 subscales of the LSEQ, participants reported that they had more problems with getting to sleep, poorer quality of sleep, greater awakening from sleep and felt worse on waking than usual. However, there were no significant differences between those allocated to the melatonin or placebo groups.

b) Mood measures:

Baseline measures were similar for BDI scores and HDRS scores. Rates of depression were all over the cut off of 17 for the BDI and none of the patients screened ≤ 7 using the HDRS. The standard deviation of the BDI score in the melatonin allocated group at baseline is almost half the mean, but this was because the data was slightly more skewed with respect to more severely depressed people. However, this was not of a sufficient degree to warrant the use of non-parametrics rather than parametric tests.

15.5. Results from analysis measures of sleep

Data presented: Intention to treat data for main and subsidiary outcome measures is presented in the Table 15.2. GLM was undertaken on these data. Intention to treat analysis was undertaken, but it is important to note that as more patients provided data using self report than using actigraphy, the intention to treat analysis for self report is undertaken on a slightly different population, with the wrist actigraphy population being a subset of the patients providing the self report data. Data for completers is provided in tables A12-15 in the appendix and comparison of these data provided in section 15.7.

a) Sleep measures:

(i) Wrist Actigraphy: Objective measures of sleep appear to have smaller standard deviations compared to subjective measures. However, eyeballing the data, with the exception of a reduction in the time awake after sleep onset with placebo, there appears to be no obvious pattern. GLM found that total sleep time lengthened over time ($F= 5.1$; $df= 2$; $P < 0.001$), but there was no time by group (melatonin or placebo) interaction. Although there was a small trend towards improved sleep efficiency in the melatonin group, it is notable that patients had significantly poorer sleep efficiency at baseline.

(ii) Sleep diaries: As shown in Table 15.2, there appears to be some reduction in the time taken to get to sleep in the placebo group. However, both the melatonin and placebo group have large standard deviations. GLM on data from sleep diaries revealed a shortened time taken to get to sleep over time, ($F= 5.2$; $df= 4$; $p = 0.03$), but this did not appear to be specific to melatonin as there was no time by group (melatonin or placebo) interaction. Sleep diaries did not find a decrease in reported number of awakenings either for the group as a whole or with melatonin.

(iii) LSEQ: Eyeballing the data suggests that awakening from sleep (AFS) and behaviour following sleep (BFS) is worse with placebo (indicated by a low score) than for melatonin and there were significant between group differences between melatonin and placebo, with participants at week 4 who were taking melatonin reporting greater alertness on awakening (AFS) ($n = 31$; $t=2.2$, $p=0.03$) and feeling less clumsy than usual (BFW) ($n = 31$; $t =2.0$; $p = 0.05$). However, GLM for these two sub-scales of the LSEQ found a significant improvements in sleep over time- GTS ($F= 8.5$; $df = 4$; $p < 0.001$), QOS ($F= 3.9$; $df = 4$; $p < 0.001$). This did not appear to be specifically an effect of melatonin as there was no time by group (melatonin or placebo) interaction. GLM did not show any differences in AFS or BFW over time.

(iv) BDI; measure of sleep: Subsidiary analysis of question 16 on the BDI was used to provide an overview of sleep over time in 31 patients. Question 16 asks the individual to rate sleep on a 4 point Likert Scale (I can sleep as well as usual, I don't sleep as well as I used to, I wake up 1-2 hours earlier than usual and find it hard to get back to sleep, I wake several hours earlier than I used to and cannot get back to sleep). This is shown in Figure 15.2. As data were not normally distributed and Likert scales used, parametric analysis using General Linear Modelling is not possible and numbers were too small for further analysis.

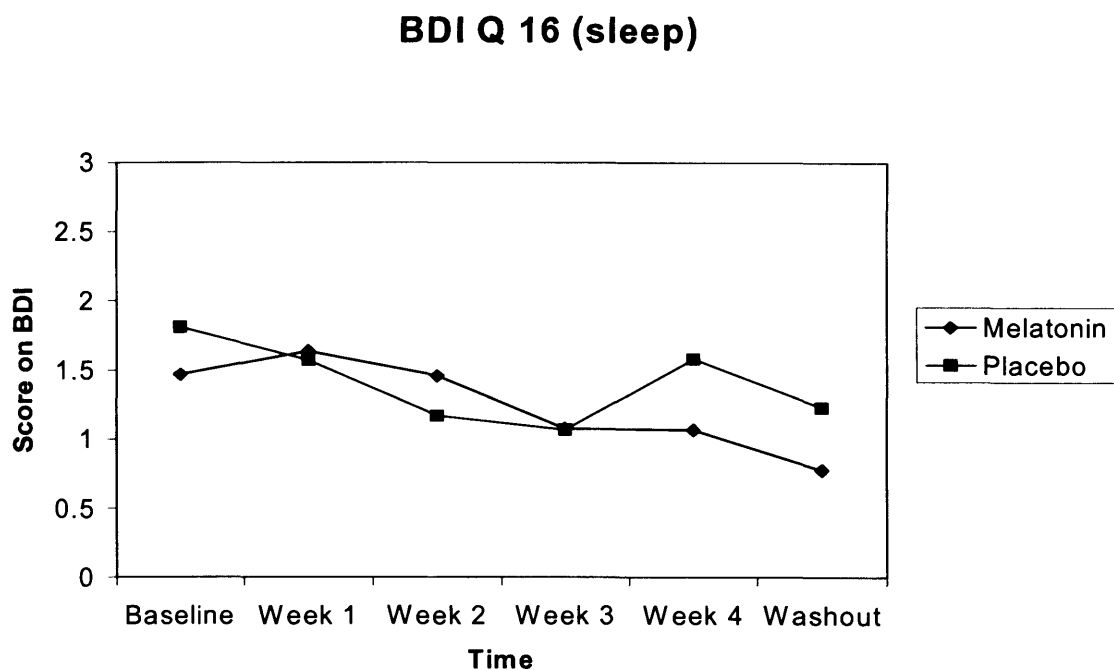


Figure 15-2 Sleep change score from question 16 on the BDI for melatonin in depression trial

15.6. Effects of melatonin on the BDI and HDRS

There were significant correlations (Pearson = 0.63; $p < 0.001$) between the HDRS and the BDI for all of the follow up points. Figure 15.3 suggests a more marked improvement in

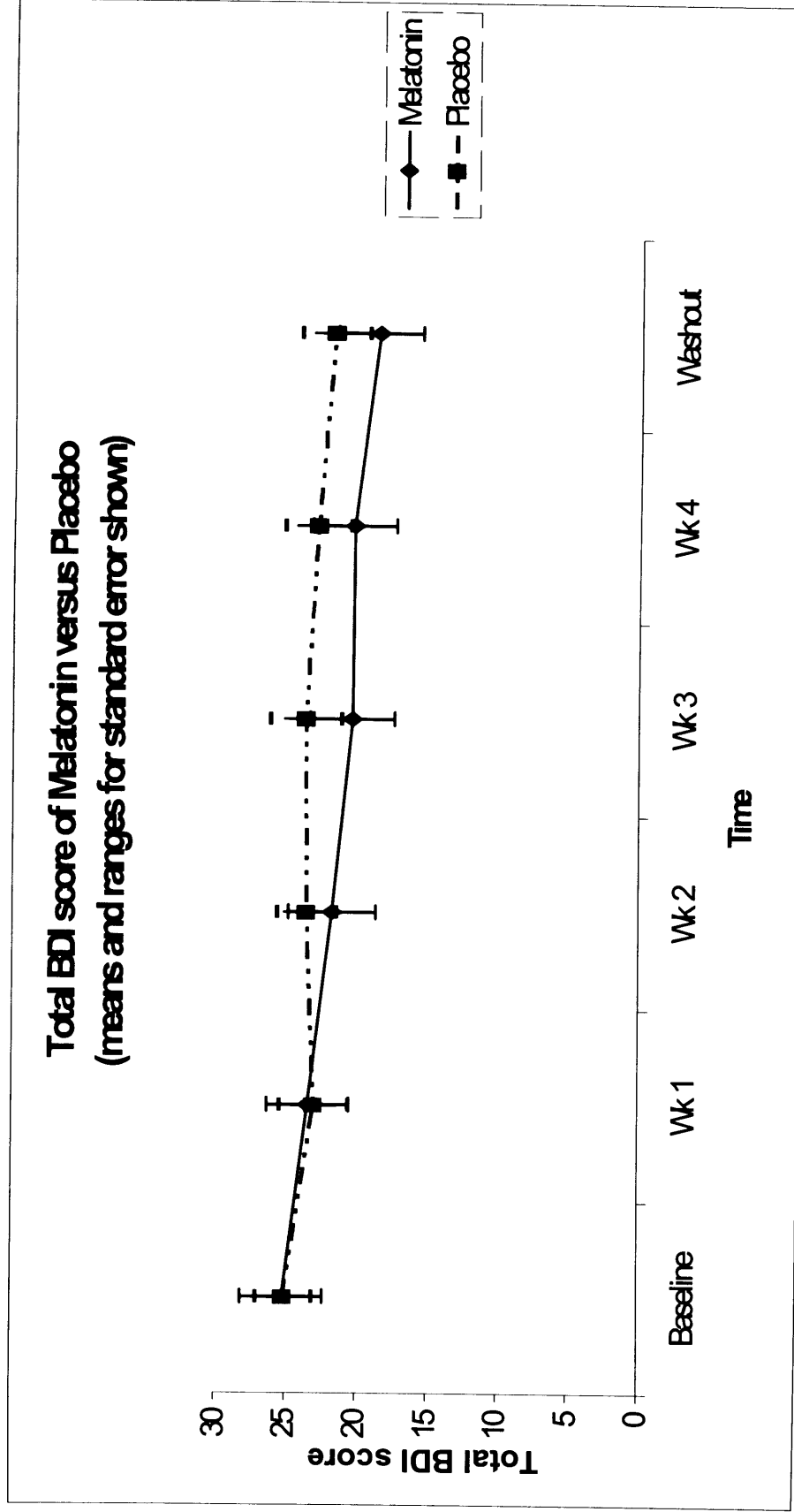
mood with melatonin than placebo. General Linear Models (GLM) analysis found significant improvements in depression ratings over time (BDI: $F= 3.2$, $df = 4$, $P = 0.01$; HDRS: $F= 7.4$, $df = 2$, $p = 0.003$) and that this relationship was linear. However, it was not specific to the melatonin group and there was no time by group (melatonin or placebo) interaction.

Table 15-2 ITT for main measures of patients allocated to melatonin or placebo in depression

Group	Baseline		Week 1		Week 4		Washout	
	M	P	M	P	M	P	M	P
Depression Measures								
BDI	25.2 (sd 11.4)	25.2 (sd 7.9)	23.4 (sd 11.1)	23.0 (sd 9.4)	20.2(sd 11.7)	22.8 (sd 9.0)	18.5 (sd 11.6)	21.7 (sd 9.6)
HDRS	16.8 (sd 6.1)	18.8 (sd 3.5)	16.0 (sd 5.3)	16.5 (sd 4.9)	13.3 (sd 6.7)	14.7 (sd 5.8)	14.9 (sd 7.9)	14.6 (sd 6.6)
Sleep Diary								
Time to sleep	69.0 (sd 44.6)	68.5 (sd 75.0)	67.5 (sd 50.0)	59.0 (sd 51.4)	52.4 (sd 40.4)	43.9 (sd 42.5)	50.9 (sd 42.2)	48.2 (sd 38.7)
Number of awakenings	3.1 (sd 2.0)	2.3 (sd 1.3)	2.3 (sd 1.5)	2.1 (sd 1.0)	2.3 (sd 1.6)	2.1 (sd 0.9)	2.6 (sd 1.9)	2.0 (sd 0.9)
LSEQ								
GTS	3.5 (sd 2.1)	3.6 (sd 1.9)	4.9 (sd 2.1)	5.3 (sd 1.7)	5.8 (sd 1.4)	4.7 (sd 1.8)	5.2 (sd 1.4)	4.4 (sd 2.1)
QOS	3.2 (sd 1.9)	3.4 (sd 2.0)	4.4 (sd 2.0)	5.0 (sd 1.9)	5.2 (sd 2.1)	4.6 (sd 1.9)	4.6 (sd 2.4)	4.8 (sd 2.3)
AFS	4.1 (sd 2.0)	4.2 (sd 1.8)	3.9 (sd 1.8)	4.8 (sd 1.7)	4.7 (sd 1.3)	3.6 (sd 1.5)*	4.9 (sd 1.8)	4.2 (sd 1.6)
BFW	4.7 (sd 1.6)	3.9 (sd 1.5)	4.7 (sd 2.1)	4.6 (sd 1.6)	5.2 (sd 1.3)	4.1 (sd 1.8)*	4.9 (sd 1.8)	3.9 (sd 1.7)
Actigraph Measures								
(In minutes)								
Time in bed	499.1 (sd 67.9)	473.7 (sd 99.3)	518.5 (sd 79.7)	511.9 (sd 91.8)	499.0 (sd 82.0)	492.6 (sd 73.8)	507.8 (sd 105.6)	486.5 (sd 69.8)
Sleep latency	39.8 (sd 31.2)	21.9 (sd 17.1)	26.9 (sd 25.9)	23.4 (sd 23.2)	33.3 (sd 31.9)	28.9 (sd 24.3)	35.6 (sd 36.1)	31.7 (sd 29.8)
Wake after sleep onset	76.0 (sd 37.4)	47.6 (sd 28.3)*	74.7 (sd 37.1)	53.8 (sd 34.7)	70.4 (sd 39.5)	44.4 (sd 32.0)*	77.9 (sd 44.8)	43.9 (sd 32.6)*
Total sleep time	370.7 (sd 49.8)	391.7 (sd 107.8)	399.0 (sd 62.7)	422.5 (sd 89.1)	385.0 (sd 49.8)	401.9 (sd 89.8)	384.9 (sd 83.4)	394.8 (sd 100.9)
Number of awakenings	29.7 (sd 12.3)	24.1 (sd 8.7)	30.4 (sd 13.1)	26.4 (sd 12.7)	28.5 (sd 13.1)	23.8 (sd 11.9)	29.3 (sd 15.5)	22.3 (sd 11.3)
Movement index	847.4 (sd 481.0)	617.1 (sd 305.6)	891.9 (sd 509.3)	584.6 (sd 339.1)	722.5 (sd 310.7)	611.0 (sd 375.0)	790.8 (sd 371.9)	664.4 (sd 448.6)
Sleep efficiency %	74.7 (sd 8.8)	82.1 (sd 7.5)*	77.5 (sd 10.4)	82.8 (sd 8.9)	78.1 (sd 9.5)	81.2 (sd 12.0)	76.3 (sd 10.6)	80.6 (sd 14.6)

Means given with (standard deviations). **Group:** M = Melatonin or P = Placebo; **Depression measures:** BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale; **Subjective measures of Sleep:** LSEQ = Leeds Sleep Evaluation Questionnaire, GTS = getting to sleep, QOS = quality of sleep, AFS = awakening from sleep, BFW = behaviour following wakefulness. **Objective measures of sleep:** TIB = Time in Bed, SL = Sleep latency, WSO = Wake after Sleep Onset, TST = Total Sleep Time, NWA = Number of Awakenings, MI = Movement Index, SE = Sleep Efficiency. * denotes P < 0.05 for unpaired t-test of between group comparisons. GLM stated in text.

Figure 15-3 Total BDI score for melatonin versus placebo for melatonin in depression



15.7. Subsidiary analyses: completers versus ITT data, compliance and blindness

Completers versus intention to treat data: As shown in Tables A12-15, means and standard deviations for subjective and objective measures of sleep, and measures of mood are virtually identical for completers data and ITT data. Standard deviations are slightly smaller in the ITT analysis and the sample size larger. The large standard deviations and small sample size should also be noted.

Subjective versus objective measures of sleep: Subjective and objective measures were compared using a Pearson correlation to assess the reliability of self report measures against wrist actigraphy where time to sleep obtained from sleep diaries was correlated with sleep latency obtained from wrist actigraphy. Similarly, a Pearson correlation analysis was undertaken between number of awakenings recorded in sleep diaries and number of awakenings obtained from wrist actigraphy. No correlation between reports from diary sheets and objective sleep data were observed.

Compliance: Assessments of compliance were made by the participants reporting on the diary sheets whether they took the melatonin/placebo. Although pill bottles were collected, the number of tablets returned was not counted. Data is given for completers only, as it is not possible to estimate compliance for the small number of people who did not complete the measures. Reported compliance with tablets was high: 27 people (14 melatonin, 13 placebo) indicated whether they had taken the tablets or not. The mean number of doses missed in the 28 day intervention period was 1.7 (sd 2.4) for melatonin and 1.3 (sd 1.6) for placebo out of a potential of 28 doses. There was no significant difference between the number of tablets missed for people who were taking melatonin or placebo.

Blindness: Both the participants and the researcher were blind to the intervention.

Blindness was maintained, with no significant difference in scores on visual analogue scales for melatonin or placebo completed by both researcher and patient at the end of the 1st week and 4th week of melatonin/placebo (Table 15.3).

Table 15-3 Melatonin in depression trial: assessment of blindness

Assessment of blindness:						
10 cm Visual Analogue Scale assessing blindness.	N	Mean	Standard deviation	df	t- value	P value
Patient blindness						
Week 1						
Melatonin	12	4.8	2.5	23	-0.79	0.43
Placebo	13	5.6	2.2			
Week 5						
Melatonin	12	5.1	2.4	23	-0.79	0.63
Placebo	11	5.7	3.1			
Researcher blindness						
Week 1						
Melatonin	12	4.7	2.3	21	-1.1	0.29
Placebo	11	5.7	3.3			
Week 5						
Melatonin	14	4.1	3.5	21	0.18	0.86
Placebo	13	3.8	3.3			

Adverse events: Of those taking melatonin, poor sleep was reported by 2 patients, vivid dreams by one, day time sleepiness by one and a fuzzy feeling the next day in another patient. Vivid dreams were also reported during the washout period of melatonin by one patient. Of those taking placebo: poor sleep was reported by 2 patients, daytime sleepiness by 1, vivid dreams by 1 and headaches by another.

15.8. Methodological issues

The Consolidated Standards of Reporting Trials (CONSORT) statement (Begg et al, 1996), revised from Moher et al (2001), suggests that certain criteria are met when reporting the results of parallel-group RCTs. This revised checklist consists of 22 items reported in four stages: enrolment, intervention allocation, followup and analysis. These issues have been addressed and reference to these is given in the Table 15.4 below.

Table 15-4 CONSORT Checklist when reporting an RCT: melatonin in depression

PAPER SECTION And topic	Item	Description	Reported Section or table or Figure.
TITLE & ABSTRACT	1	How participants were allocated to interventions (<i>e.g.</i> , "random allocation", "randomised", or "randomly assigned").	Page 4 and 14.2-3
INTRODUCTION Background	2	Scientific background and explanation of rationale.	Chapt 12
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	14.2
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	14.3
Objectives	5	Specific objectives and hypotheses.	Chapt 13
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (<i>e.g.</i> , multiple observations, training of assessors).	14.4
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	14.5
Randomization – Sequence generation	8	Method used to implement the random allocation sequence (<i>e.g.</i> , numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned	14.3
Randomization – Allocation concealment	9	Method used to implement the random allocation sequence (<i>e.g.</i> , numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	14.3
Randomization – Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	14.3
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	14.4
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	14.5

**CONSORT Checklist for reporting a randomised trial: Melatonin in depression
(continued)**

RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	Fig 15.1
Recruitment	14	Dates defining the periods of recruitment and follow-up.	15.1
Baseline data	15	Baseline demographic and clinical characteristics of each group.	15.4 Table 15.1
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	14.5 15.3 Fig 15.1
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).	15.5 Table 15.2
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	15.7
Adverse events	19	All important adverse events or side effects in each intervention group.	None reported
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	16.2-9
Generalisability	21	Generalisability (external validity) of the trial findings.	16.2-9
Overall evidence	22	General interpretation of the results in the context of current evidence.	16.2-9

Chapter 16 MELATONIN IN DEPRESSION: DISCUSSION

16.1. Recruitment issues

Although we approached all 60 practices linked to NoCTeN, of these only 18 general practices (around 50 GPs) agreed to participate to the study. It is notable that of those who did not participate, GPs suggested they did not have time for research, that research was not a priority and that they often found depressed patients too difficult to motivate. GPs were the major single referrers to the study. On a hypothetical GP list of 2,500, an average of 12 people present with severe depression per year (Royal College of General Practitioners, 1981). The numbers presenting with milder forms of depression will be considerably higher. We might therefore expect at least 700 ($50 \times 12 \times 14/12$) people with severe depression alone to present to his/her GP and then potentially be referred to the study. Only 80 people were actually referred to the study by GPs.

There are several possible reasons why the number of people referred was many less than expected. The first is that depression was rare in the catchment areas under study; the second is that people with depression did not present to primary care; the third is that although people presented with depression, they were not detected; and the fourth is that although people with depression were detected, they were not being referred to the study, but rather were being filtered out by GPs. It seems unlikely that depression rates in our sample population were significantly lower than expected as the sample population area is typical of urban General Practices. Although it may be suggested that people with depression may not be presenting to their GPs, there is evidence to suggest that if anything, people with psychiatric illnesses have higher consultation rates with their GP and are less likely to tolerate psychiatric (cf physical) symptoms (Ingham and Miller, 1976; Goldberg and Huxley, 1980).

The last two possibilities, that people with depression were not detected or referred are perhaps more likely. Although it needs to be acknowledged that GPs may only detect up to two thirds of patients who are psychiatrically ill (Goldberg and Blackwell, 1970; Goldberg et al, 1970), a low detection rate in itself could not explain the low number of referrals.

Although it may have been interesting to know why GPs chose not to refer people, this was neither a purpose of the study nor would it have been realistic to ask GPs who are already time pressured to record their reasons for not referring. Indeed, it is necessary to minimise the GPs workload in order to maximise referrals. It is notable that almost 40 % (80/203) of people referred to the study were referred by their GP and this referral source constituted almost 50% (16/33) of people who were eventually recruited to the study, thus GP referral clearly constitutes a good source of participants.

There was however some indirect evidence which may explain the low referral rates in this study. There is some evidence of bias in the way GPs refer and the bias in those who agree to participate. Almost half (84/170) of those who did not participate in the study did not have disturbance of sleep or depression. This suggests that diagnosis of sleep disturbance was not the main factor determining whether GPs considered patients suitable for referral. The prevalence of major depression in females is about twice that of males (Weissman et al, 1996), however our data show that the female to male ratio of people selected for the trial was 9 to 1 which suggests that females may be more likely to participate in research such as this. It was noted by the Research Fellow that GPs indicated that female patients had more time for research and often mentioned they were keen on natural remedies rather than antidepressants. Although we did not have information available about why GPs did not refer to the study, a number of GPs expressed the view to the research fellow that they did not want to discuss the issue of research with a patient with depression in case it upset

them. Furthermore, GPs suggested they were reluctant to enter patients into a trial in which the entry criteria specified that psychotropic (antidepressant medication and hypnotics) should, where possible, be kept constant as they felt it would not be ethical to withhold treatment. Although GPs indicated significant interest during preliminary discussions when setting up the study, there was a disparity between professed interest and actual referrals. We tried to maximise referrals by regular contact with GPs, placing posters advertising the study in waiting rooms, searching practice data bases for suitable patients and providing memory aids for GPs, such as stickers to place on computers and information sheets, but referrals were limited.

Little is known about the decision making process determining whether or not GPs refer patients to drug trials in particular. Although randomised placebo controlled trials are advocated where little is known about an intervention, GPs may feel it is unethical to refer to a placebo-controlled trial when effective treatments are known to be available. The issue of how GPs decide whether or not to refer for drug trials may best be explored further using qualitative methods, adopting a grounded theory approach to explore GPs views about involving people in drug trials. This approach could be undertaken by interviewing a selection of GPs and asking them what they think about involving people with depression in research and whether there are any special considerations where drugs are involved. All interviews would be recorded and text from transcribed interviews then imported into a data management package (NUD.IST 3: Non-numerical Unstructured Data Indexing, Searching and Theory-Building) and coded into categories of statement. This systematic analysis of qualitative data would generate information about how GPs make their decision about referral. Although we did survey GPs informally prior to the study, in practice we found that numbers of referrals were significantly less than expected. Pilot work in

selected practices to determine how many people may be referred to a study such as described may have been more helpful.

Another important factor observed in the referral process is that of referral bias. We hoped to recruit a significant number of people who were medication free, but it was surprising that of those referred, only 29% (9/31) were not on or did not want to take antidepressant medication. Detailed information on the dosages and timing of medication people were taking during the course of their illness was available, but people were prescribed different types of drugs (e.g. SSRIs, tricyclic antidepressants) at varying doses, and given the small numbers involved in this trial, it is not possible to subanalyse the data according to drug and dose. Furthermore, although antidepressants were prescribed, it is not possible to be sure about compliance as antidepressants are often not taken. However, participants were ill for an average over 6 months. It is therefore possible that people referred represented a treatment resistant group who were then more likely to be referred for alternative (melatonin) treatments. However, it is likely this sample population would have a propensity not to respond to treatment generally and this may also be associated with a reduced treatment effect with melatonin. The decision on how tight to make selection criteria is often difficult. Encouraging referral despite some use of antidepressant/hypnotic medication has to be balanced up with the pragmatic design which hopes to select patients most representative of a general practice population, so that findings may be applied to other general practice settings.

16.2. Main findings from intervention with melatonin/placebo in depression

This is the largest RCT of the use of melatonin in sleep disturbance in depression. All participants had significant baseline scores for depression using the HDRS and BDI and there

were significant improvements in these scores with time. Compared to data from a normal population (Cole et al, 1992; 1998), baseline data suggests more disturbed sleep; shortened sleep, poorer sleep efficiency and increased awakenings. At baseline (i.e. prior to melatonin/placebo), the melatonin group had significantly longer periods of wakefulness and poorer sleep efficiency overall. It may be that people allocated to the melatonin group represented a more severely disturbed population. This may in part explain why there was a failure to find an effect of melatonin on sleep. Randomisation was otherwise successful and blindness was maintained.

Sleep diaries did not reveal a difference in time taken to get to sleep or number of awakenings between groups (melatonin or placebo). Although subjective measures of sleep using the LSEQ found better sleep at 5 weeks with melatonin (being more alert on wakening and feeling less clumsy), GLM did not demonstrate an improvement with melatonin versus placebo for other measures. GLM undertaken on objective measures of sleep suggested that there was an improvement in sleep over time for the group as a whole, but that this was not associated with melatonin per se.

A number of studies have suggested that melatonin has a beneficial effect in treating disturbance of the sleep wake cycle in depression. However published work has been based on small numbers (DeVries and Peeters, 1997) (n = 1) and trials have not been randomised (Fainstein et al, (1997) (n=9) and Dalton et al, (2000) (n=9). Interpreting these reports is therefore difficult and publication bias may also reinforce claims about the benefits of melatonin for use in depression without good evidence to support this.

16.3. Reliability of outcome measures used

EEG polysomnography may be regarded as the gold standard for measuring sleep disturbance. Although wrist actigraphy is the most useful measure of distinguishing sleep from wakefulness, with a reliability of 88% (Cole et al, 1992), in an outpatient setting the lack of correlation between actigraph data and self report data highlights the problems of other studies which used self report measures of sleep. Participants in our study had impaired sleep efficiency (74.7% and 82.1% for the melatonin and placebo group respectively). Previously published data suggests that means in sleep efficiency of over 85% may be expected for normal controls and of 79% for those with insomnia (Sadeh et al, 1989; Stanley, 1997). Our findings are largely consistent with the RCT by Dolberg et al (1998) who did not find a significant improvement in sleep and mood. Although there was no improvement in most of the measures of sleep, we did find an improvement in subjective reports of sleep quality using the LSEQ (Parrot and Hindmarch, 1978) and possibly a trend towards an improvement in mood. Nevertheless, findings from our study, suggest that gains on melatonin, if anything, are modest.

Buysee et al (1989) who developed the Pittsburgh Sleep Quality Index (PSQI) advocate its use over other measures of sleep, such as the LSEQ, as it provides qualitative as well as quantitative information. Although this may have been helpful, our study was interested in how sleep changed over time with 4 weeks of melatonin. The PSQI measures change in the last month and therefore may not be appropriate for the purposes of this study which also aimed at evaluating sleep in the one week washout phase.

Actigraph data did not reveal objective improvements in sleep, however it is notable that full sets of data were not available in 28% (8/29), although of participants because of practical

problems; patients forgot to wear actigraphs or they did not function. Nevertheless, we would advise caution in interpreting self report data only. In particular, sleep/activity logs may not always be filled out accurately (Stanley, 1997). The lack of reliability between actigraphy data and self report data was highlighted by Baskett et al (2003) who were investigating the effects of melatonin in both normal and problem sleepers. They found that actigraphy records showed between 30 and 50 events were 'awakenings' whereas the participant only reported waking 2 or 3 times. Patients with depression may have some degree of cognitive difficulty and it is likely that measures which rely on self report are going to be even more inaccurate. All the trials of melatonin in depression previously described (DeVries and Peeters, 1997; Fainstein et al, 1997; Dolberg et al 1998; Dalton et al, 2000), have relied on self report data. Indeed, in the trial using wrist actigraphy to evaluate sleep in dementia described in this thesis, we also found that carer reports about sleep were unreliable (Serfaty et al, 2002). Therefore in light of evidence by Stanley (1997) and from this study, the use of objective measures, such as wrist actigraphy is recommended.

16.4. Power considerations

In our very conservative estimate of pre-study power, we suggested that a total of 34 participants were required to detect a significant difference between those receiving melatonin and placebo. This prediction was conservative, particularly given that other studies have suggested that exogenous melatonin may increase total sleep time by as much as 200% (De Vries and Peeters, 1997) and that melatonin is effective in improving sleep quality, measured using the PSQI (Buysse et al, 1989), in only 19 patients (Dolberg et al, 1998). Although it may be argued that our trial may have had insufficient power to determine whether melatonin is a natural sleep promoter and antidepressant, our findings are not consistent with previous claims suggesting that melatonin may induce a subjective improvement in sleep in depression

(Fainstein et al, 1997; De Vries and Peeters, 1997; Lewy et al, 1998, Dolberg et al, 1998; Dalton et al, 2000). A post hoc analysis on the data was conducted to determine how many people would be required to detect a beneficial effect on sleep efficiency of melatonin over placebo. Using means for melatonin, placebo and pooled means for the whole sample population at week 4 of melatonin/placebo compared to baseline, at 80% power at the 5% significance level, a total of 90 people would be required to detect an improvement in sleep efficiency. This suggests that, if anything, melatonin has only a weak effect on sleep in depression and that even if numbers suggested from our power analysis were recruited, this trial would still have been underpowered. A Hawthorn effect may reduce the power of a trial since, by virtue of being in the study, even those allocated to the placebo group may report an improvement, which further reduces the ability to detect significant differences. Nevertheless, the data presented at least provide a more precise estimate for the numbers required to detect a significant improvement in sleep. It also highlights the need to rely on objective measures of sleep rather than self report data, which may be unreliable.

16.5. Compliance.

Compliance with medication was high, with only 6.1% of the doses of the active intervention (melatonin) being missed. Both the researchers and participants were blind to whether melatonin placebo was being taken. Although compliance can be tested using salivary (Voultsios et al, 1997) or urinary (Aldhous and Arendt, 1988) 6-sulphatoxy-melatonin, this was not done because of financial considerations.

16.6. Dose, duration and dose response considerations

Varying doses of melatonin have been used in intervention trials, although, recent studies suggest significantly lower doses may be advisable. Although doses of 5-10mg were used for

people on antidepressants (Dalton 2000), there is a suggestion that considerably lower doses of 0.125mg may be effective for the treatment of winter depression (Lewy et al 1998b). Indeed, polysomnography found that in the case of age related insomnia, 0.3 mg may be the most effective dose when compared to placebo, 0.1 and 3mg (Zhadanova et al, 2001). Although it is difficult to extrapolate the effective melatonin dose for a different population, future trials to investigating its potential beneficial effects in depression should use different doses.

There may be considerable individual variations in the response to exogenous melatonin depending on the phase of circadian melatonin levels. Phase abnormalities exist in the endogenous melatonin cycle in people with seasonal affective disorders (Lewy et al 1995), but the evidence for this effect in other mood disorders is less clear. The hypnotic properties of melatonin, as well as its ability to synchronise circadian rhythms (Sack et al 2000) provided a theoretical basis to support its use in the treatment of depression. The phase typing of individuals in our sample population was unknown and it could be argued that failure to find a beneficial effect of melatonin could be explained by different phase response effects. Knowledge of an individuals melatonin cycle may be helpful so that optimal timing of administration of melatonin is possible. However, all our patients had early morning wakening, which suggests that if phase rhythm abnormalities exist at all, then those of a phase advance type may be expected. Although providing immediate release melatonin in the evening may exacerbate sleep problems by phase advancing the melatonin cycle further, it was hoped that, with the longer half life of slow release melatonin, prolongation of serum melatonin into the early hours of the morning would extend morning sleep. A small number of people in our study sample may be expected to have a phase delay in melatonin secretion, which may be expected to be associated with morning sleepiness. We would hope that these participants would benefit from the soporific properties of melatonin and that these people

were equally distributed to the melatonin/placebo group by virtue of the randomisation process.

The length of time (weeks) required for melatonin to be prescribed may also be relevant. Most studies however, have investigated the use of melatonin in depression for 3-4 weeks (Dolberg et al, 1998; Lewy et al, 1998; Dalton et al, 2000) and although a longer period of administration may be required, all studies published so far suggest that the beneficial effects occur early in treatment.

16.7. Factors which may interfere with effects of melatonin

The concomitant use of medication which may affect sleep is of particular relevance to this trial. Although hypnotic medication may be prescribed for sleep problems, only one patient was taking such medication. It is therefore unlikely that such medication is introducing a significant bias. Furthermore, the dose of hypnotic medication was stable for some months and any hypnotic effects are likely to be on initial insomnia.

Although we would have expected a smaller proportion of those referred not to be on antidepressants, as melatonin represents a “natural” compound, over seventy percent (22/31) of people recruited to the trial were receiving antidepressant therapy. There were no significant between group differences for those allocated to melatonin or placebo and taking antidepressants or not. Although no one was started on antidepressant therapy 4 weeks prior to the trial or during the trial, it seems likely that those recruited may have been non-responders to antidepressants. Such non-responders to conventional antidepressant treatment may represent a treatment resistant group and therefore are also less likely to respond to melatonin. Although there was no significant difference in antidepressant prescriptions for

either group, there is evidence that antidepressants may significantly improve sleep architecture. The effect of antidepressants in both groups would therefore reduce the power and the ability to detect an effect of melatonin. Mood improved in both groups over time. Figure 15.3 suggests that there is some evidence that melatonin may be acting as a natural antidepressant as the melatonin group appeared to improve more than the placebo. Mills and Faunce (1991) found that melatonin inhibits MAO activity and increases brain levels of serotonin, dopamine, and noradrenaline and it may be that melatonin is acting through this mechanism. Although there was no evidence of an effect of melatonin on mood when combined with fluoxetine (Dolberg et al, 1998), because of methodological issues previously described, such combinations therapies merit further evaluation.

Post hoc analysis of trial data using BDI scores (Figure 15.3) suggests a 2.6 point advantage of melatonin over placebo. This corresponds to an effect size of 0.26. In order to detect a significant effect of melatonin over placebo on mood, we would need $n=233$ in each arm of the trial. As we recruited 33 of the 34 suggested by power analysis, it is theoretically unlikely that our findings could be explained through a lack of power. However, in practice the effect sizes we found are far smaller than those reported in previous studies showing a positive effect of melatonin. Interestingly, the effect sizes shown in our, negative study are similar to those found in reportedly positive studies of agomelatine (Kennedy and Emsley, 2005; 2006).

16.8. Period of data collection

The time period of data collection may be important. Some studies investigating the use of melatonin for sleep disorders in dementia using wrist actigraphy have compared night-time activity to total daily activity (Tozawa et al, 1998; Cohen Mansfield, et al, 2000; Singer et al, 2003). Although recording night-time activity to daytime activity may be of relevance in

people with depression as they may catnap during the day, this was not part of our main hypothesis which aimed to investigate the effect of melatonin on night-time sleep and mood.

16.9. Effects of dropouts on outcome

Complete data sets through wrist actigraphy were available in 72% of participants and 88% (29/33) of participants completed the study. Dropouts are an important consideration in any study (Steiner, 2002), as participants who drop out may represent a different sample population. However, the reason for incomplete data sets in half the cases who dropped out was because the actigraphs failed to function properly. It therefore seems unlikely that this represented a different sample population. As the number of people who dropped out was small, it is not possible to determine whether drop outs represent a different population from those who completed the study. As completers data and intention to treat data were very similar and no differences in the findings observed, it seems likely that the effect of dropouts is unlikely to explain our findings.

16.10. Recommendations

Joint recommendations which apply to both studies (melatonin in depression and dementia respectively) described in this thesis are given in chapter 25. This study was a pragmatic trial in a primary care setting using objective measures of sleep using wrist actigraphy. However, in light of the findings from this and other trials, we would recommend in future studies, that varying dose regimens of melatonin (0.3mg - 6mg) are used and that qualitative measures of sleep such as the PSQI (Buysse et al, 1989) may be helpful. Evidence from this trial suggests that melatonin is not particularly helpful for treating sleep problems in depressed patients in primary care. Although too few for analysis, a number of patients reported feeling considerably better on melatonin. It may be that there exists a subset of patients who are

melatonin responders and in further studies it may be interesting to identify melatonin responders. Nevertheless, strategies that involve studying a small number of patients in detail may prove more fruitful; patients with depression would have their melatonin cycle determined using saliva and/or serum melatonin. Given knowledge of the phase response curve, melatonin/placebo could be then given at the optimal time. Its effect on sleep and mood could then be determined through EEG monitoring and the HDRS respectively. In the meantime, for people with depression, we suggest continued critical appraisal of claims of the beneficial effects of melatonin as a natural sleep promoter and antidepressant.

Chapter 17 MELATONIN IN DEPRESSION: CRITICAL ANALYSIS:

As previously described, the aim of a pragmatic trial includes describing the advantages and disadvantages of such a trial in clinical practice (Sackett and Gent, 1979).

17.1. Aims of a pragmatic trial of melatonin in depression

- (i) Does the trial address a clinically important dilemma?

Sleep disturbance is one of the major and defining characteristic of depressive disorder according to diagnostic criteria defined both in ICD10 and DSMIV. The importance of sleep in depression (Benca et al, 1992; Bersani, 1997; van Bommel, 1997; Perlis et al, 1997) has been highlighted in chapter 12. About two thirds of adults will at some time experience depression which will affect their daily activities (University of Leeds; Effective Health Care 1993). Depression is one of the most common reasons for attending a general practitioner (Goldberg & Huxley 1992). Antidepressants are the mainstay treatment of depression in primary care in the UK. There has been recent media criticism of the use of antidepressant drugs, which are increasingly perceived by patients to be either toxic or addictive. Melatonin is not classed as a medicine in the USA or the UK and non drug treatments are often welcomed by patients. It follows that the use of what is perceived as a natural compound to address a significant clinical problem would seem timely as previously no large RCTs of the use of melatonin in depressive disorder have been undertaken.

- (ii) Are the participants in the trial those patients in which the treatment would normally be considered in clinical practice?

The trial described in this thesis examined the use of melatonin in people in a primary care setting, where the majority of people with depression will be cared for. The use of

alternative treatments is very popular amongst patients, but there is little evidence base to inform practice. However, the sample population recruited included people with longstanding depressive illness and melatonin may be more effective in recent onset depression.

(iii) Is the intervention a realistic reflection of the likely good practice in the NHS?

Good practice suggests that any intervention should be of benefit to the patient and do no harm. It should also be as cheap as possible to maximise cost-effectiveness. The GP is often the first person to be approached for help. With the introduction of the SSRIs in the late 1980s there has been a dramatic increase in antidepressant prescriptions and an escalation in associated drug costs in the 1990s (<http://www.nelh.nhs.uk/guidelinesdb/html/Antidepressants-ft.htm>). Improved patient compliance because of reduced adverse effects has been one of the main factors in switching from tricyclic antidepressants. The SSRIs now account for 63% of prescribed antidepressants and contribute significantly to healthcare costs (National Institute of Clinical Excellence, 2004). Melatonin has been shown to have very few adverse effects in lower doses (Buscemi et al, 2006), is very cheap and is not subject to patent protection. It follows, that if effective, melatonin would be a safe, easy to administer compound.

17.2. Design of a pragmatic trial of melatonin in depression

(i) What was the method of randomisation and did the investigators ensure that it was adhered to?

The method of randomisation was undertaken using a random numbers generated by computer.

- (ii) Who was blind to the randomised allocation: patient, physician, the research assistant measuring the outcomes, the investigator who analysed the data?

The codes were not broken until completion of the trial and until all outcome data had been collected. This trial was actually a quadruple blind design in that the dispensing pharmacist, researcher, GP and patient were all blind to which preparation (melatonin/placebo) was dispensed. The analysis was undertaken by Dr Serfaty.

- (iii) How was blindness ensured and was it assessed?

Blindness was assessed using a VAS. The results suggest that blindness was indeed maintained as virtually identical scores were obtained for guessing whether melatonin or placebo had been given.

- (iv) Did the experimenters include an assessment of “quality of life”?

Although measures evaluating quality of sleep were made using the LSEQ, no direct measures of quality of life were taken. It is acknowledged that reliable and valid measures, such as the EuroQol (5D) (Brooks 1996) may provide information about the indirect benefits of an intervention and may be also used to estimate treatment costs (Beecham and Knapp, 1992). Researchers may desire to collect as much information as possible, but there is always a need to balance this with what is practical. It is worth noting that in pilot work the assessment process already took over an hour. Lengthy assessments may decrease patient enrolment and increase dropouts. Furthermore, lengthy assessment procedures are discouraged by ethics committees who wish to ensure that research does not cause patients additional stress.

- (v) Is there an economic assessment that measures health and social service costs not directly concerned with treatment?

One of the most commonly used measures of costs is the Client Service Receipt Inventory (CSRI; Beecham and Knapp, 1992). Using this, the researcher is able to explore the cost per quality-adjusted-life-year. Although health economic measures are increasingly used to evaluate interventions for depression in a primary care setting (e.g. Bower et al, 2000), this was not appropriate in this study. It was decided that in the first instance, it would be important to establish that melatonin has a beneficial effect in depression. Once this had been demonstrated, further work to investigate its mode of action and its cost-benefit could be undertaken.

17.3. Analysis of a pragmatic trial of melatonin in depression

- (i) Was there an imbalance between the randomised groups in any of the prognostic variables?

Results suggest that there was a differences between some of the variables which may predict outcome. The longer time to wake after sleep onset in the melatonin group at baseline (i.e. prior to receiving melatonin) may suggest that further improvement with melatonin may be less likely. Similarly poorer sleep efficiency in the melatonin group at baseline may result in an improvement with melatonin because of spontaneous remission. No differences in basic demographic information (gender, length of illness etc), prescribed medication, nor any differences in other baseline outcome measures were observed. It is worth noting that the numbers in each group were small and one cannot exclude the possibility of a type 2 error in which there is a significant difference between groups even though none exists.

(ii) How is missing data analysed? Is an intention to treat strategy used or are other statistical methods used?

A full description of how missing data were analysed was described in the methods section 14.5 and also in the results section 15.3. Both a completers analysis and an intention to treat analysis was used for the main outcome (actigraph) measure, but as they gave the same results only the ITT analysis of results was given.

(iii) Have the investigators performed multiple statistical tests on a variety of outcomes?

All statistical tests were undertaken to test our a priori hypothesis, so that spurious results were not obtained by multiple testing generating type 1 errors, demonstrating a difference and rejecting the Null hypothesis.

(iv) Was the main outcome specified before the trial was started?

The main outcome measures, sleep efficiency using wrist actigraphy and BDI (Beck et al 1961) were specified before the trial was started.

(v) Is the power calculation from the research proposal described?

The power calculation is described in section 14.5.

(vi) If a negative result, how large are the confidence intervals?

Data for sleep and depression were normally distributed and therefore means and standard deviations were given and parametric tests were used in this thesis. Confidence intervals (CI) can be calculated from standard deviations. Ninety five percent confidence intervals are calculated by $\text{mean} \pm 1.96 \text{ SD} / \sqrt{n}$, where SD is the standard deviation and n is the number of observations. In the study, roughly 15 people were assigned to each group.

Thus $1.96 \text{ SD} / \sqrt{15} = 1.96 \text{ SD} / 3.9 = 0.5 \text{ SD}$. A rough calculation of CIs may be done by mean \pm half the standard deviation. Applying this to the data on the outcome measures, it becomes clear that data collected from depression rating measures, sleep diaries, the LSEQ and wrist actigraphy, shows a considerable range in CIs and also that there is an overlap in CI between the two intervention groups for all the measures presented.

(vii) Have the investigators ruled out the possibility of an important treatment effect? Analysis of the results suggest that there is little in the way of treatment effect using melatonin for sleep disturbance of depression. Data was examined to see whether there were any trends for melatonin/placebo and seemed to indicate a trend towards improvement in the BDI with melatonin. Other investigators have performed inappropriate statistical tests such as looking for between group differences using unpaired t-tests at followup without taking into account baseline measures. Other studies have claimed a significant treatment effect when this is of doubtful clinical significance. For example in the trial by Kennedy and Emsley (2006), a placebo controlled trial of agomelatine in the treatment of major depressive disorder, the authors suggested that agomelatine was effective. However, the HAM-D total score was 28.1 in the placebo group compared with 27.7 in the agomelatine group. The clinical significance of a 0.4 reduction in HAM-D scores needs to be called into question.

17.4. Conclusions of a pragmatic trial of melatonin in depression

This study is the first RCT using objective measures of sleep to provide information about the use of melatonin in depression. Although consistent with other studies, there is some suggestion that melatonin may be helpful in subjective experiences of sleep. The effects of melatonin did not appear statistically significant on our main outcome measures of sleep

and mood, the most likely explanation is that if there is an effect of melatonin, it is if anything, very weak. Although previous trials with fewer patients, have suggested that melatonin has a beneficial effect on sleep quality, these findings need to be questioned as it is likely that the effects of melatonin on sleep are exaggerated. The effect on mood warrants further investigation and the effect size is no different from that seen in other studies claiming a positive effect of agomelatine Kennedy and Emsley (2005; 2006).

**PART III: DOUBLE BLIND RANDOMISED PLACEBO CONTROLLED CROSSOVER
TRIAL OF LOW DOSE MELATONIN TO SEE WHETHER MELATONIN IMPROVES SLEEP
AND COGNITIVE FUNCTION IN DEMENTIA**

Chapter 18 MELATONIN IN DEMENTIA: INTRODUCTION

Cognitive impairment is a characteristic feature of dementia and is a considerable problem world-wide, with over 29 million people affected (Vink et al, 2002). As the incidence of dementia increases with age, with the increasing life expectancy and smaller family size in developed countries as the “baby boomers” reach old age, it is predicted that the proportion of elderly people will increase. Dementia is therefore likely to become more prevalent in the population overall.

In normal ageing there may be fragmented nocturnal sleep, being particularly worse in the second half of the night, and daytime napping (Campbell et al, 1998). In elderly people with Alzheimer’s disease there may be an exacerbation of this pattern with loss of the circadian rhythm and delayed acrophase (Bliwise et al, 1993). As a result, a characteristic pattern of sleep disturbance is seen in dementia. This is known as “sundowning” and is characterised by increased arousal in the late afternoon, evening or night (Rindlinbacher and Hopkins, 1992; Bliwise, 1994). These impairments are well described in dementia of the Alzheimer’s type (Moe et al, 1995; Liu et al, 2000; Harper et al, 2001; Johnson et al, 2002) which makes up 64% of all cases of dementia (Canadian Study of Health and Aging Working Group, 1994). The inability to maintain a circadian pattern may also contribute to cognitive dysfunction, behavioural disturbance and depression associated with Alzheimer’s disease (Satlin et al, 1992; Bliwise et al, 1995; Mishima et al, 1999; Haffmans et al, 2001).

The accompanying behavioural and sleep disturbance, which is common in dementia, presents a significant clinical problem (McGaffigan and Bliwise, 1997). It is a cause of increased stress for caregivers (Gallagher-Thomson et al, 1992) and is one of the most important factors in deciding whether to institutionalise patients (Pollak et al, 1991; Gallagher-

Thompson et al 1992; van Someren et al, 1993; Ancoli-Israel et al, 1994). There are also of course financial implications on the health care system and more importantly for unpaid caregivers (Fast et al, 1999; Johnson et al, 2002).

Psychological methods to promote healthy sleep and appropriate behaviour are desirable (Riefler, 1996), but not always effective or practical. In particular a number of cognitive behavioural techniques used for people over 60 years of age (Montgomery et al, 2002), including relaxation exercises and the use of imagery, are unlikely to be feasible for those with marked cognitive impairment. Indeed, it is estimated that less than 15% of people of all ages with chronic insomnia receive any treatment (Mellinger et al, 1995). Hypnotics are one of the most common treatments for insomnia (Hohagen et al, 1994; Kupfer et al 1997; Morin 1999). A main reason that physicians cite for prescribing hypnotics is a lack of knowledge about non drug treatments (Baillergeon et al, 1996). Hypnotics may help with decreasing the time getting off to sleep, the number of awakenings, the sleep length and quality of sleep (Nowell et al 1997) and short term use may be useful (National Institute of Health, 1983; 1990). However, because of problems with tolerance and dependence, long term chronic use is not recommended. Benzodiazepine hypnotics should not be used for more than 4 weeks (NIH, 1983, 1990; committee of safety of medicines, 1988), which is not helpful for people with dementia who have longstanding sleep problems. Furthermore, pharmacological means to control sleep in older people may present with other problems. Older people have reduced metabolic rates for drugs and are also more likely to be affected by the daytime residues of drugs (Morgan et al, 1988; Prinz et al, 1990; Kripke et al, 2000). There may be a greater likelihood to develop sleep apnoea (Kripke et al, 1983) and the hangover effects may contribute to fractures following falls (Wettstein et al, 1992; Meyer 1998). Hypnotic use is also correlated with constipation (Campbell et al, 1993), which is a particular problem for

people with dementia who have difficulty in interoceptive awareness and communication problems. Despite all these problems peculiar to old age, older people in the USA, and those with dementia in particular, are twice as likely to be prescribed sedative-hypnotics than their younger counterpart (Baum et al, 1986). In Europe and Canada the use of hypnotics is even more prevalent (Morin et al, 1999). Other traditional pharmacological means have not proven any more fruitful; neuroleptics, prescribed in the more severe cases of behavioural disturbance, are associated with extrapyramidal side effects and worsening confusion and may not be effective (Schneider et al, 1990).

As discussed in chapters 5 and 7 respectively, melatonin has been shown to be effective in the treatment of disorders of the sleep-wake cycle, has few side effects and there is some evidence to suggest it may be effective in people with dementia (Chapter 7), although much of the theoretical basis for its use in dementia applies to patients with dementia of the Alzheimer's type who have disruption of melatonin secretion. Similar changes in melatonin secretion have also been reported in vascular dementias and Parkinson's disease (Bordet et al, 2003) and Lewy Body dementia has some similar clinical characteristics to Alzheimer's Disease and Vascular Dementia. Thus, our study aimed to assess the clinical effectiveness of exogenous low-dose slow-release melatonin given at bedtime in individuals with dementia experiencing sleep disturbance.

Finally, it has also been suggested that loss of intraventricular melatonin fluid explains some of the pathological processes seen in Alzheimer's disease and that maybe restoring physiological intraventricular levels will assist with failing memory (Maurizi, 1997).

Chapter 19 MELATONIN IN DEMENTIA: HYPOTHESIS

We undertook a randomised double blind placebo controlled trial to test the hypothesis that melatonin improves sleep and cognitive function in people with dementia.

Null hypothesis

1. Melatonin slow release 6 mg given at bedtime for 2 weeks will have no effect on sleep quality and duration in people over 65 years of age with dementia and sleep disturbance.
2. Melatonin slow release 6 mg given at bedtime for 2 weeks will have no effect on cognitive function in people over 65 years of age with dementia and sleep disturbance.

Chapter 20 MELATONIN IN DEMENTIA: METHODS

20.1. The study setting and referrals

The study was undertaken in North London between August 1998 and May 2000. The study was approved by local ethical committees. Particular consideration was given to ethical issues for people who lack the capacity to consent (Finucane et al, 1993; Wager et al, 1995). Both the participant's assent and the main carers' consent were obtained.

GP practices agreed to participate in the study through the North Central Thames Research Network (NoCTeN). This consists of a data base of around 200 practices who have registered an interest in research. The practices receive an honorarium to cover the costs of the time required to participate in research. In preliminary discussions with GPs at practices, there was a suggestion that there were significant numbers of patients with dementia who had sleep disturbance and who would be suitable candidates for taking part in the study. Referrals from old age psychiatry were from team meetings or in one case an admiral nurse. Admiral nurses are specialist dementia nurses, working in the community, with families, carers and supporters of people with dementia. Recruitment from nursing homes was via direct contact, or through CPNs, by referral from a friend or partner, or by a GP attending the nursing home. Ward referrals were from the consultant. A variety of sources of referral were used. People were referred if they had had contact with psychiatric services and a diagnosis of dementia made. People with dementia were also identified through the Patient Administration System (PAS). People were also recruited through liaison with staff at day centres and nursing homes. GPs were also aware of the study and referred directly. Flyers and posters were placed in GP Practices and nursing homes. An article about the study was published in the Ham and High, a local newspaper. People were

also referred directly from hospital wards if they had been admitted for respite care, but where their usual place of abode was in a community setting. All people with a diagnosis of dementia and with sleep problems were considered for the study.

20.2. Selection criteria

Inclusion criteria: Participants of 65 years of age or over were required to satisfy DSM-IV (American Psychiatric Association, 1994) (items A2-5 in appendix) criteria for a clinical diagnosis of dementia or Lewy Body dementia (item A6 in appendix) made by a consultant psychiatrist and also have sleep disturbance identified by the main carer. Sleep disturbance was defined as shouting or agitated behaviour and/or wandering on at least 2 nights per week. Participants were either not taking hypnotic medication or were receiving the same dose of medication for at least 4 weeks prior to entry into the trial. “As required” psychotropic medication was not used during the study period. *Exclusion criteria:* People were excluded from the study if they: had received ECT within the last 6 months; had another axis 1 diagnosis e.g. depression; could not comply with the requirements of the trial, (e.g. living alone, no night carer); had severe physical problems; would not take medication or would not wear the monitor. People were also excluded where consent/assent was not obtained from all relevant parties and where changes in psychotropic medication were planned.

20.3. Design

The design is similar to the methods described by Tozawa et al (1998) and Garfinkel et al (1995). The trial was a randomised double-blind placebo-controlled 2 period crossover design. One week of baseline data was collected prior to the first treatment period. Each treatment period was of two weeks, with a one-week washout phase at the end of each

treatment period. Participants who received melatonin in the first treatment period were given placebo in the second treatment period and vice versa. Treatment order was random and determined individually by a computer-generated algorithm as soon as consent was obtained. Both the pharmacist dispensing the trial medication and the researchers were blind to the treatment received. The code for treatment allocation was only broken once the trial was completed. Melatonin 6 mg slow-release (synthetic origin) was provided by VitaPure Ltd. Tablets were given at the participants' usual bedtime. The melatonin was a sustained release matrix for a gradual release of melatonin over 6-8 hours. The melatonin or placebo were given at bedtime. Melatonin and placebo were identical with respect to preparation and packaging and were distinguishable only by batch number held by the manufacturer.

Period of data collection:

There may be biases introduced because of a number of factors which may effect sleep. These include time of the year (people sleep slightly longer in winter), exposure to light, activity in the week and at weeks ends, meal times and whether sleep data are collected in the week or at week ends. The routine in these participants was consistent throughout the week as the majority of participants were on a ward setting or in nursing homes. Seasonal effects are likely to be minimal as people were randomised over the year. As this is a cross over design, biases will be minimised with respect to whether data is collected on the week end or in the week.

Although we would have preferred to collect data over the full 24 hour period, the memory in the actigraphs was finite and only allows for 36 hours of data collection. Therefore full

nighttime data collection only was chosen, so that at least 3 actigraph recordings could be obtained.

20.4. Outcome measures

Main outcome measures of sleep: objective measures of sleep (onset time, wakening, rest period and sleep efficiency) were obtained using wrist actigraphy monitors and analysis software supplied by Neurim Pharmaceuticals Ltd (Neurim Pharmaceuticals Ltd, 8 Hanechochet, Tel Aviv 69710, Israel). Wrist actigraphy is an established method, based on wrist movements, that can distinguish sleep from wakefulness with a reliability of 88% using an algorithm described by Cole et al (1992). When carers placed and removed the actigraph on the subject's wrist when the subject went to bed and got up respectively. At this time they were instructed to press a button on the actigraph provided an indication of the time when the person went to bed and when they got up. The parameters used are described in section 8.2.

Subsidiary measures. Melatonin has two main effects. It acts as both a hypnotic and as a zeitgeber and may synchronise rhythms of the sleep-wake cycle. Sleep diaries may thus provide indirect information about the hypnotic effects of melatonin (how long it took to fall asleep) and the number of awakenings may provide an indirect measure of depth of sleep. The protocol requested that sleep diaries and the LSEQ (Parrot and Hindmarch, 1978) be completed by participants and their carers; so that participants' sleep can be evaluated. Also a measure of carers' quality of sleep was requested; the rationale being that if the main carer lived with the older person with dementia, their sleep may also have been disrupted.

Measures of sleep included: daily diary recording by carers of information concerning bedtime, sleep onset time, estimated total sleep, wake time and comments on sleep quality,

the Sleep Evaluation Questionnaire, where visual analogue scales are used to determine subjective measures of the participants' sleep (Parrot and Hindmarch, 1978) (item A-10 in the appendix) and Likert scales to assess the quality and duration of sleep for both participants and carers. A pill count provided a guide of compliance with medication and blindness was rated using a visual analogue scale. An assessment of cognitive function using the mini mental state (item A-9 in the appendix) was undertaken at baseline and at the end of the treatment periods. The main outcome measures were collected in the last three days in each of the baseline phase, two treatment periods and two washout phases. For each of these five periods/phases of measurement an average was taken of the three data points. Where possible sleep diaries were recorded throughout the study period. Carers were also asked to report any adverse events in the sleep diaries (item A-11 in the appendix) so that consideration could be given to withdrawing the individual from the trial. Finally, an assessment of blindness was made by asking researchers, participants and carers whether melatonin or placebo was taken during each treatment period.

20.5. Statistical analysis

Pre-study power: Pre study power calculation on sleep disturbance was difficult as few studies had been carried out on this patient group. It was therefore necessary to use data available from other patient groups which may not be comparable. Based on previous studies, particularly those on healthy older people, we predicted a placebo response of approximately 20% and an improvement with melatonin of 45% in total sleep time. To achieve 80% power at 5% significance (2 tailed test) in a cross-over design, the number of participants needed to detect a difference would therefore be 62.

Analysis: Where appropriate, the following tests were used: unpaired t-test (continuous normally distributed data) and Mann-Whitney U test (continuous non-parametric data) and

Chi Squared test (categorical data). Non-parametric methods were used to analyse the main outcome measures using the Mann Whitney U test since these data were not normally distributed. Mann Whitney U test was also used to examine the sleep diary data for median number of awakenings on either melatonin or placebo.

Analysis of crossover designs is complex and only the general principles are described in this thesis, although for the mathematical derivations the reader is referred to Everitt (1994). Everitt's approach allows for baseline adjustment of data, along with testing for carryover effects and for the separation of both period and treatment effects previously described. Missing baseline data was managed by substituting the group mean or median score, depending on whether the data were normally or not normally distributed respectively. Both a completers analysis and an intention to treat analysis were undertaken. In the intention to treat analysis, last observation carried forward was employed. Subsidiary analysis aimed to determine the accuracy of report data from observers by correlating this with actigraph data.

The design of the trial has previously been described in section 10.3. Baseline measurements were taken for those allocated to receive melatonin (M_{Bas}) and placebo (P_{Bas}). Then participants proceeded to receive one of two interventions, M_1 or P_1 (melatonin or placebo) in the initial treatment period (Period 1). This intervention was then followed by a washout phase for melatonin (M_{W1}) and placebo (P_{W1}) respectively. Participants then received the alternative treatment (P_2 and M_2 respectively) and this was then followed by a second washout phase (P_{W2} and M_{W2} respectively). This design is summarised in Table 20.1 below.

Table 20-1 Summary of trial design in melatonin in dementia study

	Baseline	Period 1	Washout 1	Period 2	Washout 2
Group 1	M _{Bas}	M1	M _{W1}	P2	P _{W2}
Group 2	P _{Bas}	P1	P _{W1}	M2	M _{W2}

Bas = Baseline, M = Melatonin, P= Placebo, W = Washout.

We are interested in the different responses to the two different treatments and wish to compare differences in response to M or P. Initially eyeballing the data may be helpful, using a useful graphical aid for detecting carryover effects to supplement the formal test of crossover trials. A plot of sum and difference scores, on the x and y axes respectively, is made for the outcome measures taken during period 1 and 2 (Everitt, 1994). If the shift in a horizontal direction is small, then differential carry over effects are unlikely. Similarly, if the shift in a vertical direction is small, then treatment effects are unlikely. This approach was used and is illustrated in Figure 21.3 in the results section.

A number of approaches may be taken when analysing the 2 x 2 crossover design. In the case of the data presented in this thesis, data were not normally distributed and therefore non-parametric methods, the Mann-Whitney test, were used (Everitt, 1994). In this method, rank “sum” scores for period 1 and 2 are calculated for the two treatment groups (M1 + P1 vs M2 + P2) and compared for the two periods 1 or 2. Providing no carry over effects are present, then one may test for a treatment effect by examining difference scores for the two periods by group allocation (M1 - P2) vs (M2 - P1).

If baseline and washout measurements have been made, then using similar methods to those described above (providing no residual or carry over effects are present), a more complex analysis may be undertaken (Kenward and Jones, 1987). With these methods, the first washout periods (M_{W1} and P_{W1}) are equivalent to the initial baseline data collection points (P_{Bas} and M_{Bas} respectively). Thus baseline data for each participant is subtracted from scores in period one ($M1 - M_{Bas}$ and $P1 - P_{Bas}$) and washout 1 scores subtracted from period 2 scores for each participant ($P2 - M_{W1}$ and $M2 - P_{W1}$). The groups are then compared depending on whether treatment M or P ($M1, M2$ or $P1, P2$ respectively) was received. These methods have the effect of doubling the numbers for analysis and thereby increasing the power.

20.6. Ethical Issues

Ethical approval was sought and obtained from the local medical ethics committees responsible for the catchment areas of the study. Much consideration was given to the ethics of engaging people with dementia in research. The Nuremberg Code and the Declaration of Helsinki provide the major principles of ethical research. These principles suggest that ethical research is undertaken where there is:

1. A minimisation of harm.
2. Maximisation of benefit (beneficence).
3. Truth telling.
4. Autonomy and self determination through the process of informed consent.

For people with dementia, truth telling can present considerable problems for caregivers and people with dementia. In particular caregivers may be unwilling to allow the person to

be told their diagnosis, and even when this is done, the person may deny their disabilities because of anosognosia. The devastating nature of dementia is nevertheless of such a significant humanitarian importance that potentially more than minimal risk is acceptable if significant benefits from research are anticipated. During the process of informed consent these four principles need to be constantly balanced, depending upon the patients reactions and responses to the information they are being given (High et al, 1994a; High et al, 1994b; Post and Whitehouse, 1995).

The design of this study which involves recruiting people with dementia and giving them a drug (melatonin) raises a number of ethical issues in recruitment, identifying the nearest relative, obtaining the patients assent and obtaining the carer's or nearest relative's consent.

Participants were identified from a range of sources. The usual method of recruiting to clinical trials is to ask people to actively volunteer by, for example, responding to an information leaflet. For people considered potentially suitable for our study, information was obtained from carers and relatives without the patient necessarily being aware. This could be argued to breach the patient's confidentiality. Therefore, every effort was made to ask the carer to check with the person with dementia whether or not they minded if someone approached them from a research team. Where the main carer was not the nearest relative (e.g. those who were referred by nursing home staff or GPs), it would then be necessary to identify a nearest relative. To do this we were guided by the definition of the "nearest relative" in the Mental Health Act for England and Wales, 1983 (HMSO, 1983). Writing to a patient with severe dementia may be construed by a family member as unsympathetic. However, writing only to the caregiver might similarly cause upset. Some patients and relatives may be unaware of the diagnosis, and would be distressed if they

received a letter that mentions dementia or conditions such as Alzheimer's disease. Our initial approaches to patients referred to dementia in terms of 'memory problems' until personal contact had been established and the patients' and carers' understanding of their illness had been explored. In cases where no nearest relative was identifiable, the patient was excluded from the trial.

Once the nearest relative had been identified, then patients were approached by the researchers to provide them with more detailed information about the project. Ethics committees take particular care when 'vulnerable' subjects, such as people with dementia, are to be included in clinical research. Where some degree of understanding is possible, the information provided needs to be clearly drafted in simple language that can be understood by someone with impaired cognitive functioning (the patient with dementia) and by the carer.

The process of consent, and those involved in the process was clearly documented with the involvement of both the caregiver and an independent witness to ensure that no coercion was involved. A significant concern within the study protocol was that patients had a free choice (autonomy) to decide whether or not they wished to participate in the project, and that the approach to them for their agreement was as sympathetic as possible to avoid causing distress. The Nuremberg code and the declaration of Helsinki suggests there should be minimal risk of harm to participants. Two main considerations are worthy of note; first, asking the patient to wear an actigraph and secondly to take melatonin.

Although wearing an actigraph does not represent an invasive procedure and is unlikely to cause discomfort, withdrawal of his or her arm during attachment of the actigraph (or trying

to remove it) was taken as refusal and withdrawal of assent. Administration of any drug, in this case melatonin, is a more serious consideration as it may involve potential risk to the patient. The only significant reports of adverse side effects of melatonin were in a trial by Carman et al (1976) who used up to 500 times more than the 6 mg used in the study described in this thesis. With the exception of this paper, the beneficial effects of lower dose melatonin have been reported in a variety of setting with minimal adverse side effects. Indeed, few side effects have been reported with doses below 240 mg (Arendt et al 1997). Nevertheless we went to considerable lengths to record any side effects of melatonin.

Informed consent may be impossible in patients with severe dementia. In this case a full discussion was carried out with both family and professional caregivers, and the next of kin was asked to sign to indicate their consent for the patient to be included. The person with dementia was nevertheless still able to indicate either assent or a desire not to participate. Indeed, any indication that he/she may have changed his/her mind, such as refusing to wear the actigraph or take the melatonin, was taken as withdrawal of assent, thus respecting their free choice.

Finally, it was important to know what medication the person was taking as a number of drugs may interfere with the use of melatonin. Thus there was a need to collect some information from medical records. Participants were asked what medication they were taking, but it was acknowledged that they were unlikely to remember. Consent was sought from the nearest relative and assent was sought to access medical records from both the patient and the doctor in charge (GP).

Chapter 21 MELATONIN IN DEMENTIA: RESULTS

21.1. Referral and recruitment

Period of recruitment and recruitment location: The study was originally planned as an 18 month study from August 1998 to March 2000: two months orientation, 14 months recruitment and follow up (recruitment 54 weeks, follow up 6 weeks), and two months analysis and write up. The initial aim was to recruit an average of just over 4 participants per month from the Royal Free and University College Medical School site over 14 months in order to achieve a target of 62 participants in the trial. Participants were to be recruited from 5 boroughs in north London: Camden, Islington, Barnet, Enfield and Haringay with a total population of roughly 1,178,000 (www.upmystreet.com; electoral ward data). The recruitment base was subsequently expanded to include the boroughs of “Kensington and Chelsea” and Westminster, adding a further population of around 340,000 bringing the total population in the catchment areas to 1,518,000. This suggests that a total of 186,000 people (11.9 ± 1.8 %) in the catchment area are over 65 years of age. A population survey in north London determined the prevalence rates of dementia at 4.7% in those over 65 years (Livingston et al, 1990), so roughly 8,700 people would suffer from dementia. Although there have been no studies of sleep problems in dementia as a group, it is estimated that 45% of people with Alzheimer’s dementia have significant sleep disturbance (Swearer et al, 1988). If this holds true for other types of dementia, we would expect around 3,900 people with dementia and sleep disturbance in the study area.

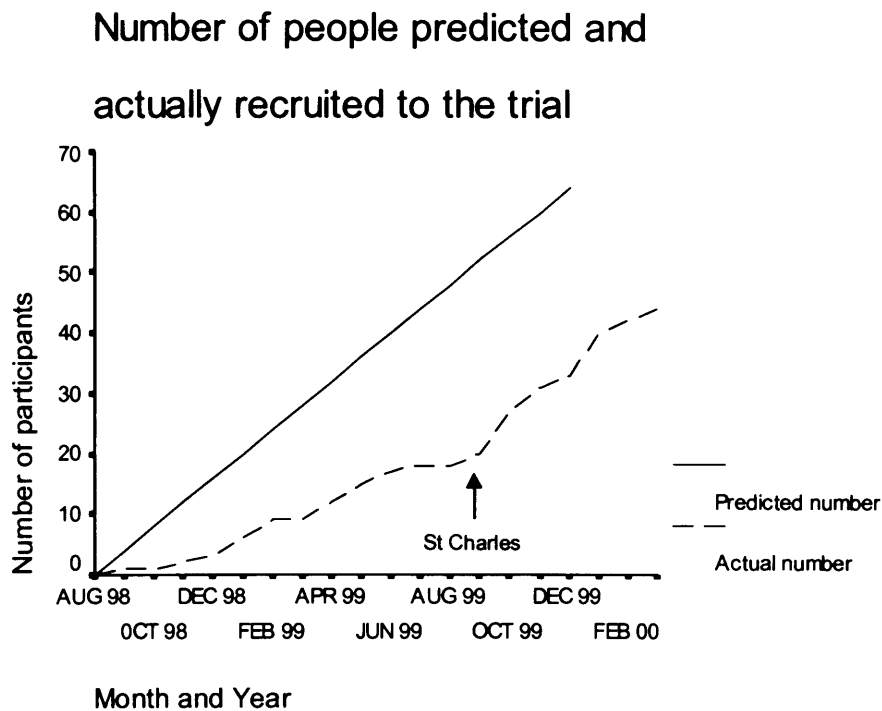
The recruitment rate was less than originally anticipated, with an average of only 1.5 people being recruited per month. Therefore additional measures to improve recruitment were adopted. These methods were as follows:

1. The recruitment period was extended from Dec 1999 to May 2000.
2. The recruitment base was expanded to include recruitment through St Charles' Hospital, West London from September 1999.
3. Attempts were made to generate interest in the project (and thus promote referrals) from articles written in the local papers (e.g. Ham and High) about the research and how to contact the research team.
4. Posters and leaflets were left in local GP waiting rooms.
5. Homes for older people receiving long term care and day centres for older people were approached and told about the study.

Although a variety of other recruitment methods were considered, such as expanding the setting to inpatient units, such methods were excluded for a variety of reasons. First, the aim of this study was to examine the efficacy of melatonin in a more naturalistic setting. Secondly, patients on Nightingale type wards or in dormitories were not considered suitable as there would be a number of extraneous factors which may interfere with sleep, such as disruption by other people with dementia.

As expanding the recruitment base through St Charles' Hospital may have introduced bias into the study, participants were randomised to the two intervention groups by site (RFUCMS or St Charles). Expansion of the recruitment base took several months to organise because of the delay by the local ethical committee for St Charles' Hospital who expressed concern about the ethics of undertaking drug trials in people in whom consent is problematic. The ethical issues have already been discussed in section 20.6. Ethical approval was given in September 1999. Below is a graph of predicted recruitment and actual recruitment.

Figure 21-1 Flow diagram of recruitment in dementia



As shown from the graph above, there was an acceleration in recruitment from September 1999 (marked by arrow) from 1.5 per month to an average of 3.6 participants per month once the recruitment base was expanded to St Charles' Hospital. Nevertheless, for a number of reasons (see discussion), it was felt that if anything our pre power analysis was excessively conservative, particularly given that there is no evidence for a placebo response in people with marked cognitive impairment. Thus, revising the power analysis, 46 people were deemed sufficient and 44 were achieved.

Referrals screened: Of 528 individuals referred and screened for the study, 497 were from the Royal Free Hospital and 31 from St Charles' Hospital. Three hundred and fifty two met the inclusion criteria.

Source of referral: Data shown in Table 21-1 below provides the source of referrals from the RFUCMS and St Charles Hospital sites combined, although a more detailed breakdown by site is given in Table A-16 in the appendix. Percentages are given in brackets for the number of people referred from a particular source. Of all those referred, only 11% were suitable. By far the greatest number of suitable referrals was from nursing homes and this also represented the greatest proportion of people suitable for the study. Although old age psychiatry provided a quarter (14/58) of those who were suitable, only 6% of the 231 referrals were suitable.

Source of referral	Number referred	Suitable (% Suitable)	In the study
<i>Old age psychiatry</i>	231	14 (6%)	8
<i>PAS list</i>	84	0 (0%)	0
<i>Flyer</i>	55	1 (2%)	1
<i>Nursing Home</i>	48	32 (67%)	27
<i>GP</i>	38	2 (5%)	2
<i>Advertising</i>	29	1 (3%)	0
<i>Day centres</i>	20	2 (10%)	1
<i>Posters</i>	12	0 (0%)	0
<i>Hospital wards</i>	11	6 (54%)	5
Total	528	58 (11%)	44

Table 21-1 Source of referral for melatonin in dementia trial

Old age psychiatry services were the main referrers, with 44% (231/528) of all patients referred coming from old age psychiatry services at the RFH. Other sources of referral included people identified on the Patient Administration System (PAS). Recruitment was also achieved from advertising through 200 flyers placed in GP waiting rooms, day centres and in nursing homes, though direct liaison with staff in 36 nursing homes and 40 General

Practices. Of the nursing homes, 36 were contacted (30 from the RFH site and 6 from St Charles' Hospital) and 25 nursing homes agreed to participate in the study, while 11 refused. Of the 25 who agreed to participate, 2 could not obtain social services approval and 12 did not have any suitable patients. Eleven nursing homes referred 32 of the patients suitable for the trial. Participation from the GP practices was achieved as follows: GPs were contacted through 216 letters sent in a mail shot (with 5 replies), through posters delivered to 85 practices, contact with 40 practices through the practice manager/receptionist and through contacting 26 GPs in person. Four adverts were placed at different times in the local paper and generated 1 person suitable out of 29 respondents. Finally referral came from hospital wards when patients were admitted for periods of respite care. It is notable that the 31 referrals from St Charles' Hospital came from only 3 sources; nursing homes (23), hospital wards for people admitted for respite (7) and old age psychiatry services (1) reflecting a different organisation of services.

Of the 528 individuals referred to the study, 58 people were eligible for the trial and 470 did not participate in the study. This was either because they were not assessed (n= 93) or did not satisfy entry criteria (n=377). Of the 93 not assessed, in 75 it was not possible to make contact: 53 had responded to flyers and provided their address but were not contactable, 10 did not respond to letters sent by their GPs, 6 were not on the patient records system, 3 refused contact and in 3 no access was possible despite organised appointments. The other 18 who were not assessed were deemed not to be suitable by nursing home staff, although usually no specific reason was given. It was felt that further enquiry would not prove productive and may indeed damage a collaborative relationship. This lack of cooperation is described more fully below and in the discussion.

Reason for failure to meet selection criteria: Of the 377 in whom contact was made but who did not satisfy entry criteria, 119 did not meet inclusion criteria and 258 met exclusion criteria. The reasons for this are given in Table 21-2 below. Just over a third (35%, 119/337) did not meet inclusion criteria, because they either did not have a sleep problem, did not have dementia or in one case were too young. It is also noted that in 79% (205/258) the setting was the main reason for exclusion.

It also of note that in the 36 nursing homes which were contacted (in which 55% of residents had dementia and 24% had sleep problems), the commonest reason for lack of referrals was difficulty in gaining collaboration from staff. Staff would often give vague reasons for why the older person was not suitable such as “I don’t think he would want to wear the monitor” or “She would put it down the loo”. The general impression was of subtle non-verbal cues that suggested a reluctance by staff to engage older people in research for which they could not consent. Indeed, nursing home staff expressed ethical objections to research being done in this patient population and were not reassured by the fact that the study had ethical approval. Staff also expressed the view that having to dispense the melatonin would be too onerous.

Table 21-2 Selection criteria for melatonin in dementia study

Reason for 337 who were contacted for not entering into the study	Number	Details
Failed to meet inclusion criteria	119	
	41	Did not have dementia
	77	Did not have sleep problems
	1	Under 65
Met exclusion criteria	258	
The setting		
Living alone	151	95 Sheltered accommodation 40 Own home 10 No night carers 5 Warden controlled flats 1 No fixed abode
Out of catchment area	30	
Still awaiting placement	19	
Relatives unable to cope	5	
Health issues	30	13 Alcohol problems 11 Had died 4 Physically ill 2 Deaf/ Blind
Contact only after recruitment period ended.	9	
No contactable next of kin	5	
Undergoing medication changes	4	
Were moving	2	
Could not speak English	1	
No longer deemed suitable by GP	1	
Could not take medication unless crushed (NB slow release preparation can't be crushed)	1	

Referral source of those recruited: Forty four people were recruited to the study. Table 21.3 shows the numbers of people entering and completing the study by referral source. For example, 5 people entered the study referred by CPN via the Royal Free, but only one completed. As can be seen from the table, just over two fifths (19/44) of those recruited to the trial were through direct contact with nursing homes. There were differences in the organisation of services at the Royal Free Hospital and St Charles' Hospital and this was reflected in the type of referral as shown in Table 21-3 below:

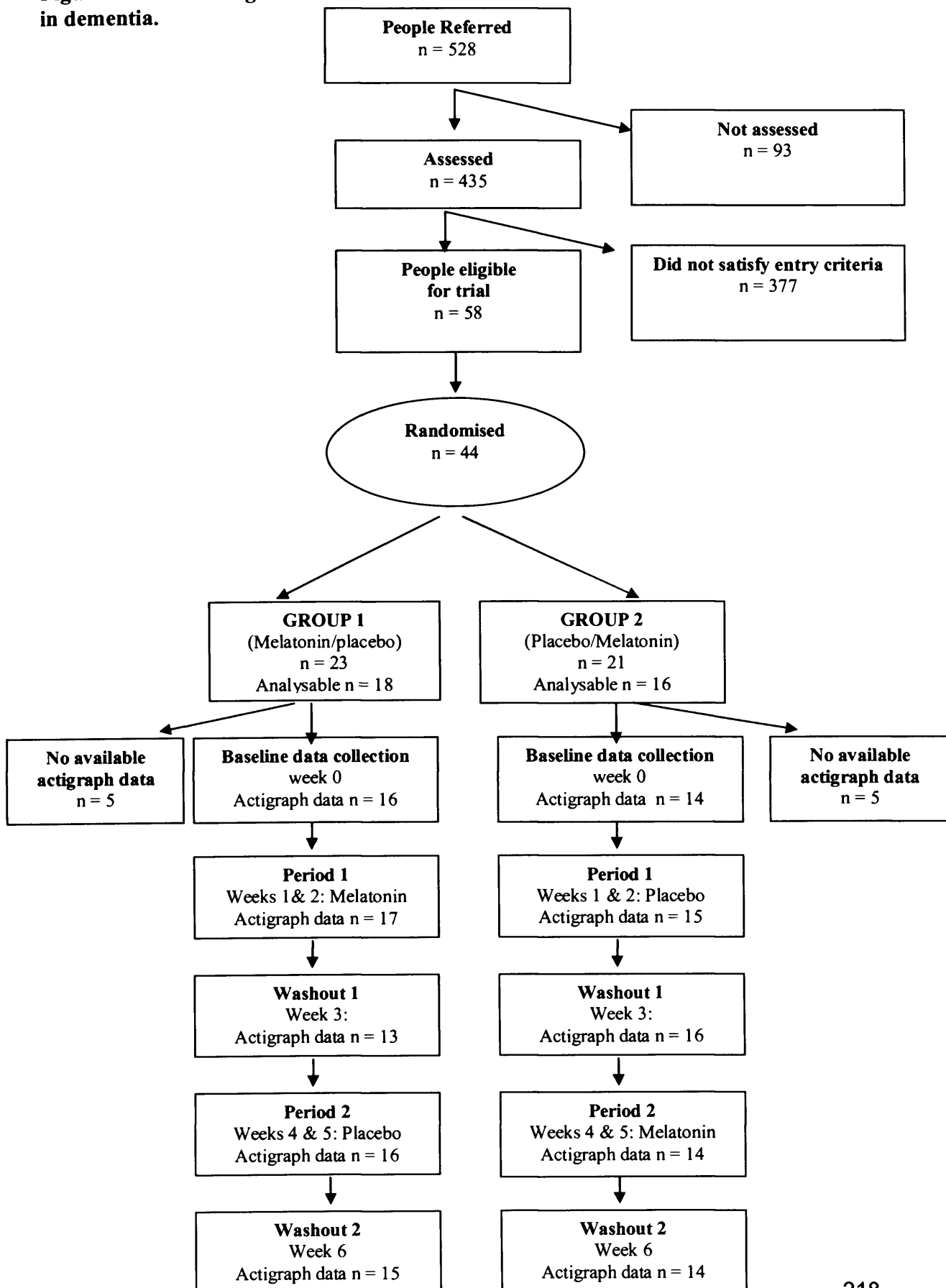
Table 21-3 Source of referral by site: melatonin in dementia trial

Type of referral	Source of referral		Total
	Royal Free	St.Charles'	
Com. Psychiatric Nurse	1/5	0/0	1/5
Day centre	1/1	0/0	1/1
Consultant	2/2	2/3	4/5
Call to nursing homes	10/19	0/0	10/19
GP	2/2	0/0	2/2
GP attending NH	0/1	0/0	0/11
Flyer response	1/1	0/0	1/1
Team meeting	0/0	3/7	3/7
Admiral nurse	0/0	1/11	1/11
Other Friend/partner	2/2	0/0	2/2
Total	19/33	6/11	25/44

21.2. Participant flow

A total of 58 people referred were considered suitable, at initial assessment. However, 14 did not participate in the study because 7 refused/ withdrew consent, 2 would not wear the monitor despite initially agreeing, 2 were too physically unwell, 2 had died within a week of the assessment and in one the sleep problems resolved. Thus 44 participated in the trial and a summary of the participant flow is given in the Figure 21.2.

Figure 21-2 Flow diagram for randomised double blind crossover trial of melatonin in dementia.



21.3. Numbers analysed and management of missing data

At Baseline:

- (i) Actigraph data: Complete actigraph data sets were available for 30 out of 44 participants at baseline. Where actigraphy data were missing at baseline, in 4 cases, group median baseline scores were substituted. In 10 participants, there were no actigraph data for any of the time-points, the reason being given in “At followup” paragraph below.
- (ii) Sleep diary data: For the subjective measures, baseline diary data were missing in 4 cases. In these, averaged median scores were substituted.
- (iii) LSEQ: Baseline data for the LSEQ for the older people with dementia was completed by 37 carers. LSEQ data were available for all participants in whom actigraphy data were used.

At follow-up:

- (i) Actigraph data: Data were available in 34 and 30 participants for periods 1 and 2 respectively and in 29 for both washout periods. Although there was incomplete data in 19 participants, it was nevertheless analysable in a significant number of participants. The main reason for data being lost or not being analysed was that there were insufficient actigraph data (9 participants repeatedly removed actigraphs, 7 participants refused to wear the actigraphs on the night, one participant had a stroke, making the actigraph data unreliable). Secondly, there was poor compliance with medication in two participants (defined as participants missing more than 3 doses of melatonin in each week), which was an a priori exclusion from data analysis. However, as one of the participant’s refused the melatonin when taking placebo in the second period and given that actigraphy recordings were made, the data were included in the analysis (see section on compliance issues in 21.7 for explanation).

(ii) Diary Data: Six data points for diary data were missing in the 34 in whom wrist actigraphy data were available.

(iii) LSEQ: Measures of participants sleep by carers using th LSEQ found that only a 17 out of 34 were completed by carers for period 1 and 2 respectively, therefore ITT analysis would not be appropriate.

Data presented:

(i) Wrist actigraphy: Data are presented as an intention to treat analysis, where the last observation is carried forward (Table 21.7). Last observation carried forward was used in 7 cases for the main analysis and in 11 cases for the carry over effect analysis. Completers data and analysis for the main outcome measure is also given in Tables A17-19 on the appendix. ITT data for wrist actigraphy are presented (Table 21.7) and analyses (Table 21.8) for 34 participants. Completers data (Table A-17) and analysis (item A-18 in the appendix) is presented in the appendix for the 25 participants in whom all data sets at treatment period 1 and treatment period 2 were available. Analysis specific to this crossover trial are shown in Table 21.9. As no carry over effects, were observed in ITT , data were “stacked” and analysed by subtracting baseline and first washout observations from period 1 and period 2 data respectively using methods previously described by Kenward and Jones, (1985) (see section 20.5) and this is given in Table 21.9.

(ii) Sleep diary: Sleep diary data are presented as ITT data (Table 21.10). Diary data are restricted to the 34 people in whom actigraph data were available so that the same sample population is represented. Data on total sleep length and quality of sleep was often omitted from sleep diary sheets by patients, with few comments being made on side effects of medication, however, carers provided good information on the time it took people to fall asleep and the number of awakenings during the night. These diary data are presented in

Table 21.10. Analysis of these diary data, using the Mann Whitney U test, are presented in Table 21.11. Although few self report measures for sleep diary data were available for ITT analysis, for thoroughness completers data is available in Table A-20 in the appendix.

Analysis using the MannWhitney U and Wilcoxon Rank sum tests are given in Table A-21.

(iii) LSEQ: Results for the LSEQ are given in Table A-20 although too few data were completed for analysis.

21.4. Examination of baseline data

Demographic and other information: Data were collected for ethnicity, gender, status, age, handedness, social class, where cared for and by whom, diagnosis, length of time to diagnosis, mini mental state and whether participants were taking hypnotic medication (Table 21-4).

Diagnosis: As summarised in Table 21.4, the diagnoses of the 44 participants who entered the study were 29 with Alzheimer's disease, 8 with vascular dementia, 6 with mixed vascular and Alzheimer's dementia and one with Lewy Body dementia. Of the 25 who completed 17 had clinical diagnoses of dementia of the Alzheimer's type, 4 had vascular infarct dementia, 3 had mixed Alzheimer's/vascular dementia and one participant had a diagnosis of Lewy body dementia (McKeith et al, 1996). Numbers were too small for analysis to determine whether there were differences in diagnosis by randomisation to either group 1 or 2 in the trial.

Table 21-4 Basic demographic and other information: melatonin in dementia trial

Basic demographic and other information of participants recruited (completed) the study. (Age and MMSE scores are given as means \pm standard deviations)			
Ethnicity:		Clinical Diagnosis:	
White	41 (23)	Alzheimer's	29(18)
Black Caribbean	1 (1)	MultiInfarct Dementia	8(4)
Black African	1 (0)	Dementia (mixed)	6(3)
Other	1 (1)	Lewy Body	1(0)
Status:		Carers	
Married	8 (6)	Multiple carers	35 (20)
Single	11 (5)	Single carer	9 (5)
Divorced	2 (2)	Where cared for:	
Widowed	23 (12)	Nursing home room	29(16)
Gender		Home setting	10 (5)
Male	32 (16)	Hospital setting	5 (4)
Female	12 (9)	Taking regular sleep medication:	
Age		Yes	16 (9)
84.2 \pm 7.6 (83.7 \pm 7.4)		No	28 (16)
Handedness:		Mean Mini Mental State score at baseline for the group as a whole.	
Right	40 (22)	11.6 \pm 7.5 (13.4 \pm 8.5)	
Left	4 (3)	Class of main job:	
Class of main job:		Professional	
Professional	4(4)	Intermediate	
Intermediate	8(5)	Skilled manual	
Skilled manual	11(7)	Skilled non-manual	
Skilled non-manual	5 (5)	Semi skilled manual	
Semi skilled manual	4 (4)		

Prescribed medication: There was a range in the number of prescribed drugs, with all of the forty four participants taking at least one prescribed medication, 19/44 (43%) on at least 5 drugs and 4 people on 7 drugs. There was a variety of prescribed medications, some of which included vitamins, minerals and drugs against constipation. Although drug interactions may exist and that interfere with melatonin secretion, because of the different classes of drugs used, dosing regimens and individual variations in drug metabolism, it is not possible to determine the precise nature of these interactions. Nor would it be ethical to expect patient to become drug free during the course of the study. It is hoped that these drug effects will be controlled for through the randomisation process. Drugs that may

affect melatonin secretion and metabolism, such as psychotropic drugs and beta blockers (see introduction), are of particular interest. For convenience all psychotropic medications which may affect sleep are listed in Table 21-5 below. All of these drugs were prescribed for at least four weeks before the start of the study and these medications were kept constant throughout the duration of the study. Of the two patients who were on atenolol, one completed the study. The psychotropic medication prescribed is given in Table 21-5.

Although medication may be prescribed for several purposes, 9 out of 25 participants who completed the study were on regular medication to help with sleep; four in group 1 and 5 in group 2, suggesting that randomisation was successful. Data were then analysed to see whether there were any differences in baseline scores for those receiving medication with hypnotic properties compared with those on no such medication. Although numbers were small, no significant between group differences were observed between those on hypnotic medication and those without. Two patients randomised to group 1 were on the β -blocker atenolol (which may interfere with melatonin secretion).

Table 21-5 Psychotropic medication prescribed: melatonin in dementia trial

Type of Medication	Name of medication	Recruited & completers in ()
Antidepressant	Amitryptiline	1 (1)
	Dothiepin	1 (0)
	Mirtazapine	1 (1)
	Venlafaxine	1 (1)
	Paroxetine	3 (2)
Anxiolytic	Diazepam	2 (0)
Hypnotic	Temazepam	5 (3)
	Nitrazepam	1 (1)
	Zopiclone	4 (2)
	Chlormethiazole	1 (1)
Antipsychotic	Risperidone	8 (6)
	Thioridazine	6 (3)
	Haloperidol	1 (1)
	Sulpiride	1 (0)
Anti-dementia	Donepezil	1 (1)

Randomisation: As shown in Table 21.6 below the randomisation was successful, with roughly equal numbers of participants being allocated to group 1 or group 2 from each site.

Table 21-6 Randomisation to melatonin or placebo by site

	<i>Group 1</i>	<i>Group 2</i>	<i>Total</i>
Referral centre	Royal Free	17	33
	St.Charles	6	11
Total	23	21	44

Outcome measures:

a) Sleep measures:

(i) Actigraphy data: There are no baseline differences in actigraph data for Time In Bed (TIB), Sleep Latency (SL), Wake After Sleep Onset (WSO), Total Sleep Time (TST), Number of awakenings (NWA), Movement index (MI) and Sleep efficiency % (SE) (Table 21.7). Although people spent a median time of at least 8 hours in bed, the median sleep time was at best only just over 6 and a half hours. Participants took about half an hour to

get to sleep and awoke at least 13 times and sleep efficiency was also low at below 75%.

Quartile ranges, given in brackets also demonstrate a wide range.

(ii) Sleep diary data: Data completed by observers suggests that participants woke infrequently and took just over half an hour to get to sleep. No significant differences in median baseline scores were observed between participants allocated to groups 1 or 2.

However, the large quartile ranges in both groups need to be noted.

(iii) LSEQ: Completers data for the LSEQ (broken down according to the four subscales: Getting To Sleep (GTS), Quality Of Sleep (QOS) Awakening From Sleep (AFS) and Behaviour Following Wakefulness (BFW)) are given in Table A-20 in the appendix. Although no significant differences were observed between groups at baseline, numbers are very small and quartile ranges large.

b) Mini Mental State Examination (MMSE):

Baseline data for the MMSE is given in Table 21.12. It is notable that participants in both groups had similar MMSE scores indicating significant cognitive impairment, with mean MMSE scores of around 12. A large standard deviation is observed.

21.5. Results from analysis of measures of sleep

(i) Actigraphy measures: The useful graphical aid for detecting carryover effects to supplement the formal test of crossover trials with a plot of sum and difference scores (Everitt, 1994) is shown in Figure 21.3 below and no obvious clustering can be seen. Statistical analyses (section 20.5) using these sum and difference scores for actigraphy data, using the Mann Whitney U test, are given in Table 21.8.

Plot of sum and difference scores for sleep efficiency in melatonin in dementia

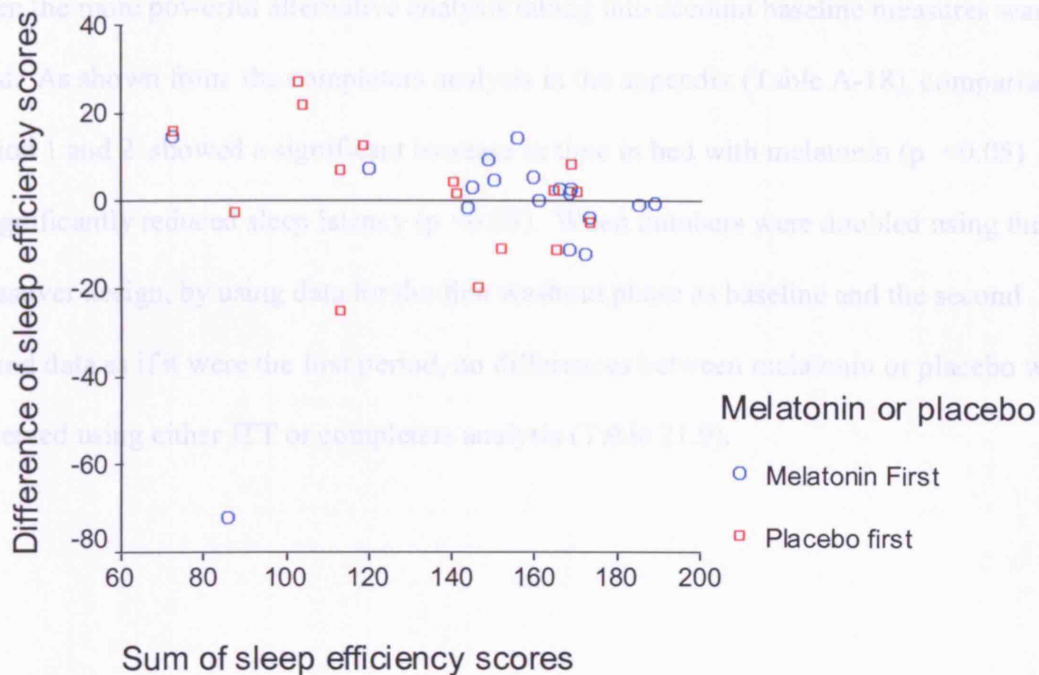


Figure 21-3 Plot of sum and difference scores for sleep efficiency for melatonin in dementia study

As shown in Table 21.7 below, the median time in bed was around an expected 8 hours, people would take at least 20 minutes to get to sleep, would usually wake within an hour, would spend around 6 hours asleep, would move considerably, would wake over 10 times and had poor sleep efficiency.

Analyses of actigraphy data (Table 21.8) suggest that during period 1 there was a significant ($p < 0.02$) treatment effect with shortening in the length of time spent awake after sleep onset with melatonin and also that the mean number of awakenings during the sleep period were significantly reduced ($p = 0.04$). There may appear to be a carry over

effect (Period 1 + Period 2) for the wake after sleep onset (WSO), but this was not evident when the more powerful alternative analysis taking into account baseline measures was used. As shown from the completers analysis in the appendix (Table A-18), comparison of period 1 and 2 showed a significant increase in time in bed with melatonin ($p < 0.05$) and a significantly reduced sleep latency ($p < 0.05$). When numbers were doubled using the crossover design, by using data for the first washout phase as baseline and the second period data as if it were the first period, no differences between melatonin or placebo were observed using either ITT or completers analysis (Table 21.9).

Table 21-7 Actigraphy data (intention to treat): melatonin in dementia trial.

		Baseline		Period 1		Washout 1		Period 2		Washout 2	
Actigraphy data (intention to treat): melatonin in dementia trial. Group 1 received melatonin in period 1 and placebo in period 2 and group 2 received placebo in period 1 and melatonin in period 2. (Medians are given with Quartiles ranges in parentheses and where appropriate time is given in mins)											
Number											
Group 1	18	18 (M)	18	18 (P)	18 (P)	18 (P)	18 (P)	18 (P)	18 (P)	18	18
Group 2	16	16 (P)	16	16 (M)	16 (M)	16 (M)	16 (M)	16 (M)	16 (M)	16	16
TIB											
Group 1	544.2 (501.3-595.3)	524.0 (444.6-605.2)	511.0 (441.1-616.9)	551.5 (442.1-597.5)	562.5 (475.5-619.8)						
Group 2	510.0 (427.1-545.4)	485.0 (441.9-534.2)	494.7 (461.7-568.3)	532.5 (485.2-592.4)	522.3 (483.6-604.7)						
SL											
Group 1	28.8(16.1-49.0)	21.2 (7.1-42.2)	21.2 (11.0-52.4)	26.5 (11.5-45.7)	26.5 (15.2-46.6)						
Group 2	26.7 (12.9-58.8)	30.0 (16.7-57.9)	21.5 (3.7-55.1)	22.0 (11.7-48.9)	47.0 (18.8-97.1)						
WSO											
Group 1	74.8 (44.6-98.7)	48.2 (26.7-72.8)	89.3 (55.7-98.8)	53.3 (34.1-89.2)	55.1 (20.5-79.1)						
Group 2	62.4 (44.4-107.6)	77.0 (53.8-132.4)	80.7 (65.1-99.1)	84.7 (64.1-128.6)	82.7 (66.1-165.4)						
TST											
Group 1	401.7 (311.0.3-473.4)	399.0 (317.5-475.5)	400.2 (301.6-475.5)	410.2 (310.3-479.1)	422.3 (358.3-479.0)						
Group 2	371.3 (244.3-3967)	318.0 (262.1-425.8)	331.3 (225.3-472.5)	378.0 (237.6-478.5)	329.1 (203.4-411.4)						
MI											
Group 1	1289.6 (877.5-2041.7)	1066.8 (500.8-1734.5)	1224.7 (547.3-2174.5)	1400.2(615.7-1939.7)	868.7 (493.2-2623.6)						
Group 2	1400.8(1141.2-1728.8)	1409.2 (936.1-1807.6)	1617.5 (685.9-2748.7)	1401.0 (937.2-1803.6)	1803.0(1183.1-2464.2)						
NWA											
Group 1	13.0 (8.6-18.6)	10.8 (3.9-16.9)	13.8 (7.4-21.4)	13.8 (7.9-17.0)	13.7 (6.0-26.1)						
Group 2	13.0 (8.1-15.7)	14.0 (10.1-20.1)	15.2 (11.9-21.4)	16.2 (12.6-21.7)	16.7 (13.0-21.2)						
SE											
Group 1	72.7 (65.2-82.9)	80.2 (73.2-85.0)	75.7 (64.7-83.7)	79.7 (70.9-88.8)	79.2 (66.7-89.2)						
Group 2	71.6 (65.9-75.9)	68.0 (60.7-81.7)	66.7 (44.0-84.0)	69.2 (47.0-82.6)	62.8 (39.7-77.3)						

Actigraphy data is given according to the following: TIB = Time in bed, SL = Sleep latency, WSO = Wake after sleep onset, TST = Total sleep time, NWA = Number of awakenings, MI = Movement index, SE = Sleep efficiency %. **Analysis is given in the text.**

	Period 1- Baseline (Treatment effect)		Period 1 + Period 2 (Carry over effect)		Period 1 - Period 2 (Treatment effect)				
	MW-U	Z score	P value	MW-U	Z score	P value			
TIB	111.5	-1.12	0.26	122	-0.76	0.4	98.0	-1.59	0.11
SL	90.5	-1.85	0.06	128	-0.55	0.16	113.0	-1.07	0.285
WSO	76.0	-2.35	<0.02	74	-2.41	<0.02	134.5	-0.32	0.74
TST	127.5	-0.57	0.57	103	-0.63	0.16	120.0	-0.82	0.48
MI	137.0	-0.24	0.89	112.0	-1.86	0.27	143.0	-0.35	0.97
NWA	84.5	-2.05	0.04	93.0	-1.76	0.08	129	-0.52	0.65
SE	97.5	-1.6	0.11	93.0	-1.76	0.08	135.5	-0.29	0.77

Statistical analysis is represented in the text. Actigraphy data is given according to the following: TIB = Time in bed, SL = Sleep latency, WSO = Wake after sleep onset, TST = Total sleep time, NWA = Number of awakenings, MI = Movement index, SE = Sleep efficiency %.

Table 21-9 Main outcome measures of sleep using ITT data adding washout 1 to baseline score and measures from period 2 to period 1

Number	Baseline/first washout	Period 1 and period 2	Mean Rank	MW-U	Z score	P
Group 1	34	34 (M)				
Group 2	34	34 (P)				
TIB						
Group 1	537.7 (482.0 – 588.0)	532.5 (463.2 – 597.4)	34.3	557.5	-0.25	0.80
Group 2	513.0 (437.0 – 563.0)	496.7 (442.4 570.2)	34.7			
SL						
Group 1	28.0 (8.0 – 48.3)	22.0 (10.2 – 46.1)	32.0	486.0	-1.13	0.26
Group 2	25.5 (12.0 – 52.7)	28.0 (13.7 – 48.9)	37.3			
WSO						
Group 1	80.0 (54.0 – 98.3)	64.7 (34.9 – 95.7)	34.1	566.5	-0.14	0.89
Group 2	66.2 (47.7 – 94.7)	63.8 (38.2 – 103.7)	34.9			
TST						
Group 1	384.0 (295.3 – 479.0)	399.0 (280.4 – 475.5)	34.8	564.0	-0.17	0.86
Group 2	384.0 (287.0 – 438.3)	378.1 (287.2- 446.8)	34.2			
MI						
Group 1	1360.7 (763.0 – 2094.5)	1251.9 (738.2 – 1732.1)	33.8	550.0	-0.34	0.73
Group 2	1360.0 (871.3- 1882.3)	1409.2 (702.2 – 1861.5)	35.2			
NWA						
Group 1	13.7 (10.3 - 19.0)	13.0 (7.7 – 20.7)	32.6	510.0	-0.83	0.40
Group 2	13.0 (8.0 -19.5)	13.8 (8.8 – 17.5)	36.6			
SE						
Group 1	72.5 (59.6 – 83.5)	72.7 (64.6 – 83.5)	35.8	522.5	-0.83	0.50
Group 2	72.7 (65.5 – 80.5)	79.5 (61.0 – 84.4)	33.0			

TIB = Time in bed, SL = Sleep latency, WSO = Wake after sleep onset, TST = Total sleep time, NWA = Number of awakenings, MI = Movement index, SE = Sleep efficiency %.

(ii) LSEQ: All patients with dementia had significant memory problems and were not able to recall how well they had slept and therefore were not able to complete the LSEQ. 39% (17/44) carers provided data (Appendix Table A-20) using the LSEQ (Parrot and Hindmarch, 1978). As numbers were small, comparison of melatonin and placebo (appendix table A-21) were made using the Wilcoxon rank sum test. However, with such a small sample size, caution is required when interpreting the results. Behaviour following awakening (BFW) improved with placebo ($p < 0.05$) (Table A-21).

(iii) Sleep diaries: All patients with dementia had significant memory problems and were not able to recall how well they had slept and therefore not able to complete sleep diaries.

Although prior to embarking on this study data about carers sleep was deemed important, only 5 participants were cared for at home. The majority (66%; 29/44) were living in a nursing home where they were cared for by staff who worked night shifts. Of the five people caring directly for the patient in their own home, none provided information about their own sleep. Provision of sleep data from shift workers caring for the patient did not seem appropriate. Data provided by carers concerning the patients' length of time to get to sleep and number of awakening (Table 21.10) were available and exceeded those obtained from wrist actigraphy (Table 21.7), although the reliability of these subjective carer measures are questionable. Mann Whitney U scores (Table 21.11) are presented below for melatonin/placebo for sleep diary data and shows no significant differences for carry over or treatment effects.

Table 21-10 Sleep diary ITT data in melatonin in dementia trial.

		Baseline		Period 1		Washout 1		Period 2		Washout 2	
Sleep Diary Group 1 Group 2		18	18 (M)	18	18 (P)	18	18 (P)	18 (P)	18	18	18
		16	16 (P)	16	16 (M)	16	16 (M)	16 (M)	16	16	16
Time to sleep (Mins) Group 1 Group 2		42.5 (24.0-66.0)	31.8 (23.7-47.1)	30.6 (23.4-56.2)	33.2 (21.9-51.5)	30.6 (23.4-56.2)	33.2 (21.9-51.5)	33.2 (21.9-51.5)	29.6 (15.0-48.5)	32.5 (14.3-66.1)	29.6 (15.0-48.5)
		35.9 (25.7-53.6)	56.9 (29.3-100.0)	40.1 (14.2-85.2)	48.7 (20.8-82.0)	40.1 (14.2-85.2)	48.7 (20.8-82.0)	48.7 (20.8-82.0)	48.7 (20.8-82.0)	32.5 (14.3-66.1)	32.5 (14.3-66.1)
Number of awakenings Group 1 Group 2		2.06 (1.45-2.26)	1.74 (1.14-2.30)	1.73 (0.50-3.00)	1.70 (0.23-2.01)	1.73 (0.50-3.00)	1.70 (0.23-2.01)	1.70 (0.23-2.01)	1.29 (0.22-2.96)	1.66 (1.00-2.68)	1.29 (0.22-2.96)
		1.69 (1.45-2.24)	1.63 (1.10-2.03)	1.41 (1.30-2.00)	1.52 (1.16-1.98)	1.41 (1.30-2.00)	1.52 (1.16-1.98)	1.52 (1.16-1.98)	1.66 (1.00-2.68)	1.66 (1.00-2.68)	1.66 (1.00-2.68)

Sleep diary ITT data in melatonin in dementia trial. ITT analysis showing main outcome measures of sleep diary during the course of the trial for those in whom actigraph data was available. Group 1 received melatonin (M) in period 1 and placebo in period 2 and group 2 received placebo (P) in period 1 and melatonin in period (Medians are given with Quartiles ranges in parentheses)

Table 21-11 Sleep diary ITT analysis: MWU and Wilcoxon for melatonin in dementia trial

		Sleep diary analysis: MWU and Wilcoxon scores of melatonin in dementia trial								
Mann Whitney U analysis for sum and difference scores for sleep diary in whom actigraph data was available in the melatonin in dementia trial.		Period 1 - Baseline (Treatment effect)		Period 1 + Period 2 (Carry over effect)		Period 1 - Period 2 (Treatment effect)				
		MW-U	Z score	P value	MW-U	Z score	P value	MW-U	Z score	P value
Sleep diary Time to sleep Number of awakenings		121.0	-0.79	0.44	117.0	-0.93	0.35	108.5	1.22	0.22
		115.5	-0.98	0.32	137.0	-0.24	0.80	139.0	-0.17	0.86

21.6. Effects of melatonin on Mini Mental State Examination

Table 21.12 presents means for mini mental state examination taken at the end of the baseline period (week 0), at the end of period one (weeks 1 and 2) in which participants received melatonin or placebo and at the end of period 2 (weeks 3 and 4) in which participants received placebo or melatonin. As data were normally distributed they are presented showing results of an unpaired t-test for treatment group A or B. It was not possible to do the Mini Mental State in one participant at baseline because he was aphasic, but nevertheless a clinical diagnosis of Alzheimer had been made by a Consultant Psychiatrist. It was not possible to undertake a Mini Mental State at the end of period 1 in 7 people because of physical problems in 3 (poor eyesight making it impossible to read or write), 3 were unable to comply/refused and one was away at a clinic visit. For period 2, repeat MMSE was not possible in 6; four had physical problems, one refused and one was away. As shown from the Table 21.12 below, there were no significant changes in the mini mental state with melatonin.

Table 21-12 Mini Mental State Examination analysis: melatonin in dementia trial

Mini Mental State Examination Scores for those in whom actigraph data was available shown for the 2 groups at baseline, the end of period 1 and period 2. Group 1 received Placebo first and melatonin 2nd and Group2 received Melatonin first and placebo second.

	N	Mean	Std. Deviation	df	t-value	P value
MMSE at Baseline				31	-0.02	0.98
Group 1	17	12.6	6.8			
Group 2	16	12.7	9.1			
MMSE end of period 1				27	0.16	0.87
Group 1	15	13.1	7.4			
Group 2	14	12.7	8.5			
MMSE end of period 2				28	-0.12	0.91
Group 1	14	12.2	8.2			
Group 2	16	12.6	9.2			

21.7. Subsidiary analyses: completers versus ITT data, compliance and blindness

Finally a number of other findings, including measures of compliance (Table 21.12), blindness (Table 21.14) and side effects are also presented.

Completers versus intention to treat data:

(i) Actigraphy data: Median scores and quartile ranges for completers data for wrist actigraphy are given in Table A-17. No significant differences were observed for completers or ITT data for any of the sleep data given in Table 21-7. It should be noted that ITT data (Table 21-7) and completers data (Table A-17) show very similar median scores and quartile ranges. As shown in table A-18 (Completers data), some differences were seen between melatonin and placebo (Period 1- Period 2) for time in bed and sleep latency between melatonin and placebo. Examination of table A-17 shows that median time in bed was longer and sleep latency was shorter in the melatonin group. However, there was also differential dropout in period 2.

(i) Sleep diary measures: More data were available for sleep diary measures than for wrist actigraphy and this is reflected in numbers of people in Table A-20. Data appear similar and quartile ranges were larger in the completers data.

(ii) LSEQ: Too few data were available for the LSEQ to allow ITT analysis to be used.

Subjective versus objective measures of sleep: A Pearson correlation between the objective measures (actigraphy) and subjective measures (carers estimation of sleep using the LSEQ) was also undertaken. This provides a proxy measure of the validity of subjective ratings. Reports of night-time activity were not correlated to actigraph generated data (n= 218,

Pearson correlation = 0.05, $p = 0.94$). The times of going to bed and getting up were too erratically recorded on diary sheets and therefore analysis would not be appropriate.

Compliance: Compliance was measured using a pill count and confirmed by carers' reports on diary sheets indicating whether participants took medication (Table 21.12). The time melatonin/placebo was given was also recorded. Melatonin and placebo was for 2 weeks each respectively. A total of 28 days of tablets per participant were prescribed. There were 34 participants in whom data analyses were possible. Thus, 476 (28x34) tablets were prescribed in period 1 and 476 in period 2. As data were skewed, non-parametric methods were employed for analysis. 6.7 % (32/476) of tablets were returned in period 1 and 14.9 % (71/476) of tablets had been returned from period 2. However, this poorer compliance in period 2 was largely accounted for by one participant who had not taken placebo for all 14 days. He nevertheless did take melatonin intermittently for a total of 8/14 days of the melatonin phase in period 1 and therefore was included in the analysis.

The major reason for not taking the medication was that there were 17 refusals in the first period and 37 refusals in the second period. On 3 occasions melatonin/placebo was recorded as given, but pill count contradicted this. As shown from the table below for the 34 participants in whom actigraph data was analysable, there was no difference in compliance between placebo and melatonin. Although restlessness was a common complaint by staff, no adverse effects were reported from the use of melatonin.

No data on adverse events were recorded by carers. People with dementia had no recollection that they were taking melatonin.

Table 21-13 Melatonin in dementia trial: compliance with medication

Melatonin or placebo received for the the 2 groups and the number of tablets counted at the end of period 1 and period 2. (Group 1 received Melatonin first and Placebo 2nd and Group2 received Placebo first and Melatonin second).

	N	Median	Lower and upper quartiles	MWU	Z score	P value 2-tailed
Number of tablets returned at end of period 1				111.5	-1.17	0.24
Group 1	18	2.0	2.0 - 6.0			
Group 2	16	2.0	0.0 - 3.75			
Number of tablets returned at end of period 2				134.0	-0.36	0.72
Group 1	18	2.0	0.0- 4.75			
Group 2	16	2.0	0.5 – 6.75			

Blindness: As a measure of blindness, patients, carers and the researcher were asked to mark on a 10cm visual analogue scale whether they thought that melatonin or placebo was given. Only data for the intention to treat analysis in the 34 participants in whom actigraph data is available is presented for the carers and researchers (Table 21.13). Only 5 participants said they could remember taking the medication and therefore statistical analysis of participant blindness was not possible because of the small numbers involved. Of the carers one did not complete the VAS at period 1 and 6 did not complete the VAS at period 2, though no reason was given. The researcher completed all VASs at the end of period 1, but was not able to interview 4 of the participants at the end of period 2; one participant was at a clinic appointment and three refused to talk. Findings suggest that neither the carers nor the researcher were able to determine whether placebo or melatonin was given and therefore blindness was maintained.

Table 21-14 Visual analogue scale (VAS) measuring blindness

VAS data showing whether melatonin or placebo was received for those allocated to the 2 groups at baseline, the end of period 1 and period 2. The score given is the mean length of the line in mm.

(Group 1 received Melatonin first and Placebo 2nd and Group 2 received Placebo first and Melatonin second).

	N	Mean	Std. Deviation	df	t-value	P value
VAS end of period 1 for carer						
Group 1	17	53.1	17.2	31	-1.46	0.154
Group 2	16	43.7	19.7			
VAS end of period 1 for researcher						
Group 1	18	50.4	3.2	34	-1.8	0.08
Group 2	16	48.5	2.9			
VAS end of period 2 for carer						
Group 1	14	56.1	22.7	26	-1.58	0.13
Group 2	14	44.6	14.9			
VAS end of period 2 for researcher						
Group 1	15	48.6	2.7	28	0.48	0.63
Group 2	15	49.0	1.7			

21.8. Methodological issues

The Consolidated Standards of Reporting Trials (CONSORT) statement (Begg et al, 1996; Moher et al, 2001) recommends criteria for reporting parallel-group RCTs. These standards were used when reporting of the melatonin in depression trial previously described in this thesis (section 15.8). These criteria have been modified for the purpose of this thesis for reporting this double blind randomized placebo controlled crossover trial of low dose melatonin for sleep disorders in dementia and are summarised in Table 21.15 below:

Table 21-15 CONSORT Checklist when reporting an RCT: melatonin in dementia

PAPER SECTION And topic	Item	Description	Reported on Page # or section or Figure # or table.
<i>TITLE & ABSTRACT</i>	1	How participants were allocated to interventions (<i>e.g.</i> , "random allocation", "randomized", or "randomly assigned").	Page 5
<i>INTRODUCTION</i> Background	2	Scientific background and explanation of rationale.	Chapt 18
<i>METHODS</i> Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	20.1-2
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	20.3
Objectives	5	Specific objectives and hypotheses.	Chapt 19
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (<i>e.g.</i> , multiple observations, training of assessors).	20.4
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	20.5
Randomization – Sequence generation	8	Method used to implement the random allocation sequence (<i>e.g.</i> , numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned	20.3
Randomization – Allocation concealment	9	Method used to implement the random allocation sequence (<i>e.g.</i> , numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	20.3
Randomization – Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	20.3
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	20.3, 21.6
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	20.5

CONSORT Checklist when reporting an RCT: melatonin in dementia (Continued)

RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	Fig 21.2
Recruitment	14	Dates defining the periods of recruitment and follow-up.	21.1 fig 21.1
Baseline data	15	Baseline demographic and clinical characteristics of each group.	Table 21.4
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (<i>e.g.</i> , 10/20, not 50%).	Fig 21.1 21.5 table 21.7
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (<i>e.g.</i> , 95% confidence interval).	Table 21.7-11
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	Chapt 21
Adverse events	19	All important adverse events or side effects in each intervention group.	None reported
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	Chapter 22
Generalisability	21	Generalisability (external validity) of the trial findings.	Chapter 22
Overall evidence	22	General interpretation of the results in the context of current evidence.	Chapter 22

Chapter 22 MELATONIN IN DEMENTIA: DISCUSSION

Several stages exist in clinical trials research which have parallels to the filter model first described by Goldberg and Huxley (1980): a) there exists a number of people with dementia and sleep disturbance, our target population. b) there is a need for identification of the target population. c) there is a need to encourage referral and finally d) the suitability for entry into the study needs to be assessed before our intervention to examine the effects of melatonin on sleep disturbance in people with dementia can be undertaken. The number of people with dementia and sleep disturbance in the community under study is likely to be high (n= 3,900), but recruiting people to the study was difficult. The discussion will therefore focus firstly on recruitment issues and associated sources of bias and secondly, why little beneficial effect of melatonin was observed.

22.1. Recruitment issues

a) The recruitment base

In our study population we would expect about 8,700 people over 65 years of age to have dementia, of whom about 3,900 will have had significant sleep disturbance. This suggests that large numbers of people are potentially available for study. However, as the study proceeded, it became clear that the number of people being referred or suitable for the study was low. Expansion to incorporate teams from St Charles' Hospital took place and the recruitment period was also lengthened. As shown in Fig 21.1, these methods were partly successful, with the recruitment numbers increasing. The rate increased from 2.5 to 3.5 participants per month which was still less than our target rate of 4.8 per month.

A major obstacle to recruitment was the delay in receiving ethical approval. The administrative process involved in undertaking research is becoming increasingly

burdensome and has been criticised for impeding research (Warlow, 2004; Jamrozik, 2004; Wald, 2004; Ward et al, 2004). Simplifying the ethics procedures by adopting a UK wide approval system is long overdue. Simplifying the ethics procedures would facilitate research by ensuring that unnecessary delays do not occur when expanding a recruitment base to different geographical areas.

b) *Identification of the target population*

We wished to identify as many people as possible who may have had dementia and sleep disturbance. Because of the nature of the problem, it is unlikely that people with dementia would respond individually to calls for research because of their cognitive deficits.

Therefore identification of cases needs to occur by proxy by targeting health professionals, social services and carers. Our findings are in agreement with the view of Singer et al (2003) that recruitment should be targeted at dementia clinics, other clinics and long-term care facilities. However, Singer et al (2003) also advocated the use of newspaper advertisements, Alzheimer's Association newsletters, public lectures and calls to individual physicians which our experience suggests would be unlikely to be particularly effective.

Although increasing awareness of the study may encourage referrals, it is also notable from Table 21.1, that the use of posters, adverts and flyers generated only one participant in total. It would have been helpful for Singer and colleagues to specify the precise routes by which referrals were achieved.

c) *Encouraging appropriate referrals to the study:*

Of a potential population of 3,900, only 528 people were referred to the study. Of these, 93 could not be assessed and 41 people referred did not even have dementia. Although we had a large recruitment base, the reason for only around one in twenty of the target

population being referred is worthy of consideration. People with dementia are usually managed through liaison with their GPs, social services and nursing homes, while secondary care may be involved in the latter stages of the disease.

Preliminary talks with GPs in the planning stage of this study suggested that they cared for significant numbers of people in the community with dementia, but it is notable that less than one percent (38/528) were referred by GPs, with 60% of all referrals coming from secondary care (Old age psychiatry and PAS). GPs informally expressed the view during the study that they were concerned about upsetting the family when considering an older person with dementia for research, particularly given ethical issues around consent.

Although the majority of people participating in the study were from nursing homes, only 9% of all referrals were from this source and again there were ethical objections by staff who were concerned about issues of consent in people with dementia. One member of staff even expressed the view that “research should not take place at all on people with dementia who are treated like guinea pigs”. However, despite these objections, there is evidence that participation in clinical trials in carers is motivated by altruism, with relatives of patients seeking enrolment to benefit other people (Karlavish et al 2001), and to help future patients and science in general (Elad et al, 2000; Masden et al, 2000). Indeed, there is evidence that participation in research may be a positive experience for relatives (Mastwyk et al, 2003).

In contrast to the non university staff, significant numbers of people were referred from old age psychiatry services which had established links with University Departments where there was an ethos of undertaking research and a more positive attitude to research. It is possible that staff who care directly for the patient were reluctant to undertake research

because of the additional time pressure which studies may impose on people who have a number of other work commitments. The research fellow (SK-W) went to considerable lengths to minimize the workload of carers, but informal interview suggested that the 5 minutes required to attach monitors, record sleep diaries and administer medication at night may have been sufficient to deter some carers from participating. Financial inducements may be beneficial in facilitating collaboration. Deehan et al (1997) found that responses to surveys increased incrementally to levels of payment. Furthermore, Foy et al (1998) point out that pharmaceutical companies offer monetary compensations to general practitioners, which they would not do unless it had a positive impact on recruitment. However, in cases where ethical issues are relevant, caution is advisable; it was important not to introduce a conflict of interest through financial inducements for collaborators, as such inducements may be the deciding factor whether people, who are not able to give informed consent, participate in a study.

Ethical issues contributing to the difficulty in recruiting patients with sleep disruption in Alzheimer's disease have previously been described (Dowling and Wiener, 1997). Our trial also highlights the need for greater understanding about why people may be reluctant to refer older people with dementia to clinical trials, where ethical considerations may well be a major rate limiting step. There are large gaps in our understanding of why people engage in research and their attitudes to the process (Mastwyk et al, 2002). This problem may best be further explored using qualitative methods, adopting a grounded theory approach. This approach could be undertaken by interviewing a selection of carers and health care professionals attending to people with dementia. These methods could involve collecting narratives on people's views about the benefits of research and the problems of involving people who may not be able to provide real consent.

Fifty five percent of our projected participant numbers were achieved. In order to meet our original target we would need to have received almost 1,000 referrals, assuming the same proportion met our study criteria. This is almost 1 in 9 (1,000/ 8,700) of all people with dementia over 65 years in the area, which is a very tall order. It is also apparent that the largest source of successful recruits to the study was from nursing homes. In retrospect, it needs to be acknowledged that pilot work would have been helpful to assess the feasibility of recruitment to the study. However, findings from this study suggest that targeting nursing homes where there are regular carers is the most likely way to yield results for this kind of research.

d) Suitability of those referred

Of the 435 assessed, only 58 people satisfied all entry criteria (Table 21-2). Forty one people did not have dementia, 77 did not have sleep problems and one was under 65 years of age a further 258 met exclusion criteria.

Although this study was targeted at people with dementia, it may seem surprising that about 10% (41/435) did not have this diagnosis. However, of those who did not have a diagnosis of dementia, 29 people were referred by a friend/relative from newspaper adverts and only one of these referrals was suitable. The relatively high proportion of people who did not have dementia may reflect the lack of knowledge about a diagnosis of dementia in the carers/relatives who responded to adverts. In retrospect, it would be more effective to focus on encouraging referral from health care professionals and from nursing homes in particular, as these sources referred well over two thirds of all people suitable for the trial.

Of those with dementia referred to the study, over 80% had significant sleep problems as defined in the study protocol. This compares favourably with 45% of all people with Alzheimer's who have sleep disturbance (Swearer et al, 1988). Optimising the number of appropriate referrals maximises the use of resources. This may be done by having tight criteria to screen out inappropriate referrals. Although the use of precise criteria (Yesavage et al, 2003) to define sleep disturbance in Alzheimer's disease may be useful for selecting people for clinical trials, these may also adversely affect referral numbers, because of the skills and extra work required to screen people. Indeed, it would not be realistic to expect referrers to be familiar with detailed protocols assessing the suitability for the study. Although other studies in other areas have employed self administered screening questionnaires, in order to encourage self referral, this is not appropriate in studies of sleep disturbance using existing questionnaires. First, current rating scales (e.g. Sleep Disorders Inventory (SDI), Singer et al, 2003; Leeds Sleep Evaluation Questionnaire, (LSEQ), Parrot and Hindmarch, 1978) require some explanation and understanding of their use. Secondly, they have not been validated as a screening tool. Thirdly, because of the cognitive deficits associated with dementia, screening would need to be done by proxy, through relatives/carers and health care professionals. Fourthly, as we have shown, reports of sleep disturbance by carers are not particularly reliable. A pragmatic approach, using a broad definition of sleep disturbance was therefore applied. This approach increases sensitivity and maximises referral, albeit at the expense of specificity.

A survey by Livingston et al (1990) in Gospel Oak, one of the catchment areas in our study, suggested that about half of people over 65 live in a nursing home or with a carer. There is, however, very little information available on the living circumstances of people with dementia. Over half (151/258) of those assessed lived alone, which we found surprising for

people with a diagnosis of dementia. Unless our sample is very unrepresentative, it seems likely that a greater proportion of people with dementia live alone than is generally realised. Even more surprisingly, precise data on this question are lacking (Graham, 2005, personal communication). A community survey might well identify the potential scale of the problem. Alternatively our sample may be unrepresentative and referral bias accounts for people who are living alone being more likely to be referred. Referral bias may be explained because greater attention may be given to people with dementia who live on their own and who have sleep disturbance because of potential dangers.

A major reason for people referred being excluded from the study was the individual's living circumstance. Carers are mandatory in a study such as this as they would be required to administer medication. Although it may be suggested that carers/ researchers could be introduced into the home during a period of study in other conditions, sending in a "living in carer/researcher", is likely to introduce a number of methodological problems peculiar to people with dementia. In particular a person with dementia is likely to be disrupted by having a stranger visit and different people may adapt to this at different rates. Thus, it follows that increasing recruitment is best served by increasing referrals of people in suitable living circumstances, rather than by making changes to their living circumstances during the course of study. Again this suggests the appropriateness of targeting recruitment from nursing homes, where people have regular carers.

f) Methodological problems and potential sources of bias associated with the referral process

Expanding the recruitment base to involve other centres presents a number of methodological problems which may introduce bias. As shown in Table 21.3, the majority

of people referred from St Charles were from team meetings, whereas the majority of people referred from the Royal Free site were through direct contact with nursing homes. It was therefore appropriate to randomise participants by site. As can be seen from Table 21.6, randomisation by site was successful, with patients from each site being roughly equally randomised to each intervention group.

g) Conclusions for recruitment to trial of melatonin in dementia

The numbers of referrals may be maximised by having a large recruitment base, whilst at the same time encouraging appropriate referrals from settings such as nursing homes where people have a regular carer. There will also be a need to ensure that potential sources of bias are addressed in the randomisation process. Further study through the use of qualitative research methods may be useful in understanding and minimising hostility to trials in people with dementia.

22.2. Results from intervention.

We did not find a therapeutic effect of slow release low dose exogenous melatonin in people with dementia and disturbance of sleep. A number of studies have demonstrated that melatonin is useful in disturbance of the sleep-wake cycle (Sack et al, 2000; Claustrat et al, 1992; Petrie et al, 1993; Skene et al, 1996; de Vries and Peeters, 1997), with possible beneficial effects for people with sleep disturbance and dementia (Brusco et al, 1999; Cohen-Mansfield et al, 2000; Tozawa et al, 1998), although this latter study was not published in a peer-reviewed journal and therefore it is difficult to determine how much authority these findings should carry. However, a large multicentred placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease has since been published

following our trial (Singer et al, 2003) and it is notable that this study showed similar findings to ours.

Selection criteria; Diagnostic considerations and validity of sleep measures

All participants in this study had a clinical diagnosis of dementia with a mean mini-mental state score of 13.3, suggesting significant cognitive impairment similar to that observed in the study by Singer et al (2003). All patients in our study had at some point been assessed by an experienced clinician who had diagnosed dementia using DSM-IV criteria (with the exception of one patient who had dementia of the Lewy body type). Although the diagnosis of dementia was not confirmed by post mortem examination, clinical diagnosis was made by experienced clinicians according to internationally recognised criteria and a high correlation exists between clinical diagnosis and post mortem diagnosis. We were therefore confident about diagnosis. More detailed assessments using diagnostic criteria of the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association; McKhann et al, 1984) for probable senile dementia of the Alzheimer's type (SDAT) were used in the Singer et al (2003) study in order to specifically identify people with probable Alzheimer's disease. This was not done in our study which was a pragmatic one investigating the effects of melatonin on a community sample of people with dementia. Nevertheless, it is important to stress that all participants in this study were only diagnosed as suffering from dementia after being thoroughly investigated as suggested by McKhann et al (1984) and McKeith (1996). Participants in the Singer et al (2003) study were therefore more accurately diagnosed, as a diagnosis of definite Alzheimer's disease requires histopathologic confirmation. However, restricting the study to a specific subtype of dementia, such as Alzheimer's disease in particular, may be more appropriate, as melatonin

dysfunction has been most extensively reported in this sub group of people with dementia. Conversely, melatonin dysfunction may be so disrupted in people with dementia of the Alzheimer's type that its therapeutic effects may be more readily observed in patients with dementia which are not of the Alzheimer's type. The sample size in our study was small and excessive restriction by diagnosis may further limit recruitment and may not allow findings to be generalisable to a normal population of people with dementia.

Yesavage et al (2003) have developed precise criteria to define sleep disturbance in Alzheimer's disease, but their use is yet to be established. Singer et al (2003) used two measures to define sleep disturbance; the Sleep Disorders Inventory (SDI) and wrist actigraphy. Singer et al (2003) specified that two or more episodes of night time behaviours per week reported by the caregivers on the Sleep Disorders Inventory (SDI) and less than 7 hours of total time immobile between 8 pm and 8 am on at least five nights of complete actigraph data collected over a single week were required for inclusion in their study. Although use of scales such as the SDI may be helpful in selecting participants for referral, our study demonstrated that caregivers assessment of the participants sleep was unreliable, and therefore it is unlikely to be a valid screening tool. The use of wrist actigraphy, as used by Singer et al (2003), may be no better in screening for entry into the study. Normative data for sleep in a normal population of a mean age of 50.2 ± 14.7 years (Cole et al, 1992) suggests that a mean of 427 ± 74.7 minutes (7 hours 6 minutes) might be expected. Sleep decreases with age. Singer et al (2003) suggested that people be referred to their study if they slept less than 7 hours on 5 out of 7 days in the week. However, given the normative data for sleep presented above, the specificity of these criteria is questionable. Furthermore, Singer et al (2003) reported a total nocturnal sleep time of 350 ± 83 minutes. The reporting of these data suggests that data were normally distributed (as

SD are given rather than Quartile ranges). From these data we can calculate the 95% confidence interval which is $(1.96 \times SD)$, which is 163 minutes. It follows that the 95% confidence intervals are (187-513 mins). 513 mins is roughly 8.5 hours, which suggests that either data were not normally distributed or inclusion criteria were unlikely not satisfied. A tighter inclusion criterion of sleeping less than 6 hours using wrist actigraphy may be preferable, but then this might exclude study of the effects of melatonin with people who have milder sleep disturbance but may nevertheless benefit from investigation.

Reliability of outcome measures

Wrist actigraphy confirmed that participants selected for the study had significant disturbance of sleep, with a median baseline total sleep time (TST) of 335.0 (250.7 - 448.2), a median number of awakenings (NWA) of 13.7 (8.6- 20.0), median time awake after sleep (WSO) of 66.2 (46.2-97.7) mins and median sleep efficiency (SE) of 69.3% (61.0 - 69.4). The validity of wrist activity as an objective measure of sleep is also suggested by independent findings from the larger larger study population in Singer et al (2003) who reported a mean TST of 350.5 (± 83.0), WSO of 62.4 (± 59.4) mins and mean SE of 69 (± 11)%. However, as with Singer et al, (2003), we also found a large night to night variability within individuals and a significant spread (quartile range) for all sleep measures. Findings also confirm the perception by carers that there is a greater degree of impairment than a non-demented elderly people with sleep problems (Garfinkel et al, 1995). However, carers' reports of the sleep problems encountered in people with dementia were not very accurate as there was no consistency with objective evidence obtained from wrist actigraphy (Pearson correlation =0.05, $p = 0.94$) and indeed Singer et al (2003) raised concerns about the reliability of caregiver reports of participants' sleep. These findings raise questions about the validity of studies, e.g. Cohen-Mansfield et al

(2000), which use carer reports of sleep as the main outcome measure. Furthermore, even if reliable, such methods are not practical in a naturalistic setting such as ours, as it would not be reasonable to expect carers to stay up all night to monitor the participants' sleep. People with dementia, by definition, experience memory problems and cannot provide accurate self-report information about their own sleep. Although controlled conditions, such as a sleep laboratory using sleep polysomnography may provide accurate measures of sleep in normal individuals, this is not appropriate for people with dementia who are likely to be disturbed by the unusual surroundings. The need for an objective and accurate measure of sleep disturbance therefore cannot be over-emphasized, but in a naturalistic setting such as ours, wrist actigraphy provides the most practical method and has also been used by others (Singer et al, 2003; Yesavage et al, 2003; Sadeh et al, 2002; Ancoli-Israel et al, 1997; Sadeh et al, 1995).

22.3. Reasons for finding no beneficial effect from melatonin

Power considerations

Contrary to theoretical and clinical evidence suggesting that melatonin may be effective in sleep disturbance in dementia, we did not find a beneficial effect and these findings are consistent with findings in the larger study by Singer et al (2003). In our study, a pre-study power analysis suggested that 62 participants were needed to complete the trial compared to 34 completers, of whom 25 had full data sets. Therefore this study could be criticized for having insufficient numbers to detect a true significant difference between melatonin and placebo. However, power considerations are unlikely to account for our findings for several reasons. First, during the course of this study significant beneficial effects of melatonin were reported in only 9 inpatients by Brusco et al (1999) and in 7 inpatients by Tozawa et al (1998). Secondly, in the case of other disorders, such as depression,

exogenous melatonin has resulted in increases of total sleep time of as much as 200% (De Vries and Peeters, 1997). In the light of recent evidence, these findings suggest that, if anything, our pre study power analysis was too conservative. Thirdly, we would argue, with hindsight, that our prediction of a 20% placebo response was also over-cautious. Although the nature of the placebo response is subject to debate, none of the older people with dementia were aware that they were in a study, nor could they remember taking medication, hence a placebo effect is unlikely to be marked, if present at all. Similarly, although it is possible that a Hawthorn effect may be observed in carers, it is unlikely that this effect would be marked in the older person with dementia.

Thus, a post hoc analysis suggests that with a 45% improvement in sleep with melatonin and no placebo response, at 80% power and 5% significance, only 23 participants would be required to demonstrate a treatment effect. It is also notable that the crossover design described in our study will have had the effect of doubling the numbers resulting in equivalent to 34 participants in the melatonin and placebo groups respectively. Singer et al (2003) suggested that at 80% power and 0.05 level of significance, 150 people would be required, with 50 people in each of three groups. This calculation was based on the prediction that a 30 minute increase in nocturnal total sleep time could be detected between the study groups. Although trials of psychotropic medications require several hundred people to demonstrate modest treatment effects (Tariot et al, 2001), as pointed out by Singer et al (2003) a change in sleep based on their power calculation would be of minimal clinical significance. Fourthly, had the results shown smaller, not statistically significant effects, all in the hypothesised direction, then the lack of statistical significance could be attributed to low power. However, the findings shown in Table 21.7 do not demonstrate any consistent trend, suggesting the lack of statistical significance is not simply due to low

power. Indeed, as shown in the study by Singer et al (2003) who randomised 157 individuals to one of three groups (melatonin 10mg, sustained release melatonin 2.5 mg or placebo) and used similar methods, no significant between group differences were observed. There seems little doubt that this is a negative trial and reasons for lack of effect of melatonin, which is of benefit in older people with sleep disturbance who do not have dementia, needs to be explained.

There did not appear to be an effect of melatonin on cognitive function which is consistent with findings by others (Singer et al, 2003; Assayma et al, 2003; Jansen et al, 2006).

Although the MMSE may be not be sufficiently sensitive to change and alternative scales such as the

Dose, preparation and timing of melatonin

The dose, preparation and timing of melatonin may be important. At higher doses (above 10 mg) melatonin is soporific (Singer et al, 1994, 1995a,b, 1997; Brzezinski, 1997; Zhdanova et al, 1997; Dawson et al, 1998; Hughes et al, 1998; Sack 1997, 1998, 1990; Sack et al, 1990; Lewy et al, 1992; Mendelson 1997; Zisapel 1999; Monti and Cardinali, 2000; Stone et al, 2000; Andrade et al, 2001; Arendt and Skene, 2005; van den Heuval et al, 2005a,b; Zhdanova, 2005a,b) and chronobiologic (Zaidan et al, 1994; Lapierre et al, 1995; Czeisler, 1997; Lewy 1997; Lockley et al, 2000; Sack et al, 2000; Arendt and Skene, 2005). Singer et al (2003) used two dose preparations; a higher dose 10 mg melatonin and a lower dose 2.5 mg sustained release. They also conducted pilot work (unpublished) in people with Alzheimer's disease which suggested that 10 mg provided a 30minute increase in actigraphically determined total sleep time, whereas 0.5mg did not (Singer et al, 1997). The dosing regimen in the Singer et al (2003) was determined following pilot data on the

two preparations which showed that both melatonin doses yielded blood levels sustained through the night. Although they state that plasma levels were higher for the higher dose preparation, but cleared in the day, mid-day levels were 67.7 ± 281 ng/dL and 28.7 ± 67 for the 10 and SR 2.5 mg doses respectively. It has been suggested that doses of exogenous melatonin for it to be effective need to elevate plasma melatonin levels to night time levels of between 60-200ng/dL as opposed to the usual daytime levels of less than 3-10 ng/dL (Dollins et al, 1994). Although there is some evidence that doses (0.2 mg) of exogenous melatonin which are not physiological may be effective in healthy elderly people with sleep problems (Singer et al, 1995a; 1995b), there is evidence that very low doses of melatonin (0.1 to 0.3mg) are at least as effective as pharmacological doses (3mg to 6mg) (Zhdanova et al, 2001). Although it may have been helpful for us to collect either plasma or salivary melatonin levels in our study, we did not have the resources available to do this. It is nevertheless possible that in both our study and that by Singer et al (2003), that high daytime residual levels of melatonin accounts for the failure to observe a chronobiological effect. Assuming our melatonin levels did demonstrate a reasonable physiological cycle, then results suggest that melatonin has only limited influence on the sleep-wake cycle in this population. It maybe that people with severe dementia have such a severe disruption of normal sleep patterns and diurnal rhythms that exogenous melatonin is not effective. Indeed it is also possible that changes in receptor sensitivity and/or density known to occur with age may account for the increased inter-individual variability in melatonin efficacy among elderly patients and patients suffering from neurodegenerative disorders (Zhdanova, 2005).

The length of time required for melatonin to be prescribed and concomitant use of medication may also be important. Of the 25 participants who completed the trial, we did

not find any “period” or “carry over” effects of melatonin and reject the hypothesis that there is a therapeutic effect of exogenous low dose melatonin. However, work using melatonin for longer periods in other conditions (Cole et al, 1992; Haimov et al, 1995) suggests that longer term treatment may be effective. Indeed, in trials in dementia, a twin study (Brusco et al, 1998a), an open trial study (Brusco et al, 1999) and a larger trial by the same group (Cardinali et al, 2002) suggests that longer term treatment may give better results. However, none of these trials were RCTs, nor did they use objective methods for evaluating sleep.

Factors which may interfere with the therapeutic effect of melatonin

Hypnotic and psychotropic medication may beneficially affect sleep or alternatively interfere with melatonin levels. Although it is unusual for older people with sleep problems not to receive any hypnotic medication, the use of concomitant medication is not reported in the study by Tozawa et al (1998). Singer et al (2003) excluded people treated with psychotropic or hypnotic medication which had been discontinued in the last 2 weeks of the screening visit, but they did not provide any information about prescribed medication. Nevertheless, it is likely that such biases will have been controlled for by the randomisation process. In our study, participants randomised to either groups 1 or 2 were on similar hypnotic and psychotropic medication, suggesting that randomisation should have addressed possible effects of medication on endogenous melatonin secretion. Furthermore, sub-analysis of our data did not demonstrate any beneficial effects of melatonin in the 16 psychotropic-free participants in our study and of those medicated, all had sleep disturbance despite stable medication regimens for at least 4 weeks prior to the trial.

It is also known that a number of other factors may interfere with an individual's circadian rhythm. Often older people living in care homes may be exposed to low levels of light in that they spend much of their time indoors. They may also have little in the way of social contacts or structured daily activities and spend their time lying down. It is possible that in such individuals, circadian entrainment of their biorhythms is less marked.

Effects of dropouts

Some difficulties associated with the use of wrist actigraphy to assess sleep in people with neurodegenerative diseases, such as Alzheimer's disease, have been described (Van Someren, 1997). A major reason for this was inability or unwillingness to wear the wrist actigraph. The stringent ethical standards required and adopted in this study interpreted a reluctance to wear the monitor as a withdrawal of consent. In retrospect, dropouts could have been eliminated had randomisation taken place after the run-in period. Wrist actigraphy still provides one of the most accurate measures of sleep in this group of patients (Singer et al, 2003; Yesavage et al, 2003; Sadeh et al, 2002; Ancoli-Israel et al, 1997; Sadeh et al, 1995).

Period of data collection

The time period of data collection may have been an explanation of why our results differed from those reported by Tozawa et al (1998) and Cohen-Mansfield et al (2000) who compared night-time activity to total daily activity. Singer et al (2003) noted that one-third of sleep occurred during the day period of the sleep wake cycle, although they did not find a significant effect of melatonin despite recording sleep over 24 hours for two weeks. Although our study examined the effects of melatonin for the night period only, as pointed out by Singer et al (2003) points out that choosing a 12 hour night time epoch to define the nocturnal period for automated scoring may not provide information about what happens

during a shorter period (e.g. midnight to 4:00 AM). In retrospect, in redesigning our study, it would be helpful to analyse sleep over a 24 hour period and to subanalyse the data to see whether there were differences in the epochs, say between midnight and 4:00 AM and 4:00 AM to 8:00 AM. Studies in children also suggest that more useful data on sleep efficiency can be achieved if the period of data collection is for more than 7 nights (Acebo et al, 1999). However, it is notable that the actigraphs used in our study are not able to record data continuously for more than a 48 hour period.

Chapter 23 METHODOLOGICAL ISSUES: CRITICAL ANALYSIS

23.1. Aims of a pragmatic trial of melatonin in dementia

- (i) Does the trial address a clinically important dilemma?

Sleep disturbance is one of the major problems in Alzheimer's disease affecting 45% of patients (Swearer et al, 1988). It is also a major stressor for families, leading to nursing home placement (Pollack et al, 1991). Melatonin is not classed as a medicine in the UK and non-drug treatments are often welcomed by patients. It follows that the use of what is perceived as a natural compound to address a significant clinical problem would seem timely as previously no large RCTs of the use of melatonin in dementia had been undertaken.

- (ii) Are the participants in the trial those patients in which the treatment would normally be considered in clinical practice?

The participants used in this trial were typical of those found in a naturalistic setting. The majority of people with dementia are cared for in either nursing homes or live with relatives (Livingston et al, 1990). If melatonin had proved to be effective for sleep disturbance in this population, many people with dementia could have benefited.

- (iii) Is the intervention a realistic reflection of the likely good practice in the NHS?

Good practice suggests that any intervention should be of benefit to the patient and do no harm. It should also be as cheap as possible to maximise cost-effectiveness. Although a significant number of older people with dementia are cared for in either nursing homes or by a relative the GP is often the first person to be approached by carers for help, which also places a number of costs on Health Service. As previously suggested, conventional pharmacological agents used for sleep problems are often not beneficial (Kripke et al, 2000;

Meyer 1998; Wettstein et al, 1992; Schneider et al, 1990; Prinz et al, 1990; Morgan et al, 1988, Kripke et al, 1983). Despite this, those with dementia are twice as likely to be prescribed sedative-hypnotics than their younger counterparts (Baum et al, 1986).

Melatonin has also been shown to have very few side effects in lower doses, is very cheap and is not subject to patent protection. It follows, that were its use have proven to be beneficial, the use of an easy to administer and safe compound would be much recommended and also decrease service demands on GPs.

23.2. Design of a pragmatic trial: melatonin in dementia

- (i) What was the method of randomisation and did the investigators ensure that it was adhered to?

The method of randomisation was undertaken using a random numbers generated by computer.

- (ii) Who was blind to the randomised allocation-patient, physician, the research assistant measuring the outcomes, the investigator who analysed the data?

The codes were not broken until completion of the trial and until all outcome data had been collected. A quadruple blind design (the dispensing pharmacist, researcher, carer and patient all being blind to which preparation (melatonin/placebo) was dispensed. The analysis was undertaken by Dr Serfaty.

- (iii) How was blindness ensured and was it assessed?

Blindness was assessed using a VAS. The results suggest that blindness was indeed maintained.

(iv) Did the experimenters include an assessment of “quality of life” ?

Although we considered assessing the quality of sleep of the carer, in fact this would have been very difficult as patients often had multiple carers. Because of the cognitive deficits experienced by the participants, it would not be possible to obtain accurate data from self report.

(v) Is there an economic assessment that measures health and social service costs not directly concerned with treatment?

One of the most commonly used measures of costs is the Client Service Receipt Inventory (CSRI; Beecham and Knapp, 1992). However, this has not been evaluated in the target population. Although it may have been helpful to obtain economic measures this was not possible within the constraints of resources available. Furthermore, some data is required using an established tool for a pre-study power analysis to be undertaken.

23.3. Analysis of a pragmatic trial of melatonin in dementia

(i) Was there an imbalance between the randomised groups in any of the prognostic variables?

Results suggest that there are no differences between the variables which may predict outcome. Although there were no differences in basic demographic information (gender, length of illness etc), prescribed medication, nor any differences in baseline outcome measures, it is worth noting that the numbers in each group were small and one cannot exclude the possibility of a type 2 error in which there is a significant difference between groups although none was detected.

- (ii) How is missing data analysed? Is an intention to treat strategy used or are other statistical methods used?

A full description of how missing data were analysed was given in section 21.2. Both a completers analysis and an intention to treat analysis was used for the main outcome measures. Because of the limited completion by carers of the observer rating scales, an intention to treat analysis would not have been appropriate, unless there was evidence for significant differences between groups for the main outcome measures using a completers analysis.

- (iii) Have the investigators performed multiple statistical tests on a variety of outcomes?

All statistical analyses were undertaken to test our a priori hypothesis, so that spurious results were not obtained by multiple testing generating type 1 errors, demonstrating a difference and rejecting the Null hypothesis.

- (iv) Was the main outcome specified before the trial was started?

The main outcome measure, sleep efficiency using wrist actigraphy, was specified before the trial was started.

- (v) Is the power calculation from the research proposal described?

The power calculation is described in section 20.5.

- (vi) If a negative result, how large are the confidence intervals?

This study shows that the data for sleep in dementia is skewed and therefore quartile ranges were given and non-parametric tests were used. It was also noted that there was a wide range of sleep quartile ranges for the main outcome measure (wrist actigraphy) used.

(vii) Have the investigators ruled out the possibility of an important treatment effect?

Analysis of the results suggest that there is little in the way of treatment effect using melatonin for sleep disturbance of dementia. Data was examined to see whether there were any trends for melatonin/placebo. The findings of this study were also confirmed by those of Singer et al (2003) who found in a larger population that melatonin was not an effective soporific agent in people with Alzheimer's disease.

23.4. Conclusions of a pragmatic trial of melatonin in dementia

In conclusion, we did not find either therapeutic or adverse effects of exogenous melatonin in the treatment of sleep disturbance in dementia, despite a strong theoretical basis and some research evidence advocating its use. A cross-over design using objective measures of sleep disturbance was ideally suited to investigating older people with dementia. However, contrary to the widely held view that sleep difficulties are common and enduring in this population, such problems may be sporadic and ethical issues contributed to making recruitment of large numbers for study over short periods of time a challenge. Although short-term use of melatonin was not helpful, the potential beneficial effects of longer-term administration cannot be discounted.

PART IV: CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

The three chapters in Part IV of this thesis will highlight first, overall conclusions from the trials investigating the use of exogenous melatonin for sleep disturbance in depression and dementia , secondly how the studies may have been improved and thirdly consider alternative strategies for further research in these disorders.

Chapter 24 OVERALL FINDINGS OF TRIALS TO EXAMINE THE EFFECT OF EXOGENOUS MELATONIN IN DEPRESSION AND DEMENTIA

24.1. Recruitment

Both studies aimed at recruiting patients through established research networks. However, people in the melatonin in depression study were mainly recruited from a GP setting, whereas those recruited to the dementia study were recruited through services which had a special interest in care of the elderly. Despite the different setting and large sample population, there were difficulties in recruiting people to both trials, with 12% and 16% percent of those screened being recruited to the depression or dementia study respectively.

24.2. Diagnosis and demographics

Referral was often made on the basis of correct diagnosis, but this was more likely for those referred to the depression study (95%) compared to the dementia study (89%). There were also demographic differences between the studies, with a preponderance of females being recruited in the depression study (90%) whereas more males were recruited in the dementia study (73%).

24.3. Dropouts and availability and reliability of data

Full actigraph data were available in 64% and 66% of people recruited to the depression and dementia trial respectively. This was either because people could not remember to use the actigraph or because the actigraphs did not function. Attempts to evaluate sleep using rating scales and sleep diaries revealed that data was often completed by depressed participants, but reports of sleep by dementia carers was scantily recorded and where recorded, inaccurate.

24.4. Prescribed medication:

The use of medication was high in people recruited to both studies. Seventy percent of patients recruited to the depression study were taking antidepressants. Of those recruited to the dementia study, all were taking at least one drug and just under half were taking at least five drugs. It is notable that 25 % of those with dementia were on hypnotics and 16% on antidepressants.

24.5. Results from studies

There is an inability to improve sleep when pre-intervention sleep is better than 90% efficiency (James et al, 1987). However, both studies found that there was significant impairment in sleep using the objective measure of wrist actigraphy. There was marked impairment in sleep using self report and diaries in the depressed. Carer report of sleep problems in the dementia study revealed significant impairment in sleep, although only around a third of measures were completed by carers.

Neither study demonstrated a conclusive therapeutic effect of melatonin on sleep. In the depression study, wrist actigraphy showed improvements in sleep over time for both melatonin and placebo. In dementia no such improvement was observed. Self report data in the depression study also revealed that participants felt more alert and less clumsy. The study of melatonin in dementia in particular also highlights the lack of reliability of carer report.

Although there have been two published meta-analyses (Bzezinski et al, 2005; Buscemi et al, 2006) on the use of exogenous melatonin against placebo for secondary sleep disorders and sleep restriction, these meta-analyses are inconsistent. A meta-analysis by Buscemi et

al (2006) into the effects of exogenous melatonin on sleep in a heterogeneous population suggested that melatonin did not have a significantly beneficial effect in treating secondary sleep disorders compared to placebo. However, the conclusions from this meta-analysis should be treated with some caution as numerous published studies, mostly with a positive result, were not included (Arendt, 2006). For example, the authors do not mention the importance of melatonin in blind sleep disorder and delayed sleep phase syndrome. Nevertheless, if we accept the findings of Buscemi et al, (2006) and Bzeinski et al, (2005), the two studies described in this thesis are consistent with the meta-analyses and suggest that the effects of melatonin are, at best, modest, with sleep latency being reduced by 13 minutes, sleep efficiency increased by 1.9 % and total sleep time increased by 15.6 minutes when compared to placebo. In the meta-analysis by Bzeinski et al (2005), melatonin treatment significantly reduced sleep onset latency by 4.0 minutes, increased sleep efficiency by 2.2% and increased total sleep duration by 12.8 minutes (Bzeinski et al, 2005). Although the evidence that melatonin is an effective hypnotic is disputed, melatonin's role in acting as a regulating switch to induce circadian phase shifts may be more relevant (Herxheimer, 2006). However, meta-analyses provide little information about what melatonin does and why it works (Herxheimer, 2006).

Both the trials in this thesis, supported by meta-analyses by Bzeinski et al, (2005) and Herxheimer (2006), suggest that as the effects of melatonin on sleep are modest and that extremely large numbers would be required to detect significant differences between melatonin and placebo. Furthermore, where a statistically significant finding has been observed, this is probably of debatable clinical significance.

The two studies described in this thesis suggested that melatonin may have a positive effect on mood in depression, but no effect was seen on cognitive function in people with dementia.

24.6. Randomisation and blindness

Objective measures of sleep using wrist actigraphy showed that depressed patients randomised to receive melatonin were awake for longer after sleep onset (WSO) and had poorer sleep efficiency (SE), at baseline, suggesting randomisation may not have been entirely successful. However, subjective measures of sleep did not reveal any significant differences at baseline. Randomisation appeared to be successful in the melatonin in dementia trial.

Both studies suggest that patient and assessor blindness was achieved.

24.7. Design

Both studies demonstrate that the design is practical. Indeed, the crossover design was particularly useful in the dementia trial, as the absence of carry over effects from melatonin increased numbers for analysis.

Chapter 25 SUGGESTED IMPROVEMENTS IN RCTs INVESTIGATING THE EFFECT OF EXOGENOUS MELATONIN IN DEPRESSION AND DEMENTIA

25.1. Recruitment issues

Recruitment to these studies was harder than anticipated. This is possibly because people perceived them as “drug trials” rather than complementary therapy with a “natural product”. In retrospect, these trials emphasise the importance of feasibility studies, designed to demonstrate the likely recruitment rate. These might also provide more accurate data upon which to conduct a power analysis, rather than rely on case reports. Qualitative methods such as focus groups may also provide useful information about reluctance by referrers to involve people who may not be able to consent.

Recruitment certainly seemed to be difficult in both trials. Where recruitment is problematic, it may be appropriate to increase the sample population by expanding the study to numerous centres around the UK. This multicentre approach was adopted by Singer et al (2003) in the USA for a large study of melatonin in dementia. In the UK, a trial such as this may be done by liaising with research networks such as Mental Health Research Network (MHRN) groupings. Such organisations are particularly useful for undertaking large multi centred trials, though it needs to be pointed out, that many organisations do not fund what they perceive as drug trials and it is unlikely that drug companies would fund a trial with a compound that has no patent protection. Furthermore, such large multicentre trials also escalate the costs because of the number of staff required to undertake assessment procedures and collect outcome data.

Research from both studies also suggested that a significant number of referrals were not appropriate, with only 16% and 8 % of people being suitable for the melatonin in depression

and melatonin in dementia studies respectively. Tighter referral criteria may increase the suitability of those referred to participate in the study. Another approach may be to relax criteria for an individual's entry into the study. The use of very tight entry criteria may have implications about the generalisability of the findings and also makes it harder to perform subgroup analysis.

25.2. Diagnosis

Diagnosis of depression was made using accepted diagnostic research criteria (Endicott and Spitzer, 1978). We are confident that all people recruited to the trial investigating the use of melatonin in depression suffered from this clinical disorder. Patients recruited to the trial of melatonin in dementia were diagnosed according to DSM-IV criteria for dementia (American Psychiatric Association, 1994,; Appendix A3-5) or according to criteria for Lewy Body Dementia (McKeith et al, 1996; Appendix A6) by an experienced clinician. However, the subtype of dementia is a post mortem diagnosis. More precise criteria such as the diagnostic criteria of the NINCDS-ADRDA (McKhann et al, 1984) may have been useful, although we were keen to limit the time of the assessment in a vulnerable population. In retrospect, it may have been more appropriate to limit the study of melatonin in dementia to a specific diagnosis, e.g. Senile Dementia of the Alzheimer's Type, as the disease process and melatonin dysfunction may be very different from that of other dementias. This approach was adopted by Singer et al (2003). Nevertheless, were it possible to investigate large numbers of patients with dementia, an alternative approach may be to stratify recruitment according to diagnosis, providing that the study is sufficiently powered to detect differences for the different diagnostic groups. Unfortunately, because of small numbers of people with vascular dementia (n=8) in our study it would not be possible to conduct a subanalysis of the data to see whether people with vascular dementias benefited from melatonin.

As described in section 5.5, there is some suggestion that exogenous melatonin may be helpful in healthy older people with sleep disturbance. Senile dementia is a gradual process and what is not clear is whether patients with milder forms of the disease who experience sleep problems would benefit from exogenous melatonin. Although statistical analysis may enter severity of dementia, judged by the Mini Mental State Examination score, as a covariate, an alternative design may be only to select patients with milder forms of dementia (for example MMSE scores 20-24). Using a similar approach, it may be that people with milder forms of depression respond more favourably to melatonin. Stratification of participants by severity of depression on the BDI may be helpful in evaluating the effect of melatonin on mood and sleep.

25.3. Reliability of the outcome measures used

Measures of sleep:

Both studies were pragmatic trials using objective measures of sleep and both demonstrate that subjective evaluations of sleep are not reliable. These studies highlight the need for practical and accurate objective measures to evaluate sleep. However, it is also evident that collecting data using wrist actigraphy may have problems associated with actigraphs either because of hardware malfunction or because of lack of participant co-operation. In the study by Singer et al (2003) they reported that only 3 out of 157 participants did not wear the same actigraph throughout the study suggesting a far lower failure rate with the Actiwatch AW64 series model produced by Mini-Mitter Inc (Sunriver, Oregon).

Both the Mini Mental State (Folstein et al, 1975) and the Beck Depression Inventory (Beck et al, 1961) have been well validated and are easy to use. However, the study in depression may be refined using the newer version of the BDI, the BDI second edition (Beck et al, 1996).

25.4. Duration of data collection

The period when wrist actigraphy data is collected may be important. In particular, as a result of experience gained in these studies, we would recommend that data about the sleep wake cycle is collected over the full 24 hour period and that this provides a better measure of sleep efficiency (Roehrs et al, 2000). This would enable comparison of sleep and wake periods, particular in dementia where sundowning and daytime sleeping has been widely reported. However, this was not possible in our study because the Somnitors had a finite memory. Newer technology, as in the case of the study by Singer et al (2003), suggests that the length of time covered by actigraphs may be extended to two weeks. This may provide more accurate information about average sleep pattern, given that there seems to be considerable variation in sleep both within and between individuals. It needs to be stressed, however, that wrist actigraphy alone cannot provide useful qualitative measures of sleep.

25.5. The dose, preparation and timing of melatonin

The precise dose, timing, type of preparation and duration of treatment with melatonin requires further evaluation. The extremely high doses (up to 1600 mg per day) reported in the first study of exogenous melatonin (Carmen et al, 1976) study are five thousand times higher than the low doses (0.3mg) shown to be effective (Lewy et al, 2001; Zhdanova et al, 2001).

Although we used sustained release melatonin, in the treatment of jet lag there is some suggestion that melatonin 0.5mg and 5mg rapid release is better than melatonin 2mg slow release (Suhner et al, 1998a). However, there was no effect using different types of preparation or dose in dementia (Singer et al, 2003). In our study of melatonin in depression we found a trend towards an improvement in mood with melatonin, and in light of the study by Suhner et al (1998a), it may be that a pulse of melatonin may be more effective. Thus, our

study investigating the effects of melatonin in depression may be improved by using different doses and formulations of melatonin and comparing these against placebo. However, as pointed out by Arendt (1995), there are large individual differences in the pharmacokinetics of oral melatonin. Indeed, a 1,000 fold increase in plasma melatonin level may be seen after ingestion of a 10mg dose in young people (Zhdanova, 2005) and as pointed out by Scheer and Czeisler (2005), there are inter-individual differences in melatonin receptor sensitivity and/or density and some evidence for a threshold phenomenon in the dose response relationship to melatonin. These findings suggest that exploration and interpretation of the effects of dose response effects is likely to be complicated.

The timing of melatonin is also important. Ideally each individual should be phase typed in order to establish the optimum timing for melatonin administration, especially given that older people have a variable phase (Kripke et al, 2005). However, phase typing would be difficult in a dementia trial, but should be possible in a depression trial (Raven et al, 1996).

The length of time that melatonin is given may be important. Administration of a daily repeated dose of melatonin before bedtime over several weeks has been reported as more effective in elderly insomniacs with low melatonin levels (Haimov et al, 1995; Scheer et al, 2005).

There appears to be some evidence that some individuals may be “responders” to melatonin (Singer et al, 2003). Although not always practical in a pragmatic trial, precise phase typing of people’s melatonin cycle may be helpful when examining responses to melatonin.

Obtaining more accurate information about whether people who enter the study have a phase

advance or delay in their melatonin secretion may be useful to determine whether patients respond differentially to exogenously administered melatonin.

25.6. Modification of current design

Unlike its use in dementia, it seems unlikely that a crossover trial is the best design for a trial of melatonin in depression, as there may be carry over effects where the treatment by the active ingredient (in this case melatonin) carries over into the second period, making analysis of the second period data problematic.

25.7. Control of factors which may reduce the efficacy of the intervention

The study by Singer et al (2003) provides some additional useful exclusion criteria. Although we did not explicitly specify a number of the criteria, such as having no mobile upper extremity, this was done as part of the assessment procedure. However, Singer et al (2003) also excluded people who may not sleep because of pain, asked participants to maintain abstinence from caffeine after 2pm for the duration of the protocol and excluded patients who were unwilling to comply with a maximum of two alcoholic drinks per day. Although alcohol abuse would have been excluded in our depressed sample using the SADS (Endicott and Spitzer, 1978), physical tests were not undertaken to confirm the reliability of self report data. In the melatonin in dementia study, the majority of people were referred from nursing homes and alcohol is not routinely given to the residents. Caffeine intake was not monitored and in retrospect this may have been a useful exclusion, However, it is not always possible to control for all factors which may influence outcome and it was hoped that the unknown use of caffeine was addressed through the randomisation process.

25.8. Stratified randomisation

As previously described, the RCT is regarded as the Gold Standard in trial design.

Although the randomisation process aims to control for both known and unknown biases, a modification of an RCT is to use a process of stratification. This process aims to minimise some of the imbalances known to influence the outcome. In the melatonin in depression study, the outcome may be predicted by the severity of depression at baseline. Similarly in the melatonin in dementia study, response to treatment may be associated with severity of cognitive impairment. Using a stratification process it would be possible to band participants by severity of depression or dementia and then randomise them to one of the two treatment groups. This process would hopefully ensure that a representative sample of people, by severity of depression/dementia, were allocated to each group and thus one could examine the effects of the intervention. An alternative approach is to use a post hoc analysis. However, in trials in which numbers in each intervention group may not be representative, stratified randomisation may be a useful way to overcome this problem.

25.9. Improved methods of data analysis

Missing data is common in most studies with increasing attrition over time. When data are missing, replacement with the group mean leads to an underestimation of the standard deviation and inflation of the type I error. Although using last observation carried forward may preserve the sample size, it makes unwarranted assumptions about the missing data. Using regression estimates using multiple data imputation methods may be a way of preserving the estimate of the mean and standard deviation (Streiner 2002).

Chapter 26 ALTERNATIVE RESEARCH STRATEGIES TO INVESTGATE EFFECTS OF MELATONIN IN DEPRESSION AND DEMENTIA

26.1. Small case studies

The RCTs undertaken in this thesis assumed that people with depression or dementia have a specific dysregulation of the sleep wake cycle and melatonin secretion. However, there is still little known about the precise nature of the dysregulation of melatonin secretion in non-seasonal depression and dementia. As previously discussed in section 5.5 there is some evidence to suggest that in dementia melatonin secretion is decreased in amplitude and the circadian rhythm is lost (Bliwise, 1993). However, there is a dearth of information on how these changes relate to the severity of dementia, or indeed to different subtypes of dementia, and this area is worthy of further research. In the case of depression, it has been suggested that there is a phase delay in SAD and possibly a phase advance in non seasonal depression.

A pure science approach prior to embarking on RCTs may be helpful in gleaning more understanding about the nature of melatonin secretion and its link to the sleep-wake cycle in non-seasonal depression. This approach could involve studying a small number of highly selected patients in great detail, although caution will need to be exercised about the generalisability of the findings. It may be helpful to study a specific group under laboratory conditions, thus controlling for some of the factors which are known to affect melatonin secretion and the sleep wake cycle . Male patients (as melatonin may vary with the menstrual cycle), in the 30-50 age range, who are medication free, satisfying RDC for depression (non-seasonal type) and who have no previous history of depression would be favourable for some of the reasons described. Baseline measures of sleep using EEG polysomnography, wrist actigraphy as well as subjective measures of sleep could be taken.

People should also be asked to complete the automated morningness-eveningness questionnaire (MEQ; Horne and Ostberg, 1976), available on the world wide web (www.cet.org), and serial melatonin measurements to determine melatonin offset time and measures of mood should also be made. This information could then be used to build up a more precise picture about melatonin secretion, sleep and mood so that an optimum intervention may be considered with a few to then undertaking some open label studies prior to a full RCT. Although these methods could also be used to study patients with dementia, the nature of the illness and ethical issues would present considerable difficulties.

26.2. Determining phase type

The first step in small case studies would be to screen people with sleep disturbance in depression and dementia using a questionnaire (the morningness-eveningness questionnaire (MEQ); Horne and Ostberg, 1976) and gain some information about the individual's circadian rhythm type. An on-line version of this scale, the automatic morningness eveningness questionnaire (www.cet.org) is available. The MEQ correlates strongly with objective measures of the circadian phase (Terman and Terman, 2001). An advantage of this scale is that it can also be used by an informant, although its use in dementia has not been validated.

Nevertheless, these data, in conjunction with objective tests of the melatonin cycle, would provide useful preliminary data on whether patients with non-seasonal depression or dementia are more likely to experience specific (phase advance, phase delay or no phase shifts) disturbance of the sleep wake cycle.

A precise measure of the secretory phase of melatonin in an individual could then be confirmed under strict laboratory conditions, as, in healthy individuals, the human melatonin cycle is highly reproducible within an individual. Accurately determining the time at which melatonin secretion rises above 10 pg per millilitre (DLMO) provides a reliable marker of the phase of the endogenous circadian cycle (Lewy et al, 1997b). Phase typing is particularly important because the optimal timing of administration of exogenous melatonin can then be determined using our established knowledge of the phase-response curve, which describes the relation between the time in the circadian cycle that melatonin is given and its effects on the circadian rhythm.

26.3. An alternative study setting

Ideally, objective measures of circadian phase could be made under laboratory conditions. For example, for maximal effect melatonin needs to be taken in dim light conditions and the person needs to be supine. However, such strict laboratory conditions are unlikely to be fruitful when examining the use of melatonin in dementia because of first, the ethical problem with obtaining informed consent, secondly the practical problems associated with obtaining samples, thirdly because rigorous test conditions are likely to increase agitation because of the change in environment and this will affect sleep. Furthermore rigorous test conditions may generate the justified criticism that the results would not be generalisable to the population of interest and we would suggest that the crossover design described in this thesis remains the intervention of choice.

26.4. Alternative measures of sleep

Both studies have also highlighted the need for a variety and combination of outcome measures to evaluate sleep (in the case of dementia) and sleep and mood (in the case of

depression). Wrist actigraphy is particularly useful for evaluating sleep in people in whom subjective measures may be unreliable. However, our experience was that wrist actigraphy is not without problems for two reasons. First, as highlighted by both studies, it was not possible to collect data on sleep in about a third of patients using wrist actigraphy and secondly this method provides no subjective information about sleep. Investigating the precise nature of sleep problems in a small number of patients with depression using EEG polysomnography may yield more accurate information. Indeed, this approach has been used when investigating the use of agomelatine, a melatonin agonist, in healthy older people (Leproult et al, 2005). Admitting depressed patients to a sleep laboratory where the melatonin cycle can be determined and sleep pattern accurately assessed using sleep polysomnography, may thus provide complementary information to a large randomised controlled trial in a primary care setting.

26.5. Length of administration of melatonin

Although we did not find a therapeutic effect of melatonin in dementia, an Argentinian group has suggested that melatonin is effective in people with dementia when used for longer periods of 3 years (Brusco et al, 1998), 22-35 months (Brusco et al , 1999; 2000) and 4 months (Cardinali et al, 2002a,b). However, none of these trials were RCTs and no objective measures of sleep were used. Nevertheless, it may be preferable in future trials evaluating the effects of melatonin in dementia to consider using melatonin for at least 4 months.

26.6. Open label studies

A randomised controlled trial aims to control for a number of factors which may influence the outcome. Randomisation may result in participants not getting the treatment of their

choice (melatonin) and is one of the only ways of eliminating *unknown* biases from treatment allocation (Bradford Hill, 1961; Cawley, 1983, Fox, 1998; Spiegel, 1998).

Randomisation is also useful in controlling for known biases. In *open label* trials, a small number of patients could be given melatonin using different times of administration, using different formulations and doses. In this way investigators may obtain an idea of how melatonin might affect the sleep wake cycle and endogenous melatonin rhythm. Indeed, this type of small intervention has been fruitful in a number of studies investigating the use of exogenous melatonin; for example in blind people (e.g. Lockley et al, 2000; Sack et al, 2000; Lewy et al, 2002).

For reasons previously described, we do not think it would be feasible to adopt this kind of approach for people with dementia, but open label studies may be helpful in non-seasonal depression. In the case of dementia we would still advocate that a randomised crossover trial similar to ours and that subsequently undertaken by Singer et al (2003) is the most pragmatic way of investigating the use of melatonin in dementia, although in retrospect controlling for known biases by using tight selection criteria would seem preferable. The tighter selection criteria in the RCT crossover trial by Singer et al (2003) ensured that participants were medication free, caffeine free and did not consume alcoholic beverages at least 2 weeks prior to and during the course of the study.

26.7. Combination treatment

Drugs given in combination may exert a synergistic effect. There is little information available on the use of melatonin in combination with other medication. One study has been published which investigated the use of melatonin in combination with an SSRI (Dolberg et al, 1998). In this study melatonin or placebo was added to fluoxetine.

Although there was no improvement in mood, the authors did report an improvement in sleep at four weeks with melatonin. A factorial design may be an alternative way of investigating the use of combination treatment. In this design, patients would receive either placebo, melatonin, fluoxetine or melatonin plus fluoxetine. Results would then be analysed to see whether the combination of fluoxetine with melatonin resulted in a significantly greater response than would be expected for either treatment alone. Factorial designs are considered an efficient way to test medicines in combination, but their results are not always easy to interpret (Montgomery et al, 2003).

26.8. Melatonin agonists; ramelteon and agomelatine.

Two melatonin agonists have been developed; ramelteon and agomelatine. Ramelteon is a selective MT₁/MT₂ receptor agonist, approved by the US Food and Drug Administration in 2005, for the treatment of insomnia. Although statistically significant improvements in sleep latency, total sleep time and sleep efficiency (using sleep polysomnography) were reported with ramelteon 4 and 8mg (Roth et al, 2005; 2006), these findings were selectively presented. There were differing results depending on dose and time of followup and some of the data showed no statistically significant differences between ramelteon and placebo. Furthermore, in the largest study (n=829) by Roth et al (2006), sponsored by Takeda Pharmaceuticals, the authors suggest ramelteon improves sleep latency at 5 weeks by around 21 minutes ((13+29)/2). However, if Figure 1 presented in the paper is examined, there is a placebo effect of around 12 minutes. Therefore, though statistically significant, a 9 minute improvement in sleep is of questionable clinical significance. Furthermore, the use of this compound has not been investigated in psychiatric patients (Becker, 2006) and more placebo controlled trials should be undertaken before judgments concerning the efficacy of ramelteon can be made (Bellon, 2006).

Recent studies suggest that agomelatine (S-20098), a melatonineric agonist and selective 5-HT_{2c} antagonist may be promising as an anxiolytic and antidepressant.

In rats agomelatine may have anxiolytic properties not observed by melatonin alone (Millan et al, 2005). Animal models of depression and anxiety (Seligman and Beagly, 1975; Porsolt et al, 1977; Papp et al, 1996) have been used to investigate the effects of drugs. Such animal models suggest that agomelatine may be beneficial (Bourin et al, 2004; Papp et al, 2004). Although agomelatine has 5-HT_{2c} antagonist action, data suggest that the beneficial effects in these models are not mediated through the same mechanisms as Serotonin Reuptake Inhibitors or tricyclics (Hanoun, 2004).

There have been few studies of the use of agomelatine in humans. Seven hundred people with DSM-IV major depressive disorder were randomised double blind to 3 doses of agomelatine (1, 5 and 25mg) or placebo (Loo et al, 2002). The authors concluded that agomelatine 25 mg may be effective in reducing HDRS. Agomelatine was also effective in alleviating anxiety and has a side effect profile similar to placebo (Loo et al, 2002). The same group (Loo et al 2003) also undertook an open label study of agomelatine (5 or 100 mg) given for 4 to 8 weeks to 30 patients with DSM III-R criteria for major depressive disorder and noted an improvement on the MADRS for both groups.

Olie and Emsley (2005) report data from two studies in which 212 and 238 patients were randomised to 25-50 mg of agomelatine or placebo. The authors suggest that agomelatine was significantly better at reducing HDRS scores in major depressive disorder.

A more recent 6 week placebo controlled trial of agomelatine in the treatment of major depressive disorder (Kennedy and Emsley, 2005;2006) randomised 212 patients to agomelatine or placebo. Although the authors report a significant reduction in HDRS compared to placebo, the difference in scores (14.4 ± 7.9 vs 17.3 ± 7.2 for agomelatine and placebo respectively) was small and the clinical significance of this is questionable. The authors do however point out that this difference compares favourably with other antidepressants.

Agomelatine may have hypnotic effects and this may predict the difference in HDRS scores on agomelatine compared to placebo. However, a statistical difference is still present even when adjustments are made for the positive effects on sleep and anxiety (Montgomery, 2006). The mode of action of agomelatine in depression is unclear and preliminary studies suggest that the magnitude of the antidepressant effect with agomelatine may be similar to the antidepressant effect of melatonin observed in our study. Although the greater effect of agomelatine on mood may be associated with its 5-HT_{2c} antagonist action, it would still be of interest to further examine any beneficial hypnotic properties of agomelatine given alone or as an adjunct to antidepressant therapy for people with sleep disorder in depression.

Preliminary studies investigating the use of agomelatine are particularly promising given that it appears to have little in the way of adverse effects (Kennedy and Emsley, 2006) and does not seem to be associated with a discontinuation syndrome. Indeed, a randomised double blind placebo controlled discontinuation study did not find that 12 weeks of daily agomelatine 25 mg (compared against paroxetine 20mg) was associated with a discontinuation syndrome when patients were transferred to 2 weeks of placebo (Montgomery et al, 2004). In a double blind crossover trial by Leproult et al (2005), two

15 day periods of agomelatine (50 mg)/placebo were given separated by a 2 week washout period. Agomelatine/placebo was given at 6.30 pm to eight healthy men of mean age 60 years who normally go to bed at 11pm. Sleep was assessed using polysomnography. The effects of melatonin on growth hormone, prolactin secretion and body temperature were also assessed. Agomelatine induced a phase advance in temperature, cortisol and plasma TSH, stimulated growth hormone and a transient elevation of prolactin levels in the wake period, but did not affect any of the sleep variables. This is consistent with the known effects of melatonin, which is only effective in older people with sleep disturbance (Zhdanova et al, 2001).

Agomelatine is being advocated as a new antidepressant. However the effect size observed is similar to that observed in our study. Although the use of agomelatine as an antidepressant may be promising, it is also worth noting that unlike melatonin, agomelatine would be subject to copyright and therefore the financial implications associated with marketing this new drug could be considerable. The role of agomelatine in sleep in depression and dementia in particular remains to be evaluated.

26.9. Summary of suggested future research strategies using melatonin in depression and dementia

There may be some advantage in studies using small numbers of cases investigated in detail. In such studies there should be an accurate determination of the individuals phase type. The use of a sleep laboratory may be helpful in depression, though this is not feasible in dementia. Although wrist actigraphy is the most practical way of monitoring sleep in people with dementia, there was a high failure rate and EEG sleep polysomnography may be better for people with depression. Though there is little information on the precise dose, timing and

length of administration of melatonin, 0.5 mg at CT 14 for at least 4 weeks is recommended. Ideally controlling for factors known to affect melatonin metabolism is recommended, however in practice this may not always be practical. Little is known about the synergistic effect of melatonin in combination with other treatments, SRIs in particular, and this is worthy of exploration. The synthetic melatonin agonist, agomelatine, appears promising and certainly warrants further exploration in disorders of sleep-wake cycle in depression and dementia.

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APPENDIX

A-1. List of abbreviations used:

AFS:	Awakening from Sleep
BDI:	Depression Inventory (BDI; Beck et al, 1961),
BFW	Behaviour Following Wakefulness
DLMO	Dim Light Melatonin Onset time
DLMOff	Dim Light Melatonin Offset time
GTS:	Getting to Sleep
HDRS:	Hamilton Rating Depression Scale (Hamilton 1960),
LSEQ:	Leeds Sleep Evaluation Questionnaire (Parrot and Hindmarch, 1978)
MI:	Movement index
MADRS	Montgomery-Asberg Depression Rating Scale
MMSE:	Mini Mental State Examination
NWA	Number of awakenings
PRC	Phase response curve
QOS	Quality of Sleep (QOS)
SCN	Suprachiasmatic nucleus
SE:	Sleep efficiency %
SL	Sleep latency
SynOff	Synthesis offset time
TIB	Time in bed
TST	Total sleep time
WSO:	Wake after sleep onset

DIAGNOSTIC CRITERIA

A-2. DSM-IV diagnostic criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Major Depressive Disorder

Single Episode

A. Presence of a single Major Depressive Episode

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

Note: This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Recurrent

A. Presence of two or more Major Depressive Episodes.

Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects or a general medical condition.

Specify (for current or most recent episode):

Severity/Psychotic/Remission Specifiers

Chronic

With Catatonic Features

With Atypical Features

With Postpartum Onset

Specify

Longitudinal Course Specifiers (With and Without Interepisode Recovery)

With Seasonal Pattern

A-3. DSM-IV Diagnostic criteria for Dementia of the Alzheimer's Type

- A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information.)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
- B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterized by gradual onset and continuing cognitive decline.
- D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
(1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
(2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
(3) substance-induced conditions
- E. The deficits do not occur exclusively during the course of a delirium.
- F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Code based on type of onset and predominant features:

With Early Onset: if delirium is superimposed on the dementia

290.11 With Delirium: if delirium is superimposed on the dementia

290.12 With Delusions: if delusions are the predominant feature

290.13 With Depressed Mood: if depressed mood (including presentations that meet full

symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.10 Uncomplicated: if none of the above predominated in the current clinical presentation

With Late Onset: if onset is after age 65 years.

290.3 With Delirium: if delirium is superimposed on the dementia

290.20 With Delusions: if delusions are the predominant feature

290.21 With Depressed Mood: if depressed mood (including presentations that meet full

symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.0 Uncomplicated: if none of the above predominates in the current clinical presentation

Specify if:

With Behavioral Disturbance

Coding note: Also code 331.0 Alzheimer's disease on Axis III

A-4. DSM-IV criteria for the diagnosis of vascular dementia

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:
 - (a) aphasia (language disturbance)
 - (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) agnosia (failure to recognize or identify objects despite intact sensory function)
 - (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during the course of a delirium.

Code based on predominant features

290.41 With Delirium: if delirium is superimposed on the dementia

290.42 With Delusions: if delusions are the predominant feature

290.43 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.44 Uncomplicated: if none of the above predominates in the current clinical presentation

Specify if (can be applied to any of the above subtypes):

With Behavioral Disturbance: if there is clinically significant behavioral disturbance (i.e., wandering)

Coding note: Also code cerebrovascular condition on Axis III.

A-5. DSM-IV criteria for Dementia Due to Multiple Etiologies

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:
 - (a) aphasia (language disturbance)
 - (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) agnosia (failure to recognize or identify objects despite intact sensory function)
 - (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance has more than one etiology (e.g., head trauma plus chronic alcohol use, Dementia of the Alzheimer's type with the subsequent development of Vascular Dementia).

D. The deficits do not occur exclusively during the course of a delirium.

Coding note: Use multiple codes based on specific dementias and specific etiologies, e.g. 290.0 Dementia of the Alzheimer's Type, With Late Onset, Uncomplicated; 290.40 Vascular Dementia, Uncomplicated.

A-6. Diagnostic criteria for dementia with Lewy bodies (DLB)

(according to the criteria proposed by McKeith et al., 1996)

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of fronto-subcortical skills and visuospatial ability may be especially prominent.

2. Two of the following core features are essential for a diagnosis of PROBABLE DLB:
 - a) Fluctuating cognition with pronounced variations in attention and alertness
 - b) Recurrent visual hallucinations that are typically well formed and detailed
 - c) Spontaneous motor features of parkinsonism

3. Features supportive of the diagnosis are
 - a) Repeated falls
 - b) Syncope
 - c) Transient loss of consciousness
 - d) Neuroleptic sensitivity
 - e) Systematized delusions
 - f) Hallucinations in other modalities

4. A diagnosis of DLB is less likely in the presence of
 - a) Stroke disease, evident as focal neurologic signs or on brain imaging
 - b) Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture.

RATING SCALES

A-7. The Beck Depression Inventory

Name: _____

Date: _____

On this questionnaire are a group of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling the past week, including today. Circle the number beside the statement you picked. Be sure to read all the statements in each group before making your choice.

- 1 0-I do not feel sad
 1-I feel sad
 2-I am sad all the time and I can't snap out of it
 3-I am so sad or unhappy that I can't stand it

2. 0-I am not particularly discouraged about the future
 1-I feel discouraged about the future
 2-I feel like I have nothing to look forward to
 3-I feel like the future is hopeless and that things cannot improve

3. 0-I do not feel like a failure
 1-I feel like I have failed more than the average person
 2-As I look back in my life, all I can see is a lot of failures
 3-I feel like I am a complete failure as a person

4. 0-I get as much satisfaction out of things as I used to
 1-I don't enjoy things the way I used to
 2-I don't get real satisfaction out of anything anymore
 3-I am dissatisfied or bored with everything

- 5 0-I don't feel particularly guilty
 1-I feel guilty a good part of the time
 2-I feel guilty most of the time
 3-I feel guilty all of the time

6. 0-I don't feel I am being punished
 1-I feel I may be punished
 2-I expect to be punished
 3-I feel I am being punished

7. 0-I don't feel disappointed in myself
 1-I am disappointed in myself
 2-I am disgusted with myself
 3-I hate myself

8. 0-I don't feel I am any worse than anybody else
 1-I am critical of myself for my weakness or mistakes
 2-I blame myself all the time for my faults
 3-I blame myself for everything bad that happens
9. 0-I don't have thoughts of killing myself
 1-I have thoughts of killing myself, but would not carry them out
 2-I would like to kill myself
 3-I would kill myself if I had the chance
10. 0-I don't cry any more than usual
 1-I cry more now than I used to
 2-I cry all the time now
 3-I used to be able to cry, but now I can't cry even though I want to
11. 0-I am no more irritated now than I ever am
 1-I get annoyed or irritated more easily than I used to
 2-I feel irritated all the time now
 3-I don't get irritated at all by the things that used to irritate me
12. 0-I have not lost interest in other people
 1-I am less interested in other people than I used to be
 2-I have lost most of my interest in other people
 3-I have lost all my interest in other people
13. 0-I make decisions about as well as I ever could
 1-I put off making decisions more than I used to
 2-I have greater difficulty in making decisions than before
 3-I can't make decisions at all anymore
14. 0-I don't feel I look any worse than I used to
 1-I am worried that I am looking old or unattractive
 2-I feel that there are permanent changes in my appearance that make me look unattractive
 3-I believe that I look ugly
15. 0-I can work as well as before
 1-It takes an extra effort to get started at doing something
 2-I have to push myself very hard to do something
 3-I can't do any work at all
16. 0-I can sleep as well as usual
 1-I don't sleep as well as I used to
 2-I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
 3-I wake up several hours earlier than I used to and cannot get back to sleep
17. 0-I don't get more tired than usual
 1-I get tired more easily than I used to
 2-I get tired from doing almost anything
 3-I am too tired to do anything

18. 0-My appetite is no worse than usual
1-My appetite is not as good as it used to be
2-My appetite is much worse now
3-I have no appetite at all anymore
19. 0-I haven't lost much weight, if any, lately
1-I have lost more than 5 pounds
2-I have lost more than 10 pounds
3-I have lost more than 15 pounds
I am purposely trying to lose weight by eating less
Yes _____ No _____
20. 0-I am no more worried about my health than usual
1-I am worried about physical problems such as aches and pains; or upset stomach; or constipation
2-I am very worried about physical problems and it's hard to think of much else
3-I am so worried about my physical problems that I cannot think about anything else
21. 0-I have not noticed any recent change in my interest in sex
1-I am less interested in sex than I used to be
2-I am much less interested in sex now
3-I have lost interest in sex completely

A-8. Hamilton Rating Scale for Depression

1. **DEPRESSED MOOD (Sad, hopeless, helpless, worthless)**
 - 0 = Absent
 - 1 = These feelings stated only on questioning
 - 2 = These feelings stated spontaneously reported verbally
 - 3 = Communicates feeling states non-verbally-i.e. through facial expression, posture, voice, and a tendency to weep.
 - 4 = Patient reports VIRTUALLY ONLY these feelings states in his spontaneous verbal and non-verbal communication.

2. **FEELINGS OF GUILT**
 - 0 = Absent
 - 1 = Self-reproach, feels he/she has let people down
 - 2 = Ideas of guilt or rumination over past errors or sinful deeds
 - 3 = Present illness is punishment. Delusions of guilt.
 - 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3. **SUICIDE**
 - 0 = Absent
 - 1 = Feels life is not worth living
 - 2 = Wishes he/she were dead, or any thoughts of possible death to self
 - 3 = Suicide, ideas or half-hearted attempt
 - 4 = Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA, EARLY**
 - 0 = No difficulty falling asleep
 - 1 = Complaints of occasional difficulty in falling asleep i.e. more than half-hour
 - 2 = Complaints of nightly difficulty falling asleep

5. **INSOMNIA, MIDDLE**
 - 0 = No difficulty
 - 1 = Patient complains of being restless and disturbed during the night
 - 2 = Walking during the night – any getting out of bed rates 2 (except voiding bladder)

6. **INSOMNIA, LATE**
 - 0 = No difficulty
 - 1 = Waking in the early hours of the morning but goes back to sleep
 - 2 = Unable to fall asleep again if he/she gets out of bed

7. **WORK AND ACTIVITIES**

- 0 = No difficulty
- 1 = Thoughts and feelings of incapacity related to activities: work or hobbies
- 2 = Loss of interest in activity – hobbies or work – either directly reported by patient or indirectly seen in listlessness, in decisions and vacillation (feels he/she has to push self to work or activities)
- 3 = 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
- 4 = Stopped working because of present illness. In hospital rate 4 if patient engages in no activities except supervised ward chores

8. **RETARDATION**

Slowness of thought and speech; impaired ability to concentrate; decreased motor activity

- 0 = Normal speech and thought
- 1 = Slight retardation at interview
- 2 = Obvious retardation at interview
- 3 = Interview difficult
- 4 = Complete stupor

9. **AGITATION**

- 0 = None
- 1 = Fidgetiness
- 2 = Playing with hands, hair, obvious restlessness
- 3 = Moving about; can't sit still
- 4 = Hand wringing, nail biting, hair pulling, biting of lips

10. **ANXIETY, (PSYCHOLOGICAL)**

- 0 = No difficulty
- 1 = subjective tension and irritability
- 2 = Worrying about minor matters
- 3 = Apprehension attitude apparent in face or speech
- 4 = Fears expressed without questioning

11. **ANXIETY, SOMATIC:** Physiological concomitants of anxiety: (i.e. effects of autonomic over-activity, "butterflies", indigestion, stomach cramps, belching, diarrhoea, palpitations, hyperventilation, paraesthesia, sweating, flushing tremor headache, urinary frequency). Avoid asking about possible medication effects (i.e. dry mouth, constipation).

- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Incapacitating

12. **SOMATIC SYMPTOMS: GASTROINTESTINAL**

0 = None

1 = Loss of appetite but eating without encouragement from others.
Food intake about normal.

2 = Difficulty in eating without urging from others. Marked reduction in
appetite and food intake.

13. **SOMATIC SYMPTOMS: GENERAL**

0 = None

1 = Heaviness in limbs, back or head; backaches, headaches, muscle
aches, loss of energy, fatigability

2 = Any clear-cut symptom rates 2

14. **GENITAL SYMPTOMS** (Symptoms such as: loss of libido, impaired sexual
performance, menstrual disturbances)

0 = Absent

1 = Mild

2 = Severe

15. **HYPOCHONDRIASIS**

0 = Not present

1 = Self-absorption (bodily)

2 = Preoccupation with health

3 = Frequent complaints, requests for help etc

4 = Hypochondriacal delusions

16. **LOSS OF WEIGHT**

Rate either 'A' or 'B':

A When rating by history

0 = No weight loss

1 = Probable weight loss associated with present illness

2 = Definite (according to patient) weight loss

B On weekly ratings by ward psychiatrist, when actual weight changes are
measured

0 = Less than 1 lb (0.5 kg) weight loss in one week

1 = 1-2 lb (0.5 kg-1.0 kg) weight loss in week

2 = Greater than 2 lb (1 kg) weight loss in week

3 = Not assessed

17. **INSIGHT**

0 = Acknowledges being depressed and ill

1 = Acknowledges illness but attributes cause to bad food, overwork,
virus, need for rest, etc.

2 = Denies being ill at all

18. **DIURNAL VARIATION**

A Rate whether symptoms are worse in the morning or evening. If NO diurnal variation mark none:

- 0 = No variation
- 1 = Worse in A.M.
- 2 = Worse in P.M.

B When present mark the severity of the variation. Mark "None" if no variation

- 0 = None
- 1 = Mild
- 2 = Severe
- 3 = Not assessed

19. **DEPERSONALISATION AND DEREALIZATION** (Such as: feelings of unreality; nihilistic ideas)

- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Incapacitating

20. **PARANOID SYMPTOMS**

- 0 = None
- 1 = Suspicious
- 2 = Ideas of reference
- 3 = Delusions of reference and persecution

21. **OBSESSIVE AND COMPULSIVE SYMPTOMS**

- 0 = Absent
- 1 = Mild
- 2 = Severe

18. **DIURNAL VARIATION**

A Rate whether symptoms are worse in the morning or evening. If NO diurnal variation mark none:

- 0 = No variation
- 1 = Worse in A.M.
- 2 = Worse in P.M.

B When present mark the severity of the variation. Mark "None" if no variation

- 0 = None
- 1 = Mild
- 2 = Severe
- 3 = Not assessed

19. **DEPERSONALISATION AND DEREALIZATION** (Such as: feelings of unreality; nihilistic ideas)

- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Incapacitating

20. **PARANOID SYMPTOMS**

- 0 = None
- 1 = Suspicious
- 2 = Ideas of reference
- 3 = Delusions of reference and persecution

21. **OBSessional AND COMPULSIVE SYMPTOMS**

- 0 = Absent
- 1 = Mild
- 2 = Severe

A-9. The Mini-Mental State Exam

Patient _____

Examiner _____

Date _____

Maximum Score

Orientation

- 5 () What is the (year) (season) (date) (day) (month)?
- 5 () Where are we (state) (country) (town) (hospital) (floor)?

Registration

- 3 () Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record.
Trials _____

Attention and Calculation

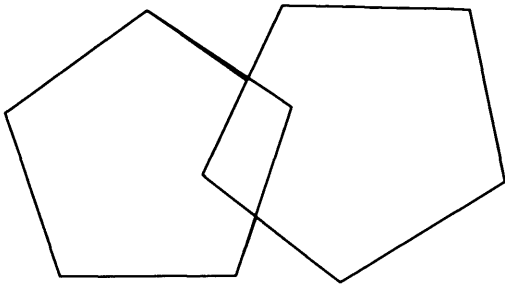
- 5 () Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.

Recall

- 3 () Ask for the 3 objects repeated above. Give 1 point for each correct answer.

Language

- 2 () Name a pencil and watch.
- 1 () Repeat the following "No ifs, ands, or buts"
- 3 () Follow a 3-stage command:
"Take a paper in your hand, fold it in half, and put it on the floor."
- 1 () Read and obey the following: CLOSE YOUR EYES
- 1 () Write a sentence.
- 1 () Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert

Drowsy Stupor

Coma

A-10. Leeds Sleep Evaluation Questionnaire

Leeds Sleep Evaluation Questionnaire:

I. How would you compare getting to sleep with getting to sleep normally?

1.

Harder than usual	About the same	Easier than usual
_____	_____	_____

2.

Slower than usual	About the same	Quicker than usual
_____	_____	_____

3.

Felt less drowsy than usual	About the same	Felt more drowsy than usual
_____	_____	_____

II. How would you compare the quality of sleep compared to you usual sleep?

4.

More restless than usual	About the same	Less restless than usual
_____	_____	_____

5.

More periods of wakefulness than usual	About the same	More periods of wakefulness than usual
_____	_____	_____

III. How does your awakening compare to your usual pattern of awakening?

6.

More difficult than usual	About the same	Less difficult than usual
_____	_____	_____

7.

Took longer than usual	About the same	Took shorter than usual
_____	_____	_____

IV. How did you feel on waking?

8.

More tired
than usual

About
the same

More alert
than usual

--	--	--

V. How do you feel now?

9.

More tired
than usual

About
the same

More alert
than usual

--	--	--

VI. How was your sense of balance and coordination upon getting up?

10.

More clumsy
than usual

About
the same

Less clumsy
than usual

--	--	--

VII. What is your level of alertness compared to usual?

11.

More alert
than usual

About
the same

More drowsy
than usual

--	--	--

VII. Are you experiencing any confusion?

12.

More confused
than usual

About
the same

Less confused
than usual

--	--	--

A-11. Sleep diary

SLEEP DIARY TO BE COMPLETED BY PATIENT - WITH THE HELP OF THE CARER.

Please write down all times in hours and minutes.

Week Please enter date here: -----	Did you take the melatonin / placebo? Please ring	What time did you go to bed?	How long were you awake before falling asleep?	How many times do you think you woke during the night ?	What time did you eventually wake up?	What time did you get up out of bed?	COMMENTS Please write any additional information you think may be useful in the spaces below. Include any possible side effects from medication:
Day 1	YES/NO						
Day 2	YES/NO						
Day 3	YES/NO						
Day 4	YES/NO						
Day 5	YES/NO						
Day 6	YES/NO						
Day 7	YES/NO						

SUPPLEMENTARY DATA

A-12. BDI Scores: completers and ITT data: melatonin in depression.

BDI Scores comparing completers and intention to treat data: melatonin in depression.

The numbers (n) for the intention to treat are not presented for convenience of space. In the ITT groups n = 15 for melatonin and n = 16 for placebo group. Means (\bar{x}_m) for melatonin and (\bar{x}_p) for placebo are also given along with standard deviations (SD).

	Melatonin						Placebo			
	<i>Completers</i>			<i>Intention to Treat</i>			<i>Completers</i>		<i>Intention to Treat</i>	
	n	\bar{x}_m	SD	\bar{x}_m	SD	n	\bar{x}_p	SD	\bar{x}_p	SD
BDI Score										
Week 0 (Baseline)	15	26.2	± 10.9	25.2	± 11.4		24.1	± 7.3	25.2	± 7.9
Week 1	14	24.3	± 10.8	23.4	± 11.1	16	22.2	± 7.9	23.0	± 9.4
Week 2	13	22.6	± 11.8	21.7	± 11.8	15	22.8	± 6.5	23.5	± 8.6
Week 3	13	21.0	± 11.6	20.3	± 11.6	12	22.9	± 8.5	23.6	± 9.9
Week 4	14	20.9	± 11.8	20.2	± 11.7	12	22.0	± 7.1	22.8	± 9.0
Week 5 (Washout)	14	19.1	± 11.8	18.5	± 11.6	12	20.7	± 7.9	21.7	± 9.6

A-13. HDRS Scores: completers and ITT data: melatonin in depression.

HDRS Scores comparing completers and intention to treat data: melatonin in depression.

The numbers (n) for the intention to treat are not presented for convenience of space. In the ITT groups n = 15 for melatonin and n = 16 for placebo group. Means (\bar{x}_m) for melatonin and (\bar{x}_p) for placebo are also given along with standard deviations (SD).

HDRS Score	Melatonin					Placebo				
	Completers			Intention to Treat		Completers			Intention to Treat	
	n	\bar{x}_m	SD	\bar{x}_m	SD	n	\bar{x}_p	SD	\bar{x}_p	SD
Week 0 (Baseline)	15	17.2	± 6.1	16.8	± 6.1	16	18.0	± 3.0	18.8	± 3.5
Week 1	14	16.3	± 5.4	16.0	± 5.3	15	16.1	± 3.9	16.5	± 4.9
Week 4	14	13.4	± 6.9	13.3	± 6.7	12	13.7	± 4.8	14.7	± 5.8
Week 5 (Washout)	14	15.1	± 8.1	14.9	± 7.9	13	13.8	± 6.1	14.6	± 6.6

A-14. LSEQ comparing data: completers and ITT data: melatonin in depression.

LSEQ comparing data for completers only and intention to treat data: melatonin in depression.

The numbers (n) for the intention to treat are not presented for convenience of space. In the ITT groups n = 15 for melatonin and n = 16 for placebo group. Means (\bar{x}_m) for melatonin and (\bar{x}_p) for placebo are also given along with standard deviations (SD). Units are given as a measurement in cm on a 10cm visual analogue scale.

	Melatonin					Placebo				
	Completers		Intention to Treat			Completers		Intention to Treat		
	n	\bar{x}_m	SD	\bar{x}_m	SD	n	\bar{x}_p	SD	\bar{x}_p	SD
Getting to sleep										
Week 0 (Baseline)	15	3.5	± 2.1	3.5	± 2.1	16	3.6	± 1.9	3.6	± 1.9
Week 1	14	5.1	± 2.1	5.0	± 2.1	15	5.6	± 1.2	5.3	± 1.7
Week 2	13	4.9	± 1.5	5.0	± 1.8	12	4.9	± 2.4	4.7	± 2.3
Week 3	13	5.6	± 1.2	5.6	± 1.6	12	4.8	± 1.4	4.6	± 1.6
Week 4	14	6.1	± 1.1	5.8	± 1.4	12	4.9	± 1.6	4.7	± 1.8
Week 5 (Washout)	14	5.4	± 1.2	5.2	± 1.4	13	4.5	± 2.1	4.4	± 2.1
Quality of sleep										
Week 0 (Baseline)	15	3.2	± 1.9	3.2	± 1.9	16	3.4	± 2.0	3.4	± 2.0
Week 1	14	4.3	± 2.0	4.4	± 2.0	15	5.3	± 1.5	5.0	± 1.9
Week 2	13	4.5	± 1.8	4.5	± 1.7	12	4.5	± 2.1	4.3	± 2.2
Week 3	13	5.3	± 1.6	5.2	± 1.5	12	4.5	± 2.4	4.3	± 2.3
Week 4	14	5.2	± 2.1	5.2	± 2.1	12	4.9	± 1.7	4.6	± 1.9
Week 5 (Washout)	14	4.5	± 2.4	4.6	± 2.4	13	5.0	± 2.2	4.8	± 2.3
Awakenings										
Week 0 (Baseline)	15	4.1	± 2.0	4.1	± 2.0	16	4.2	± 1.9	4.2	± 1.9
Week 1	14	3.8	± 1.8	3.9	± 1.8	15	4.8	± 1.8	4.9	± 1.7
Week 2	13	3.9	± 0.9	4.0	± 0.9	12	4.2	± 1.4	3.9	± 1.5
Week 3	13	4.4	± 1.7	4.4	± 1.6	12	4.2	± 1.6	4.0	± 1.7
Week 4	14	4.7	± 1.4	4.7	± 1.3	12	3.7	± 1.4	3.6	± 1.5
Week 5 (Washout)	14	4.9	± 1.9	4.9	± 1.8	13	4.6	± 1.3	4.3	± 1.6
Behaviour following wakefulness										
Week 0 (Baseline)	15	4.7	± 1.6	4.7	± 1.6	16	3.9	± 1.5	3.9	± 1.5
Week 1	14	4.7	± 2.2	4.7	± 2.1	15	4.9	± 1.2	4.6	± 1.6
Week 2	13	4.2	± 1.4	4.6	± 2.1	12	4.6	± 0.9	4.3	± 1.5
Week 3	13	4.9	± 1.5	5.3	± 2.0	12	4.5	± 1.4	4.3	± 1.7
Week 4	14	5.3	± 1.4	5.2	± 1.4	12	4.3	± 1.5	4.1	± 1.8
Week 5 (Washout)	14	4.9	± 1.8	4.9	± 1.8	13	4.1	± 1.3	3.9	± 1.7

A-15. Actigraph data: comparison of completers and ITT data: melatonin in depression.

Actigraph data: completers and intention to treat data: melatonin in depression.

The numbers (n) for the intention to treat are not presented for convenience of space. In the ITT groups n = 15 for melatonin and n = 16 for placebo group. Means (\bar{x}_m) for melatonin and (\bar{x}_p) for placebo are given along with standard deviations (SD).

	Melatonin				Placebo					
	Completers n	mean	SD	Intention to Treat mean	SD	Completers n	mean	SD	Intention to Treat mean	SD
Time in bed										
Week 0 (Baseline)	13	499.3	± 76.6	499.1	± 67.9	14	473.7	± 106.7	473.7	± 99.3
Week 1	14	519.9	± 82.5	518.5	± 79.7	13	502.6	± 84.6	511.9	± 91.8
Week 4	12	490.7	± 84.8	499.0	± 82.0	13	487.8	± 47.1	492.6	± 73.8
Week 5 (Washout)	9	477.7	± 99.6	507.8	± 105.6	12	485.1	± 30.6	486.5	± 69.8
Sleep latency										
Week 0 (Baseline)	13	39.8	± 36.0	39.8	± 31.2	14	21.9	± 17.1	21.9	± 17.1
Week 1	14	28.1	± 26.4	26.9	± 25.9	13	26.1	± 24.1	23.4	± 23.2
Week 4	12	34.1	± 27.3	33.3	± 31.9	13	34.9	± 24.9	28.9	± 24.3
Week 5 (Washout)	9	25.6	± 27.1	35.6	± 36.1	12	37.9	± 32.1	31.7	± 29.8
Wake after sleep onset										
Week 0 (Baseline)	13	76.0	± 40.6	76.0	± 37.4	14	47.6	± 28.3	47.6	± 28.3
Week 1	14	73.9	± 38.4	74.7	± 37.1	13	57.5	± 35.9	53.8	± 34.7
Week 4	12	72.3	± 43.3	70.4	± 39.5	13	45.5	± 37.0	44.4	± 32.0
Week 5 (Washout)	9	68.8	± 47.8	77.9	± 44.8	12	49.2	± 36.0	43.9	± 32.6
Total sleep time										
Week 0 (Baseline)	13	370.7	± 56.2	370.7	± 49.8	14	391.2	± 107.8	391.7	± 107.8
Week 1	14	399.5	± 65.0	399.0	± 62.7	13	407.6	± 62.1	422.5	± 89.1
Week 4	12	378.7	± 54.1	385.0	± 49.8	13	391.5	± 67.8	401.9	± 89.8
Week 5 (Washout)	9	372.0	± 97.1	384.9	± 83.4	12	384.1	± 79.8	394.8	± 100.9
Number of awakenings										
Week 0 (Baseline)	13	29.7	± 14.0	29.7	± 12.3	14	24.1	± 9.4	24.1	± 8.7
Week 1	14	28.9	± 12.2	30.4	± 13.1	13	26.3	± 13.7	26.4	± 12.7
Week 4	12	29.0	± 14.5	28.5	± 13.1	13	25.0	± 15.3	23.8	± 11.9
Week 5 (Washout)	9	26.7	± 14.6	29.3	± 15.5	12	24.2	± 12.4	22.3	± 11.3
Movement index										
Week 0 (Baseline)	13	847.4	± 542.7	847.4	± 481.0	14	617.1	± 328.2	617.1	± 305.6
Week 1	14	919.1	± 517.1	891.9	± 509.3	13	623.9	± 346.6	684.6	± 339.1
Week 4	12	745.5	± 334.3	722.5	± 310.7	13	638.4	± 387.1	611.0	± 375.0
Week 5	9	765.6	± 398.9	790.8	± 371.9	12	692.8	± 460.1	664.4	± 448.6
Sleep efficiency %										
Week 0 (Baseline)	13	74.9	± 10.0	74.7	± 8.8	14	82.1	± 7.5	82.1	± 7.5
Week 1	14	77.5	± 10.8	77.5	± 10.4	13	81.8	± 8.8	82.8	± 8.9
Week 4	12	72.7	± 21.1	78.1	± 9.5	13	80.3	± 13.1	81.2	± 12.0
Week 5 (Washout)	9	77.8	± 10.7	76.3	± 10.6	12	79.0	± 16.2	80.6	± 14.6

A-16. Melatonin in dementia trial: Source of referral by site

Source of referral	Site	Number referred	Suitable	In the study
Old age psychiatry	RFH	230	13	7
	St Ch	1	1	1
PAS List	RFH	84	0	0
	St Ch	0	0	0
Flyer	RFH	55	1	1
	St Ch	0	0	0
Homes	RFH	25	21	20
	St Ch	23	11	7
GP	RFH	38	2	2
	St Ch	0	0	0
Adverts	RFH	29	1	0
	St Ch	0	0	0
Day centres	RFH	20	2	1
	St Ch	0	0	0
Posters	RFH	12	0	0
	St Ch	0	0	0
Hospital	RFH	4	2	2
	St Ch	7	4	3
Total	RFH	497	42	33
	St Ch	31	16	11

A-17. Actigraph (completers) data: melatonin in dementia trial.

		Actigraphy (completers) data: melatonin in dementia trial.			
		Group 1 received melatonin in period 1 and placebo in period 2 and group 2 received placebo in period 1 and melatonin in period 2 (Medians are given with Quartiles ranges in parentheses and where appropriate time is given in minutes)			
	Baseline	Period 1	Washout 1	Period 2	Washout 2
Number					
Group 1	16	17 (M)	13	16 (P)	15
Group 2	14	14 (P)	15	14 (M)	13
TIB					
Group 1	551.7 (524.7-610.0)	513.0 (451.2-594.5)	491.7 (436.5-628.6)	555.0 (438.2-605.8)	575.0 (475.7-636.0)
Group 2	492 (414.4-545.7)	485.0 (424.7-543.2)	498.3 (455.0-570.0)	541.7 (494.9-599.9)	514.6 (460.8-624.5)
SL					
Group 1	29.8(10.4-50.3)	19.5 (6.2-44.0)	20.3 (10.0-52.5)	23.0 (10.5-42.6)	30.7 (16.0-47.0)
Group 2	22.2 (10.7-63.7)	30.0 (16.7-52.6)	24.0 (2.3-62.3)	20.7 (10.7-46.7)	63.7 (19.0-95.2)
WSO					
Group 1	84.3 (42.5-99.6)	42.0 (25.5-63.7)	90.0 (51.5-111.6)	53.3 (36.0-96.2)	57.0 (20.7-70.5)
Group 2	58.2 (39.5-120.1)	77.0 (51.1-126.1)	81.0 (74.3-103.0)	83.0 (55.2-131.2)	80.7 (54.7-156.8)
TST					
Group 1	429.8 (297.7-477.1)	399.0 (308.8-458.7)	344.3 (262.2-376.2)	406.7 (309.7-493.2)	418.0 (350.3-476.0)
Group 2	350.8 (234.3-404.5)	318.0 (277.4-438.2)	(202.2-485.0)	(280.4-495.0)	335.5 (214.5-430.0)
MI					
Group 1	1105.0 (773.2-2042.3)	1091.6(498.2-1778.3)	1706.0(841.6-2511.2)	1400.2(475.2-1969.0)	1187.3 (534.7-2769.3)
Group 2	1490.0 (1060.8-1797.8)	1409.2 (847.9-1713.9)	1768.7 (966.0-2816.0)	1328.9 (836.2-1585.5)	1869.0(1213.0- 2442.7)
NWA					
Group 1	13.2 (8.5-18.8)	11.0 (3.8-18.8)	13.3 (7.4-19.2)	13.8 (8.5-16.8)	13.5 (4.0-26.0)
Group 2	13.0 (8.0-17.5)	14.0 (10.4-19.7)	15.3 (13.0-22.0)	14.7 (12.0-21.4)	16.0 (11.1-21.2)
SE					
Group 1	74.1 (61.7-83.3)	80.5 (72.5-85.0)	72.7 (57.5-85.0)	78.0 (70.7-89.4)	75.0 (62.5-86.5)
Group 2	70.3 (64.6-76.7)	68.0 (62.2-78.7)	66.0 (41.0-81.0)	74.7 (53.0-83.5)	63.3 (44.0-76.2)

A-18. Actigraph (completers) data: Mann Whitney U; sum & difference scores: melatonin in dementia

	Period 1 - Baseline (Treatment effect)		Period 1 + Period 2 (Carry over effect)		Period 1 - Period 2 (Treatment effect)				
	MW-U	Z score	P value	MW-U	Z score	P value	MW-U	Z score	P value
TIB	59.0	-1.51	0.13	85.0	-0.24	0.80	66.5	-1.15	0.05
SL	57.0	-1.60	0.11	78.0	-0.59	0.57	50.5	-1.93	0.05
WSO	55.0	-1.71	<0.08	58.0	-1.56	0.56	70.0	-0.98	0.33
TST	86.5	-0.17	0.86	78.0	-0.59	0.56	61.0	-1.41	0.16
MI	83.0	-0.34	0.19	90.0	-0.00	1.00	67.0	-1.12	0.26
NWA	63.0	-1.32	0.19	67.0	-1.12	0.26	86.5	-0.17	0.86
SE	75.5	-0.71	0.48	68.5	-1.05	0.29	68.0	-1.07	0.28

Statistical analysis is represented in the text. Actigraphy data is given according to the following: TIB = Time in bed, SL = Sleep latency, WSO = Wake after sleep onset, TST = Total sleep time, NWA = Number of awakenings, MI = Movement index, SE = Sleep efficiency %.

A-19. Actigraphy (completers data): Mann Whitney U analysis for difference scores (period 1 – baseline and period 2 – first washout) Taking into account stacked data for crossover trial.

	Melatonin or Placebo	Numbers	Mean Rank	MW-U	Z score	P value
Time in Bed	Melatonin	28	25.9	319.5	-0.30	0.76
	Placebo	24	27.2			
	Total	52				
Sleep latency	Melatonin	28	24.1	270.0	-1.21	0.23
	Placebo	24	29.2			
	Total	52				
Wake after sleep onset	Melatonin	28	26.7	329.5	-1.12	0.90
	Placebo	24	26.2			
	Total	52				
Total Sleep Time	Melatonin	28	26.4	333.0	-0.06	0.96
	Placebo	24	26.6			
	Total	52				
Movement Index	Melatonin	28	25.1	297.0	-0.72	0.47
	Placebo	24	28.1			
	Total	52				
Mean Number of Awakenings	Melatonin	28	26.1	325.5	-0.19	0.85
	Placebo	24	26.9			
	Total	52				
Sleep Efficiency	Melatonin	28	27.0	321.5	-0.27	0.79
	Placebo	24	25.9			
	Total	52				

A-20. Completers data for sleep diary and LSEQ: melatonin in dementia trial.

Group 1 received melatonin in period 1 and placebo in period 2 and group 2 received placebo in period 1 and melatonin in period 2 (Medians are given with Quartiles ranges in parentheses).					
	Baseline	Period 1	Washout 1	Period 2	Washout 2
Group 1	18	20 (M)	19	17 (P)	17 (P)
Group 2	19	17 (P)	16	17 (M)	17 (M)
Sleep Diary					
Time to sleep (Mins)					
Group 1	37.4 (24.0-76.0)	33.5 (24.5-57.4)	30.0 (20.7-55.0)	34.3 (20.4-54.8)	24.3 (13.8-47.3)
Group 2	39.3 (25.0-77.5)	55.4 (29.3-90.7)	40.1 (14.2-77.1)	48.9 (21.2-76.2)	33.6 (15.5-68.0)
Number of awakenings					
Group 1	2.00 (1.22-2.63)	1.81 (1.22-2.34)	1.73 (0.61-2.02)	1.70 (0.61-2.02)	1.55 (0.73-2.95)
Group 2	1.62 (1.00-2.19)	1.60 (1.11-1.99)	1.55 (1.30-2.00)	1.44 (1.04-1.93)	1.59 (1.00-2.68)
LSEQ					
Group 1	10	9 (M)	7	9 (P)	8
Group 2	7	8 (P)	7	8 (M)	7
GTS					
Group 1	47.4 (42.5-62.8)	52.2 (42.2-69.8)	53.7 (37.5-54.4)	58.6 (42.4-60.6)	50.2 (41.8-58.5)
Group 2	54.1 (38.3-62.6)	54.8 (45.3-69.0)	47.2 (44.4-62.8)	58.5 (46.4-81.7)	52.0 (46.7-53.3)
QOS					
Group 1	48.0 (35.4-65.6)	57.7 (33.6-63.7)	60.7 (35.2-64.2)	65.3 (40.1-57.3)	59.2 (40.2-57.3)
Group 2	47.1 (36.2-65.1)	57.8 (47.7-74.1)	50.4 (41.9-67.0)	78.0 (46.9-86.6)	64.3 (49.4-79.2)
AFS					
Group 1	50.5 (40.2-57.3)	49.7 (31.0-55.5)	51.5 (45.9-64.2)	54.5 (38.5-65.2)	52.3 (35.8-66.3)
Group 2	58.8 (42.8-66.7)	47.0 (41.2-71.1)	42.5 (33.0-60.0)	48.8 (23.1-75.5)	68.7 (54.9-88.0)
BFW					
Group 1	44.7 (36.1-57.2)	50.6 (38.8-62.0)	50.0 (41.0-61.5)	52.0 (36.9-64.7)	52.6 (39.4-56.4)
Group 2	49.6 (47.4-61.5)	65.8 (56.4-79.2)	57.3 (40.0-92.3)	48.7 (45.7-64.8)	48.2 (41.9-60.0)

Statistical analysis is presented in the text. Sleep evaluation questionnaire: GTS = Getting to Sleep, QOS = Quality of Sleep, AFS = Awakening from Sleep and BFW = Behaviour Following Wakefulness.

A-21. Sleep diary and LSEQ analysis: MWU and Wilcoxon for melatonin in dementia trial.

Sleep diary and LSEQ analysis: MWU and Wilcoxon scores of melatonin in dementia trial Mann Whitney U analysis for sum and difference scores for sleep diary and Wilcoxon Rank Sum Test for LSEQ for completers in whom actigraph data was available in the melatonin in dementia trial.											
	Period 1 - Baseline (Treatment effect)			Period 1 + Period 2 (Carry over effect)			Period 1 - Period 2 (Treatment effect)				
	MW-U	Z score	P value	MW-U	Z score	P value	MW-U	Z score	P value		
Sleep diary											
Time to sleep	103.5	-0.35	0.78	100.0	-0.17	0.86	83.5	-1.19	0.23		
Number of awakenings	83.5	-1.18	0.23	92.0	-0.57	0.57	86.0	-0.83	0.40		
LSEQ											
GTS	69.0	-0.35	0.72	52.0	-0.46	0.64	58.0	-0.69	0.49		
QOS	67.0	-1.06	0.31	61.0	-0.53	0.72	52.0	-0.46	0.64		
AFS	59.0	-0.13	0.90	36.0	-0.86	0.39	35.0	-1.0	0.31		
BFW	72.0	-0.47	0.63	51.0	-0.19	0.84	37.0	-2.0	0.05		

