The sleep of stable bipolar outpatients: a controlled naturalistic study using actigraphy

& Research Portfolio

PART ONE
(Part two bound separately)

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31st July 2001

ACKNOWLEDGEMENTS

I am extremely grateful to everyone who participated in my study for their time and effort. I am also indebted to everyone from the various Community Mental Health Teams, and psychiatric outpatients departments who helped me recruit by identifying potentially suitable subjects. Particular thanks are due to Catherine Hamilton, Community Psychiatric Nurse at Riverside Resource Centre, Glasgow; and to Dr Martin Livingston, Consultant Psychiatrist, and the rest of the team at the psychiatric outpatient clinic based at Southern General Hospital, Glasgow.

Thanks are due to my Research Supervisor, Professor Colin Espie, for his encouragement and for comments on drafts of the thesis.

I would also like to thank "Study Group" for support over the last three years, and my friends and family for their patience and encouragement.

Finally, I would especially like to thank Robert, for all his support during the preparation of this thesis, for many helpful discussions of the ideas involved, and for persuading me to persist in applying to Clinical Training in the first place.

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CHAPTER 1:
SMALL-SCALE SERVICE RELATED RESEARCH PROJECT

Allocation to group therapy for anxiety: what issues do clinical psychologists think are important?

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Prepared in accordance with guidelines for submission to *Health Bulletin* (Appendix 1.1)

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ABSTRACT

Objective: To determine which issues clinical psychologists think are important in decisions about allocating patients to anxiety management groups, and to determine whether they are in agreement about the allocation of patients.

Design: A survey design by questionnaire was implemented.

Setting: Trust primary health care settings in all sectors of Glasgow.

Participants: Thirty-five qualified clinical psychologists working in adult mental health within Glasgow Trust were surveyed. Twenty-three responded and were included.

Results: The majority (74%) thought anxiety management groups were useful, and could be used as the sole intervention in some cases.

In decisions about allocation the patient's presentation (ie nature and chronicity of anxiety) and some practical issues, such as the likely mix of people in the group, were rated as being important. Demographic variables (eg age, occupation) were relatively unimportant in the decision. Clinicians were less likely to include patients with a severe level of anxiety (as opposed to mild/ moderate), and those whose problem had been present for more than three years. Comorbid problems most likely to lead to exclusion from groups were severe depression, substance or alcohol abuse, current criminal behaviour, and personality disorder. However there was a wide range of opinions about appropriate inclusion, which was also reflected in clinicians' decisions about particular cases (based on case vignettes).

Conclusion: The wide range of opinion perhaps demonstrates the need for standardisation. Further outcome research aimed at identifying those who benefit most from group management would allow criteria for allocation to be outlined.

INTRODUCTION

CBT (Cognitive Behaviour Therapy) techniques have been shown to be effective in the management of Generalised Anxiety Disorder (GAD), specific phobias and panic disorder with/ without agoraphobia[1,2,3], and the common focus on education/ information and cognitive-behavioural techniques for symptom management make treatment of anxiety disorders an area where group management is appropriate. Groups based on a cognitive-behavioural model of anxiety disorders incorporate elements such as education/ information about anxiety, applied relaxation and teaching cognitive and behavioural techniques for managing anxiety. This psycho-educational group approach has been shown to be effective, and information about anxiety and stress, and the experience of meeting others with similar problems have been identified as the most helpful components of group management[4,5]. This finding highlights the importance of non-specific therapeutic effects of groups, such as the process of "normalisation" which occurs through the opportunity to "share problems with others in the same boat"[6], and also through learning about anxiety and panic.

In recent years pressure of waiting lists, and the imbalance between demand and therapeutic resources has resulted in service development, and innovative cognitive-behavioural practices such as group therapies and self-help packages have become increasingly prevalent.[7,8] In addition to the therapeutic effects of groups outlined above, there are clearly practical advantages to group management of anxiety problems. On a practical level, appropriate use of group management of anxiety may be advantageous, in that it may reduce waiting lists, and free up clinician time for one-to-one interventions with complex problems. However, while the use of group work may be efficient, in order to be efficacious it must be demonstrated that allocation to group therapy is appropriate in each case. The danger of misallocation is highlighted by findings on the effects of comorbidity and complexity on treatment outcome in anxious patients. Brown and Barlow[9] suggest that poorer responses to conventional treatments for anxiety disorders are likely if there is comorbid occurrence of major depression or personality disorder. Such findings highlight the need for detailed assessment of patients prior to devising a treatment plan. The implications for group management of anxiety disorders are that misallocation of patients may result in important issues and problems being missed and therefore untreated. Accurate allocation should be related to outcome, in that patients allocated to groups should be those who have potential for gaining most benefit from the group.

Outcome research to date has not attempted to describe in detail which factors mediate outcome from group treatment, and therefore no guidelines exist about which patients are suitable for inclusion in anxiety management groups. Clinical psychologists working in adult mental health make decisions daily about which patients to allocate to group management, and yet there has been no attempt to describe or formally operationalise the method of allocation. As a first stage in this process it may be useful to identify which issues clinicians think are important in decisions about allocation to anxiety management groups. The aim of this study is to identify the important issues for clinical psychologists making such decisions, and to determine whether or not clinicians are in agreement about the important issues, and about which patients should be included in group approaches.

OBJECTIVES

1. To determine clinical psychologists' views on the usefulness of different elements of anxiety management groups.
2. To determine which issues clinicians perceive as important in deciding to allocate patients to anxiety management groups.
3. To determine the extent to which clinicians agree about which patients should be allocated to group management for anxiety.

METHODS

Setting: Trust primary health care settings in all sectors of Glasgow.

Design: A survey method was used and participants were asked to complete a questionnaire, which contained open-ended and structured questions.

***Participants*:** All qualified clinical psychologists involved in primary care, in all four sectors of the Glasgow Trust were sampled (35 were given questionnaires), and twenty-three who returned completed questionnaires were included in the study.

Procedure:

Development of the questionnaire: A questionnaire containing open-ended and structured questions was devised (Appendix 1.2). A definition of group treatment, in line with standard practice was provided in the questionnaire. The questionnaire asked for background information regarding participants' practice and experience. Clinicians were asked what size

they thought groups should be, and which elements they thought were important in groups. The questionnaire also focused on issues affecting the decision to allocate to group management. Clinicians were asked to rate (on a five point Likert type scale) the importance of different patient and group variables in the decision to allocate to group therapy. Open-ended questions provided scope for clinicians to identify other important issues, and other information which would lead them to exclude cases. Five illustrative case vignettes were devised (adapted from a range of actual cases) and included in the questionnaire. It was thought that the inclusion of case vignettes would result in greater ecological validity, in that clinicians would have to make decisions about realistic cases. Each vignette contained a brief GP referral letter, baseline scores on the Hospital Anxiety and Depression Scale, and some brief comments made by a Clinical Psychologist following first assessment (re diagnosis etc). Clinicians were asked whether they would include the patient described in an anxiety management group, and whether they thought individual therapy would be necessary in addition.

Pilot study: A pilot study was conducted in order to refine the questionnaire (Appendix 1.3).

Questionnaire analysis: The questionnaire yielded mainly descriptive data. Mean and modal ratings of the importance of a range of issues and variables can be calculated. Mean/modal ratings of the likelihood of including patients with certain characteristics or comorbid problems are also described. The inclusion of case vignettes means that the proportions of clinicians who would include and exclude certain cases can be documented, reflecting the level of agreement across cases.

RESULTS

- ***Characteristics of the respondents***

Twenty-three respondents who returned questionnaires (response rate of 66%) were included in the study. All were working in Glasgow Trust primary health care settings. The majority spent 100% of their work time in adult mental health, though five of the twenty-three spent a percentage of time in another specialty (eg addictions service, forensic service). Several respondents specified a percentage of time spent in Community Mental Health Teams (CMHTs). The vast majority (78%) predominantly adhered to a CBT model in their clinical work. Others described their approach as behavioural, as

CBT/psychodynamic or as eclectic. Twenty-one of the respondents had previous experience of working with anxiety management groups.

- ***Respondents' views on the useful elements of anxiety management groups***

The majority of respondents (74%) agreed that anxiety management groups were generally useful, and only four of the 23 thought that groups should only be used in combination with individual therapy. The majority (68%) thought that groups should include between 6 and 10 patients.

Respondents rated information/ education about anxiety and teaching cognitive and behavioural techniques for managing anxiety as the most important components. Applied relaxation was perceived as more useful than relaxation training per se. Opportunity for group members to discuss personal experiences was rated as the least important function of anxiety management groups. Ratings of the different components are illustrated in Figure 1.

Insert Figure 1

- ***Respondents' views on issues affecting the decision to allocate to groups***

Figures i – v in Appendix 1.4 illustrate in detail psychologists' ratings of the importance of a range of issues affecting allocation to groups. Together with patient's marital satisfaction and available social support, demographic variables were perceived by the sample of psychologists as the least important factors (modes of 1). The patient's level of motivation, medical history, previous referrals to psychology/ psychiatry, and the likely mix of people in the group were most frequently rated as very important in making decisions about allocation to groups (modes of 4). Level of anxiety was also rated as important (mode=4), and the chronicity of the problem as moderately important (mode=3). Figures 2 and 3 illustrate that clinicians are increasingly unlikely to include patients as the severity and duration of the patient's anxiety symptoms increase.

Insert Figures 2 and 3

- ***Respondents' views on the influence of comorbid problems/ diagnoses***

Table I shows mean and modal ratings which reflect the likelihood of patients with certain comorbid problems or disorders being included in groups.

Insert Table I

Clinicians were least likely to include patients with current substance or alcohol abuse, current criminal behaviour, borderline personality disorder, antisocial personality disorder, or severe depression. Figure 4 demonstrates that clinicians are increasingly unlikely to include patients as the patient's level of depression increases.

Insert Figure 4

They were frequently undecided about the inclusion of patients with a range of comorbid problems or disorders:- specifically bipolar disorder, obsessive-compulsive disorder (OCD), eating disorders, medical disorders, those with marked social problems or a history of sexual abuse, or those with a moderate level of depression. The problems/ diagnoses which clinicians were most likely to include patients with, were a mild level of depression, agoraphobic symptoms and social phobia. However one of the most striking features about Table I is the range of ratings apparent for most disorders/ problems.

- ***Other issues mentioned by respondents***

Respondents seemed to find the questionnaire comprehensive, in that few additional issues were highlighted. The most frequent additional reasons for excluding patients mentioned were psychotic symptoms, or the presence of brain injury. Several respondents mentioned the need to exclude anyone who would potentially disrupt the group; and within this context the need to exclude patients who met diagnostic criteria for any personality disorder, and those who were currently abusing alcohol or drugs, was emphasised again by some respondents. Other broader issues for consideration which were highlighted included the

patient's preference, the patient's history of attendance and previous experience of groups; and issues of staff motivation, staff expertise, and available resources.

- ***Respondents' views on allocation of case vignettes***

Figure 5 (a-e) illustrates the proportions of clinicians who decided to include and exclude each case within an anxiety management group, based on what they read in the vignettes. Key features of each case are listed on the figure (see Appendix 1.2 for full versions of vignettes).

Insert Figure 5a-e

Respondents were largely in agreement about case 1 - a 51 year old woman with a long history of anxiety and somatising. This was the case most likely to be allocated to group management. Opinions were more divided on the other cases; most notably on case 3 (a 33 year old man with stress symptoms and sleep disturbance relating to work pressure, and a current problem with alcohol abuse) where the respondents were split in almost equal numbers.

DISCUSSION

The majority of this sample of clinical psychologists working in adult mental health was in favour of anxiety management groups, and most of the sample had been involved in groups. It is therefore likely that the sample comprised clinicians who regularly allocated patients to groups.

Clinicians' views of the most and least useful elements of groups suggests that this sample favour the model outlined as standard practice; with applied relaxation, information/ education, and teaching of cognitive and behavioural techniques for managing anxiety as the key components of group management. The perceived lack of importance of the opportunity for group members to discuss personal experiences suggests a preference for a psycho-educational, skills-based approach to group management, rather than an approach which emphasises group processes themselves as a curative vehicle. The preference for this style of group management is consistent with the majority of respondents' adherence to a CBT model. Information and education about anxiety symptoms have been highlighted as

among the most beneficial aspects of groups[5], however, outcome research has also emphasised the therapeutic importance of "normalisation", which comes from meeting others with the same problems and sharing experiences.

In deciding to allocate patients, demographic variables, such as the patient's age and occupation, were perceived as the least important issue, however there are indications that age of the patient does have implications for treatment of anxiety, particularly where older adults are concerned.[10] Patient motivation was perceived as important, as was certain information to do with history of treatment (such as previous referrals to psychiatry/ psychology, and medical history). The patient's degree of insight and interpersonal/ communication skills were perceived as less important, and willingness to disclose in a group even less so. The ratings suggest that patients most likely to be included in group management are those most able to engage in a learning process and acquire specific skills for managing their anxiety. The ability and willingness to share experiences are not perceived as necessary patient characteristics by the majority of this sample of clinicians; and this may again reflect the preference for a predominantly psycho-educational, skills-based approach within this sample. The low ratings of the importance of marital satisfaction and social support are surprising, since it seems probable that the patients most likely to improve within a group would be those who are relatively independent and well-supported.

Ratings of the importance of group issues suggest that practical considerations such as the mix of people in the group do influence clinicians when they have to decide whether to allocate patients to group therapy. It is likely that clinical decisions about individuals involve balancing therapeutic considerations against practical issues.

In terms of comorbidity, clinicians were most likely to include patients with a mild level of depression, agoraphobic symptoms and social phobia; and least likely to include patients with severe depression, comorbid alcohol or substance abuse, borderline personality disorder or antisocial personality disorder. These decisions are in line with the limited outcome literature. For example, studies have shown that group management of anxiety may also reduce depressive symptoms where depression is mild[11], and group management of patients with agoraphobia and social phobia provides in vivo exposure, and has been shown to be effective.[12] Higher levels of depression have been shown to predict poorer outcome from cognitive-behavioural group therapy for social phobia[13] and from treatment

programs for agoraphobia and Panic Disorder.[14] Other findings with Panic Disorder patients suggest that those with major depression are less likely to recover over a two year period.[15] A diagnosis of avoidant personality disorder has been shown to predict poor response to cognitive-behavioural management of social phobia.[16,17,18] Conventional wisdom suggests that the presence of significant substance or alcohol abuse in patients (particularly where dependency is involved) precludes treatment of other disorders until issues of abuse and dependency are tackled and treated.[19] There was a great deal of uncertainty about many comorbid problems asked about, which perhaps reflects the lack of research on the effects of comorbidity on outcome.

Decisions on case vignettes to some degree reflected what clinicians as a group had already stated about important issues and factors. For example, most clinicians (70%) chose to exclude case 2, possibly because of the significant level of depression and interpersonal and social problems described. The highest level of agreement was about the suitability of case 1 (a woman with a probable diagnosis of GAD, and a history of somatising), whom the majority (91%) said was suitable for group management. The fact that clinicians as a group were prepared to allocate this case despite the somatic nature of the presentation is consistent with their ratings of the nature of the symptoms (whether somatic, behavioural, cognitive) as unimportant. Interestingly, the vignette did indicate that the problems were of chronic duration. Despite clinicians being less likely to include patients whose problems had been present for more than three years in groups the majority still chose to include this woman. This reflects the complexity of the decision making process, and suggests that clinical judgement involves the weighing up of different factors or issues.

Further evidence of the complexity of the clinical decision process is provided by the pattern of results on Case Vignettes 3 and 5. Case 5 is the only case where previous psychiatric referrals are mentioned (the woman described has a history of psychiatric problems, relationship difficulties, and one known suicide attempt, although her current presentation is with anxiety/ agoraphobic problems), and in that respect it is surprising that the majority of clinicians (78%) said this case was appropriate for group management (particularly since previous psychiatric referrals was rated as one of the most influential issues in decisions about allocation). Again, the decision probably reflects a weighing up of current difficulties against history. In addition, thirteen of the eighteen clinicians who thought the case was appropriate for a group thought individual therapy was also necessary.

Case 3 provided the greatest split of opinion in the sample. Just over half of the respondents thought the case was suitable for group management, despite the fact that binge drinking was mentioned as a feature of the case. The majority decision on this case is clearly inconsistent with the ratings of current alcohol abuse as one of the problems most likely to lead to exclusion from a group. However other than the mention of heavy drinking the case (presentation with work stress etc) does sound suitable for inclusion in an anxiety management group. In addition the case description suggests that alcohol abuse has been a problem for some time, and that current levels of drinking are not as heavy as previous levels. It is likely that this information would be part of a decision process involving weighing up the indications and contraindications for group management.

CONCLUSIONS AND IMPLICATIONS

This sample of clinical psychologists, working in adult mental health, are largely in favour of psycho-educational anxiety management groups. They rate certain issues such as patient motivation and history of treatment as more important than others (eg demographic factors) in making decisions about suitability for group management. Clinicians' ratings of the comorbid problems most and least likely to be included in groups were in line with the available literature on outcome. Greater uncertainty was apparent with problems and issues where research evidence is more limited.

However, the range of opinion within this small sample of clinicians about how comorbid problems should affect treatment, and how case vignettes should be allocated, reflects the complexity of clinical decision making and suggests a diversity of practice.

An evaluation of outcome from anxiety management groups across the Glasgow Trust would allow identification and description of treatment successes and failures, and would represent a first step towards devising guidelines for allocation.

More broadly, further outcome research aimed at identifying those who benefit most from anxiety management groups would allow some criteria for allocation to be outlined, and could result in greater standardisation.

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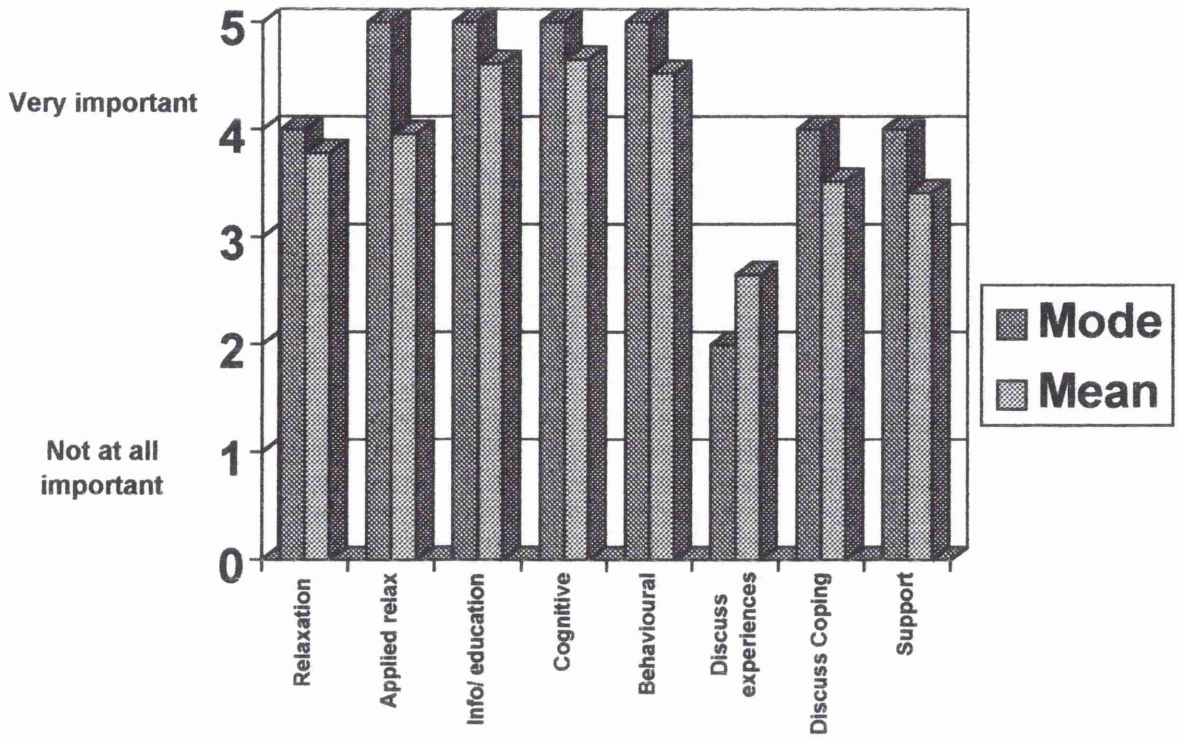
Figure 1
Clinical psychologists' ratings of the relative importance of different components of anxiety management groups



Details of components as described in questionnaire:

- Relaxation training
- Applied relaxation
- Information/ education about anxiety
- Teaching cognitive techniques for managing anxiety
- Teaching behavioural techniques for managing anxiety
- Opportunity to discuss personal experiences with group members
- Opportunity to discuss coping strategies with other group members
- Support

Figure 2
Clinicians' ratings of likelihood of including patients with increasing duration of anxiety

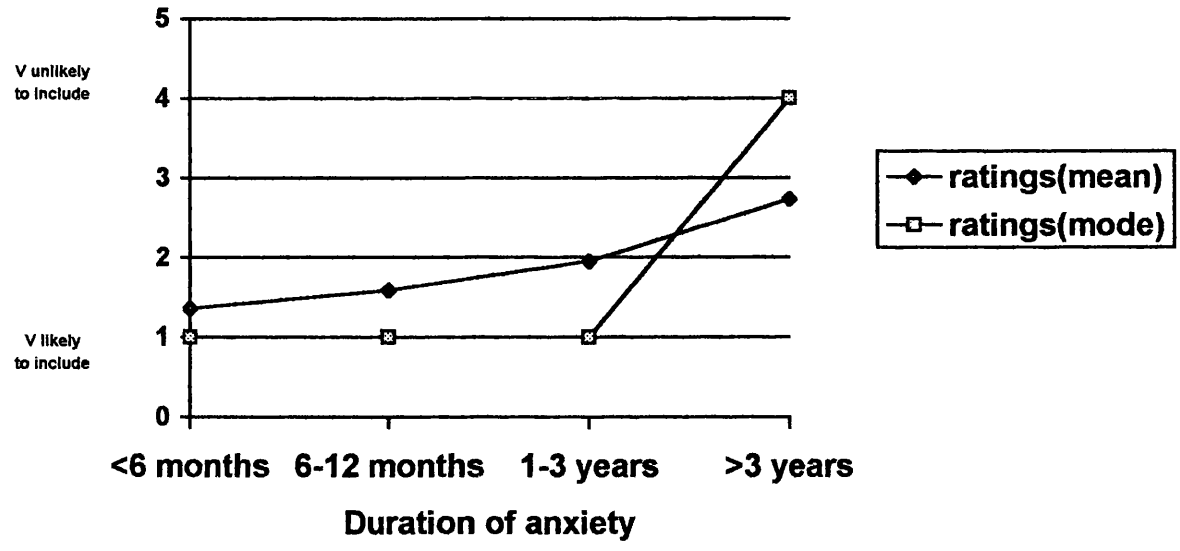


Figure 3
Clinicians' ratings of likelihood of including patients with different levels of anxiety

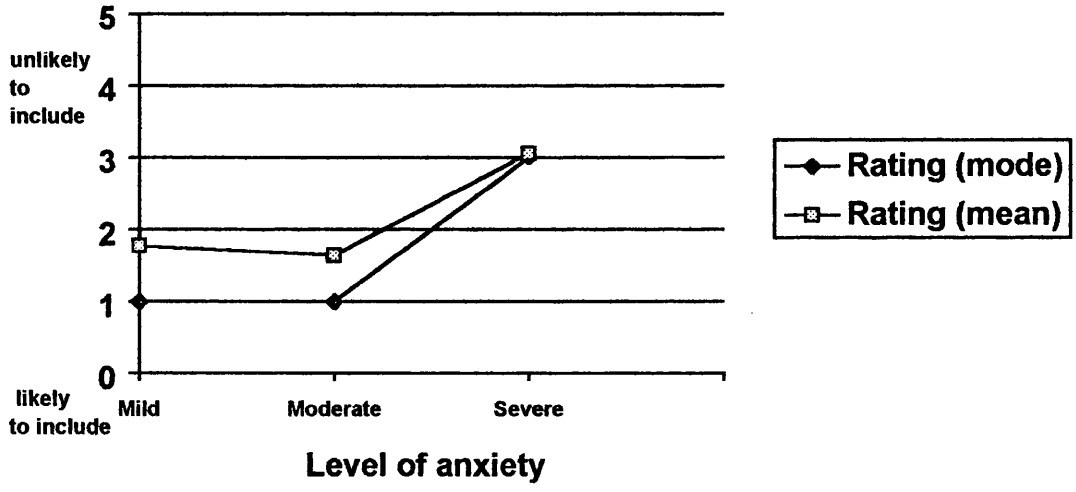


Figure 4
Clinicians' ratings of likelihood of including patients with different levels of depression

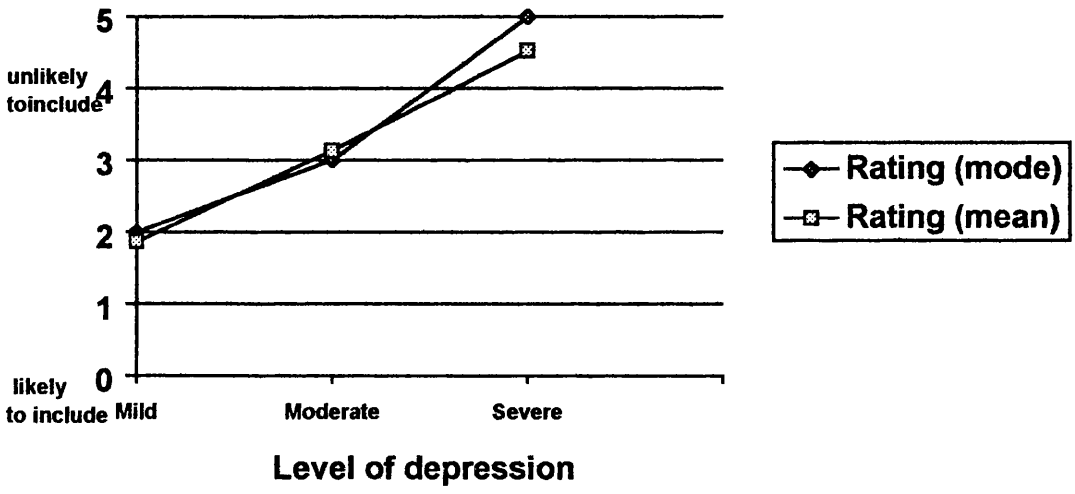
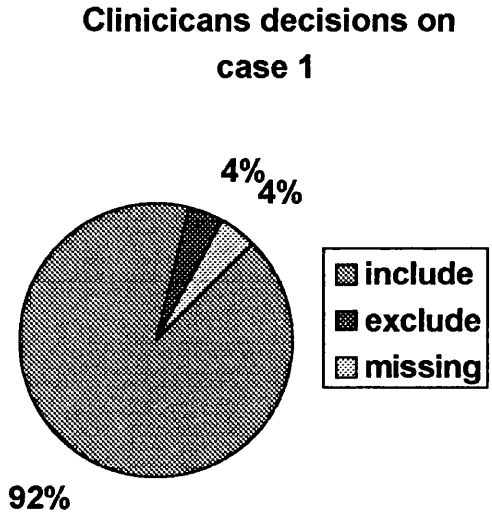


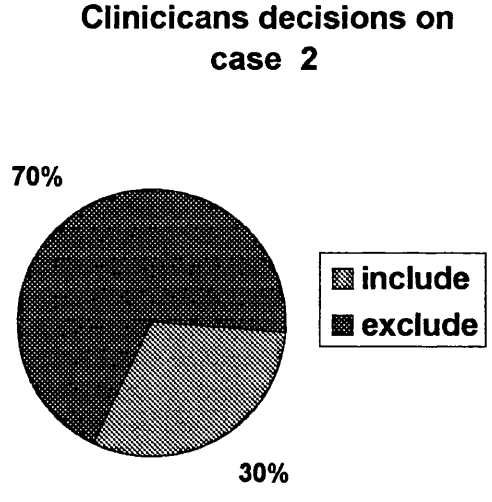
Figure 5
Proportions of clinicians who decided to include and exclude sample cases within an anxiety management group

Figure 5a



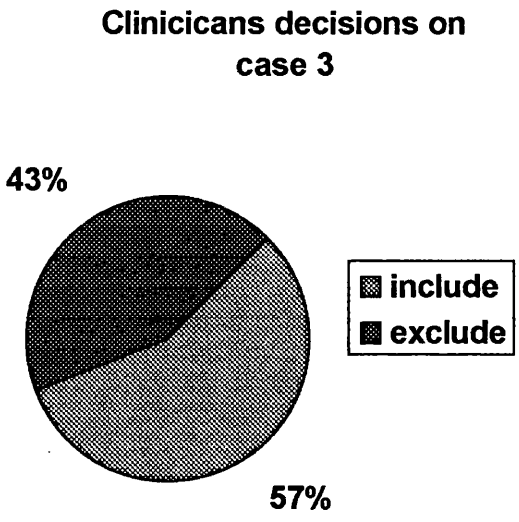
***Key features of case 1**: female aged 51, no particular social or marital difficulties, long history of somatic symptoms probably due to anxiety, has undergone medical investigations*

Figure 5b



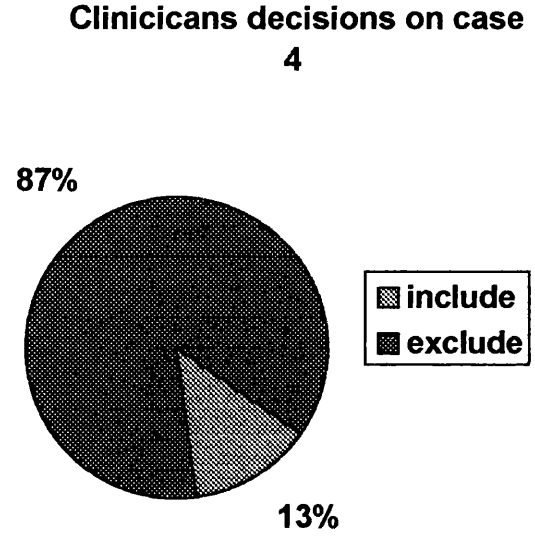
***Key features of case 2**: female aged 31, significant depression as well as anxiety; significant social and family problems*

Figure 5c



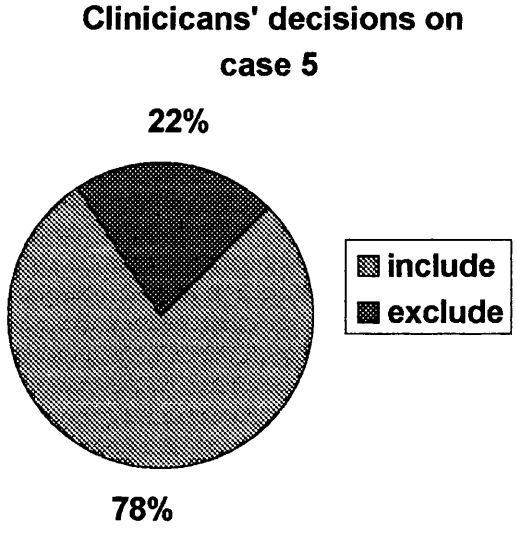
***Key features of case 3**: male aged 33; work stress - realistic appraisal; sleep problems and other anxiety symptoms; abusing alcohol -(binge drinking)*

Figure 5d



***Key features of case 4**: female aged 33, postnatal anxiety and depression symptoms following traumatic labour; hypomanic presentation*

Figure 5e



***Key features of case 5**: female aged 20; psychiatric history; previous suicide attempt; long history of rapid mood changes and low self-esteem; currently reports anxiety as her main problem, but possible personality issues*

Table I
Participants mean and modal ratings for likelihood of including patient with comorbid problem in a group

Comorbid disorder/ problem	Mean rating	Modal rating	Minimum	Maximum	Valid cases (n)
Comorbid medical condition	2.22	3	1	4	23
Bipolar disorder	3.70	3*	2	5	23
Comorbid depression (mild)	1.87	2	1	4	23
Moderate depression	3.13	3	1	5	23
Severe depression	4.52	5	1	5	23
Agroaphobia	1.70	1	1	4	23
Obsessive-compulsive disorder	3.00	3	1	5	23
Comorbid substance abuse	4.39	5	2	5	23
Eating disorder(s)	3.61	3	2	5	23
Current alcohol abuse	4.65	5	2	5	23
Current criminal behaviour	3.83	5	1	5	23
Relationship problems	2.35	2*	1	5	23
Social phobia	2.00	2	1	5	23
Borderline personality disorder	4.22	4	1	5	23
Antisocial personality disorder	4.57	5	1	5	23
Marked social problems	2.74	3	1	5	23
History of sexual abuse	3.18	3	1	5	22

* Multiple modes exist. The smallest value is shown.
Note Ratings were on a five point Likert scale from 1= very likely to include a patient with this disorder/ problem in a group through to 5 = Very unlikely to include a patient with this problem in a group.

CHAPTER 2:
MAJOR RESEARCH PROJECT LITERATURE REVIEW

Sleep, activity and mood in bipolar disorder: a review

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Prepared in accordance with guidelines for submission to *The Journal of Affective Disorders* (Appendix 2.1)

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ABSTRACT

The pervasiveness of sleep disturbances in mood disorders suggests that they may be central to the aetiology of such disorders. This review focuses on the relationship between sleep, activity and mood in mood disorders, with an emphasis on bipolar mood disorder. Methodological issues in the measurement of the sleep-wake cycle in mood-disordered subjects are considered briefly. The evidence linking disruptions of the sleep-wake cycle to mood symptoms during episodes of mood disorder is examined, and possible differences in sleep between bipolar and unipolar depression are discussed. Evidence that sleep abnormalities are stable characteristics of mood-disordered subjects which persist during remission is evaluated. The clinical relevance of findings on sleep and mood in bipolar disorder is discussed. Finally, future research directions are suggested, and the need for further research in euthymic bipolar subjects highlighted.

KEYWORDS: Bipolar mood disorder, Sleep, Activity

Introduction

Sleep disturbances have been considered as cardinal symptoms of depression and mania for as long as these states have been recognised. The pervasiveness of sleep disturbances in mood disorders suggests that they are not merely symptomatic but may be central to the aetiology of such conditions. According to Goodwin and Jamison, the episodic and recurrent nature of bipolar and unipolar depressive disorders, together with the circadian disruption that accompanies mood episodes, could indicate "malfunctions in a master biological clock" (1990; p542). This review aims to examine the evidence linking disruptions of the sleep-wake cycle to mood symptoms in mood disorders, and to consider briefly the mechanism by which sleep-wake cycle changes may trigger mood changes. Possible differences between the sleep patterns of bipolar and unipolar depressives will be discussed and the suggestion that long-term sleep abnormalities may exist in these disorders will be evaluated. Finally, the therapeutic relevance of research in this area will be highlighted and suggestions advanced for future research strategies. Initially, however, it may be useful to consider methodological issues around the measurement of the sleep-wake cycle. Two of the major techniques for investigating sleep-wake patterns are outlined in the following section.

The measurement of sleep-wake patterns– methodological considerations

Many sleep studies rely on polysomnography. Polysomnography utilises EEG techniques to record electrical activity from the scalp, monitoring the characteristic neural signatures associated with different sleep and waking states. However, although polysomnography allows accurate measurement of many sleep variables, it is primarily a laboratory-based technique. For logistic reasons, laboratory sleep studies are usually confined to one or two nights, making it difficult to obtain the longer-term data required by studies concerned with circadian rhythms. Moreover, other practical issues have given rise to doubts about the ecological validity of the data obtained in such settings (Goodwin and Jamison, 1990). The artificial nature of the sleep laboratory may itself disrupt natural rhythms, and evidence for a strong "first night" adaptation effect provides support for this claim. Moreover, many laboratories constrain subjects' sleep schedules by waking them at predetermined times. Sleep duration may thus be underestimated, and this concern applies especially to hypersomnic patients. A case study by Wehr et al (1985) found that the daily sleep periods of a depressed bipolar patient who was permitted to sleep freely reached 12 hours and

encompassed as many as nine cycles of REM and non-REM sleep. These figures far exceed those generally reported by EEG laboratories. Similarly, there is preliminary evidence that where EEG monitoring takes place in a subject's home, the data have more ecological validity (Edinger et al, 1997). Polysomnography provides highly refined objective measures of sleep, but the conditions under which recordings are made limit the issues that it can address and may confound the interpretation of results.

A potential solution to some of the above problems is offered by the technique of actigraphy. Actigraphy employs a small motion-sensitive device, worn like a wristwatch, that samples physical activity levels continuously for prolonged time periods (Sadeh et al, 1995) (periods of 72 hours are common, though sampling is now possible for up to 40 days and nights). From this raw data, a range of sleep-related variables can be estimated (e.g. sleep onset time, sleep onset latency, sleep duration, amount of wake time during the night, and "sleep efficiency"). Although actigraphy is less precise than polysomnography, and less able to discriminate sleep phases, comparative studies have reported 80-90% agreement between polysomnographic and actigraphic recordings with respect to determination of sleep and wakefulness (Sadeh et al, 1989). The practical advantages of actigraphy are that recordings of daytime and night-time activity can be made over extended periods with minimal disruption to a subject's normal life. Accordingly, this technique is well suited to investigating patterns of sleep and activity over time, and its value in the study of sleep disorders has been clearly demonstrated (American Sleep Disorders Association, 1995; Hauri and Wiseby, 1992; Sadeh et al, 1995). Actigraphy has now been applied to a range of clinical populations, including mood disordered subjects.

In the following sections, some of the major findings generated by studies of sleep and activity in mood disordered subjects are reviewed. Many of these studies have employed either actigraphy or polysomnography. The strengths and limitations of these techniques, highlighted above, should be borne in mind when evaluating the evidence presented.

Sleep and activity in manic and depressed states

Depression in bipolar populations is characterised by a lethargic state, whilst hypomania manifests as heightened activation. Leibenluft et al (1995) sought to determine the consistency of the major symptoms of hypomania and depression across repeated episodes in rapid cycling bipolar patients. Patients made twice daily ratings of their mood on a

visual analogue scale. This was subsequently used to determine the number of mood episodes experienced, and only patients followed through at least three depressive or hypomanic episodes were included in the analysis. Observer ratings of mania and depression were recorded at intervals of three weeks. During the period of observation nine patients who had a total of 30 depressive episodes and 31 hypomanic episodes were included in the study. The symptoms most consistently noted during depressive episodes were fatiguability, decreased work activities and hypersomnia. In hypomanic episodes, the most consistent symptoms were decreased need for sleep, increased work activities and increased social activities.

Leibenluft et al's (1995) study confirmed that hyposomnia and hyperactivity are two defining features of mania. However, there is growing evidence that changes in sleep and activity could potentially act as sensitive markers for relapse in bipolar illness. Klein et al (1991) studied four remitted bipolar patients during discontinuation of longterm lithium therapy. Actigraphic data were collected over 72 hours during the baseline period, and 72 hour actigraphic recordings were subsequently taken every two-three weeks following discontinuation of medication. Two of the four subjects developed manic symptoms within two weeks of ceasing medication, while the other two remained stable, and showed no clinical evidence of relapse even at one year follow-up. Actigraphic data showed that the two patients who relapsed had a marked reduction in nightly sleep duration and sleep efficiency on discontinuation of lithium. Similar changes were not apparent in the two patients who remained euthymic. In a subsequent study, Klein et al (1992) followed ten further euthymic patients undergoing lithium discontinuation. Actigraphic recordings were performed during baseline and after lithium discontinuation for 72 hour periods. Within three months, seven of the ten patients had relapsed. A retrospective analysis of the actigraphic data failed to identify any differences between relapsers and non-relapsers in measures of sleep efficiency or night-time (sleep) activity. However, a significant difference in daytime activity was found, indicating that the relapsers had had higher mean activity levels both on and off lithium. Considering the small subject numbers involved, it is unsurprising that the findings of the later study did not duplicate those of the first. Nonetheless, both outcomes are consistent with the view that characteristic patterns of hyposomnia and hyperactivity may precede a manic episode.

Further support for this proposal comes from a number of correlational studies that have used more qualitative means of sleep assessment. Leibenluft et al (1996) explored the relationships between daily self-ratings of mood and sleep logs in 11 rapid cycling bipolar out-patients. Sleep duration was identified as the best single predictor of mania or hypomania the following day. In a similar study, Barbini et al (1996) assessed the relationship between sleep duration (as rated by nursing staff) and manic symptoms in 34 manic bipolar inpatients. A significant inverse correlation was found between sleep duration and key manic symptoms the following day ($r = - 0.43$, $p < 0.05$). Finally, Nowlin-Finch et al (1994) retrospectively studied 34 patients with a diagnosis of bipolar disorder, all of whom had been admitted to an adult inpatient unit with a manic episode. Seven patients were categorised as "rapid responders" on the basis of having shown a "moderate" or better improvement in symptoms by the second day of hospitalisation. Sleep records, medical and demographic data were reviewed by researchers blind to the patient's response status. The seven rapid responders were found to have slept significantly longer on the first night of hospitalisation than the 27 other patients. Given the design of this study, it is possible that the increased sleep of the rapid responders could itself have reflected their rapid response to medication, rather than having been a causal factor in their improvement. Nonetheless, the finding is fully consistent with the other studies cited here. If reduced sleep duration is associated with increased manic symptoms, it seems probable that increased sleep should be associated with the remission of those symptoms.

In unipolar depressed subjects studies have demonstrated that activity levels and immobility parameters (at night and during the day) provided by actigraphic recordings are a good indicator of subjective severity of depressive state, with less activity signifying greater depression (Benoit et al, 1985; Royant-Parola et al, 1986).

The most reliable EEG sleep abnormality documented is a shortened REM latency throughout episodes of unipolar depression (eg Coble et al, 1981). There has been less investigation of sleep architecture in bipolar depressed subjects compared to controls. One study by Thase et al (1989) compared 19 anergic bipolar depressed outpatients with 26 age and sex matched controls on EEG variables recorded in a sleep laboratory over two nights. The study found that patients and controls did not differ significantly in sleep duration or efficiency. Moreover, the groups did not differ in terms of mean REM latency or REM density. However, the study did identify a trend for more REM time in the bipolar group,

and bipolar subjects had a significantly lower percentage of stage 1 sleep than controls. It may be that the lack of difference in variables such as sleep duration in this study is accounted for by constraints imposed by sleep-laboratory recording, since it has frequently been suggested that hypersomnia characterises bipolar depression (eg Kupfer et al, 1972), while hyposomnia is more common in unipolar depression (eg Detre et al, 1972; Reynolds & Kupfer, 1987). However, the evidence on sleep and depression is complex, and findings about similarities between bipolar and unipolar depression are frequently contrasting. These findings are discussed in more detail in a later section.

The antidepressant effect of sleep deprivation in bipolar illness

Research discussed previously documents an association between reduced sleep and elevated mood. A number of other studies have taken a more experimental approach, measuring the effects of enforced sleep deprivation in mood disordered patients, and these studies report an antidepressant effect of sleep deprivation. In an early study performed by Wehr et al (1982), nine depressed rapid cycling bipolar patients were required to simulate a 48 hour sleep-wake cycle by remaining awake for 40 hours. Eight of the nine patients switched out of depression and seven were rated as manic or hypomanic. This study demonstrated that sleep loss may be powerfully antidepressant, at least in rapid cycling bipolar illness. Subsequent work has suggested that that these effects may be partly a function of time into a depressive episode, with a positive response becoming more likely as the episode progresses (Gill et al, 1993).

Recently, Neumeister et al (1998) assessed the effects of sleep deprivation (39 hours) on 30 depressed inpatients (20 patients had a diagnosis of major depressive disorder, 6 had a history of bipolar I, and 4 has a history of bipolar II[2]). A positive response (> 40% reduction in scores on the Hamilton Depression Rating Scale) was observed in 22 cases, indicating that sleep deprivation may be effective in depressed states across a variety of diagnoses. However, Barbini et al (1998) have suggested that the effects are greater in bipolar than in unipolar subjects. Barbini et al subjected 51 depressed inpatients (bipolar I or II, n = 25; major depressive disorder, n = 26) to total sleep deprivation (TSD) over three cycles (one TSD cycle is composed of a night of TSD followed by a recovery night), and

[2] Those with a diagnosis of bipolar I had a history of manic episodes severe enough to require treatment (usually hospitalisation); patients receiving a diagnosis of bipolar II had a history of major depressive episodes predominantly, with some evidence of hypomania or mania

reported mood elevation in all diagnostic subgroups. All patients in the study showed improvement in mood levels following TSD, but the effects were greater in the bipolar groups than in the unipolar subgroup.

The antidepressant action of sleep loss in mood disorder is interesting from a theoretical perspective. It also suggests that sleep deprivation may be useful in the treatment of depression, though the danger of precipitating manic episodes in some bipolar subjects must be acknowledged (Wehr et al, 1982). As yet, there is no consensus regarding the mechanism by which sleep deprivation exerts its influence, but several authors have proposed that increased light exposure may be critical (e.g. Lewy, 1985; Neumeister et al, 1998). Indeed, Lewy has postulated that bipolar patients with susceptibility to mania have seritonergic systems that are particularly light-sensitive. Identifying the precise mode of action of sleep deprivation in mood disorder is clearly an important issue for future research. For present purposes, however, the findings cited here can be taken as a further indication that the study of patterns of sleep and activity may be central to a full understanding of mood disorders, both unipolar and bipolar.

Sleep disturbance in bipolar and unipolar depression

Barbini et al's finding that sleep deprivation impacts differentially in unipolar and bipolar depression raises the possibility that differences between these disorders may be reflected in sleep-related variables. Beauchemin and Hays (1996) monitored characteristics of sleep (such as REM latency), dream content and mood in bipolar and unipolar patients hospitalised for depression. They found that REM latency tends to increase as mood improves in bipolar depressives, but is stable or even decreases with mood improvements in unipolar depressives. Duncan et al (1979) compared 36 normal volunteers, with 36 patients with unipolar depression, and 22 patients with bipolar depression on a range of sleep EEG variables over a one night observation. All bipolar and unipolar patients were judged to be clinically depressed at the time. The study found that the unipolar and bipolar subjects had significantly greater fragmentation of REM periods than controls. However the study also showed significantly greater fragmentation of REM periods in bipolar subjects compared to unipolar subjects. In general the study found that sleep in unipolar subjects deviated more from controls than did sleep in bipolar subjects. Bipolar patients had a greater incidence of hypersomnia than unipolar, and as a group the unipolar subjects had a significantly reduced total sleep period relative to controls whereas the sleep of the

bipolar patients did not differ significantly. Overall the study suggests key differences between the two depressed states.

Giles et al (1986) compared bipolar I depressed subjects (n=10) and bipolar II depressed subjects (n=12) with age, sex and severity of depression matched unipolar subjects (n=22) on polysomnographic variables meaned over two nights. Bipolar I and bipolar II subjects were similar on all polysomnographic measures, but bipolar II subjects differed from unipolar subjects in that they had more hypersomnia, higher REM latencies, and more non-REM time. The authors conclude with the suggestion that the sleep physiology of bipolar II depression may be different from unipolar depression, with the bipolar I subjects falling somewhere in between. The authors also draw attention to the complexity of their pattern of findings, and the need for carefully controlled studies.

The majority of studies directly comparing unipolar and bipolar depression has used polysomnography. To date, actigraphic studies have provided little confirmatory evidence of consistent differences between unipolar and bipolar populations. The suggestion that lower actigraphic activity levels indicate a more severe depressed state in unipolar depression (Benoit et al, 1985; Royant-Parola et al, 1986) implies similarities between unipolar depression and the description of bipolar depression as a lethargic hypoactive state (Leibenluft et al, 1995). Activity levels have been compared directly between unipolar (n=25) and bipolar (n=12) depressed patients using 48-hour actigraphic monitoring (Kuhs and Reschke, 1992). This study reported no differences between the patient groups once the influence of age and gender were controlled for. However, the study did not directly compare the groups on sleep variables.

These preliminary findings highlight the need for further carefully controlled actigraphic studies of sleep in bipolar and unipolar depression before any firm conclusions are drawn.

Circadian rhythm disturbance as a trait marker in mood disorders

The studies discussed so far have focused on sleep disturbances immediately prior to and during episodes of mood disorder. However, to understand fully the importance of sleep in the aetiology of mood disorders it may be necessary to consider the circadian rhythms of symptom-free (euthymic) subjects with a history of mood disorder. Leibenluft and Suppes (1999) discuss the fact that many bipolar individuals have difficulty maintaining a stable

sleep-wake schedule. Ashman et al (1999) further note that phase delay, in which both bedtime and waking time are retarded, is common in rapid cycling bipolar disorder, even during euthymia. This section will review emerging evidence that sleep abnormalities are relatively stable traits associated with mood disorders.

Using EEG, Sitaram et al (1982) monitored sleep in 14 patients with remitted bipolar disorder. An increased density and percentage of REM sleep was observed in the remitted bipolar patients relative to a control group. The study also found that the patients were more sensitive to the effects of arecoline, an acetylcholine agonist that can reduce REM latency. EEG assessment of remitted bipolar patients (n = 10) was also performed by Knowles et al (1986), with recordings made on five consecutive nights. In most major respects, the sleep of the remitted patients was similar to that of controls. The one reliable difference was that the patients had more shifts to stage 1, awake and movement time from other stages of sleep. Together with higher values for the total percentage time in stage 1 sleep, these data suggest more disturbed sleep than in controls, and are consistent with the view that remitted bipolar patients have characteristic sleep disturbances. However, the finding of a higher proportion of time in stage 1 sleep relative to controls is in direct contrast with the findings of Thase et al (1989) discussed earlier.

Other studies of sleep patterns in remitted patients with mood disorder have focused on unipolar depression. Rush et al (1986) found no significant changes in sleep variables six months after depressed patients became symptom-free. The EEG traces of these patients continued to show a reduced REM latency relative to controls. Similarly, Giles et al (1990) used a cross-sectional design to study REM latency over the course of depression, matching patients in a first depressive episode with age-matched patients with recurrent depression, non-age matched patients with recurrent depression (but who were matched for age of onset of depression) and age-matched controls. All three depressed groups had shorter REM latencies than controls and no reliable differences were found between the patient groups. In a later study, Giles et al (1993) recorded sleep in 29 patients with major depression prior to treatment, and followed this up with monthly sleep EEG assessments after remission. Most EEG measures remained stable from the depressive episode through prolonged periods of remission. Where evidence of change was found, the effect was modest and due to a small subset of patients. These findings offer compelling evidence that certain sleep disturbances are trait-like and may be useful for identifying individuals at risk

from major depression. This conclusion is further supported by the work of Lauer et al (1995), who have estimated that one fifth of healthy individuals with no lifetime current diagnosis of psychiatric disorder, but with at least one first degree relative with mood disorder, show abnormal (depression-like) EEG patterns during sleep.

In summary, the evidence for enduring sleep abnormalities (e.g. shortened REM latencies) seems to be strong in the case of unipolar depression. In bipolar illness, the picture is less clear but there is some suggestion of differences from controls even in euthymic subjects. Clearly, further studies of euthymic bipolar subjects are required. It is suggested that this is one area where actigraphic monitoring would provide a valuable complement to polysomnographic research. As already noted, one advantage of actigraphic recording is that it can be extended over long periods with minimal disruption to the subject's normal routine. This offers the potential for longer-term naturalistic assessments of circadian patterns, which would not be accessible to study by polysomnographic means.

Clinical relevance of findings on the sleep-wake cycle and mood in bipolar disorder

Findings discussed above suggest that sleep disturbances commonly precede manic episodes and sleep deprivation can have antidepressant effects in bipolar illness. Wehr (1989, 1990) has emphasised the probable role of sleep loss in the natural course of bipolar disorder, and there is evidence that life events which are rated as causing severe disruption to social rhythms precipitate manic (though not necessarily depressed) episodes (Malkoff-Schwartz et al, 1998). Wehr proposes that psychosocial factors that trigger the onset of mania could do so through their ability to cause sleep deprivation, and Barbini et al (1996) note that sleep loss may augment ongoing manic episodes. Moreover, Ashman (1999) has produced evidence that bipolar subjects have difficulties maintaining stable social rhythms and daily routines. The therapeutic implication of this body of literature is clearly that stabilising sleep-wake cycles should impact positively on mood symptoms, and there is recent evidence that this is the case.

A case study conducted by Wehr et al (1998) used actigraphy in conjunction with sleep logs in a rapidly cycling bipolar man (51-years old). The study aimed to increase and stabilise the number of hours the patient slept each night. He was asked to remain at bedrest in the dark for 14 hours each night (gradually reduced to ten hours). His progress was followed over several years with self and observer mood ratings and continuous

actigraphic monitoring. The patient, who had been cycling rapidly between mania and depression every 6-8 weeks, with concurrent fluctuations in the timing and duration of sleep, stabilised in terms of mood and sleep over the course of treatment. Leibenluft and Suppes (1999) reported the case of a 42 year old woman, diagnosed with bipolar disorder at the age of 23. She experienced rapid mood cycling that was exacerbated by shift work. Regularisation of her sleep-wake cycle through changes in work conditions led to a sufficient stabilisation of mood for her drug regimen to be reduced. Leibenluft and Suppes concluded that bipolar patients may be particularly intolerant of irregular work schedules since hypomania or mania may onset after even one night's sleep deprivation. The authors advocated lifestyle interventions that allow the maintenance of stable sleep-wake patterns where chronic sleep disruption coexists with mood cycling.

Findings like the above have led to an increasing focus on lifestyle issues in psychotherapies for bipolar disorder. Miklowitz and Frank (1999) highlighted the limitations of pharmacotherapy in bipolar disorder and emphasised the need for psychotherapies that acknowledge the bi-directional interplay between biological vulnerability and psychosocial stress (i.e. stressful life events may elicit the expression of biological vulnerabilities by disrupting daily routines and circadian rhythms).

Contemporary Cognitive Behavioural Therapy for bipolar disorder often promotes self-management of prodromes in the illness (Lam et al, 1999). This involves the identification of early warning signs through the therapeutic alliance, with the patient taking a more active role in symptom management by developing a regular sleep-wake cycle and stable circadian rhythms. The process of learning to recognise specific "relapse signatures" is intended to promote earlier clinical presentation and thus to reduce the frequency and severity of episodes (Scott, 1996). So far, evidence for the effectiveness of this approach seems highly favourable. A recent randomised controlled trial (Perry et al, 1999), found that teaching patients to recognise manic prodromes (including biological symptoms such as changes in sleep), can significantly reduce both the number of relapses and the time to first relapse.

Conclusions and future research directions

Several patterns have emerged from this brief review of the literature concerning sleep and activity in mood disorders. It is clear that characteristic changes in sleep may precede

clinically significant mood changes, and the antidepressant effects of sleep deprivation in bipolar subjects imply that the relationship between sleep and mood is causal. The mechanisms underlying this link have yet to be established, but the application of these findings to clinical practice has already yielded therapeutic benefits. In addition to acute sleep disturbances, there is now growing evidence to suggest the presence of chronic sleep abnormalities in mood disordered patients, and this is one target area for future research. The evidence so far indicates that instability in the sleep-wake cycle and abnormalities of sleep architecture may act as trait or vulnerability markers for mood disorders. These markers may predate symptom onset and persist through euthymic periods. At present, the case for such abnormalities is stronger in unipolar than in bipolar disorder but more work is required to evaluate the sleep of euthymic bipolar subjects. Most research in this area has so far been based on polysomnographic techniques. It may be partly as a consequence of this bias that abnormalities relating to sleep architecture (particularly REM sleep) have been emphasised. However, given the possibility that circadian abnormalities are involved in mood disorders, it may be valuable to explore patterns of sleep and activity over extended periods in more naturalistic environments. It is therefore proposed that the actigraphic monitoring of euthymic bipolar subjects is a research strategy with the potential to uncover trait-level disturbances that are not visible in the sleep laboratory, but which might usefully inform emerging lifestyle-based therapies for bipolar disorder.

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CHAPTER 3:
MAJOR RESEARCH PROJECT PROPOSAL

The sleep of stable bipolar outpatients: a controlled naturalistic study using actigraphy

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Prepared in accordance with guidelines in the D.Clin.Psy. handbook, based on application for a mini project grant (SOHHD Chief Scientist Office) (Appendix 3.1).

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TITLE:

The sleep of stable bipolar outpatients: a controlled naturalistic study using actigraphy

SUMMARY:

In bipolar mood disorder there is evidence that acute changes in sleep are related to the onset of manic and depressed episodes. In addition, it seems that sleep abnormalities are relatively stable traits associated with mood disorder, which persist even during remission. In bipolar disorder there is preliminary evidence for differences in sleep architecture between remitted bipolar patients and controls. However, the reliance on polysomnography in these studies is a limitation, since studies are usually confined to one or two nights. Actigraphy uses a small motion-sensitive device that samples physical activity levels continuously to estimate sleep parameters (Sadeh et al, 1995); and allows prolonged measurement in a naturalistic environment. This study aims to compare the sleep of subjects with bipolar disorder who are euthymic with controls using objective (actigraphic) and subjective (sleep log) parameters of sleep over a five day period. It is hypothesised that bipolar subjects will display greater variability in sleep parameters than controls across the five days. Bipolar subjects will be recruited through CMHTs, and other settings. Control subjects included will be individually age and sex-matched to bipolar subjects. Based on a power calculation, we aim to recruit 20-25 subjects in each group. Information about sleep history will be recorded at initial interview. Objective parameters of sleep will be recorded over a five day period using actiwatches. During this period, subjects will also complete sleep logs to generate equivalent subjective sleep parameters, and visual analogue scale ratings of mood, to provide an index of mood variability. The groups will be compared on the different sets of sleep parameters using multivariate (MANOVA) techniques. Univariate group comparisons will then be conducted for each sleep measure using one way analyses of variance (ANOVA). Finally, the association between objective and subjective sleep parameters will also be measured.

INTRODUCTION

In bipolar mood disorder, hyposomnia and hyperactivity are two of the defining features of mania, while reduced activity and hypersomnia characterise bipolar depression (Leibenluft et al, 1995). Changes in sleep and activity may act as sensitive markers for relapse in bipolar illness, with reduced sleep and increased activity being associated with the onset of a manic episode (Barbini et al, 1996; Klein et al, 1991, 1992; Leibenluft et al, 1996; Nowlin-Finch et al, 1994). Experimental studies of the effect of enforced sleep deprivation have demonstrated that sleep loss may have a powerful antidepressant effect in mood disorders, causing remission of symptoms of depression (eg Neuimeister et al, 1998) and in some cases triggering mania (Wehr et al, 1982).

In terms of sleep architecture, the most robust finding is the presence of a shortened REM latency in unipolar depression (eg Coble et al, 1981). There is limited evidence that bipolar subjects who are depressed differ from controls in terms of sleep architecture. Duncan et al (1979) compared a unipolar group, a bipolar group and a normal control group on sleep variables, and found mood disordered subjects had significantly greater fragmentation of REM periods than controls, and that fragmentation was greater in bipolar than in unipolar subjects. Thase et al (1989) compared bipolar depressed patients and controls, and found a trend for more REM time in bipolar subjects, and a lower percentage of stage 1 sleep.

There is compelling evidence that sleep abnormalities are relatively stable traits associated with mood disorder, which persist even when subjects are symptom free or euthymic. This evidence is clearest in the case of unipolar depression, where it seems that reduced REM latency may be a stable characteristic in those with a history of unipolar depression, even when recovered (Giles et al, 1990, 1993; Rush et al, 1986). In bipolar disorder there have been fewer studies, and the evidence is less clear. Using EEG, Sitaram et al (1982) monitored sleep in 14 patients with remitted bipolar disorder. An increased density and percentage of REM sleep was observed in the remitted bipolar patients relative to a control group. EEG assessment of remitted bipolar patients (n = 10) was also performed by Knowles et al (1986), with recordings made on five consecutive nights. In most major respects, the sleep of the remitted patients was similar to that of controls (n=10). The one reliable difference was that the patients had more shifts to stage 1, awake and movement

time from other stages of sleep. Together with higher values for the total percentage time in stage 1 sleep, these data suggest more disturbed sleep than in controls, and are consistent with the view that remitted bipolar patients have characteristic sleep disturbances.

A limitation of studies comparing bipolar subjects and controls to date is the reliance on polysomnography to measure sleep. For logistic reasons polysomnographic studies are usually confined to one or two nights. In addition, the artificial nature of the sleep laboratory may disrupt natural rhythms. For example, the fact that subjects are woken at predetermined times may lead to underestimation of sleep duration in hypersomnic subjects (eg Wehr et al, 1985).

A potential solution to these problems is offered by the technique of actigraphy, which employs a small motion-sensitive device, worn like a wristwatch, that samples physical activity levels continuously for prolonged time periods (Sadeh et al, 1995). Periods of 72 hours are common, though sampling is now possible for up to 40 days and nights. A range of sleep-related variables can be calculated from raw data according to a predetermined set of algorithms (e.g. sleep onset time, sleep onset latency, sleep duration, amount of wake time during the night, and "sleep efficiency"). Although actigraphy is less precise than polysomnography, and less able to discriminate sleep phases, comparative studies have reported 80-90% agreement between polysomnographic and actigraphic recordings with respect to determination of sleep and wakefulness (Sadeh et al, 1989). The practical advantage of actigraphy is that recordings of daytime and night-time activity can be made over extended periods with minimal disruption to a subject's normal life.

There is some evidence that individuals with bipolar disorder may have difficulty maintaining stable sleep-wake cycles, and regular daily routines and rhythms (Ashman et al, 1999; Leibenluft & Suppes, 1999). It may be that these instabilities reflect underlying circadian abnormalities involved in the aetiology of bipolar mood disorder. Actigraphic measurement has been utilised successfully with other subject groups where stability of the sleep-wake cycle is of particular interest. For example, Gruber et al, (2000) used actigraphy to compare children with Attention Deficit Hyperactivity Disorder (ADHD) and controls, and found increased instability in the ADHD children over a five day measurement period. Actigraphic monitoring of the sleep-wake cycle in euthymic bipolar

subjects would allow more prolonged naturalistic measurement, which could then form the basis for comparison with controls.

AIMS AND HYPOTHESES

The present study has the following aims:

1. To compare euthymic bipolar subjects with age and sex matched control subjects on a number of objective sleep variables using actigraphic recordings made over a five day period.

2. To compare euthymic bipolar subjects with age and sex matched controls on a number of subjective sleep variables calculated from sleep logs completed for a five day period.

Given the suggestion that subjects with bipolar mood disorder have difficulty in maintaining stable sleep-wake patterns and regular daily routines, the study aims to test the following hypotheses:

1. Euthymic bipolar subjects will display greater variability in certain actigraphic sleep variables (sleep duration, sleep onset latency, sleep "efficiency", and amount of night waking time) across the five day period than control subjects.

2. Euthymic bipolar subjects will display greater variability in equivalent subjective sleep variables across the five day period than control subjects.

The study will also explore the correlation between objective and subjective sleep parameters in each group.

Finally, the study will compare the two groups on self-reported daily mood ratings over the five day period (in terms of means and variability).

PLAN OF INVESTIGATION

The study will be conducted in the Department of Psychological Medicine over a 16 month period. Some actigraphic data may subsequently be used as pilot sleep measurement for

the longitudinal study "Psychobiosocial functioning in bipolar disorders" taking place in the Department of Psychological Medicine.

SUBJECTS

Mood disordered subjects

Subjects with a confirmed psychiatric diagnosis of bipolar mood disorder will be recruited via Community Mental Health Teams and other appropriate settings over a 6 month period.

Inclusion and exclusion criteria – Subjects must fulfil DSM-IV criteria for bipolar disorder (American Psychiatric Association; 1995), according to casenotes and psychiatric diagnosis. Only subjects who are currently euthymic will be included in the study. Information about the mood status of subjects will be provided by the referring psychiatrist or key mental health worker (eg Community Psychiatric Nurse), and independently validated by the researcher, and the subject's self-reported mood at initial interview. Subjects must show willingness to provide informed consent (Appendix 3.2). Bipolar subjects who currently meet criteria for a hypomanic, manic or depressed episode according to psychiatric diagnosis, or the clinical judgement of the researcher (referring to DSM-IV criteria) will be excluded. Subjects must not meet DSM-IV criteria for major psychiatric disorder other than bipolar disorder according to casenotes. Subjects currently being treated for drug or alcohol problems will be excluded, as will those currently involved in another research study.

Control subjects

Control subjects will be recruited on a voluntary basis (via personal and occupational links) from a range of settings. Control subjects will be individually sex and age matched to bipolar subjects. As far as possible, an effort will be made to recruit from a diverse range of occupational and social class groups, and to match control subjects with bipolar subjects on variables such as occupation.

Inclusion and exclusion criteria – control subjects must show willingness to provide informed consent, and should have no history of major psychiatric disorder.

Shift workers will be excluded from the control group.

DESIGN

A cross-sectional design will be implemented to compare subjects with bipolar mood disorder with controls.

PROCEDURE

Following identification of potentially suitable mood disordered subjects by key mental health workers and psychiatrists, a brief individual interview will be conducted by the researcher in order to confirm the current mood status of the subject. If the subject is judged suitable for inclusion in the study, further background information will be collected at interview. A brief history of the subject's mood disorder will be taken, (including time since diagnosis and time since last episode). Information about current medication will also be recorded. Information about sleep patterns and any history of sleep disorder will be recorded using a Sleep History Questionnaire (based on Morin, 1993); (Appendix 3.3). Age and sex matched control subjects will be recruited in parallel. Following identification of age and sex matched control subjects, a brief initial interview will be conducted. Subjects will be asked about current and lifetime history of major psychiatric disorder, and the sections of the SCID-I interview schedule relevant to affective disorders will be administered (Structured Clinical Interview for DSM-IV Axis-I Disorders: SCID-I, Clinician version; First et al, 1997). If subjects are judged suitable for inclusion then information about sleep history will be recorded using the Sleep History Questionnaire, as above.

Following initial interviews with mood disordered and control subjects, each subject will be given an 'actiwatch', together with a pack including measures for the five day period. Subjects will be provided with an information sheet with details of the study (Appendix 3.4), and with a contact telephone number, in case they have any difficulties or questions over the five days. Over the five day period then, objective sleep parameters will be recorded in all subjects. In addition, all subjects will complete the following measures for the same five day period:

- sleep diaries / logs (Espie, 1991) (Appendix 3.5) completed in the morning upon rising, to provide subjective sleep parameters.
- a simple visual analogue measure of mood rated 0-100 (Whybrow & Guylia, 1995) (Appendix 3.6) completed twice daily; once in the morning upon rising, and once in the evening, to provide some index of mood variability.

STATISTICAL POWER

In consideration of statistical power it should be noted that existing studies using actigraphy in bipolar subjects have tended to employ longitudinal designs to examine the relationship between sleep and mood (eg Leibenluft et al, 1996); or to use experimental designs to measure the impact of sleep deprivation on mood (eg Wehr, 1982). The only studies to have compared euthymic bipolar subjects with controls on sleep parameters used polysomnography to elicit sleep parameters (Knowles et al, 1986; Sitaram et al, 1982). These studies did find differences between the two groups in terms of sleep architecture despite small sample sizes (n=10 per group in study by Knowles et al; n=14 per group in Sitaram et al study). However, the small number of significant differences in these studies may be explained partly by the constraints imposed by laboratory measurement, as outlined, and partly by the small sample sizes. No previous study has used actigraphy to compare remitted bipolar subjects with controls, but it seems likely that more prolonged measurement in a more naturalistic setting will be advantageous in eliciting differences between the two groups, particularly if there are differences in night to night variability. A power calculation (using G POWER*) assuming a significance level of 0.05, and a power of 0.8, suggests that a total sample size of 42 would enable an effect size of 0.8 to be detected between bipolar and control groups (n=21 in each group). On the basis of related literature discussed, and this calculation, we aim to recruit 20-25 euthymic bipolar subjects and 20-25 age and sex matched controls over a 6 month period.

SETTINGS AND EQUIPMENT

Initial interviews with bipolar subjects will take place either at the Community Mental Health Team Resource Centre, the relevant Psychology/Psychiatry department, or the Department of Psychological Medicine at Gartnavel Royal Hospital. Control subjects will be interviewed either in the Department of Psychological Medicine, or at another convenient location. Wrist actigraphs (Cambridge Neurotechnology Ltd Actiwatch-R Model AW2) will be borrowed from the Department of Psychological Medicine at Gartnavel Royal Hospital. Data from actiwatches will be downloaded onto PC within the Department of Psychological Medicine using available software. Sleep variables will be calculated using the programme SLEEPWATCH*.

DATA ANALYSIS

Data will be stored in a lockable filing cabinet at the Department of Psychological Medicine, and entered anonymously onto a data base (with codes attached). The statistical package SPSS FOR WINDOWS (version 10)* will be used to analyse data.

The primary analysis will involve comparing the groups on objective and subjective sleep parameters of sleep duration, sleep onset latency, "sleep efficiency", and night waking time. Data will be averaged across the five nights, and since night to night variability is of interest, the raw score standard deviation over the five nights will also be calculated. Four multivariate analyses of variance (MANOVA) will then be conducted on sleep data, to compare the groups on averaged actigraphic sleep measures, night to night variability of actigraphic measures, averaged subjective measures and night to night variability of sleep measures (using the summary variables described, and following the protocol of Gruber et al, 2000). Following each multivariate analysis, univariate group comparisons will be conducted for each sleep measure using one way analyses of variance (ANOVA).

The groups will also be compared on mood ratings; again both in terms of average ratings, and variability over the five days (raw score standard deviations over the five nights will be calculated for this comparison).

Finally, correlations between objective and subjective sleep variables will be measured (separately for each group, and for all subjects).

PRACTICAL APPLICATIONS

Wehr (1989, 1990) has emphasised the probable role of sleep loss in the natural course of bipolar disorder, and there is evidence that life events which are rated as causing severe disruption to social rhythms precipitate manic (though not necessarily depressed) episodes (Malkoff-Schwartz et al, 1998). Moreover, Ashman (1999) has produced evidence that bipolar subjects have difficulties maintaining stable social rhythms and daily routines. The obvious therapeutic implication of this body of literature is that stabilising sleep-wake cycles should impact positively on mood symptoms; and there is recent evidence that this is the case (eg Wehr et al, 1998; Leibenluft and Suppes, 1999). These findings have led to increasing focus on lifestyle issues in the psychotherapies for bipolar disorder. Contemporary CBT for the disorder promotes self-management of prodromes (Lam et al,

1999); and recent evidence has suggested that teaching patients to recognise and manage prodromal symptoms (including sleep disturbance) significantly reduces the number of subsequent relapses, as well as time to next relapse (Perry et al, 1999).
Further research into the natural sleep-wake cycles of euthymic bipolar subjects is necessary to clarify whether and how these subjects differ from controls. Such research has the potential to uncover trait level disturbances that are not visible in the sleep laboratory, but which may usefully inform ongoing lifestyle based therapies for bipolar disorder.

TIMES SCALES

April - October 2000

Proposal accepted and ethical approval sought.

November 2000 – April 2001

Subjects recruited and data collection.

May 2001 – July 2001

Data analysed and written up.

ETHICAL APPROVAL

Ethical approval is being sought from Glasgow Primary Care NHS Trust Ethics Committee.

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AMENDMENTS TO RESEARCH PROPOSAL

ETHICAL APPROVAL

The project received ethical approval from Greater Glasgow Primary Care NHS Trust Ethics Committee on July 27th 2000 within the context of the larger pilot study of the longitudinal project "Psychobiosocial functioning in bipolar disorders" being undertaken in the department of Psychological Medicine, Glasgow University, by Professor Jan Scott and Ms Alison Tait (Appendix 3.7).

Independent ethical approval was sought from Argyll and Clyde Health Board Local Research Ethics Committee in order to extend recruitment to Renfrewshire; and was granted on 24th January 2001 (Appendix 3.7).

SAMPLE SIZE

Recruitment of suitable subjects proved extremely difficult, and it was for this reason that it was extended beyond Glasgow to the Renfrewshire area. Over a six month period 32 suitable subjects were identified by mental health workers and psychiatrists for potential inclusion in the study, and had the study explained to them. However, eleven of these chose not to take part, and of the 21 who consented to participate two subjects dropped out within the first day of the study. The bipolar group therefore comprised 19 subjects in total, rather than the sample of 20-25 subjects proposed.

STATISTICAL ANALYSES

All of the analyses proposed were conducted, however in addition the relationship between sleep variables, mood ratings and disorder status was explored, using logistic regression techniques.

PREVIOUS RESEARCH PROPOSAL

It should be noted that initially in March 2000, a different but related research project was proposed and passed. This proposal was entitled "Sleep and activity as markers for mood change in bipolar disorder", (see Appendix 3.8 for a copy of the proposal), and aimed to compare subjects with bipolar disorder in different illness phases (ie a manic group, a depressed group and a euthymic group) on measures of sleep and activity (using actiwatches), and on a measure of "behavioural engagement". In the early stages of

recruitment it became apparent that it was not going to be possible to recruit an adequate number in the manic/ hypomanic or depressed subgroups. In fact most of the subjects identified by mental health workers who seemed willing and able to carry out the study were euthymic. For these reasons the present proposal was drafted, and data collection began in November, 2000.

CHAPTER 4:
MAJOR RESEARCH PROJECT PAPER

The sleep of stable bipolar outpatients: a controlled naturalistic study using actigraphy

Audrey Millar[1]

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Prepared in accordance with guidelines for submission to *The Journal of Affective Disorders* (Appendix 4.1)

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ABSTRACT

Background

In bipolar disorder, several studies suggest that sleep abnormalities are stable and persist during remission; however, a reliance on polysomnography has confined measurement to one or two nights in sleep laboratories. This study compared remitted bipolar subjects with controls on actigraphic and subjective sleep parameters in a naturalistic setting over five nights.

Methods

Nineteen bipolar subjects and 19 age and sex-matched controls were included. Objective sleep parameters were recorded using wrist actigraphs. Sleep diaries and mood ratings were completed for the same period. Sleep data were averaged for each subject across nights, and raw score standard deviations were calculated as a measure of within-subject variability. Multivariate analyses of variance were conducted to compare groups on sets of sleep measures. The relationship between sleep variables, mood and disorder status was explored using logistic regression techniques.

Results

Multivariate analyses found significant group differences for both actigraphic ($F(4,33)=3.80$, $p=.012$) and subjective measures ($F(4,31)=3.18$, $p=.027$). Univariate analyses identified reliable differences in sleep onset latency (subjective), sleep duration (subjective), and variability of sleep duration and night wake time (actigraphic). Logistic regression demonstrated that a combination of sleep and mood measures correctly predicted disorder status in 84.2% of cases.

Limitations

Failure to match on employment status is a limitation that may provide an alternative explanation for some findings.

Conclusions

The study nonetheless suggests that the sleep of stable bipolar outpatients is abnormal relative to controls: bipolar subjects sleep longer, report longer onset latencies, and display greater variability across nights.

KEYWORDS: Actigraphy, Bipolar mood disorder, Euthymia, Sleep disturbance

1. INTRODUCTION

Bipolar disorder is a common, severe and persistent disorder which affects 1.3-1.7% of the population, and is characterised by episodes of depression and mania (Kessler et al, 1996). Hyposomnia and hyperactivity are two defining features of mania, while reduced activity and hypersomnia characterise bipolar depression (Leibenluft et al, 1995). The pervasiveness of sleep disturbances in both bipolar and unipolar mood disorders suggests that they are not merely symptomatic, but may be central in the aetiology of symptoms.

There is growing evidence that changes in sleep and activity may act as sensitive markers for relapse in bipolar illness, with reduced sleep and increased activity being associated with the onset of a manic episode (Barbini et al, 1996; Klein et al, 1991, 1992; Leibenluft et al, 1996; Nowlin-Finch et al, 1994). Experimental studies of the effects of sleep deprivation in bipolar depression suggest that sleep loss may have a powerful antidepressant effect, causing remission of symptoms of depression, and in some cases triggering mania (Neuimeister et al, 1998; Wehr et al, 1982).

There is also compelling evidence that sleep abnormalities are relatively stable traits associated with mood disorder, which persist even when subjects are symptom free or euthymic. The evidence is more clear in the case of unipolar depression, where it has been shown that reduced REM latency is a stable sleep characteristic in those with a history of unipolar depression, even when recovered (Rush et al, 1986; Giles et al, 1990; Giles et al, 1993). Moreover, one fifth of healthy individuals with no current or lifetime diagnosis of psychiatric disorder, but with at least one first degree relative with mood disorder, show abnormal, depression-like EEG patterns during sleep (Lauer et al, 1995).

In one of the few studies exploring sleep characteristics of euthymic bipolar subjects, Sitaram et al (1982) used EEG to monitor sleep in 14 patients with remitted bipolar disorder. An increased density and percentage of REM sleep was observed in the remitted bipolar patients compared to a control group. The study also found that the patients were more sensitive to the effects of arecoline, an acetylcholine agonist that can reduce REM latency. EEG assessment of remitted bipolar patients (n = 10) was also performed by Knowles et al (1986), with recordings made on five consecutive nights. In most major respects, the sleep of the remitted patients was similar to that of controls (n=10). The one reliable difference was that the patients had more shifts to stage 1, awake and movement

time from other stages of sleep. Together with higher values for the total percentage time in stage 1 sleep, these data suggest more disturbed sleep in remitted bipolar patients than in controls, and are consistent with the view that these patients may have characteristic sleep disturbances.

A limitation of studies comparing euthymic bipolar subjects and controls to date is the reliance on polysomnography. The failure to find more significant differences between the groups may be partly due to constraints imposed by this type of measurement. For logistic reasons polysomnographic studies are usually confined to one or two nights. In addition, the artificial nature of the sleep laboratory may disrupt natural rhythms. For example, the fact that subjects are woken at predetermined times may lead to underestimation of sleep duration in hypersomnic subjects (eg Wehr et al, 1985).

A potential solution to these problems is offered by actigraphy, which employs a small motion-sensitive device, worn like a wristwatch, that can sample physical activity levels continuously for prolonged periods (Sadeh et al, 1995). A range of sleep-related variables are calculated from raw data according to a predetermined set of algorithms (e.g. sleep onset time, sleep onset latency, sleep duration, amount of wake time during the night, and "sleep efficiency"). Although actigraphy is less precise than polysomnography, and less able to discriminate sleep phases, comparative studies have reported 80-90% agreement between polysomnographic and actigraphic recordings with respect to determination of sleep and wakefulness (Sadeh et al, 1989). The practical advantage of actigraphy is that recordings of daytime and night-time activity can be made with minimal disruption to a subject's normal life. This technique is well suited to investigating patterns of sleep and activity over time.

Actigraphic measurement has been utilised successfully in group comparisons where stability of the sleep-wake cycle is of particular interest. For example, Gruber et al, (2000) used actigraphy to compare children with Attention Deficit Hyperactivity Disorder (ADHD) with controls, and found reduced stability in sleep onset, sleep efficiency and true sleep in the ADHD group over a five day measurement period. Case studies have similarly shown actigraphy to be a useful method for prolonged naturalistic measurement of sleep patterns in bipolar subjects (eg Wehr et al, 1998). This capacity for naturalistic

measurement makes actigraphy the obvious choice to study underlying circadian abnormalities in bipolar subjects.

The present study compared a group of euthymic bipolar subjects with age and sex matched controls on a number of objective sleep variables using actigraphic recordings made over a five day period. The study also compared the euthymic bipolar group with controls on a number of subjective sleep variables calculated from sleep logs completed for the same period. Finally, the study explored the relationship between sleep variables, mood ratings and disorder status to determine whether objective and subjective sleep parameters and daily mood ratings act as predictors of illness. Given the suggestion that subjects with bipolar mood disorder may have difficulty in maintaining stable sleep-wake patterns and daily routines even during euthymic phases (Leibenluft & Suppes, 1999; Ashman et al, 1999), it was hypothesised that bipolar subjects would differ from controls in actigraphic and subjective sleep measures. In particular, it was predicted that they would display greater variability across the five days.

2. METHODS

2.1 DESIGN

A cross-sectional design was implemented to compare subjects with a confirmed psychiatric diagnosis of bipolar disorder with healthy age and sex matched controls on a number of sleep parameters.

2.2 SUBJECTS

Mood disordered subjects

Mood disordered subjects were recruited via Community Mental Health Teams, Clinical Psychology departments, and Psychiatric outpatients clinics in Glasgow and Renfrewshire over a six month period.

Inclusion and exclusion criteria – Subjects with a confirmed psychiatric diagnosis of bipolar disorder were included in the study. All mood-disordered subjects fulfilled DSM-IV criteria for bipolar disorder (American Psychiatric Association; 1995), according to casenotes and psychiatric diagnosis. Information about the mood status of subjects was provided by the referring psychiatrist or key mental health worker (eg Community

Psychiatric Nurse), and independently validated by the researcher using DSM-IV diagnostic criteria, and the subject's self-reported mood at initial interview. Only those who were currently euthymic were included.

Mood-disordered subjects who met the criteria for a major psychiatric disorder other than bipolar disorder were excluded. Subjects being treated for drug or alcohol problems were excluded, as were those involved in any other research study. Over a six month period, 32 suitable subjects were identified for potential inclusion. Eleven of these chose not to take part and, of the 21 who consented to participate, two subjects dropped out within the first day of the study. A total of 19 subjects therefore comprised the mood-disordered group (8 males and 11 females). Ages ranged from 26-68 years (mean = 47.3, SD=10.61).

Control subjects

Control subjects were recruited on a voluntary basis via personal and occupational links. Controls were sex and age matched with bipolar subjects. As far as possible, an effort was made to recruit from a diverse range of occupational and social class groups, and to match control subjects with bipolar subjects on variables such as occupation.

Inclusion and exclusion criteria – Controls were asked about current and lifetime history of major psychiatric disorder, and sections of the SCID-I interview schedule relevant to affective disorders were administered (Structured Clinical Interview for DSM-IV Axis-I Disorders: SCID-I, Clinician version; First et al, 1997). Control subjects provided informed consent, and had no history of major psychiatric disorder. Shift workers were excluded from the control group. Over a six month period, 19 suitable age and sex matched controls were recruited.

Ages in the control group ranged from 27-67 (mean = 45.8, SD = 10.93). There was no significant difference between mood-disordered subjects and controls in age ($t(36) = .422$, $p=.676$). Similarly, there was no significant difference between groups in terms of marital status ($\chi^2(2) = 2.9$, $p=.234$). Despite efforts to match for occupation, the groups differed in employment status with a significantly smaller proportion of the mood-disordered group in part or full-time employment (37% vs 95% of the control group; $\chi^2(1)=14.2$, $p<.001$). Employment details of the two samples are provided in Appendix 4.2.

2.3 PROCEDURE

Following inclusion of mood-disordered subjects to the study, background information including the history of the mood disorder and information about current medication was recorded at interview. The time since diagnosis ranged from 1-35 years (mean=14.5(9.0), median=15). Time since last episode reported by the group ranged from 1 month – 8 years (mean 2.1 years (2.6); median 12 months; mode 6 months). Eighteen of the nineteen subjects in the bipolar group were receiving psychotropic medication (mainly mood stabilisers). Details of medication and disorder history are provided in Appendix 4.3.

A brief initial interview was conducted with control subjects to screen for history of mood disorder or other major psychiatric disorder. A number of measures were then recorded in both groups over a five day period.

2.4 MEASURES

Background information on sleep and any history of sleep problems was recorded using a Sleep History Questionnaire (based on Morin, 1993).

Actigraphy was used to obtain objective estimates of sleep over a five day period. Each subject was given an "actiwatch", worn like a wristwatch on the non-dominant arm for five consecutive days and nights. Actiwatches used were Actiwatch-R Model AW2, developed by Cambridge Neurotechnology Ltd. Raw actigraphic data was then downloaded using SLEEPWATCH*, and the following objective parameters calculated: sleep duration, "sleep efficiency" (the percentage of time in bed spent asleep), sleep onset latency, and wake time during the night.

Subjective measurement of sleep variables was obtained for the same five day period using sleep logs (Espie, 1991), which participants completed each morning on rising. The daily logs allowed calculation of the same sleep parameters as measured by the actigraphs.

All subjects gave a mood rating twice daily for the same five day period, using a simple visual analogue scale (VAS) of mood rated 0-100 (on a 100mm line), from 0 – *"most depressed/down I've ever felt"* to 100 – *"most high/ manic I've ever felt"*; with a *"well"* range defined from 35 mm – 65 mm (Whybrow & Guylia, 1995). This was completed once in the morning on rising, and once last thing in the evening before retiring.

2.5 ANALYSES

Data were averaged for each subject across the five nights on key actigraphic and subjective parameters. In addition, since night to night variability on sleep parameters was of interest, the raw score standard deviation over the five nights was also calculated for each variable. This was shown to be a useful measure of sleep variability in the study by Gruber et al (2000). The two experimental groups were then compared on objective and subjective sleep parameters using separate multivariate analyses of variance (MANOVA) for each set of sleep measures. These analyses were conducted to test the hypothesis that there are group differences in the sets of sleep measures, while controlling for multiple comparisons. Four multivariate analyses were conducted on sleep data: the groups were compared on averaged actigraphic sleep measures, night to night variability of actigraphic measures, averaged subjective sleep measures, and night to night variability of subjective sleep measures (using the summary variables described above, and following the protocol of Gruber et al, 2000). In keeping with the assumptions of MANOVA the distribution of subjects responding on all parameters was assessed using the Shapiro-Wilks test of normality. In cases where the distributed data were not normal natural log transformations were conducted prior to entry of the variable into MANOVA testing. The following three actigraphic variables were log transformed: averaged onset latency, standard deviation of onset latency, and standard deviation of sleep efficiency. Four subjective sleep variables were transformed: averaged onset latency, averaged night waking time, standard deviation of onset latency, and standard deviation of night waking time. Following each multivariate analysis, univariate group comparisons were conducted for each sleep measure using one way analyses of variance (ANOVAs).

Correlations between objective (actigraphic) and subjective sleep variables were computed across all subjects, and for each group separately. Finally, the relationship between sleep variables, mood ratings and disorder status was explored, using logistic regression techniques.

3. RESULTS

3.1 Comparison of groups on sleep history variables

The Sleep History Questionaire conducted at the point of entry to the study revealed consistent differences between the sleep histories of the two groups. All 19 bipolar subjects reported longstanding sleep disturbance, compared with only four of the control group

(21%). There was an associated difference in how the groups rated the stability of their sleep pattern (from month to month, and year to year) on a four point scale of 1 - *"very stable"* to 4 - *"very unstable"*, with the bipolar group reporting less stable patterns (χ^2 (3)=21.2, p<.0001). Unsurprisingly, therefore, a larger proportion of the bipolar group reported having ever used sleeping pills (73.7% vs 15.8%; χ^2 (1)= 14.3, p<.001) or alcohol to aid sleep (47.4% vs. 5.3%; χ^2 (1)= 9.4, p=.002).

In contrast to these long-term differences, the groups did not differ in their reported use of sleeping pills (15.8% of bipolar group vs 10.5% of controls; χ^2 (1) = .298, p=.585) or alcohol to aid sleep in the last four weeks (10.5% of bipolar group vs 0% of controls; χ^2 (1)= 2.23, p=.135). Similarly, there was no difference between their ratings of sleep quality over the last four weeks, on a four point scale of 4 - *"very good"* to 1 - *"very poor"* (χ^2 (1)= 1.69, p=.639). This may be related to the fact that the majority of the bipolar group had been taking mood stabilising medication since diagnosis, and that all were euthymic during the study.

3.2 Comparison of groups on averaged mood measures and mood variability

On the 0-100 VAS, the bipolar group rated themselves as significantly more depressed than the control group (43.2(10.5) vs 50.0(5.1); t(36)=-2.6, p=.015), though the variability of subjective mood across the five days did not differ significantly (bipolar group = 1.8(.96), control group = 1.3(.74); t(36)=1.7, p=.100). However, although bipolar subjects scored significantly lower for subjective mood than controls, both groups fell within the "well" range of the scale. Coupled with the lack of difference in the variability scores, these data tend to confirm the euthymic status of the bipolar subjects. They also suggest that euthymia, while representing optimal functioning in bipolar disorder, may represent slightly depressed mood relative to normal controls. The distributions of mood ratings in each group are illustrated in Appendix 4.4.

3.3 Comparison of groups on objective and subjective sleep measures[2]

Insert Table I

Objective sleep variables

The MANOVA comparing groups on combined averaged actigraphic measures of sleep duration, onset latency, sleep efficiency and wake time yielded a significant overall group effect ($F(4,33)=3.80$, $p=.012$). Results of separate univariate ANOVAs for each sleep measure, did not find any significant group differences. However there were trends towards the bipolar group sleeping longer, taking longer to fall asleep, and sleeping less efficiently than controls (Table 1).

The MANOVA comparing groups on standard deviations of sleep duration, onset latency, sleep efficiency, and wake time did not show any significant difference between the two groups ($F(4,33)=2.45$, $p=.066$), although separate ANOVAs of each measure suggested significant group differences in variability of sleep duration and night waking time, with the bipolar group being more variable in both cases (Table 1).

Subjective sleep variables

Results of the MANOVA which compared groups on combined subjective averages of sleep duration, onset latency, sleep efficiency and wake time revealed an overall multivariate effect ($F(4,31)=3.18$, $p=.027$). Separate univariate ANOVAs confirmed significant group differences in average sleep duration and onset latency; with the bipolar group sleeping longer and having a longer onset latency (Table 1). These findings are broadly similar to the trends observed in the objective sleep data.

The MANOVA using a combination of the standard deviations of subjective sleep duration, subjective onset latency, subjective sleep efficiency and subjective wake time did not show an overall difference between the two groups ($F(4,31)=1.79$, $p=.156$); however separate univariate analyses suggested significant group differences in the variability of

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[2] *Two subjects (one from the bipolar group and one from the control group) had sleep logs with missing data, and were therefore excluded from the multivariate analysis of subjective sleep variables.*

sleep duration, sleep onset latency and sleep efficiency; with the bipolar group showing greater variability on each measure (Table 1).

3.4 Relationship between objective and subjective sleep measures

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Insert Table II

Correlations between objective and subjective sleep variables for all subjects are illustrated in Table II. Significant correlations between objective and subjective scores were observed for sleep duration, variability of sleep duration and mean wake time. Similar patterns of correlations were observed within each group separately, though the relationship between objective and subjective parameters of sleep duration was the only one that consistently reached significance (see Appendix 4.5).

3.5 Logistic regression analyses

To assess the ability to distinguish between subjects with bipolar disorder and controls on the basis of sleep and mood measures, direct logistic regression analyses were applied with group membership (2 levels) as the dependent variable, and different combinations of objective and subjective sleep parameters and mood variables as predictor variables. The best model extracted involved a combination of four predictor variables: one actigraphic variable (variability of sleep duration) with two subjective sleep variables (average sleep duration, and average onset latency) and averaged mood ratings over the five days. A test of the full model with these predictors against a constant only model was significant (χ^2 (4)=23.7, $p<.0001$) suggesting that this set of predictors reliably distinguished between bipolar subjects and control subjects. This model predicted 84.2% of cases correctly (78.9% of the bipolar sample and 89.5% of the control group). Table III shows regression coefficients, odds ratios and other relevant statistics for each predictor variable.

Insert Table III

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4. DISCUSSION

The present study is the first to use actigraphy in a sample of euthymic bipolar subjects to compare sleep parameters obtained in a naturalistic setting with those measured in controls. It was hypothesised that the bipolar group would differ from the control group on actigraphic and subjective sleep variables, and particularly that the sleep of the bipolar subjects would be more variable than that of the controls. Although the MANOVAs, which entered a combination of variability measures, failed to find a significant group difference, univariate analyses showed trends towards significant group differences on within-subject variability of actigraphic measures. The bipolar group showed significantly greater night to night variability in sleep duration, and in night waking time. Subjective sleep data further supported the hypothesis of greater variability in the bipolar subjects, in that univariate analyses showed significantly greater night-to-night variability in bipolar subjects for sleep duration, sleep onset latency, and sleep efficiency. These findings provide preliminary support for the hypothesis stated, but should be interpreted cautiously given the relatively small sample size, and the null findings of the multivariate analyses.

The study also aimed to compare the groups on averaged sleep measures over the five day period, although no directional hypotheses were stated. The groups differed on both averaged subjective parameters, and averaged actigraphic parameters on multivariate analyses. For subjective data, univariate analyses demonstrated a significant group difference in average sleep duration, and average onset latency, with the bipolar group reporting sleeping longer and a longer sleep onset latency relative to controls. Similar trends were apparent in the actigraphic data, although group differences did not reach significance.

Across all subjects, objective and subjective parameters of sleep duration correlated significantly, as did objective and subjective parameters of mean wake time. There was no significant relationship between objective and subjective parameters of onset latency, or sleep efficiency. This pattern perhaps relates to findings that while actigraphy accurately reflects trends in overall sleep-wake patterns, the absolute values may be imprecise. In particular, actigraphic parameters of sleep onset latency are more likely to be inaccurate, since these measures tend to be underestimated in subjects who lie still for prolonged periods of time while remaining awake (American Sleep Disorders Association Report, 1995). Nevertheless, actigraphy is believed to provide a more accurate assessment of

general sleep-wake patterns of patients with sleep problems associated with mental disorders (American Sleep Disorders Association Report, 1995). The present data suggest that actigraphs and sleep logs may provide unrelated measures on certain parameters, which strengthens the case for using both types of measurement in a comprehensive study of sleep.

The results presented must be considered preliminary. Nevertheless, the present study suggests that the sleep of stable bipolar outpatients is characteristically different from controls. The findings have clinical implications, in that they suggest that even during periods of optimal functioning, subjects with bipolar disorder have difficulties in maintaining stable and adaptive sleep-wake cycles. This is consistent with the findings of Ashman et al (1999) on daily routines and social rhythms. The limitations of pharmacotherapy in bipolar disorder have increasingly highlighted the need for psychotherapies that acknowledge the bi-directional interplay between biological vulnerability and psychosocial stress (Miklowitz and Frank, 1999). Stressful life events may elicit the expression of biological vulnerabilities by disrupting daily routines and circadian rhythms. For these reasons the role of lifestyle factors is increasingly emphasised in contemporary cognitive-behavioural therapy (CBT); and there is evidence that teaching patients to recognise and manage prodromal symptoms (including changes in sleep) reduces the number of relapses (Perry et al, 1999). The findings of the present study support such approaches, and in addition suggest that a combination of actigraphic monitoring and sleep logs may provide valuable markers of the sleep-wake cycle as part of a monitoring programme.

Finally, the logistic regression analysis found that a combination of variability in objective sleep duration, subjective measures of onset latency and sleep duration, and averaged mood ratings on a VAS, correctly categorised 84.2% of the present subject population. It should be noted that the accuracy of this combination of measures in predicting disorder status in other psychiatric groups has not been tested by this study. Therefore, it is possible that the findings regarding predictors and group differences are not unique to bipolar disorder. Even so, the broad implication of this result is that a relatively simple package of measures could be used to support clinical diagnostic information with a high degree of accuracy.

5. LIMITATIONS

Evidence of differences in the sleep-wake cycle of remitted bipolar outpatients provided by this study should be regarded as preliminary, and interpreted cautiously given the relatively small sample size. It is possible that with a larger sample some of the trends towards group differences would have reached significance. Nonetheless the study provides preliminary evidence for differences in sleep of euthymic bipolar outpatients and controls, and suggests fruitful directions for future large-scale studies. In addition, it should be noted that the sample size compares favourably with previous studies cited, perhaps reflecting the practical difficulties of working with this subject group. The failure to match groups on employment status is recognised as a weakness of the study that may provide an alternative explanation for group differences in variability of the sleep-wake cycle. Difficulties of matching groups on this variable reflect the illness status of the bipolar group, since many of the bipolar group had discontinued work. It would be hard to control for this, since an age-matched healthy control group with the same proportions of unemployment would not necessarily provide a meaningful comparison, and would be unlikely to have the same diversity of occupational histories. It may be that subjects who are earlier in the course of mood disorder would be more likely to be employed, and would be easier to match with controls; although this raises diagnostic issues, since bipolar disorder is often not diagnosed until several episodes have occurred.

6. CONCLUSIONS

This study, the first to use actigraphic monitoring in combination with sleep logs to measure the sleep of a group of outpatients with remitted bipolar disorder, suggests that the more prolonged, naturalistic measurement offered by actigraphic techniques is a useful method for revealing sleep-wake cycle abnormalities in this group. It is worth noting that the differences in sleep parameters between bipolar outpatients and controls identified would almost certainly have been masked by the constraints of laboratory-based methods of sleep measurement. The study suggests that even in the absence of mood symptoms, the sleep of bipolar outpatients is abnormal relative to controls. Bipolar subjects sleep longer than healthy controls, report longer sleep onset latencies and display greater night to night variability in a number of objective and subjective sleep parameters. They also report less stable sleep histories. The suggestion of abnormal sleep patterns, and particularly increased instability in the sleep-wake cycle in bipolar disorder, is consistent with the hypothesis that circadian rhythm disruption is crucial in the aetiology of the disorder.

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Table I
Means and standard deviations of bipolar group and controls on actigraphic and subjective sleep parameters (averaged and variability measures), and results of univariate analyses

Variable	Bipolar group Mean(SD)	Control group Mean(SD)	df	Statistic F	*P value*
Averaged actigraphic measures					
Sleep duration	434.2(91.7)	387.5(53.0)	37	3.69	.063
[a]#Onset latency	19.5(22.1)	8.0(6.9)	37	3.66	.064
Sleep efficiency (%)	83.0(9.2)	86.9(3.6)	37	3.04	.090
Night waking time	59.0(26.0)	49.2(17.5)	37	1.83	.184
Standard deviations of actigraphic measures					
Sleep duration	70.0(39.6)	44.8(24.6)	37	5.53	.024*
#Onset latency	21.4(28.7)	8.8(12.2)	37	3.27	.079
#Sleep efficiency (%)	6.6(6.3)	4.3(2.3)	37	.936	.340
Night waking time	23.6(15.1)	15.4(8.1)	37	4.33	.045*
Averaged subjective measures					
Sleep duration	473.5(112.9)	411.7(56.1)	35	4.19	.048*
#Onset latency	40.9(45.3)	17.3(11.0)	35	9.01	.005**
Sleep efficiency (%)	85.7(8.7)	89.3(10.3)	35	1.32	.258
#Night waking time	38.8(40.8)	30.2(51.0)	35	.362	.552
Standard deviations of subjective measures					
Sleep duration	91.9(63.2)	55.6(31.8)	35	5.19	.029*
#Onset latency	31.2(54.9)	11.6(13.5)	35	4.86	.034*
Sleep efficiency (%)	12.5(8.4)	6.9(5.4)	35	6.23	.018*
#Night waking time	37.2(39.2)	20.8(25.3)	35	1.00	.324

[a]*Note: In table I # indicates that the variable was transformed for the purpose of analyses. In these cases statistics (F values) are the result of analysis conducted on the transformed variable, but means and standard deviations reported were calculated on raw(untransformed) data.*

Variable	r	p value
Sleep duration (mean)	.69	<.001
Sleep duration (SD)	.60	<.001
Efficiency (mean)	.24	.159
Efficiency (SD)	.05	.784
Wake time (mean)	.34	.037
Wake time (SD)	.13	.459
Onset latency (mean)	.23	.175
Onset latency (SD)	.24	.110

Table II
Correlations between objective and subjective sleep parameters[b]
(All subjects)

[b] Pearson correlations are reported for the first three variables, and Spearman's r values for the remaining five variables, in accordance with the distributions of the variables, and the assumptions of parametric statistics

Variables	B	Wald test	df	P value	Odds ratio (Exp(B))
Actigraphic variability of sleep duration	-.037	4.40	1	.036	.964
Subjective – average sleep duration	-.016	3.98	1	.046	.984
Subjective – average onset latency	-.102	3.94	1	.047	.903
Mean mood ratings	.131	2.83	1	.093	1.14
Constant	5.02	.948			

Table III
Results of logistic regression analysis of disorder status as a function of sleep and mood variables

CHAPTER 5
SINGLE CASE RESEARCH STUDY
(Abstract)

An experimental evaluation of the impact of Methylphenidate (Ritalin) and of a behavioural intervention on compulsive checking in a 10 year old boy with Attention Deficit Hyperactivity Disorder (ADHD)

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ABSTRACT

Psychostimulant medication has been shown to be effective in reducing the symptoms of ADHD (Spencer et al, 1996), but can cause side effects including tics and repetitive and compulsive behaviours. This experimental evaluation of the effects of psychostimulant medication (methylphenidate) on compulsive checking behaviour exhibited by a ten year old boy with Attention Deficit Hyperactivity Disorder (ADHD) did not find any difference in the frequency of checking behaviour during two periods of medication withdrawal. However the implementation of a behavioural intervention comprising exposure and response-prevention resulted in immediate extinction of checking behaviour, and this empirically and clinically significant effect was maintained at six-week follow-up. The study suggests that systematic monitoring of possible side effects in children with ADHD who are treated with methylphenidate may represent effective clinical practice, and may usefully inform treatment decisions. Finally, the study adds to the increasing body of evidence in favour of behavioural treatments incorporating exposure and response-prevention for obsessive-compulsive symptoms in children; although further research is necessary to clarify the effective components of treatment and isolate the precise mechanisms of change.

KEYWORDS: ADHD; Exposure and response-prevention; Methylphenidate, Obsessive-compulsive symptoms

1. APPENDICES FOR SMALL-SCALE SERVICE EVALUATION PROJECT

1.1 Copy of notes for contributors to *Health Bulletin*
1.2 Copy of questionnaire
1.3 Description of pilot study
1.4 Psychologists' ratings of the importance of different groups of variables in deciding to allocate to anxiety management groups

1.1 Copy of notes for contributors to *Health Bulletin*

Notes for Contributors

Papers, articles and other contributions should be sent to the Editor, *Health Bulletin*, Scottish Executive Health Department, Room IE05, St Andrew's House, Edinburgh EH1 3DE. They must be submitted exclusively for *Health Bulletin*. Acceptance is on the understanding that editorial revision may be necessary. All papers are reviewed by the Editor and by peer review, referees being drawn from a panel of appropriate professionals. No correspondence can be entered into in relation to articles found to be unsuitable and returned to authors.

Potential contributions can be submitted in two ways. Material submitted for publication must be typewritten on one side of the paper only, in double spacing and with adequate margins, and each page should be numbered. The top typed copy should be submitted, with four other copies. We are willing to receive one copy typewritten in the above format and accompanied by a disk (Microsoft Word version 98, Excel for tables and figures). All papers should be prefaced by a structured Abstract, of about 250 words in length. It should normally contain six clearly headed sections entitled Objective, Design, Setting, Subjects, Results and Conclusion. The name, appointment and place of work of the authors should be supplied on a separate title page. This same page should include the full postal address of one author, to whom correspondence and reprints will be directed. There should be adequate references to any relevant previous work on the subject: these references should appear at the end of the material on a separate page or pages, using the Vancouver style, which in the case of papers in journals includes:

Surname and initials of author(s)
Title of paper
Full name of journal
Year published
Volume number
Opening and closing page numbers

Reference to books should similarly include author's name and initials, full title, edition (if necessary), place of publication, publisher's name, year and, if required, volume number, chapter number or page number.

Short Communications. *Health Bulletin* publishes short communications (not exceeding four pages in length) as a separate section, and we aim to offer speedier publication for these. Material intended for this section should be submitted in the above form, and the covering letter should state the intention.

Proofs

Contributors will receive one set of proofs. This should be read carefully for printer's errors, and any tables, figures and legends should be checked. Alterations should be kept to a minimum, and the proofs should be returned promptly.

Reprints

Ten reprints will be supplied free of charge.

Appendix 1.2. Copy of questionnaire

Sector:

This questionnaire is concerned with the allocation of patients to anxiety management groups. It focuses on some of the issues which clinicians may consider when allocating patients. There are no right or wrong answers; the questions are aimed at finding out the range of *opinions* of clinicians working in the Glasgow Trust. Your help in completing it is much appreciated. It should take approximately 15-20 minutes to complete.

Thankyou very much for your help.

Section 1 General information

Please answer the following general questions in the spaces provided:

1. How long have you been qualified? ----------*Years* ----------*Months*

2. How is your clinical time currently spent? (eg 100% adult mental health, 50% adult mental health 50% learning disability).

---

3. Have you ever had experience of running/ or involvement in an anxiety management group?
   Yes/No (please delete)

If yes, please describe nature of your involvement and the nature of group.

---

4. Do you predominantly adhere to a particular model (or models) in your clinical work? If yes, which model/ models (eg CBT, psychodynamic)?

---

5. In general, to what extent do you agree with the following statements about anxiety management groups?

They are generally extremely useful

Strongly agree 1 2 3 4 5 6 *Strongly disagree*

6. They should only be used in combination with other treatments/ individual therapy

Strongly agree 1 2 3 4 5 6 *Strongly disagree*

7. What size do you think groups should ideally be? (please circle one)

5 or less people *6-10 people* *11-15 people* *More that 15 people*

8. How important/useful do you think each of the following elements of an anxiety management group is? (Please rate, by putting a number beside each)

V important	1	2	3	4	5	Not at all important
Relaxation training						
Applied relaxation						
Information/education about anxiety						
Teaching cognitive techniques for managing anxiety						
Teaching behavioural techniques for managing anxiety						
Opportunity to discuss personal experiences with other group members						
Opportunity to discuss coping strategies with other group members						
Support						
Other (please specify) ---------- ----------						

Section 2 - Factors affecting allocation to anxiety management groups

The following questions deal with some of the factors and issues which may influence decisions to allocate patients to group therapy. Again there are no right or wrong answers.

When considering the questions which follow you should bear in mind that "a group for anxiety management" should be thought of in terms of standard practice - ie a group of 10-15 patients (maximum), lasting for 6-10 sessions, and combining a range of techniques including education, relaxation training, cognitive-behavioural techniques for anxiety management, and opportunities for the sharing of coping strategies.

9. How much influence would the following **demographic** factors have in your decision about whether to include patients in an anxiety management group? (Please rate the importance of each factor/ characteristic by writing a number in the box beside it).

Please give a reason for your answer in the space provided if applicable.

No influence 1 2 3 4 5 A great deal of influence

		Reason
Age of the patient		
Gender		
Social class		
Level/ years of education		
Marital status		
Employment/ occupation		

10. How much influence would the following **patient characteristics** have on your decision to include in an anxiety management group? Please rate as before, and please give a reason if possible.

No influence 1 2 3 4 5 A great deal of influence

		Reason
Patient's motivation for treatment		
Patient's interpersonal/communication skills		
Patient's willingness to disclose information in a group		
Level/ years of education		
Patient's cognitive style		

No influence	1	2	3	4	5	A great deal of influence

Patient's marital/ relationship satisfaction		
Degree of social support available to patient		

11. How much influence would the following **factors connected with the patient's history of treatment** have on your decision to allocate to an anxiety management group? Again please give a reason if possible and applicable.

No influence	1	2	3	4	5	A great deal of influence

		Reason
Medical history		
Previous referrals to psychology/ psychiatry		
History of being treated individually		
Current medical treatment		
Previous medical treatment for psychiatric/ psychological problem		

The following questions are connected with the nature of the anxiety presentation, and whether factors related to sympotomatology and chronicity of problems would affect allocation.

12. Please rate how much influence the following **characteristics of the presentation** would have on your decision and give a reason if possible.

No influence	1	2	3	4	5	A great deal of influence

		Reason
Nature of anxiety symptoms (ie whether primarily cognitive, behavioural, somatic)		
Chronicity of anxiety problem		
Level of anxiety		

13. How likely is it that you would include a patient with the following characteristics of presentation in an anxiety management group? Please rate each on the following scale, and give a reason if appropriate.

Very likely to include in group 1 2 3 4 5 Very unlikely to include in group

		Reason	
Primarily cognitive anxiety symptoms			
Primarily behavioural presentation			
Primarily somatic symptoms of anxiety			
Mild level of anxiety			
Moderate level of anxiety			
Severe level of anxiety			
Problem present for less than 6 months			
Problem present for 6-12 months			
Problem present for 1-3 years			
Problem present for more than 3 years			

The following questions are concerned with the importance of other problems experienced by patients and with the influence of comorbid diagnoses in making decisions about allocations to group treatment.

14. How likely is it that you would include a patient with the following problems/ comorbid diagnoses in a group.

Very likely to include in group 1 2 3 4 5 Very unlikely to include in group

Comorbid medical condition		Diagnosis of OCD	
Bipolar disorder		Comorbid substance abuse	
Comorbid depression (mild)		Comorbid eating disorder	
Moderate depression		Current alcohol abuse	
Severe depression		Current criminal behaviour	

Very likely to include in group 1 2 3 4 5 Very unlikely to include in group

Agoraphobia		Relationship/ interpersonal difficulties	
Social phobia		Marked social problems	
Borderline personality disorder		History of sexual abuse	
Antisocial personality disorder			

15. Are there any problems, characteristics or comorbid diagnoses which would definitely lead you to exclude a patient from a group. Please list, and give a reason if appropriate (NB the list can include any of the factors or problems identified above plus any others you think would definitely lead you to exclude a patient).

The following question focuses on the importance of group factors and practical issues in the decision to include patients in anxiety management groups.

16. How much in general do you think the following **group factors and practical issues** would influence your decision to allocate to group therapy? Please provide a rating in the box.

No influence 1 2 3 4 5 A great deal of influence

Waiting list/ time before individual appointment possible	
Likely mix of people in the group	
Who is leading the group	

17. Are there any *other* factors not mentioned so far which you would consider important in deciding whether to allocate a patient to group or individual therapy? (Please list)

Section 3 - Case Vignettes

In the final short section you are asked to read some brief case vignettes designed to represent a range of possible referrals involving anxiety. You must decide whether each patient would be suitable for inclusion in an anxiety management group. Each vignette consists of a GP referral letter, scores on the Hospital Anxiety and Depression Scale for Anxiety and Depression, and some brief notes, made by a psychologist following first assessment.

Case 1 - Mrs Jean Donalds,
Date of Birth: 9.1.48

GP Referral letter:
I would appreciate your opinion of Mrs Donalds, aged 51, who appears as an anxious lady. However her main symptoms are physical, in particular sweating and dizzy spells, which she has most days. She has recently been assessed by ENT regarding the dizzy spells, and no clear organic pathology was identified. However she has a long history of physical problems, such as headaches, which may be anxiety related. Mrs Donalds says that she is happily married, and has no particular difficulties in her life.

HADS-Anxiety = 18
HADS-Depression = 8

Clinical Psychologist Notes at end of session :
Patient reports longterm history of tension with physical symptoms. Also chronic worrying and poor sleep and concentration. Feels she takes on others' worries. Probable diagnosis of GAD.

1. How likely is it that you would allocate the above patient to a group?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

2. How likely is it that individual therapy would be necessary (in addition)?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

Case 2 - Mrs Ann Brown
Date of Birth: 23.11.67

GP Referral letter:
This pleasant 31 year old woman has been suffering from marked anxiety and depression (which has responded to some extent to Amitryptaline - 100mg/ nocte). She has a number of domestic problems, including her husband's repeated infidelity, and her 17 year old son's involvement in drug dealing.

HADS-Anxiety = 19
HADS-Depression = 14

Clinical Psychologist Notes at end of session :
Patient reports severe stress and depression relating to life events. Husband has had several affairs and has a child with someone else. Husband drinks and uses drugs, son following in his footsteps. Possible domestic violence. Meets DSM criteria for depression and panic disorder.

1. How likely is it that you would allocate the above patient to a group?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

2. How likely is it that individual therapy would be necessary (in addition)?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

Case 3 - John Muir
Date of Birth: 7.1.66.

GP Referral letter:
Thankyou for seeing Mr Muir, aged 33, who presented requesting help with stress at work. He has been finding it increasingly difficult to cope over the past few months, and requested a sick line which I gave him. He has been sufffering from sleep difficulties for some time, and has been drinking heavily at weekends for some time.

HADS-Anxiety = 11
HADS-Depression = 6

Clinical Psychologist Notes at end of session :
Marked anxiety symptoms - difficulty sleeping, worry, headaches, breathlessness and sweating. Has had several panic attacks. Probably symptoms being exacerbated by alcohol. Although drinking a lot at weekends has drunk more heavily in the past. Work situation does seem unreasonable, so a realistic response.

1. How likely is it that you would allocate the above patient to a group?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

2. How likely is it that individual therapy would be necessary (in addition)?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

Case 4 - Mrs Claire Holland
Date of Birth: 21.12.65.

GP Referral letter:
Thankyou for seeing this lady who has developed anxiety and some depressive symptoms since the birth of her baby 6 months ago. She had a very difficult labour and this seems to have triggered the problem. At present she says she is "hyperactive", finds it hard to sit still, and feels frightened all the time. She has lost a considerable amount of weight.

HADS-Anxiety = 18
HADS-Depression = 9

Clinical Psychologist Notes at end of session :
Poor concentration, pressure of speech, some somatic symptoms, hypomanic episode?.

1. How likely is it that you would allocate the above patient to a group?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

2. How likely is it that individual therapy would be necessary (in addition)?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

Case 5 - Helen Dunbar
Date of Birth: 31.1.79.

GP Referral letter:
I would appreciate your assessment of this young woman who complains of low self-esteem, depression and anxiety since her teens. She attempted suicide aged 16 and is known to psychiatric services. In recent years she has coped well, but says that anxiety remains her main problem, especially in social situations which she avoids. She has never had many friends.

HADS-Anxiety = 17
HADS-Depression = 8

Clinical Psychologist Notes at end of session :
Reports a long history of rapid mood changes and inability to cope, but says not so much in recent years. Currently complains of anxiety, particularly in social situations - trembling, sweating. Some agoraphobic avoidance.

1. How likely is it that you would allocate the above patient to a group?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

2. How likely is it that individual therapy would be necessary (in addition)?

Definitely	*Very likely*	*Probably would*	*Probably wouldn't*	*Very unlikely*	*Definitely not:*

Thankyou very much for your time and effort.

Appendix 1.3
Description of pilot study

Sixteen trainee clinical psychologists (in the first year of training) were sampled for the pilot. They were asked to complete the questionnaire, and also to record the time taken to do so, and to provide comments about the process of completion, and about the questionnaire (eg whether they thought any important factors were missed). Twelve out of 16 returned the questionnaire, and the time taken to complete it ranged from 20 minutes to 50 minutes. The pilot study led to a second version of the questionnaire which was significantly shorter and in which the layout of particular questions was changed to provide greater clarity. Since response rate was anticipated as a problem in the study, it was thought important to reduce the length of the questionnaire in order to maximise the response rate. In addition the questionnaire became more structured following the pilot, with three separate sections: general information (including information about experience/ training etc); factors influencing allocation to groups (containing mainly structured questions with rating scales); and case vignettes (containing the five vignettes).

Appendix 1.4
Psychologists' ratings of the importance of different groups of variables in deciding to allocate to anxiety management groups (Figures i – v)

Figure i
Ratings of the importance of demographic variables

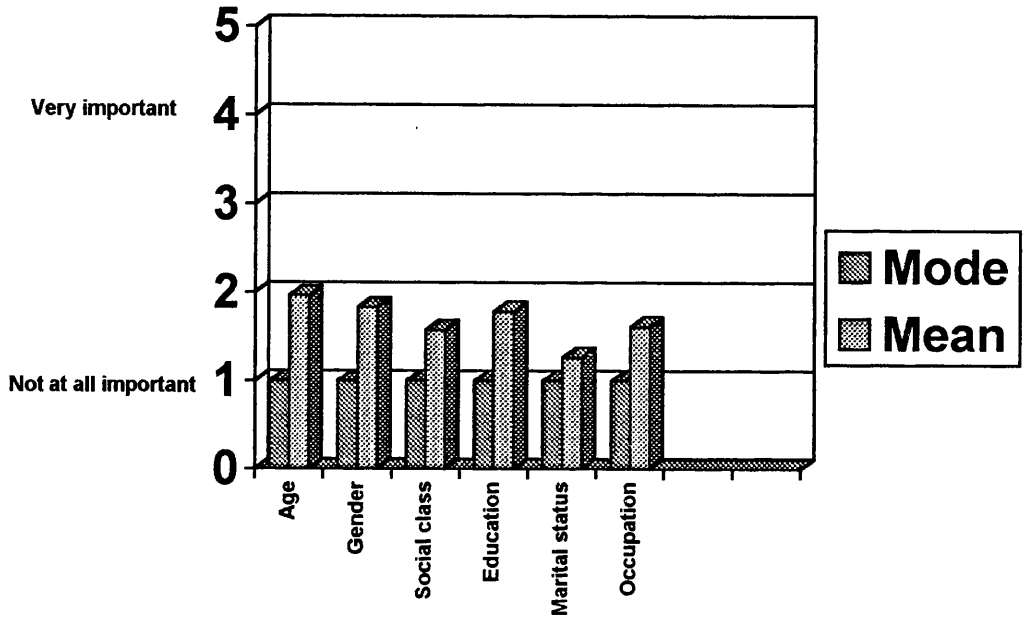


Figure ii
Ratings of the importance of patient characteristics

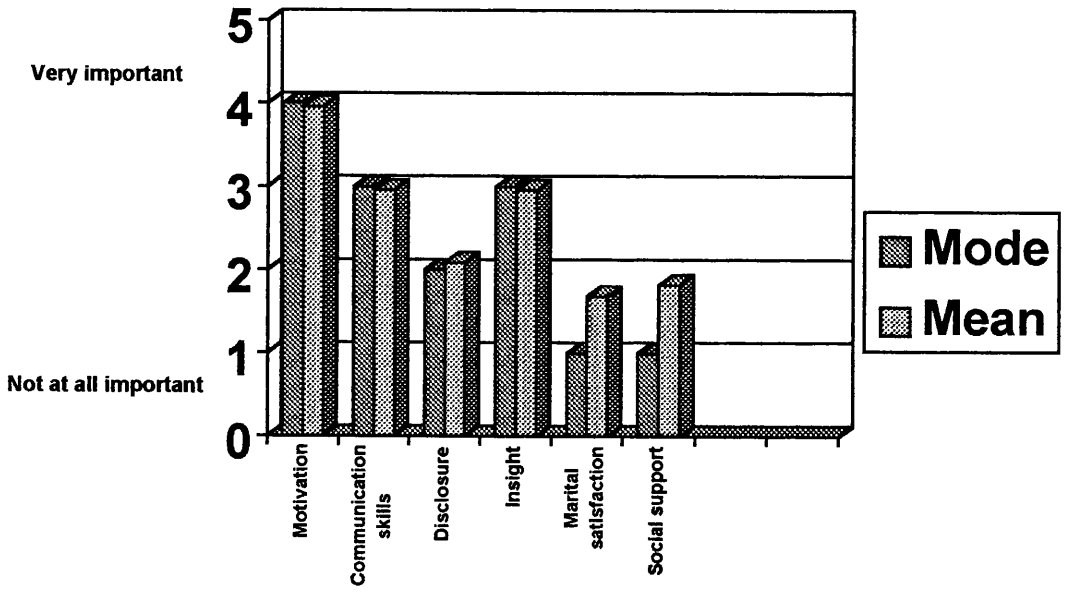


Figure iii
Ratings of the importance of the patient's history of treatment

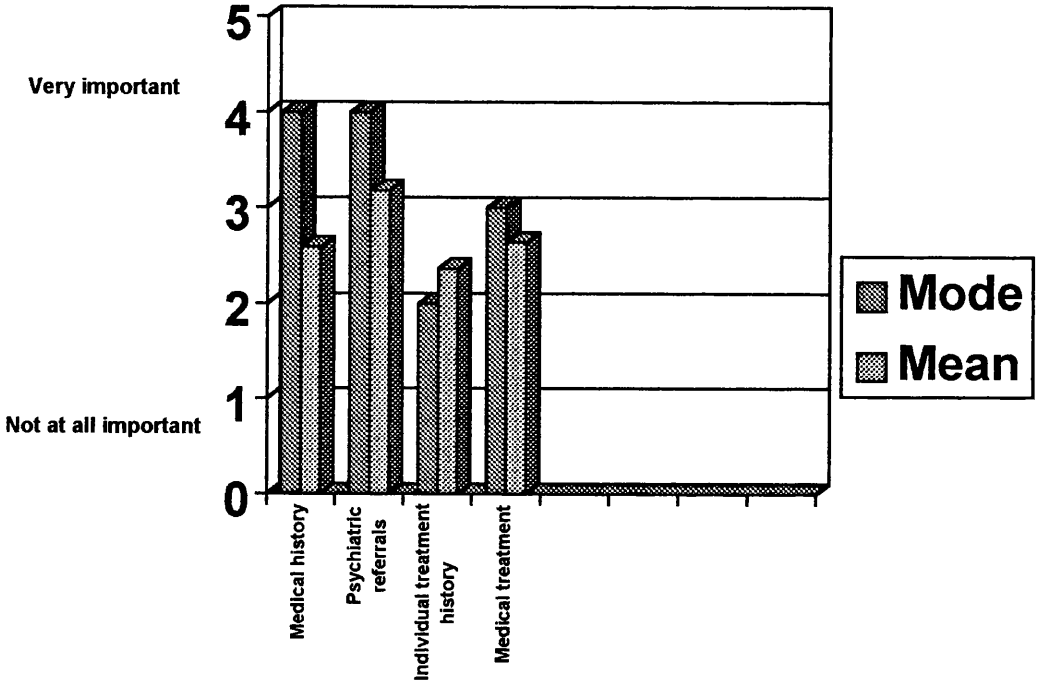


Figure iv
Ratings of the importance of practical/ group issues

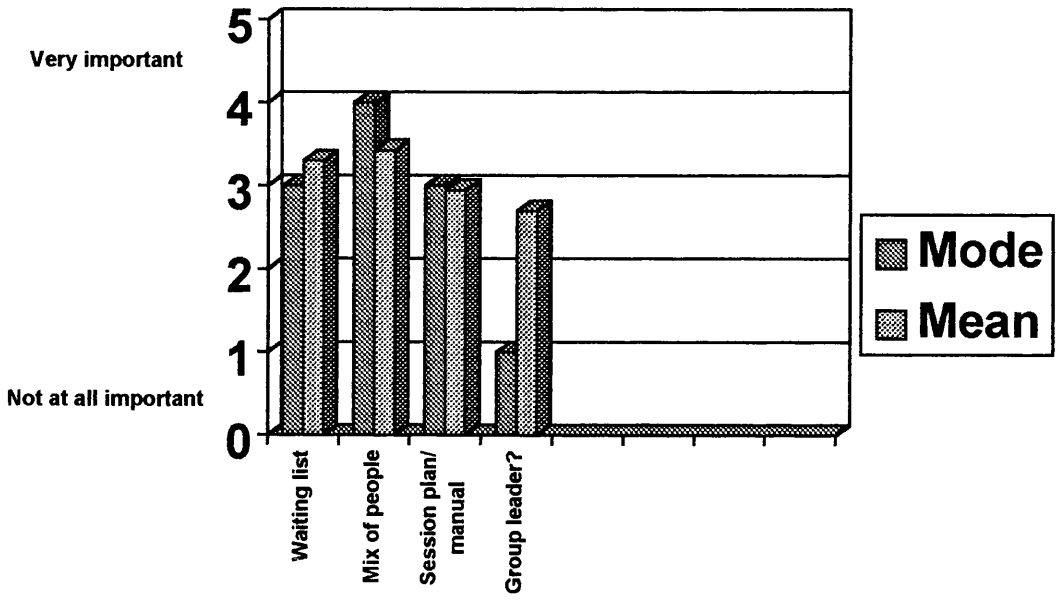
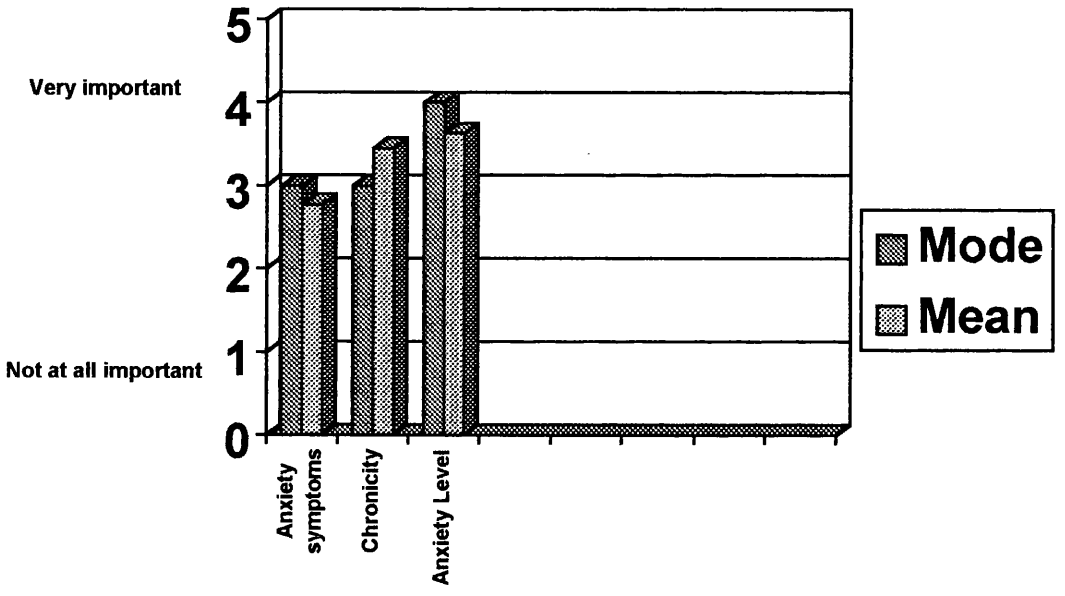


Figure v
Ratings of the importance of the nature of the anxiety presentation



2. APPENDICES FOR MAJOR RESEARCH PROJECT LITERATURE REVIEW

2.1 Copy of instructions to authors for *Journal of Affective Disorders*

ELSEVIER

Journal of Affective Disorders 65 (2001) 217–218

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Instructions to Authors

Manuscript Submission

Submission of a manuscript implies that it contains original work and has not been published or submitted for publication elsewhere. It also implies the transfer of the copyright from the author to the publisher. Four copies of all papers and illustrations are to be submitted along with a letter of transmittal and computer disk (see below) to the appropriate Editor-in-Chief:

For Europe, Asia (except Japan), and Australasia: **C. Katona**, University College London Medical School, Department of Psychiatry, Wolfson Building, Middlesex Hospital, Riding House St., London W1N 8AA, UK.

For the American Hemisphere, Africa, and Japan: **H. S. Akiskal**, University of California at San Diego, V.A. Psychiatry Service (116A), 3350 La Jolla Village Dr., San Diego, CA 92161, USA.

Authors should include permission to reproduce any previously published material. Any potential conflict of interest should be disclosed in the letter of submission. Authors are also requested to include contact information (name, address, telephone, fax, and e-mail) for three potential peer reviewers, to be used at the Editor's discretion. The review process requires 2 to 5 months. All questions concerning the review process should be directed to the appropriate editorial office.

Types of Papers

The Journal primarily publishes full-length *Research Reports* describing original work (a 15-page limit, exclusive of title page, tables, and figures, is requested), but will also accept a small number of *Brief Reports* (10 pages) and evidence-based *Review Articles* (20 pages). *Rapid Communications* (12 pages) will be accepted for expedited publication. Papers that are not developed enough to be research reports, yet offer a new approach can be designated as *Preliminary Communications* (12 pages). *Letters to the Editor* commenting on published material are encouraged and may be submitted electronically (a 500-word and 5-reference limit is requested); these might be sent to the original authors for comment. Books for review should be sent to the appropriate editorial office (see above).

Preparation of Manuscripts

Articles should be in English, typed with double spacing on only one side of consecutively numbered pages. The title page should appear as a separate sheet bearing title (without article type), author names and affiliations, and a footnote with the corresponding author's full contact information, including address, telephone and fax numbers, and e-mail address (failure to include an e-mail address can delay processing of the manuscript). Each author should have participated sufficiently in the work to merit authorship, and any conflict of interest should be disclosed in the letter of submission as well as, if appropriate, in an Acknowledgments section after the text (e.g., if support was received from a pharmaceutical or other sponsor).

Papers should be divided into sections headed by a caption (e.g., Introduction, Methods, Results, Discussion). A *structured abstract* of no more than 250 words should appear on a separate page with the following headings and order: Background, Methods, Results, Limitations, Conclusions (which should contain a statement about the clinical relevance of the research). A list of three to six key words should appear under the abstract.

0165-0327/01/$ – see front matter
PII: S0165-0327(01)00363-9

Submission of Disk

A floppy disk containing a file identical to the four printed copies should be included with the initial submission. MS-DOS format is preferred, although other systems such as Macintosh are also acceptable (but do *not* save in MS-DOS format). Please specify the type of computer and word-processing program used (do not convert your textfile to plain ASCII). Do not write-protect the disk.

Do not justify margins or hyphenate words at line breaks. Please adhere strictly to the general instructions on style, in particular for the references. Ensure that characters (such as letter 'l' and digit '1'; letter 'O' and digit '0') have been used properly and article formatted (tabs, indents, etc.) consistently. Characters not available on the word processor should be indicated by a unique code (such as gralpha, @, or # for the Greek letter ') that is used consistently throughout the text and a key to such codes provided.

Tables and Figures

Tables and Figures should be limited to necessary data that cannot be incorporated in the text.

Line drawings (including graphs) should be in black ink on white paper or on tracing paper with blue or faint grey rulings; graduation will not be reproduced. Lettering should be large enough to permit photographic reduction. If figures are not to be reduced, their format should not exceed 16 × 20 cm. Photographs (or half-tone illustrations) must be good-quality black-and-white prints on glossy paper with as much contrast as possible. Figures should be clearly marked on the reverse side with the number (arabic numerals), orientation (top), and author's name; a felt-tipped pen or soft pencil should be used for such markings. The legends should be typed separately and included in the manuscript double spaced.

Each table should appear on a separate sheet, numbered with arabic numerals and provided a short descriptive title and footnotes identified by superscript letters (^{a}, ^{b}, ^{c}, etc.).

References should be cited in text by authors' names and year of publication (Harvard system). When referring to a work of more than two authors, the name of the first author should be used with 'et al.' (examples: Brown, 1992; Brown and Bifulco, 1992; Brown et al., 1993, a, b).

All references cited in text should be listed at the end of the paper (double spaced) arranged in alphabetical order of first author. More than one paper from the same author in the same year should be identified by the letter (a, b, c, etc.) after the year of publication.

The reference list should contain names and initials of all authors, year, title of paper referred to, abbreviated title of periodical (per *Index Medicus*), volume, and inclusive page numbers. This Journal should be cited in the list of references as J. Affect. Disord. Periodicals, books, and multi-author titles should accord with the following examples:

Bauer, M.S., Shea, N., McBride, L., Gavin, C., 1997. Predictors of service utilization in veterans with bipolar disorder: a prospective study. J. Affect. Disord. 44, 159–168.

Gelenberg, A.J., Bassuk, E.L., Schoonover, S.C., 1991. The Practitioner's Guide to Psychoactive Drugs. Plenum Medical Book Company, New York, NY.

Willner, P., 1995. Dopaminergic mechanisms in depression and mania. In: Bloom, F.E. and Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press, NY, pp. 921–931.

Proofs and Reprints

One set of proofs will be sent to the author to be checked for typographical errors. No other alterations will be accepted. Fifty reprints are provided free of charge. Additional copies may be ordered via the reprint order form sent with the proofs. There will be no page charges.

Questions arising after acceptance of the manuscript, especially those relating to proofs, should be directed to Elsevier Science Ireland Ltd., Elsevier House, Brookvale Plaza, East Park, Shannon, Co. Clare, Ireland. Tel (+ 353-61) 709600. Fax (+ 353-61) 709100.

3. APPENDICES FOR MAJOR RESEARCH PROJECT PROPOSAL

3.1 Copy of guidelines for application for a mini-project grant (SOHHD Chief Scientist Office).
3.2 Consent form
3.3 Sleep History Questionnaire
3.4 Information sheet for subjects
3.5 Sleep diary
3.6 Daily mood rating scale
3.7 Ethical approval letters
3.8 Copy of previous research proposal

3.1 Copy of guidelines for application for a mini-project grant

1.1 Applicants - names and addresses including the names of co-workers and supervisor(s) if known.

1.2 Title - no more than 15 words.

1.3 Summary - No more than 300 words, including a reference to where the study will be carried out.

1.4 Introduction - of less than 600 words summarising previous work in the field, drawing attention to gaps in present knowledge and stating how the project will add to knowledge and understanding.

1.5 Aims and hypothesis to be tested - these should wherever possible be stated as a list of questions to which answers will be sought.

1.6 Plan of investigation - consisting of a statement of the practical details of how it is proposed to obtain answers to the questions posed. The proposal should contain information on Research Methods and Design i.e.

1.6.1 Subjects - a brief statement of inclusion and exclusion criteria and anticipated number of participants.

1.6.2 Measures - a brief explanation of interviews/observations/ rating scales etc. to be employed, including references where appropriate.

1.6.3 Design and Procedure - a brief explanation of the overall experimental design with reference to comparisons to be made, control populations, timing of measurements, etc. A summary chart may be helpful to explain the research process.

1.6.4 Settings and equipment - a statement on the location(s) to be used and resources or equipment which will be employed (if any).

1.6.5 Data analysis - a brief explanation of how data will be collated, stored and analysed.

1.7 Practical applications - the applicants should state the practical use to which the research findings could be put.

1.8 Timescales - the proposed starting date and duration of the project.

1.9 Ethical approval - stating whether this is necessary and, if so, whether it has been obtained.

Division of Clinical Psychology

Direct Line: 0141-211
Fax: 0141-357 4899
E-mail:

Appendix 3.2 Consent Form

UNIVERSITY *of* GLASGOW

Consent Form

Project title: Sleep patterns, activity and mood.

Before you sign:

- You should have been given an explanation of the research in which you are being invited to take part
- You should have had the opportunity to read an Information Sheet with details about the study and what you would be required to do (you can keep this sheet)
- You should have had the opportunity to ask questions
- There is no obligation to take part – you do not need to take part, and if you agree to do so you can withdraw at any time
- Participation or non-participation will not affect your treatment or routine care in any way

I _____ (name in block letters)

hereby give consent to be included in the above research project being undertaken at the Department of Psychological Medicine by Audrey Millar, Clinical Psychologist in training, and Professor Colin Espie.

The project has been described to me by

_____

(name in block letters)

Signature _____ Date _____

Researcher signature _____ Date _____

Appendix 3.3. Sleep History Questionnaire

Sleep History Questionnaire

Section 1: Current sleep-wake schedule

1. What is your usual bedtime on weekdays? _____
2. At what time do you last awaken in the morning (on weekdays)_____
3. What is your usual rising time on weekdays? _____
4. Do you have the same sleep-wake schedule at weekends? **Yes/ No**
5. If not, how does your sleep pattern differ at weekends?

   _____
6. During the past month, how many hours of actual sleep did you get a night? (This may be different than the number of hours spent in bed).

   _____
7. During the past month, how would you rate your sleep quality overall?

   Very good Fairly good Fairly bad Very bad

Section 2: Sleep/ wake difficulties

1. Do you have a problem with falling asleep?	No	Mild	Moderate	Severe
2. Do you have a problem with staying asleep?	No	Mild	Moderate	Severe
3. Do you have a problem with waking up too early in the morning?	No	Mild	Moderate	Severe
4. Do you have a problem with staying awake during the day?	No	Mild	Moderate	Severe

5. How many nights a week on average do you have a problem with falling/ staying asleep?

   _____
6. On a typical night (past month), how long does it take you to fall asleep after you go to bed and turn the lights off?

   _____ hours _____ minutes
7. On a typical night (past month), how many times do you wake up during the middle of the night?

   _____ times

8. What wakes you up at night? (eg pain, noise, child, spontaneous)

_____

9. On a typical night, how long do you spend awake in the middle of the night?

_____ hours _____ minutes

Section 3: Sleep history

1. Is your sleep pattern stable across time – ie from month to month and year to year?

Very unstable Fairly unstable Fairly Stable Very stable

(If variable, in what way does it vary?)

_____

2. If you suffer from difficulties sleeping how long has this been a problem?

_____ years _____ months

3. Was the onset of your sleep difficulties gradual or sudden? _____

4. What has been the course of your insomnia problem since its onset? (eg persistent, episodic, seasonal)

_____

Section 4: Coping with sleep difficulties

1. How concerned are you about sleep and sleep difficulties

Not at all concerned Fairly unconcerned Fairly concerned Extremely concerned

2. What impact does insomnia/ sleep difficulties have on your life? (eg mood, alertness, performance)

_____

_____

3. What types of factors improve your sleep?

_____

_____

4. What types of factors exacerbate your difficulties with sleep, if any?

_____

_____

5. Have you ever used sleeping pills or other medication to aid sleep? Yes/ No

If yes....
Which drugs/ medicines? _____
What dosage? _____
On how many nights per week? _____

6. In the past 4 weeks have you used sleeping pills/ medication?
   _____

7. Have you ever used alcohol to help you sleep? **Yes/ No**

If yes.....

In the past 4 weeks have you used alcohol as a sleep aid? **Yes/No**

Division of Clinical Psychology

Direct Line: 0141-211
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E-mail:

Appendix 3.4

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of
GLASGOW

Information sheet for Participants in Clinical Research Study

Project title: Sleep patterns, activity and mood.

Summary:

You are being invited to take part in a study of sleep patterns, and the relationship between these and mood. This study is being carried out at the Department of Psychological Medicine at Glasgow University, by Audrey Millar (Clinical Psychologist in training), and Professor Colin Espie.

This study aims to find out whether sleep pattern and changes in sleep pattern may be important in relation to mood in people with a history of mood problems. It is thought that sleep and activity levels may be important factors, but there is not a great deal of detail known about the area. By taking part you will be helping to increase the knowledge about mood disorders. This may in turn help to improve care in the future.
Your participation is voluntary. Whether or not you decide to take part will have no effect on your treatment or routine care. You can refuse to take part or can withdraw from the study at any time, and this will have no effect on your treatment.

What will happen if you agree to take part?

You will meet with Audrey Millar, one of the researchers who will explain more about the project. If you agree to take part, you will be asked to complete one questionnaire about your sleep pattern.

You will be shown an "actiwatch". This is a device that looks like a wrist watch. You wear it on your wrist and it automatically records how much activity you do. It helps us to measure your sleep.

You will be asked to wear the watch constantly for 5 days and nights.

During the time you are wearing the watch you will be asked to complete the following:

- a simple sleep log /diary each morning when you wake
- a simple rating of your mood twice each day, once in the morning and once in the evening

PLEASE TURN OVER/

In total, this should only take a few minutes of your time each day. You will have all of the measures shown and explained to you at the beginning, and will have a chance to ask questions. During the time when you are wearing the watch and completing the measures you will be given a contact number in case you have any questions or queries.

After the agreed number of days are up you can take the watch off. You will be given another appointment to meet and return the watch and diaries. You will again have the chance to ask questions at this point.

All of the information recorded will be **CONFIDENTIAL.** This means that the information will be recorded anonymously and will not be passed to anyone outside the study. You will not be identifiable since a code will be attached to your diaries, rather than your name.

The study is not linked to your treatment or routine care in any way.

Appendix 3.5

Sleep diary

To be completed *every morning*, *starting tomorrow*

Please complete this sheet each day as soon as you get up. **Thank you**.

	Day 1	Day 2	Day 3	Day 4	Day 5
At what time did you get up this morning?					
At what time did you go to bed last night?					
How long did it take you to fall asleep (minutes)?					
How many times did you waken up during the night?					
How many times were you awake for longer than 10 minutes?					
How long were you awake during the night in total?					
About how long did you sleep altogether? (hours/ minutes)					

Appendix 3.6

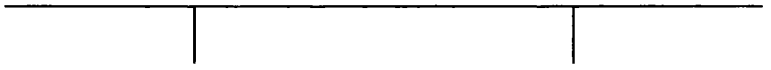
Daily mood rating

Please put a cross mark X on the line at the point that best represents your mood (how you are feeling).

Please do this *twice* daily.

Rate your mood <u>once in the morning</u> when you get up, and <u>once last thing at night</u>, before you go to bed.

Morning



Most depressed/ down I've ever felt	Well	Most manic/ 'high' I've ever felt

Evening

Most depressed/ down I've ever felt	Well	Most manic/ 'high' I've ever felt

Appendix 3.7
Ethical approval letters

Note: Ethical approval was gained from Greater Glasgow Primary Care NHS Trust Ethics Committee within the context of the larger scale pilot study: A pilot study of psychobiosocial functioning in bipolar disorder; being conducted within the Department of Psychological Medicine by Miss Alison Tait and Professor Jan Scott. Independent ethical approval was sought and gained from Argyll and Clyde Health Board Local Research Ethics Committee.

Our Ref: BR/AW/APP

GREATER GLASGOW
PRIMARY CARE
NHS TRUST

27 July 2000

Ms A Tait
Research Associate
Department of Psychological Medicine
Gartnavel Royal Hospital
105 Great Western Road
Glasgow
G12 0XH

Dear Ms Tait

Project Reference Number: **00AM04**
Project Title: **A pilot study of psychobiosocial functioning in bipolar disorders**

The above research project has now received the approval of the Research and Development Directorate. Therefore, if you have received the approval of the Ethics Committee, your research may commence.

The enclosed computer print-out shows your project details which have been entered on the Trust's R & D database. The information we collect follows Chief Scientist Office guidelines and will be entered on the National Research Register in due course. You should therefore check the information entered, correct any errors and return to the Research & Development Directorate as soon as possible.

Information on the database will be up-dated from time to time and I would appreciate if you would inform the R & D office of any change of details. A final report should also be submitted when the project is complete.

Do not hesitate to contact the R & D office if you need any assistance in submitting the necessary information.

Your help is much appreciated.

Yours sincerely

BRIAN RAE
Research Manager

Enc.

Research & Development Directorate, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH
Tel 0141 211 3661 Fax 0141 211 3814 e.mail annette.watt@gartnavel.glacomen.scot.nhs.uk

Ref: AMcM

GREATER GLASGOW
PRIMARY CARE
NHS TRUST

28 April, 2000

Ms Alison Tait
Academic Centre
Gartnavel Royal Hospital
1055 Gt Western Road
Glasgow
G12 0XH

Dear Ms Tait

PROJECT: ***A pilot study of psychobiosocial functioning in bipolar disorder***

Many thanks for sending the required amendments to the above named submission to the Research Ethics Committee - I am pleased to be able to tell you that the Committee now has no objections from an ethical point of view, to this project proceeding and ethical approval is formally granted. Before your project commences you will also require to obtain management approval via the Research & Development Directorate, Gartnavel Royal Hospital.

I would also like to take this opportunity to remind you that you should notify the Committee if there are any changes, or untoward developments, connected with the study – the Committee would then require to further reconsider your application for approval. The Committee expect to receive a brief regular update every 6 months, and then a brief final report on your project when the study reaches its conclusion. (Failure to keep the Committee abreast of the status of the project can eventually lead to ethical approval being withdrawn)

May I wish you every success with your study.

Yours sincerely

A W McMAHON
Administrator – Research Ethics Committee

cc B Rae

Direct Line: 0141 842 7266
Karen Harkins
Direct Fax: 0141 842 7308

Your Ref:

Our Ref: LREC 85/00

Date: 24th January 2001

Ms Audrey Millar
Clinical Psychologist in Training
Dept. of Psychological Medicine
Gartnavel Royal Hospital
1055 Great Western Road
GLASGOW
G12

Dear Ms Millar

SLEEP AND ACTIVITY AS MARKERS FOR MOOD CHANGE IN BIPOLAR ILLNESS

Thank you for forwarding a copy of your C.V. as requested in my last letter dated 11th December 2000.

I can confirm that there is no objection on ethical grounds to the proposed study and I write to give you our approval to proceed on the understanding that: -

a. All patients recruited to the study will be interviewed by the Clinician responsible for the conduct of the trial or a member of the Clinical Team who will obtain consent. This will not be delegated to an external agency.

b. You will notify the Medical Director of any hospital whose facilities you may use during the conduct of the study.

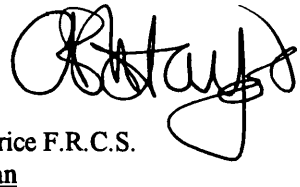
c. You submit a progress report to this Committee one-year from the date of this letter.

In reaching the decision the following documents were reviewed:-

Protocol
Application Form
Participant Information Sheet
Participant Consent Form
GP/Consultant Letter
GP/Consultant Information Sheet
Instructions for wearing an "actiwatch"
Sleep Diary
Daily Mood Rating
Sleep History Questionnaire
BIS/BAS Scales
C.V.

A list of Committee Members present at the meeting held on 6th December 2000 is appended.

Yours sincerely



J.J. Morrice F.R.C.S.
Chairman

cc. Elaine Garman, Director of Clinical Development

Appendix 3.8 Copy of previous Research Project Proposal

Major Research Project Proposal

Trainee: Audrey Millar

Supervisor: Professor Colin A Espie

Date submitted: 29 March, 2000

Applicants:

Audrey Millar,
Trainee Clinical Psychologist,
Department of Psychological Medicine,
Gartnavel Royal Hospital,
1055 Great Western Road,
GLASGOW
G12 0XH

Professor Colin A Espie,
Department of Psychological Medicine,
Gartnavel Royal Hospital,
1055 Great Western Road,
GLASGOW
G12 0XH

Title

Sleep and psychomotor activity as markers for mood change in bipolar illness

Summary

Although no causal relationship has been described it is clear that changes in activity levels and sleep pattern co-occur in mood disorders, and that these relate to changes in mood. In bipolar disorder there is evidence that shifts in sleep and activity patterns may predict relapse. One explanation for this lies with theories of "behavioural engagement" systems or general motivational systems; hypothesised to be neurobehavioural systems underlying behaviour and affect. Existing research leads to the prediction that sleep, activity, and levels of behavioural "engagement" will differ according to illness-phase in bipolar disorder, however to date there has been no attempt to compare subjects in different illness phases of bipolar disorder on all of these variables.

This study aims to explore the relationship between sleep, psychomotor activity; a measure of behavioural "engagement", and mood in bipolar subjects, using a cross-sectional design. Subjects with a confirmed psychiatric diagnosis of bipolar disorder will be recruited via Clinical Psychology Departments and Community Mental Health Teams, and allocated to one of three groups: 1. Current manic/ hypomanic mood state. 2. Current depressive mood. 3. Euthymic/ stable. Allocation will be based on the keyworker's assessment of the subject's mood state, together with self-reported mood ratings provided by the subject. psychiatric diagnosis, together with information from the SCID-IV interview conducted by the researcher. Based on a power calculation, we aim to recruit 7-10 subjects in each group. Brief information will be recorded on current medication use. Subjects will provide brief information about their sleep history (within the form of a questionnaire based on the Sleep History Questionnaire), and will also complete the Behavioural Inhibition/ Behavioural Activation Scale (Carver and White, 1994) to provide a measure of behavioural engagement. Objective parameters of sleep and psychomotor activity will be recorded over a five day period using actiwatches. During this period subjects will also complete brief sleep logs daily, and will rate their mood on a visual analogue scale twice daily. Groups will be compared using ANOVAS with illness phase as a between subjects factor.

Introduction

Objective measurement and quantification of sleep and activity is possible using computerised wrist actigraphs (Sadeh et al, 1995). Actigraphy allows continuous monitoring of sleep-wake cycles in a naturalistic environment over a prolonged period (usually 72 hours, but can be used for up to 20 days/nights). Actigraphic recordings provide data from which variables on a range of features related to sleep can be calculated; eg sleep onset time, sleep duration, wake time after sleep onset and "sleep efficiency". Actigraphy also allows psychomotor activity to be continuously monitored over time.

To date, research in a number of diverse areas has shown actigraphy to be a useful, and valid method of measurement. Several studies illustrate the validity of using actigraphic measurement in mood disordered subjects. Many of these studies also suggest that shifts in patterns of activity and in the sleep-wake cycle are strongly associated with changes in mood.

Using actigraphy Klein et al (1991) found that bipolar patients who relapsed on discontinuation of lithium demonstrated higher levels of activity at baseline. A related study showed that relapsers (as opposed to non-relapsers) demonstrated a marked reduction in nightly sleep duration (total sleep time) and in "sleep efficiency" on discontinuation of lithium (Klein et al, 1992). Wehr et al (1982) recorded wrist motor activity and sleep using actigraphy in 9 rapidly-cycling bipolar patients in a depressive phase. Subjects simulated a 48 hour sleep-wake cycle by remaining awake for 40 hours (one night's total sleep deprivation). Eight of the nine subjects switched out of depression, and seven were rated as manic/ hypomanic, suggesting that sleep loss may have an antidepressant effect in this group, and may trigger switches from depression to mania. A case study conducted over a period of several years, used actigraphic wrist motor recordings in conjunction with sleep logs in a rapidly-cycling bipolar patient. The study provides further evidence of the relationship between sleep pattern changes and mood change, in that it demonstrated that mood can be stabilised by adherence to a regime of extended bed-rest and darkness (Wehr, 1998).

Actigraphy has also been used in depressed subjects to explore the relationship between sleep and mood. Studies have demonstrated that activity levels (and immobility parameters

provided by actigraphic recordings) are a good indicator of subjective severity of depressive state (Benoit et al, 1985; Royant-Parola et al, 1986).

Findings on the importance of the sleep-mood relationship in mood disordered subjects using actigraphy are supported by a wider literature using other sleep measures. In an experimental study Barbini et al (1998) demonstrate that depressed mood can be treated using sleep deprivation; and that this is more effective in bipolar depression than in unipolar depression.

In a longitudinal, naturalistic study Leibenluft et al (1996) used logistic regression analysis to explore the relationship between daily self-ratings of mood, and sleep logs in eleven rapidly-cycling bipolar patients. The study found that decreased sleep duration was the best predictor of mania or hypomania the next day, and that the association between sleep and mood was more consistent for mania than for depression. In a correlational study Barbini et al (1996) explored the association between sleep duration and manic symptoms in 34 manic bipolar inpatients. Sleep variables were rated by nursing staff, and the study found a significant inverse correlation between sleep duration and manic symptomatology.

Overall, research to date suggests that sleep and activity levels have a significant relationship to mood in both unipolar and bipolar mood disorders. One explanation for this relationship may lie in a connected group of theories which focus on general motivational systems underlying behaviour and affect. Although theorists differ in their views of how such a system might operate, there is some agreement that such a system is likely to be important in bipolar disorder. Depue and Iacono (1989) describe a "behavioural facilitation system" (BFS), which mobilises behaviour so that active "engagement" with the environment occurs under appropriate stimulus conditions. They suggest that functional disturbance in the BFS results in the broad diversity of engagement behaviours affected in bipolar disorders. According to this model symptoms of bipolar depression and hypomania/ mania represent opposite extremes of a normal behavioural dimension; with retarded bipolar depression characterised by lack of affective reactivity at one end of the spectrum, and mania/hypomania at the other end, characterised by high incentive-reward motivation and excitement/ positive affect.

Gray's (1981, 1982) model of behavioural engagement is similar to this, but rather than a unidimensional model Gray postulates two general motivational systems underlying behaviour and affect – a behavioural inhibition system (BIS) and a behavioural activation system (BAS). The two systems proposed are like the poles or extremes in Depue's single dimension of the BFS. Gray's model is also implicated as being important in understanding affect and personality, however the dimensions are conceptualised more in terms of stable individual differences in responsiveness which represent personality tendencies. Carver and White used Gray's model to devise a scale designed to measure BAS/BIS sensitivity (Carver and White, 1994). If bipolar disorder can be understood in terms of disturbance within the BFS (whether unidimensional or bidimensional), it may be that some measure of "engagement" (perhaps based on the scale devised by Carver and White) can tap into different levels of behavioural engagement in bipolar subjects.

Literature to date suggests that "biological" symptoms such as sleep and activity levels may act as markers for mood change and relapse in bipolar illness. It may be that changes in sleep and activity are indicative of shifts in a broader neurobehavioural system of behavioural engagement. In any case, it is probable that changes in these different features co-occur, and that there will be a measurable relationship between sleep variables, levels of psychomotor activity, "engagement" variables and mood state variables. Although writers such as Depue have postulated particular types of relationship between these different groups of variables no study has specifically explored or described the relationship(s) between sleep, mood *and* a measure of "engagement" in a bipolar group. In addition, no previous study has compared actigraphic data on sleep and activity from bipolar subjects in different illness phases (ie manic, depressed, euthymic).

Aims and hypotheses

This study has the following aims:

1. to describe the effect of illness phase/ mood state on measures of sleep, psychomotor activity, and "behavioural engagement" in bipolar subjects over a five day observation period, by comparing subject groups during different illness phases/ mood states

2. to explore the relationships between sleep parameters, objective parameters of psychomotor activity, a measure of "engagement" and self-reported mood in a group of bipolar subjects over a five-day observation period

The study aims to test the following hypotheses:-

1. total sleep duration will be significantly less in the manic/ hypomanic group than in euthymic or depressed bipolar subjects

2. total levels of psychomotor activity will be greater in the manic/ hypomanic subjects than in the euthymic or depressed subjects

3. subjects whose mood is hypomanic will differ from those in the depressed or euthymic groups on measures of "engagement" (ie being more highly "engaged")

4. the different groups of variables will be related, in that reduced sleep duration will be associated with increased psychomotor activity, increased levels of behavioural "engagement" (activation), and elevated mood; while increased sleep duration will be associated with less activity, less "engagement" and low mood.

The study will also explore possible differences between subject groups in the level of agreement between subjective parameters of sleep/ activity, and parameters yielded by actigraphy on sleep and activity.

Plan of investigation

The study will run independently over a 12 month period, but data will be collected within the wider context of the MDF-funded longitudinal study "psychobiosocial functioning in bipolar disorders" taking place in the Department of Psychological Medicine, Glasgow University. Some data may subsequently act as a pilot for sleep measurement within this longitudinal study.

Subjects

Subjects with a confirmed psychiatric diagnosis of bipolar disorder (I or II) will be recruited via a CMHT on the outskirts of Glasgow over a 6 month period.

Inclusion criteria - subjects must fulfil DSM-IV criteria for bipolar disorder, according to casenotes and psychiatric diagnosis. Subjects must show willingness to provide informed consent. Subjects should be aged 18-65 years.
Exclusion criteria - Subjects unable to provide informed consent will be excluded. Subjects must not meet DSM-IV criteria for major psychiatric disorders other than bipolar disorder (ie personality disorders, schizophrenia). Subjects should not be currently being treated for any drug or alcohol problems, or currently be involved in another research study.

Design and procedure

In order to test the hypothesis that sleep, psychomotor activity, and a measure of "engagement" vary according to illness-phase in bipolar illness it is necessary to compare data from different phases of bipolar disorder. Ideally this would be done using a within subjects longitudinal design. However as a preliminary investigation, (and as a potential pilot study for this aspect of the longitudinal study described above) a controlled cross-sectional design will be implemented.

Bipolar subjects will be recruited through Clinical Psychology departments and from CMHTs, and allocated to one of three groups - 1. Current hypomania 2. Current depression 3. Euthymic - currently stable. This allocation will be based on key mental health worker's opinion or psychiatric diagnosis using DSM-IV criteria, and independently confirmed by the self-reported mood rating provided by the subject at entry to the study. Following recruitment to one of the three groups a brief initial interview will be conducted in order to administer a Sleep History Questionnaire (based on Morin, 1993) and to record some basic information about current medication. The Behavioural Inhibition/ Behavioural Activation Scales (Carver and White, 1994) will also be administered at this point. Objective measures of psychomotor activity and sleep parameters will be provided by wrist actigraphs worn over a 5 day period (see Sadeh, 1995). In addition, the following measures will be completed daily over the same period:-

- sleep diaries / logs (Espie, 1991) completed in the morning upon rising
- a simple visual analogue measure of mood rated 0-100 (Whybrow & Guylia, 1995) completed twice daily; once in the morning upon rising, and once in the evening

Statistical power

In consideration of statistical power it should be noted that existing studies using actigraphy in bipolar subjects, have employed longitudinal designs (Leibenluft et al, 1996), correlational analyses between sleep and mood variables measured over a short period (eg Barbini et al, 1996), or experimental group designs (eg Barbini et al, 1998; Wehr et al, 1982). To date no study has used actigraphic measures in this subject group in a cross-sectional design, however existing research cited suggests a large effect size between the hypomanic/ manic subjects and the other groups on parameters of sleep such as sleep duration. A power calculation conducted on the basis of a large effect size, a significance (alpha) level of 0.05, and statistical power of 0.8, for a three group ANOVA design suggests that n= 21 in each group will result in a study with sufficient power (Cohen, 1992). As stated, a minimum of 5 days and nights will be sampled from each subject on each measure. Following the protocol of Wicklow and Espie in a study utilising actigraphy in insomniacs, (Wicklow and Espie, 2000) "subject nights" will form the basis of the comparison between the three groups, taking account of correlation between participants' consecutive nights in the analysis.

On this basis 21 subject "nights" per group are necessary for the purposes of this study (for example seven subjects x 3 "nights" observation per group). Over a 6 month period therefore we aim to recruit 7-10 subjects to each group (20-30 bipolar subjects in total). Previous studies cited above indicate this will result in sufficient power.

Information about medication use and sleep history will be routinely recorded at first contact. Where possible, participants recruited to each group will be matched on these and other variables (age, sex) to reduce extraneous effects.

Settings and equipment

Following identification of subjects, initial brief interviews to record information re medication, administer a Sleep History Questionnaire (Morin, 1993), the BIS/BAS Scales (Carver and White, 1994) and explain all measures will take place either at the Community Mental Health Team Resource Centre, the relevant Psychology department, or the Department of Psychological Medicine at Gartnavel Royal. Wrist actigraphs (Cambridge

Neurotechnology "Actiwatch-score" models) will be borrowed from the Department of Psychological Medicine at Gartnavel Royal Hospital. Subjects will be given instructions re wearing the actiwatch and completing the daily package of measures. Subjects will be provided with a telephone contact number for the five days of measurement, so that if problems or queries arise with regard to any of the measures they can contact the researcher. Another appointment will be arranged to meet with the researcher and return measures and the actiwatch at the end of five days. Data from actiwatches will be downloaded onto PC within the Department of Psychological Medicine using available software.

Data analysis

Data will be stored in a lockable filing cabinet at the Department of Psychological Medicine, and entered anonymously onto a data base (with codes attached). The package SPSS for Windows will be used to analyse data, and a series of ANOVAs with illness phase/ group as the between subjects factor will be conducted on key outcome variables (sleep and activity) with post hoc tests to identify the source of significant effects. Correlational analyses will be conducted to explore associations between groups of variables (eg sleep and mood). Hypotheses relating to the interrelationship of the measures will be tested by the within subjects aspect of the design, separating for each phase of the illness.

Practical applications

Greater understanding of the relationship between 'biological' variables such as sleep and psychomotor activity, and subjective experiences of mood and "engagement" in bipolar disorders should lead to more understanding of the course of the illness, and the signs associated with movement between different phases in the illness. A recent randomised controlled trial (Perry et al, 1999), provides evidence that teaching patients to recognise manic prodromes (including recognising and monitoring biological symptoms such as changes in sleep), can significantly reduce relapse rates (number of relapses, and time to first relapse). There is increasing emphasis on the idea that identifying specific "relapse signatures" and sensitising patients to early warning signs within a CBT approach to bipolar disorder can result in earlier clinical presentation, and therefore can reduce the frequency and severity of episodes (Scott, 1996). This study aims to conduct a preliminary investigation into the nature of the relationship between sleep, activity, engagement and

mood in bipolar subjects in different illness phases, as a contribution to understanding the course of the disorder.

Timescales

March - October 2000

Proposal accepted and ethical approval sought

November 2000 – April 2001

Subjects recruited and data collection

May 2001 – July 2001

Data analysed and written up

Ethical approval

Ethical approval will be sought from Glasgow Primary Care NHS Trust.

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4. APPENDICES FOR MAJOR RESEARCH PROJECT PAPER

4.1 Copy of instructions to authors for *Journal of Affective Disorders*
4.2 Employment details of the two samples
4.3 History of the disorder, and medication details for the bipolar sample
4.4 Distributions of mood ratings in each group on the Visual Analogue Scale
4.5 Correlations between objective and subjective sleep parameters

Appendix 4.1
Copy of instructions to authors for *Journal of Affective Disorders*

ELSEVIER

Journal of Affective Disorders 65 (2001) 217–218

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Instructions to Authors

Manuscript Submission

Submission of a manuscript implies that it contains original work and has not been published or submitted for publication elsewhere. It also implies the transfer of the copyright from the author to the publisher. Four copies of all papers and illustrations are to be submitted along with a letter of transmittal and computer disk (see below) to the appropriate Editor-in-Chief:

For Europe, Asia (except Japan), and Australasia: **C. Katona**, University College London Medical School, Department of Psychiatry, Wolfson Building, Middlesex Hospital, Riding House St., London W1N 8AA, UK.

For the American Hemisphere, Africa, and Japan: **H. S. Akiskal**, University of California at San Diego, V.A. Psychiatry Service (116A), 3350 La Jolla Village Dr., San Diego, CA 92161, USA.

Authors should include permission to reproduce any previously published material. Any potential conflict of interest should be disclosed in the letter of submission. Authors are also requested to include contact information (name, address, telephone, fax, and e-mail) for three potential peer reviewers, to be used at the Editor's discretion. The review process requires 2 to 5 months. All questions concerning the review process should be directed to the appropriate editorial office.

Types of Papers

The Journal primarily publishes full-length *Research Reports* describing original work (a 15-page limit, exclusive of title page, tables, and figures, is requested), but will also accept a small number of *Brief Reports* (10 pages) and evidence-based *Review Articles* (20 pages). *Rapid Communications* (12 pages) will be accepted for expedited publication. Papers that are not developed enough to be research reports, yet offer a new approach can be designated as *Preliminary Communications* (12 pages). *Letters to the Editor* commenting on published material are encouraged and may be submitted electronically (a 500-word and 5-reference limit is requested); these might be sent to the original authors for comment. Books for review should be sent to the appropriate editorial office (see above).

Preparation of Manuscripts

Articles should be in English, typed with double spacing on only one side of consecutively numbered pages. The title page should appear as a separate sheet bearing title (without article type), author names and affiliations, and a footnote with the corresponding author's full contact information, including address, telephone and fax numbers, and e-mail address (failure to include an e-mail address can delay processing of the manuscript). Each author should have participated sufficiently in the work to merit authorship, and any conflict of interest should be disclosed in the letter of submission as well as, if appropriate, in an Acknowledgments section after the text (e.g., if support was received from a pharmaceutical or other sponsor).

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0165-0327/01/$ – see front matter
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The reference list should contain names and initials of all authors, year, title of paper referred to, abbreviated title of periodical (per *Index Medicus*), volume, and inclusive page numbers. This Journal should be cited in the list of references as J. Affect. Disord. Periodicals, books, and multi-author titles should accord with the following examples:

Bauer, M.S., Shea, N., McBride, L., Gavin, C., 1997. Predictors of service utilization in veterans with bipolar disorder: a prospective study. J. Affect. Disord. 44, 159–168.

Gelenberg, A.J., Bassuk, E.L., Schoonover, S.C., 1991. The Practitioner's Guide to Psychoactive Drugs. Plenum Medical Book Company, New York, NY.

Willner, P., 1995. Dopaminergie mechanisms in depression and mania. In: Bloom, F.E. and Kupfer, D.J. (Eds.). Psychopharmacology: The Fourth Generation of Progress. Raven Press, NY. pp. 921–931.

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Appendix 4.2 - Employment details of the sample

Control subjects

Number	Sex	Age	Occupation	Employment status
Control 1	F	67	Shop assistant	Retired
Control 2	F	32	Child Psychologist	Employed
Control 3	M	32	Student	Employed
Control 4	F	52	Further education lecturer	Employed
Control 5	M	27	Research assistant	Employed
Control 6	M	30	Research fellow	Employed
Control 7	F	36	Psychiatrist	Employed
Control 8	M	55	Quantity surveyor	Employed
Control 9	M	58	Retired/ part-time manager	Employed
Control 10	F	58	Part-time physiotherapist	Employed
Control 11	F	52	Administrator	Employed
Control 12	M	40	Clinical Psychologist	Employed
Control 13	F	48	Secretary	Employed
Control 14	F	41	Office worker	Employed
Control 15	M	50	Professor	Employed
Control 16	F	50	Secretary	Employed
Control 17	F	49	Secretary	Employed
Control 18	M	42	Professor	Employed
Control 19	F	50	Office administrator	Employed

Appendix 4.2 (continued)
Bipolar subjects

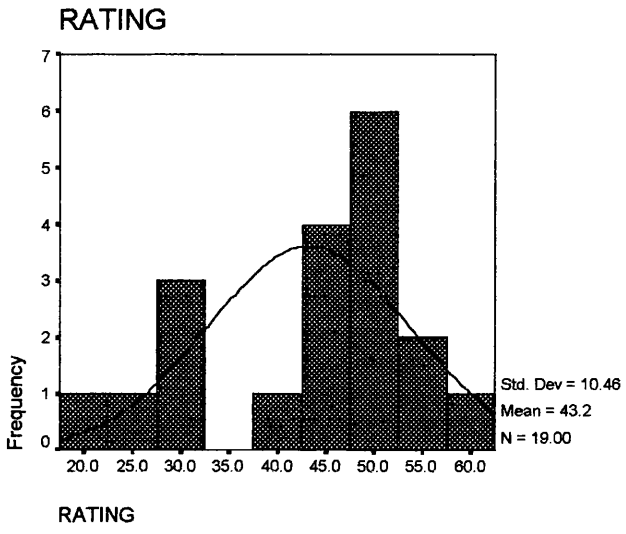
Number	Sex	Age	Occupation	Employment status
1	M	32	Social worker	Employed
2	M	49	Engineer	Sickness benefit
3	M	26	Student	Employed
4	F	42	Housewife	Unemployed
5	F	52	Further education lecturer – retired/ health grounds. Voluntary art teacher.	Employed
6	M	50	Welder	Unemployed/ sickness benefit
7	F	44	Never worked	Unemployed/ Sickness benefit
8	F	68	Housewife	Unemployed/ Sickness benefit
9	F	63	Housewife	Unemployed/ Sickness benefit
10	M	58	Engineer	Unemployed/ Sickness benefit
11	F	46	Housewife/ Cleaner	Unemployed/ Sickness benefit
12	F	57	Housewife	Unemployed/ Sickness benefit
13	M	51	Lawyer	Unemployed/ Retired – health grounds
14	F	44	Voluntary worker/ mental health advocate	Employed
15	F	37	Voluntary worker – charity shops	Employed
16	M	39	Supported employment project – Rehab Scotland/ Trainee	Employed
17	M	42	Supported employment project/ Woodwork/ Joinery	Employed
18	F	44	Housewife	Unemployed/ Sickness benefit
19	F	46	Never worked	Unemployed/ Sickness benefit

Appendix 4.3
Description of the bipolar group (history of the disorder, and medication)

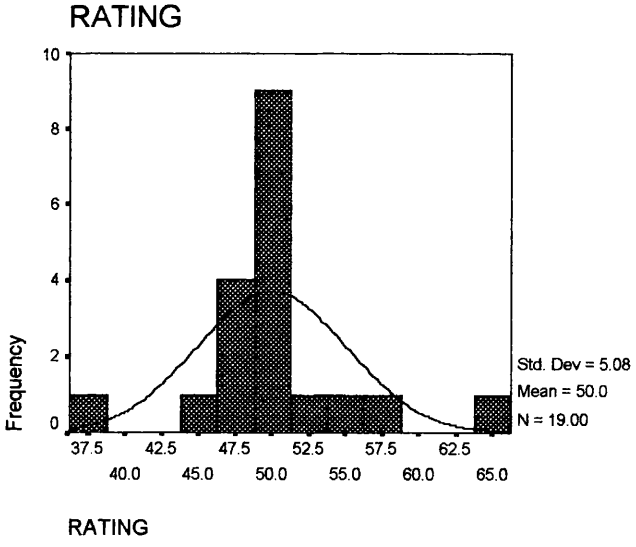
Subject no.	Age	Sex	Time since diagnosis	Time since last episode	Current medication (Daily, unless otherwise specified)
1	32	M	1 yr	6 months	Lithium carbonate 900mg Temazepam 10mg
2	49	M	15 yrs	1 yr	Lithium 400mg, Fluoxetine 20 mg, Chlorpromazine prn
3	27	M	9 yrs	1 yr	Lithium 1400mg, Efexor 375 mg
4	42	F	17 yrs	6 mnths	Nil
5	51	F	1 yr	6 mnths	Risperidone 1 mg, Ventlafaxine 225 mg
6	49	M	10 yrs	7 yrs	Carbamazepine 200 mg, Imipramine 25 mg, Chlorpromazine 25 mg
7	44	F	20 yrs	7 mnths	Lithium 800 mg, Melleril 10 mg
8	68	F	35 yrs	2 mnths	Chlopixol 75mg (depot injection - fortnightly), Melleril 10mg
9	63	F	20 yrs	1 yr	Nitrazepam 5mg, Melleril 25mg, Gaminol 140mg, Lithium (Priadel) 400mg
10	59	M	25 yrs	6 mnths	Fluoxetine 20 mg, Chlorpromazine prn
11	46	F	22 yrs	7 yrs	Lithium (Priadel) 800 mg, Lofepramine 20 mg
12	57	F	8 yrs	4 yrs	Lithium 800mg, Serequel 100 mg, Paroxetine 30 mg
13	51	M	10 yrs	3 mnths	Lithium 1000mg
14	44	F	8 yrs	8 yrs	Sodium Valproate 1500 mg, Seroxat 20 mg
15	37	F	5 yrs	3 yrs	Lithium (Priadel) 400 mg, Carbamazepine, 600mg
16	39	M	15 yrs	1 mnth	Lithium (Priadel) 1200mg, Carbamazepine 400mg, Chlopixol 20 mg, Procyclidine 10 mg
17	42	M	10 yrs	3 yrs	Lithium (Priadel) 800 mg, Ventlafaxine 325mg, Chlorpromazine 300 mg
18	44	F	28 yrs	1 yr	Lithium 800mg, Seroxat 20 mg
19	46	F	17 yrs	4 mnths	Chlopixol 300mg (depot injection - fortnightly), Carbamazepine 200 mg, Priadel (lithium) 1000mg, Procyclidine 15mg

Appendix 4.4
Distribution of mood ratings on VAS in each group

Group 1, Mood-disordered group – n=19



Group 2, Healthy control group – n=19



Appendix 4.5
Correlations between objective and subjective sleep parameters[1]

Bipolar group

Variable	r	p value
Sleep duration (mean)	.75	<.001
Sleep duration (SD)	.58	<.05
Efficiency (mean)	.23	.367
Efficiency (SD)	.19	.463
Wake time (mean)	.24	.328
Wake time (SD)	.17	.477
Onset latency (mean)	-.05	.830
Onset latency (SD)	.07	.786

Control group

Variable	r	p value
Sleep duration (mean)	.51	.024
Sleep duration (SD)	.44	.063
Efficiency (mean)	.20	.414
Efficiency (SD)	-.20	.416
Wake time (mean)	.23	.370
Wake time (SD)	-.11	.671
Onset latency (mean)	.43	.064
Onset latency (SD)	.42	.073

[1] Pearson correlations are reported for the first three variables, and Spearman's r values for the remaining five variables, in accordance with the distributions of the variables, and the assumptions of parametric statistics