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Title	Sleep disturbance in adjustment disorder and depressive episode
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Publication Date	2019-03-26
Publication Information	Doherty, A., Lorenz, L., Jabbar, F., O'Leary, E., & Casey, P. (2019). Sleep Disturbance in Adjustment Disorder and Depressive Episode. <i>International Journal of Environmental Research and Public Health</i> , 16(6), 1083. http://dx.doi.org/10.3390/ijerph16061083
Publisher	MDPI
Link to publisher's version	http://dx.doi.org/10.3390/ijerph16061083
Item record	http://hdl.handle.net/10379/15400
DOI	http://dx.doi.org/10.3390/ijerph16061083

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1 Type of the Paper (Article)

2 Sleep disturbance in adjustment disorder and 3 depressive episode

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14 Received: 28 January 2019; Accepted: date; Published: date

15 **Abstract:** *Background:* In this paper, we aimed to examine the patterns of sleep disturbance in
16 adjustment disorder (AD) and depressive episode (DE), to examine the variables associated with
17 sleep disturbance in AD and DE, and associated impairment in functioning. *Methods:* This is a multi-
18 centre case-control study of 370 patients: 185 patients with AD and 185 patients with a diagnosis of
19 DE, recruited from the liaison psychiatry services of three Dublin hospitals. We examined the
20 participants' sleep pathology using the sleep disturbance items on the Schedule for Clinical
21 Assessment in Neuropsychiatry, and the Inventory of Depressive Symptoms – Clinician-rated-30.
22 *Results:* Patients with a diagnosis of AD were less likely to report disturbed sleep than those with a
23 diagnosis of DE ($p=0.002$). On multivariate analysis, sleep disturbance was significantly associated
24 with greater severity of certain depressive symptoms decreased appetite ($p<0.001$) and psychomotor
25 agitation ($P=0.009$). Decreased appetite, younger age and single marital status were significantly
26 associated with sleep disturbance in male patients, and decreased appetite and psychomotor
27 agitation were significantly associated with sleep disturbance in female participants. *Conclusions:*
28 This is the largest study to date which has examined sleep disturbance in adjustment disorder.
29 Disturbance of sleep is a significant symptom in AD, and may represent a potential target for
30 treatment. With further research, patterns of sleep disturbance may be useful in differentiating AD
31 from DE.

32 **Keywords:** Adjustment disorder; depressive episode; sleep initiation and maintenance disorders;
33 liaison psychiatry; diagnosis; sleep
34

35 1. Introduction

36 Sleep disturbance is a common symptom of many psychiatric disorders, and is included as a
37 diagnostic criterion in many conditions, most notably depression [1]. Adjustment disorder (AD) is
38 defined by the World Health Organisation (WHO) in the tenth edition of The International
39 Classification of Diseases: Classification of Mental and Behavioural Disorders (ICD-10) as a
40 state of “subjective distress and emotional disturbance, usually interfering with social functioning
41 and performance, and arising in the period of adaptation to a significant life change or to the

42 consequences of a stressful life event" [1]. A diagnosis of AD requires the presence of a precipitating
43 stressor, resolution of symptoms within six months of the termination of the stressor and the absence
44 of another mental disorder. The ICD-10 diagnostic criteria do not specify the symptoms we expect
45 to see in AD beyond "those found in any of the affective disorders", but some indication of this is
46 given in the sub-groupings of AD in ICD-10, where there are subcategories including "brief
47 depressive reaction", "prolonged depressive reaction", "mixed anxiety and depressive reaction"
48 indicate the common presentations of the condition [1]. Similarly, DSM-5 has categories "with
49 depressed mood", "with anxiety" and "with mixed anxiety and depressed mood" [2]. Given that AD
50 has symptomatic overlap with depression and anxiety, it may be associated with sleep disturbance
51 although there is little in the literature regarding this.

52 AD is a common disorder in liaison psychiatry [3]. It is a disorder which has attracted some
53 controversy regarding its role in the classifications systems, and its nomenclature has undergone
54 some transformation over the past 60 years, although it has retained its key clinical characteristics.
55 These characteristics include symptoms common to those seen in both anxiety and depressive
56 episodes. Unlike those conditions where a list of required symptoms is provided, the classification
57 systems ICD-10 and DSM-5 do not provide a list of potential symptoms. It is well recognized that
58 many of the biological symptoms of depression are commonly seen in AD [4,5], and certain
59 symptoms such as suicidal ideation are equally common in both conditions [6]. Sleep is one of these
60 symptoms, and to date there has been little research specifically examining the role of sleep in AD,
61 whether as a symptom or indeed as a precipitant of other symptoms such as suicidal ideation.

62 Previous research has suggested that there may be significant differences in risk variables and
63 in socio-demographic profile between those with a diagnosis of DE and those with a diagnosis of AD
64 [7,8]. These have not identified sleep as a symptom associated with the diagnosis of AD (factor),
65 although it appears that sleep was not considered in these studies. Chellappa found an association
66 between insomnia and increased suicidality in depressed patients [9]. Cheung, in a population of
67 Taiwanese adolescents found that sleep was associated with both major depression and AD, but not
68 directly associated with suicidal ideation [10].

69 Zimmerman found that patients with a diagnosis of AD reported more insomnia compared with
70 those with a diagnosis of a DE [11]. Mezzich found that depressive symptoms (including sleep
71 disturbance) were more common in DE than AD, but more common in AD than in individuals with
72 no diagnosis [12]. Lijun et al likewise found that DE had a stronger association with sleep disturbance
73 than AD, but despite this those with AD had more significant early waking [13].

74 Several studies have reported an association between certain life events including workplace
75 difficulties and racial discrimination with sleep disturbance, but these studies were symptom-based,
76 and did not use a formal diagnosis of AD, or indeed any diagnosis of any mental disorder [14-16].
77 Pillai found an association with poor adaptation to stress and insomnia, but again, no formal
78 diagnosis was used [17]. Lallukka found a significant relationship between sleep disturbance
79 requiring hypnotic medications and stress related to family or work conflicts in women [18].

80 In this study we aimed to examine the patterns of sleep disturbance in AD in comparison to DE,
81 to study the variables associated with sleep disturbance in each diagnosis and to examine the
82 relationship between sleep disturbance and disturbance in functioning.

83 Our hypothesis is that patients with AD are as likely to suffer from sleep disturbance as those
84 with a diagnosis of a DE, and that there is no difference in the patterns of sleep disturbance between
85 the two conditions.

86 2. Materials and methods

87 The methods of this study have been previously described in detail and are summarized briefly
88 here [19]. Participants were recruited from patients referred to the liaison psychiatry services at three
89 Dublin hospitals, and diagnosed by the liaison psychiatrists with either a DE or AD. Patients were
90 excluded if they had a substance abuse disorder, cognitive impairment, psychotic symptoms, were
91 under 18 or unable to give informed consent. Participants were interviewed at time of diagnosis, and
92 again after six months, for stability of diagnosis.

93 In examining sleep, the sleep disturbance items on the Schedule for Clinical Assessment in
94 Neuropsychiatry (SCAN) version 2, and the Inventory of Depressive Symptoms – Clinician-rated-30
95 (IDS-C30) were used [20,21]. SCAN is a semi-structured interview schedule created by the WHO and
96 the gold standard in the diagnosis and measurement of mental illness [20]. Specifically, we used
97 question 8.009 from SCAN, which examined sleep disturbance globally asking: “Have you had any
98 trouble with sleep in the past 2 weeks?”. This is endorsed if the participant reported disturbed sleep
99 in the preceding two weeks. For the variable of decreased function, we used ‘interference with
100 activities due to sleep problems’ in SCAN (variable 8.021: “How much interference has there been
101 with your everyday activities because of your problems sleeping?”). This is endorsed where the
102 patient reported that sleep disturbance is causing the functional problems.

103 Both of these variables are rated on a scale from 0 to 3, scoring 0 if there is a “positive rating of
104 absence”, scoring 1 where a symptom is present but to “such a minor degree that it is not
105 appropriate for use in classification”, scoring 2 where the symptoms “is present to a level sufficient
106 to use in classification”, and a score of 3 is given where “the symptom is present in severe form for
107 most of the period”. For logistic regression we divided the participants into those without the
108 symptom (scoring 0 or 1), and compared them with those participants who endorsed the symptoms
109 (scoring 2 or 3).

110 IDS-C30 was used to measure overall depressive symptoms [21]. It is a clinician administered
111 30 item scale, which is used to examine specific depressive symptoms in detail, each of which is
112 rated on a scale of 0-3 it has a high level of internal consistency with a Cronbach’s alpha of 0.892.

113 We used the first four questions of IDS-C30 which examine specific types of sleep disturbance:
114 “sleep onset insomnia”, “middle insomnia”, “early morning insomnia” and “hypersomnia”, each on
115 a scale 0-3 [21]. Sleep onset insomnia was scored 0 if the participant “never takes longer than 30
116 minutes to fall asleep”, scored 1 if the participant “takes at least 30 minutes to fall asleep, less than
117 half the time”, scored 2 if the participant “takes at least 30 minutes to fall asleep, more than half the
118 time”, and scored 3 if the participant “takes at least 60 minutes to fall asleep, more than half the time”.
119 Mid-nocturnal insomnia was scored 0 if the participant “does not wake up at night”, scored 1 if the
120 participant reports a “restless, light sleep with few awakenings”, scored 2 if the participant “wakes
121 up at least once a night, but goes back to sleep easily”, and scored 3 if the participant “wakes up more
122 than once a night and stays awake for 20 minutes or more, more than half the time”. Early morning
123 insomnia was scored 0 if the participant “less than half the time, awakens no more than 30 minutes
124 before necessary”, scored 1 if the participant: “more than half the time, awakens more than 30 minutes
125 before need be”, scored 2 if the participant “awakens at least one hour before need be, more than half
126 the time,” and scored 3 if the participant “awakens at least two hour before need be, more than half
127 the time”. Hypersomnia was scored 0 if the participant “sleeps no longer than 7-8 hours/night,
128 without naps”, scored 1 if the participant “sleeps no longer than 10 hours in a 24 hour period (include
129 naps)”, scored 2 if the participant “sleeps no longer than 12 hours in a 24 hour period (include naps)”,
130 and scored 3 if the participant “sleeps longer than 12 hours in a 24 hour period (include naps)”.

131 We explored the relationship of disturbed sleep to diagnosis, depressive symptoms and other
132 variables related to this relationship, including life events, social functioning and personality. In
133 multivariate analysis, for depressive symptoms we used the total score of IDS-C30, minus those
134 scores derived from the sleep items [21].

135 The power calculations performed were based on methods described by Smith and Morrow [22].
136 To have 95% confidence of detecting a difference in depressive symptomatology of similar magnitude
137 to that detected in Casey et al [23], at a significance level of $p < 0.05$, we required 185 individuals with
138 AD and 185 individuals with DE. Statistics were calculated using SPSSv24 [24]. Univariate analysis
139 was conducted using Independent Samples T-test, Mann-Whitney U Test and Chi-Square Test. The
140 outlier analysis using the Mahalanobis Distance detected no multivariate outliers in the data.

141 Multivariate analysis was conducted using logistic regression, with the variables disturbance of sleep
 142 and impairment of function as the binary dependent variables respectively, as described above. The
 143 independent variables entered into each model were sex, age, marital status and those variables
 144 which were found to have a significant association with the dependent variable. **We decided to**
 145 **combine the two diagnostic categories in order to examine sleep disturbance and related functional**
 146 **impairment in the population as a whole, as this study was underpowered for this post hoc analysis.**

147 Ethical approval was granted by the Mater University Hospital Research Ethics Committee
 148 Ref/1/378/1146.

149 3. Results

150 A total of 370 patients were recruited to this study. Of these, 185 (50%) had a diagnosis of AD;
 151 the remainder were diagnosed with DE. A majority, 235 (63.5%) participants were female. The
 152 average age was 43.8 years (SD 14.2), and the mean age of patients with a diagnosis of AD were older
 153 (but not significantly older) than those diagnosed with DE. There were no significant differences
 154 between the two diagnostic groups in the socio-demographic variables of gender and marital status.
 155 Patients with a diagnosis of AD were significantly less likely to report disturbed sleep than those
 156 with a diagnosis of DE (Table 1). There were no significant differences in early onset sleep disturbance
 157 or oversleeping, but mid-nocturnal sleep disturbance and early wakening were significantly more
 158 commonly reported in patients with a diagnosis of DE, who were likewise significantly more likely
 159 to report disturbance of functioning due to sleep problems than those with AD. Patients with AD
 160 were significantly less likely ($p < 0.001$) to have been prescribed hypnotics. When we examined the
 161 patterns of disturbed sleep by gender, there were no significant differences between male and female
 162 participants in this study.

163 **Table 1.** Demographic and clinical characteristics of patients divided by diagnosis.

Characteristics		Total	Adjustmen t Disorder	Depressive episode	p value
Age	Mean (SD)	43.8 (14.2)	43.5 (14.5)	44.1 (13.9)	0.676 ^a
Gender	Male (%)	135 (36.5)	66 (48.9)	69 (51.1)	0.746 ^b
	Female (%)	235 (63.5)	119 (50.6)	116 (49.4)	
Marital Status	Single, n (%)	131 (36.0)	65 (35.5)	66 (36.4)	0.422 ^b
	Married/Cohabiting, n (%)	163 (44.8)	78 (42.6)	85 (47.9)	
	Sep/Div/Widowed, n (%)	70 (19.2)	40 (21.9)	30 (16.6)	
Depressive symptoms: mean IDSC-30 total score, range 0-90 %	Mean (SD)	34.9 (12.7)	30.8 (12.3)	38.8 (11.9)	<0.001^a
Depressive symptoms: mean IDSC-30 total score minus sleep item, range 0-78%	Mean (SD)	30.1 (11.0)	26.6 (10.6)	33.5 (10.4)	<0.001^a
Sleep disturbance, range 0-3*	Mean (SD)	1.5 (1.0)	1.4 (1)	1.7 (0.9)	0.002^a
Impairment of function, range 0-3*	Mean (SD)	1.1 (0.9)	0.9 (0.8)	1.3 (0.9)	<0.001^a
Early insomnia, range 0-3%	Mean (SD)	1.6 (1.1)	1.5 (1.1)	1.7 (1)	0.251 ^a

Mid nocturnal insomnia, range 0-3%	Mean (SD)	1.6 (1.1)	1.4 (1.1)	1.7 (1)	0.003^a
Early waking, range 0-3%	Mean (SD)	1.4 (1.2)	1.1 (1.1)	1.6 (1.1)	<0.001^a
Hypersomnia, range 0-3%	Mean (SD)	0.3 (0.6)	0.2 (0.6)	0.3 (0.7)	0.072 ^a
Hypnotic use	N (%)	135 (38.8)	46 (26.6)	89 (50.9)	<0.001^b

164 a=Independent samples t-test; b=chi square; %variables from IDS-C30, higher scores denote greater
165 symptoms burden; *variables from SCAN, higher scores denote greater symptoms burden.

166 When participants who reported disturbed sleep were compared to those who did not, the group
167 with disturbed sleep reported significantly more depressive symptoms and were significantly more
168 likely to have a diagnosis of DE rather than AD (table 2). They were significantly more likely to report
169 other depressive symptoms as measured by the IDS-C30 including disturbance of mood, decreased
170 appetite, decreased concentration, negative outlook towards self and future, poor energy, decreased
171 enjoyment, reduced sexual interest, psychomotor agitation and leaden paralysis. They had higher
172 mean scores on IDS-C30, indicating a greater burden of depressive symptoms.

173 **Table 2.** Demographic and clinical characteristics of patients divided by sleep disturbance.

Characteristics		Total n = 344	Sleep disturbance* n=181	No sleep disturbance* n=163	p value
Age	Mean (SD)	43.6 (14.3)	43.5 (13.9)	43.7 (14.9)	0.865 ^a
Gender	Male (%)	120 (34.9)	70 (38.7)	50 (30.7)	0.120 ^b
	Female (%)	224 (65.1)	111 (61.3)	113 (69.3)	
Marital Status	Single, n (%)	119 (35.2)	64 (36.2)	55 (34.2)	0.781 ^b
	Married/Cohabiting, n (%)	155 (45.9)	78 (44.1)	77 (47.8)	
	Sep/Div/Widowed, n (%)	64 (18.9)	35 (19.8)	29 (18.0)	
Depressive symptoms: mean IDSC-30 total score, range 0-90 %	Mean (SD)	34.9 (12.7)	40.2 (11.4)	29 (11.4)	<0.001^a
Depressive symptoms: mean IDSC-30 total minus sleep items, range 0-78%	Mean (SD)	30.1 (11)	34.2 (10.3)	25.6 (10.1)	<0.001^a
Clinical diagnosis	Adjustment Disorder (%)	172 (50)	77 (42.5)	95 (58.3)	0.004^b
	Depressive episode (%)	172 (50)	104 (57.5)	68 (41.7)	
Other depressive symptoms from IDSC30%					
Mood sad	Mean (SD)	1.9 (0.9)	2.0 (0.8)	1.7 (0.9)	0.002^a
Mood irritable	Mean (SD)	1.5 (0.9)	1.6 (0.8)	1.2 (0.9)	<0.001^a
Mood anxious	Mean (SD)	1.7 (0.9)	1.8 (0.9)	1.4 (0.9)	<0.001^a

Reactivity of mood	Mean (SD)	1.1 (0.9)	1.2 (0.9)	0.9 (0.9)	0.003^a
Mood variation	Mean (SD)	0.9 (1.0)	1.0 (1.0)	0.8 (1.0)	0.112 ^a
Mood worse in morn	Mean (SD)	0.5 (0.8)	0.4 (0.7)	0.7 (0.9)	0.003^a
Mood variation due to environment	Mean (SD)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.142 ^a
Quality of mood	Mean (SD)	1.4 (1.0)	1.4 (0.9)	1.2 (1.1)	0.057 ^a
Appetite decreased	Mean (SD)	1.0 (0.9)	1.2 (0.9)	0.7 (0.9)	<0.001^a
Appetite increased	Mean (SD)	0.3 (0.9)	0.3 (0.9)	0.4 (1.0)	0.211 ^a
Weight decrease 2 weeks	Mean (SD)	0.7 (0.9)	0.7 (0.9)	0.6 (1.0)	0.431 ^a
Weight increase 2 weeks	Mean (SD)	0.3 (0.7)	0.3 (0.6)	0.4 (0.9)	0.105 ^a
Concentration/decision making	Mean (SD)	1.5 (0.8)	1.6 (0.8)	1.3 (0.8)	0.001^a
Outlook self	Mean (SD)	1.3 (1.0)	1.4 (1.0)	1.1 (0.9)	0.016^a
Outlook future	Mean (SD)	1.6 (0.9)	1.7 (0.9)	1.5 (0.9)	0.025^a
Involvement	Mean (SD)	1.6 (0.9)	1.7 (0.9)	1.4 (1.0)	0.008^a
Energy/fatigubility	Mean (SD)	1.7 (1.0)	1.6 (0.8)	1.3 (0.9)	0.028^a
Pleasure/enjoyment	Mean (SD)	1.5 (0.9)	1.6 (0.8)	1.3 (0.9)	0.009^a
Sexual interest	Mean (SD)	1.7 (1.0)	1.8 (0.9)	1.4 (1.0)	<0.001^a
Psychomotor slowing	Mean (SD)	0.6 (0.7)	0.6 (0.8)	0.6 (0.7)	0.895 ^a
Psychomotor agitation	Mean (SD)	0.8 (0.8)	0.8 (0.8)	0.6 (0.7)	0.002^a
Somatic complaints	Mean (SD)	0.9 (0.8)	0.9 (0.9)	0.9 (0.8)	0.488 ^a
Sympathetic arousal	Mean (SD)	0.8 (0.9)	0.8 (0.8)	0.8 (1.2)	0.854 ^a
Panic/phobic symptoms	Mean (SD)	0.9 (0.9)	1.0 (0.9)	0.8 (0.8)	0.061 ^a
GIT	Mean (SD)	0.7 (0.9)	0.7 (1.0)	0.6 (0.7)	0.9 ^a
Interpersonal sensitivity	Mean (SD)	1.5 (0.9)	1.5 (1.0)	1.4 (0.8)	0.074 ^a
Leadened paralysis	Mean (SD)	1.2 (0.9)	1.4 (0.9)	1.0 (0.8)	0.001^a

174 a=Independent samples t-test; b=chi square; * Schedule for Clinical Assessment in Neuropsychiatry
 175 (SCAN), variable 8.009; %variables from the Inventory of Depressive Symptoms – Clinician-rated-30
 176 (IDS-C30): higher scores denote greater symptoms burden;

177 Participants who reported disturbance of function due to disturbed sleep reported significantly
 178 more depressive symptoms, fewer dysfunctional personality traits and an excess of stressful life
 179 events compared with those who did not report disturbance of functioning. They were significantly
 180 more likely to have a diagnosis of DE rather than AD. They had higher mean scores on IDS-C30,
 181 indicating a greater burden of depressive symptoms. They were significantly more likely to report
 182 other depressive symptoms as measured by the IDSC-C30 including disturbance of mood, decreased
 183 appetite, decreased concentration, negative outlook towards self and future, poor energy, decreased
 184 enjoyment, reduced sexual interest and interpersonal sensitivity (table 3).

185 **Table 3.** Demographic and clinical characteristics of patients divided by disturbance in function
 186 attributed to sleep difficulties.

Characteristics	Total n = 345	Functional difficulties due to sleep	No functional problems due to sleep	p value
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			disturbance*	disturbance*	
			n=137	n=208	
Age	Mean (SD)	43.6 (14.3)	43.5 (14.5)	43.7 (14.3)	0.921 ^a
Gender	Male n(%)	122 (35.4)	50 (36.5)	72 (34.6)	0.721 ^b
	Female n(%)	223 (64.6)	87 (63.5)	136 (65.4)	
Marital Status	Single, n(%)	119 (35.1)	43 (32.1)	76 (37.1)	0.643 ^b
	Married/Cohabiting, n(%)	155 (45.7)	64 (47.8)	91 (44.4)	
	Sep/Div/Widowed, n(%)	65 (19.2)	27 (20.1)	38 (18.5)	
Depressive symptoms: mean IDSC-30 total score, range 0-90%	Mean (SD)	35 (12.6)	39.2 (12.4)	32.3 (12)	<0.001^a
Depressive symptoms: mean IDSC-30 total score minus sleep item, range 0-78%	Mean (SD)	30.2 (11)	33.7 (10.7)	27.9 (10.5)	<0.001^a
Clinical diagnosis	Adjustment Disorder (%)	175 (50.7)	49 (35.8)	121 (58.2)	<0.001 ^b
	Depressive episode (%)	172 (50)	104 (57.5)	68 (41.7)	
Other depressive symptoms from IDSC30%	Mean (SD)	1.9 (0.9)	2.2 (0.8)	1.7 (0.9)	<0.001^a
Mood sad	Mean (SD)	1.5 (0.9)	1.8 (0.8)	1.3 (0.9)	<0.001 ^a
Mood irritable	Mean (SD)	1.7 (0.9)	1.9 (0.9)	1.5 (0.9)	<0.001 ^a
Mood anxious	Mean (SD)	1.1 (0.9)	1.3 (0.9)	1.0 (0.9)	0.014 ^a
Reactivity of mood	Mean (SD)	0.9 (1.0)	1.1 (1.1)	0.8 (1.0)	0.017 ^a
Mood variation	Mean (SD)	0.5 (0.8)	0.3 (0.7)	0.6 (0.8)	0.003 ^a
Mood worse in morn	Mean (SD)	0.3 (0.5)	0.2 (0.4)	0.3 (0.5)	0.079 ^a
Mood variation due to environment	Mean (SD)	1.4 (1.0)	1.5 (0.9)	1.3 (1.0)	0.011 ^a
Quality of mood	Mean (SD)	1.0 (0.9)	1.3 (0.9)	0.8 (0.9)	<0.001 ^a
Appetite decreased	Mean (SD)	0.3 (0.9)	0.2 (0.9)	0.4 (0.9)	0.165 ^a
Appetite increased	Mean (SD)	0.7 (0.9)	0.7 (0.9)	0.7 (1.0)	0.916 ^a
Weight decrease 2 weeks	Mean (SD)	0.3 (0.7)	0.2 (0.6)	0.4 (0.8)	0.052 ^a
Weight increase 2 weeks	Mean (SD)	1.5 (0.8)	1.7 (0.7)	1.4 (0.8)	0.001 ^a
Concentration/decision making	Mean (SD)	1.3 (1.0)	1.5 (1.0)	1.2 (0.9)	0.003 ^a
Outlook self	Mean (SD)	1.6 (0.9)	1.8 (0.9)	1.5 (0.9)	0.003 ^a
Outlook future	Mean (SD)	1.6 (0.9)	1.8 (0.9)	1.4 (0.9)	<0.001 ^a
Involvement	Mean (SD)	1.7 (1.0)	1.9 (0.8)	1.6 (0.8)	<0.001 ^a
Energy/fatigubility	Mean (SD)	1.5 (0.9)	1.7 (0.9)	1.3 (0.8)	<0.001 ^a
Pleasure/enjoyment	Mean (SD)	1.7 (1.0)	1.9 (0.9)	1.6 (1.0)	0.004 ^a
Sexual interest	Mean (SD)	0.6 (0.7)	0.6 (0.8)	0.6 (0.7)	0.856 ^a
Psychomotor slowing	Mean (SD)	0.8 (0.8)	1.0 (0.9)	0.6 (0.8)	<0.001 ^a
Psychomotor agitation	Mean (SD)	0.9 (0.8)	1.0 (0.9)	0.9 (0.8)	0.328 ^a
Somatic complaints	Mean (SD)	0.8 (0.9)	0.8 (0.9)	0.7 (1.0)	0.352 ^a
Sympathetic arousal	Mean (SD)	0.9 (0.9)	1.0 (0.9)	0.9 (0.9)	0.286 ^a
Panic/phobic symptoms	Mean (SD)	0.7 (0.9)	0.7 (1.1)	0.6 (0.7)	0.331 ^a
GIT	Mean (SD)	1.5 (0.9)	1.6 (1.0)	1.4 (0.9)	0.038 ^a
Interpersonal sensitivity	Mean (SD)	1.2 (0.9)	1.3 (1.0)	1.2 (0.9)	0.332 ^a
Leaden paralysis	Mean (SD)				

187 a=Independent samples t-test; b=chi square; * Schedule for Clinical Assessment in Neuropsychiatry
 188 (SCAN), variable 8.021; %variables from the Inventory of Depressive Symptoms – Clinician-rated-30
 189 (IDS-C30): higher scores denote greater symptoms burden;

190 On multivariate analysis, where sleep disturbance was the dependent variable, it was
 191 significantly associated with the following specific depressive symptoms: decreased appetite, and
 192 psychomotor in the study population as a whole, after controlling for age, gender and marital status
 193 (table 4). **We decided to combine the two diagnostic categories in order to examine sleep disturbance and**
 194 **related functional impairment in the population as a whole, as when treated separately, the findings were**
 195 **non-significant, likely as this study was underpowered for this post hoc analysis.**

196 When the sample was divided by gender, there were differences between the male and female
 197 participants. Among female participants decreased appetite and psychomotor agitation were
 198 associated with sleep disturbance. Among male participants, younger age, single marital status and
 199 decreased appetite were associated with sleep disturbance.
 200

201 **Table 4.** Multivariate analysis: logistic regression, with sleep disturbance as the dependent binary
 202 variable, in AD and DE combined (i.e the entire sample)

	Total			Male (n=135)			Female (n=235)		
	p	B	CI	p	B	CI	p	B	CI
Age	0.218	-0.002	-0.006 – 0.001	0.013	-0.059	0.900 – 0.988	0.440	-0.012	-0.959 – 1.018
Gender	0.767	-0.015	-0.115 – 0.085	-	-	-	-	-	-
Marital status	0.155	0.024	-0.012 – 0.077	0.002	-2.956	0.008 – 0.350	0.783	-0.117	-0.387 – 2.045
Clinical diagnosis	0.101	0.084	-0.016 – 0.184	0.851	-0.144	0.193 – 3.893	0.087	-0.788	-0.184 – 1.122
Depressed mood%	0.394	0.029	-0.044 – 0.101	0.197	0.637	0.719 – 4.975	0.655	-0.136	-0.480 – 1.587
Decreased appetite%	<0.001	0.103	0.048 – 0.159	0.009	1.546	1.462 – 15.119	0.009	0.794	1.217 – 4.019
Outlook for future%	0.979	0.001	-0.062 – 0.063	0.706	0.155	0.522 – 2.614	0.956	-0.016	-0.565 – 1.716
Energy%	0.492	-0.022	-0.094 – 0.05	0.174	0.646	0.752 – 4.836	0.832	-0.066	-0.506 – 1.729
Pleasure/enjoyment%	0.431	-0.032	-0.112 – 0.048	0.810	0.138	-0.371 – 3.551	0.149	0.472	-0.845 – 3.043
Sexual interest%	0.098	0.059	0.003 – 0.12	0.910	-0.050	0.398 – 2.271	0.570	0.146	0.7 – 1.911
Psychomotor agitation%	0.009	0.077	0.017 – 0.137	0.459	0.331	0.580 – 3.342	0.181	-0.341	0.432 – 1.171
Leadend paralysis%	0.061	0.062	0.001 – 0.124	0.399	-0.394	0.270 – 1.686	0.191	0.402	0.819 – 2.728

203 %variables from IDS-C30, higher scores denote greater symptom burden.

204 We performed multivariate analysis with disturbance of function due to disturbed sleep as
 205 the dependent variable. In the population as a whole, it was significantly associated with a
 206 diagnosis of DE and single marital status, and with the following specific depressive
 207 symptoms: decreased appetite, decreased energy and psychomotor agitation, after
 208 controlling for age and gender (table 5). When the sample was divided by gender, there were
 209 differences between the male and female participants. Among female participants a clinical
 210 diagnosis of DE, low mood, decreased appetite and reduced enjoyment were associated with
 211 greater impairment of function attributed to sleep disturbance. Among male participants, younger

212 age, decreased appetite, psychomotor agitation and reduced leaden paralysis were associated with
 213 sleep disturbance.
 214

215 **Table 5.** Multivariate analysis: logistic regression, with disturbance in function due to sleep problems
 216 as the dependent binary variable, in AD and DE combined (i.e the entire sample)

	Total			Male (n=135)			Female (n=235)		
	p	B	CI	p	B	CI	p	B	CI
Age	0.716	-0.001	-0.008 – 0.005	0.412	-0.014	0.954 – 1.020	0.846	0.002	-0.98 – 1.025
Gender	0.963	-0.004	-0.182 – 0.191	-	-	-	-	-	-
Marital status	0.038	0.089	0.005 – 0.173	0.293	-0.529	0.220 – 1.579	0.831	-0.070	-0.492 – 1.766
Clinical diagnosis	<0.001	0.365	0.179 – 0.551	0.284	-0.564	0.203 – 1.595	0.001	-1.174	0.159 – 0.600
Depressed mood%	0.095	0.115	-0.02 – 0.25	0.147	-0.533	0.285 – 1.207	0.004	0.766	-1.283 – 3.608
Decreased appetite%	0.005	0.149	0.046 – 0.252	0.010	0.743	1.193 – 3.702	0.054	0.338	0.994 – 1.977
Outlook for future%	0.294	0.062	-0.052 – 0.179	0.252	0.375	0.766 – 2.762	0.533	-0.130	-0.585 – 1.320
Energy%	0.038	0.142	-0.008 – 0.276	0.064	0.806	0.955 – 5.255	0.117	0.364	-0.913 – 2.269
Pleasure/enjoyment%	0.654	0.004	-0.145 – 0.154	0.007	1.391	1.467 – 11.017	0.048	-0.511	0.362 – 0.995
Sexual interest%	0.329	-0.057	-0.171 – 0.058	0.052	-0.764	0.215 – 1.007	0.307	0.201	0.831 – 1.800
Psychomotor agitation%	0.001	0.19	0.078 – 0.301	0.002	1.085	1.479 – 5.92	0.069	0.349	0.973 – 2.067
Leaden paralysis%	0.716	-0.001	-0.008 – 0.005	0.036	-0.612	0.306 – 1.579	0.836	-0.044	0.632 – 1.450

217 %variables from IDS-C30, higher scores denote greater symptom burden.

218

219 4. Discussion

220 In examining the patterns of sleep disturbance in AD and DE, we found that certain symptoms
221 were equally common in both conditions, namely “sleep onset insomnia” and “hypersomnia, while
222 others (middle insomnia and early morning insomnia) were more common in DE. Depressive
223 symptoms were significantly associated with sleep disturbance in the two diagnostic groups, both
224 combined and separately. On multivariable analysis, decreased appetite and psychomotor agitation
225 were associated with sleep disturbance. A diagnosis of DE, decreased appetite, decreased energy and
226 psychomotor agitation were associated with impairment of function due to disturbed sleep.

227 We found that sleep disturbance was associated with different variables in male and female
228 individuals with adjustment disorder or depression in a liaison psychiatry setting. Decreased
229 appetite was significantly associated with sleep disturbance in both genders. As both disturbance of
230 sleep and disturbance of appetite are important biological symptoms of depression, this is not
231 unexpected [1,2]. In addition, younger age and single marital status were associated with sleep
232 disturbance in male patients, and psychomotor agitation was significantly associated with sleep
233 disturbance in female participants. These findings have not previously been examined in the
234 literature, and suggest that females with AD and DE, symptoms of depression are most associated
235 with sleep disturbance, whereas psychosocial variables have a greater impact in males with AD and
236 DE.

237 Decreased appetite was likewise significantly associated with impairment of functioning
238 attributable to sleep disturbance in both genders. In addition, a clinical diagnosis of DE, low mood,
239 and reduced enjoyment were significantly associated with impairment of functioning attributable
240 to sleep disturbance in female participants, and younger age, psychomotor agitation and reduced
241 leaden paralysis were associated with impairment of functioning attributable to sleep disturbance
242 in male patients. These findings are consistent with existing evidence which has demonstrated
243 gender-based differences in the covariates of both sleep disturbance and associated functional
244 impairment [25-26]. Like Chasens et al, we found significant gender-based expression of impaired
245 sleep on functional outcomes [25]. Previous work by Hyde has suggested that any gender-based
246 differences in functional impairment due to sleep disturbance were likely to be small [27]. In
247 contrast to Hyde, it is difficult to comment on the strength of these differences given that the study
248 was not powered for these post hoc analyses.

249 With respect to our hypothesis, that patients with AD are as likely to suffer from sleep
250 disturbance as those with a diagnosis of DE, we found that sleep disturbance is common in both
251 conditions but significantly more common in DE. We found that a diagnosis of DE was associated
252 with sleep disturbance in females, but that there was no difference between the two diagnoses in
253 males.

254 This study confirms that sleep disturbance is a common symptom in AD and one which is
255 associated with significant disturbance of functioning. It also indicates gender-related differences in
256 this cohort of patients with low mood attending a liaison psychiatry service. No previous study has
257 examined the patterns of sleep disturbance in this level of detail: indeed, only two have examined
258 sleep disturbance in AD at all, and these studies have produced conflicting evidence. Like
259 Zimmerman we found significant degrees of reported sleep disturbance in AD, and like Mezzich we
260 found greater symptom severity in DE compared with AD [11,12]. Certain symptoms were similarly
261 common in both conditions, such as sleep onset insomnia and hypersomnia. Others, insomnia and
262 early morning insomnia, were more common in DE. The association of functional impairment
263 attributable to disturbed sleep with specific depressive symptom severity in AD and DE on
264 multivariable testing has not been previously demonstrated.

265 This study is one of few which have examined the association of AD with sleep disturbance, and
266 the first to examine the sleep pattern seen in AD and to investigate the other variables associated with
267 both sleep disturbance and functional impairment associated with sleep disturbance. It is one of the
268 first to examine gender related differences in sleep in a cohort of patients with AD. This study
269 included a large number of patients with AD: the relatively large sample size derived from our power
270 calculations. This is the largest study yet to have been conducted examining sleep disturbance and in
271 patients with AD and DE. Previous studies examining the relationship between AD and sleep have
272 been of smaller sample size [28]. This study used instruments which have been validated in similar
273 populations to assess a broad range of parameters including depressive symptoms [21], which
274 allowed us to control for a wide range of confounding variables. A systematic review found that sleep
275 disturbance is associated with increased suicidal behaviour, and although this was not a finding of
276 our study, it is an important target for treatment in people with impairment of psychosocial function
277 in adjustment disorder [29]. No previous studies have examined gender based differences in sleep
278 disturbance in AD.

279
280 The limitations of this study include the use of clinical diagnosis. We chose the clinical diagnosis
281 from the two options available (clinical diagnosis and SCAN diagnosis) as the gold standard for the
282 purpose of this study. Clinical diagnoses are informed by the ICD-10 diagnostic guidelines in a broad
283 fashion and take into account the context within which symptoms arise. This optimises the
284 applicability of findings to everyday clinical practice. Unlike clinical diagnosis, SCAN diagnosis
285 looks at symptoms only, without taking account of context, and context is essential in making a
286 diagnosis of AD. We expected that as a result of this inherent flaw in the diagnostic instruments, the
287 use of SCAN would result in a conflation of AD with DE, and as a result would not be useful in
288 distinguishing between the two diagnoses [5]. In our comparison of the two diagnoses this proved to
289 be well-founded, as 73.4% of those participants with a clinical diagnosis of AD were diagnosed with
290 DE by SCAN, resulting in a giving a sensitivity of 91.8% and a specificity of 57.2%. The heterogeneity
291 of clinical presentation in AD, including fluctuating psychological symptoms, behavioural
292 disturbances and physical symptoms which can characterise certain clinical presentations with AD
293 add to the complexity of this diagnosis [28]. Other limitations include the small numbers with sleep
294 disturbance.

295 Finally, participants were recruited from a consultation-liaison psychiatry population in two
296 general hospitals and one maternity hospital. While this might be regarded as limiting the
297 generalisability of findings to this population and being of less relevance to other populations such
298 as community-based mental health services or primary care, it has the merit of focusing on a
299 population in which AD is particularly common and thus is well appointed to provide useful
300 information for consultation-liaison psychiatry teams [29]. This diversity of participants also spans
301 the full range of severity, from less severe cases treated as outpatients to more severe cases presenting
302 to the emergency department with acute and severe symptoms.

303 This paper is novel in its examination of the disturbance of sleep which occurs not only in DE,
304 but also in AD. We have demonstrated an association between sleep disturbance and other
305 depressive symptoms in both diagnostic groups and that where sleep disturbance is present, patients
306 reports a greater severity of depressive symptoms, irrespective of diagnosis. Sleep disturbance may
307 represent a new focus for treatments such as cognitive behavioural therapy, which has a strong
308 evidence base in the treatment of sleep disturbance.

309 5. Conclusion

310 This study found that while sleep disturbance is more severe in DE, it is also common in AD
311 and is frequently associated with disturbance of function. It is a significant symptom in AD, and one
312 which may be amenable to a behavioural approach, given that psychotropics have a poor evidence
313 base within this diagnostic group. Further research is required to identify if patterns of sleep
314 disturbance may be useful in the clinical challenge of differentiating AD from DE.

315 **Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1, Table S1:
316 Demographic and clinical characteristics of patients divided by gender.

317 **Author Contributions:** Conceptualisation: P.C., A.M.D., F.J.; Methodology P.C., A.M.D., F.J.;
318 Software, P.C., A.M.D., E.O'L.; Validation, P.C., A.M.D., E.O'L.; Formal Analysis, P.C., A.M.D., L.L.,
319 E.O'L.; Investigation, P.C., A.M.D., F.J.; Resources, P.C., A.M.D., F.J.; Data Curation, A.M.D., L.L.,
320 E.O'L.; Writing – Original Draft Preparation, A.D.; Writing – Review & Editing, P.C., A.M.D., L.L.,
321 F.J., E.O'L.; Visualization, P.C., A.M.D., F.J.; Supervision, P.C.; Project Administration, A.M.D., F.J.

322 **Funding:** This research received no external funding.

323 **Acknowledgments:** We would like to acknowledge the support of Geraldine Byrne and Maura
324 Costello.

325 **Conflicts of Interest:** The authors declare no conflict of interest.

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328 Organisation, Geneva, 1992.
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395 Supplementary Table 1: Demographic and clinical characteristics of patients divided by gender

Characteristics		Total	Male	Female	p value
Age	Mean (SD)	43.8 (14.2)	44.1 (14.6)	43.6 (14.0)	0.753 ^a
Marital Status	Single, n (%)	131 (36.0)	56 (42.1)	75 (32.5)	0.156 ^b
	Married/Cohabiting, n (%)	163 (44.8)	52 (39.1)	111 (48.1)	
	Sep/Div/Widowed, n (%)	70 (19.2)	25 (18.8)	45 (19.5)	
Clinical diagnosis	Adjustment disorder (%)	135 (36.5)	66 (18.8)	69 (51.1)	0.746 ^b
	Depressive episode (%)	235 (63.5)	119 (50.6)	116 (49.4)	
Depressive symptoms: mean IDSC-30 total score, range 0-90 %	Mean (SD)	34.9 (12.7)	34.0 (12.1)	35.3 (13.0)	0.37 ^a
Depressive symptoms: mean IDSC-30 total score minus sleep items, range 0-78%	Mean (SD)	30.1 (11.0)	29.2 (10.6)	30.5 (11.3)	0.295 ^a
Sleep disturbance, range 0-3*	Mean (SD)	1.5 (1.0)	1.6 (1)	1.5 (0.9)	0.10 ^a
Impairment of function, range 0-3*	Mean (SD)	1.1 (0.9)	1.1 (1.0)	1.1 (0.9)	0.77 ^a
Early insomnia, range 0- 3%	Mean (SD)	1.6 (1.1)	1.6 (1.1)	1.6 (1)	0.625 ^a
Mid nocturnal insomnia, range 0-3%	Mean (SD)	1.6 (1.1)	1.5 (1.1)	1.6 (1.1)	0.657 ^a
Early waking, range 0- 3%	Mean (SD)	1.4 (1.2)	1.4 (1.2)	1.4 (1.2)	0.7 ^a
Hypersomnia, range 0- 3%	Mean (SD)	0.3 (0.6)	0.3 (0.7)	0.2 (0.6)	0.139 ^a
Hypnotic use	N (%)	135 (38.8)	45 (36.9)	90 (39.8)	0.592 ^b
a=Independent samples t-test; b=chi square;					
%variables from IDS-C30, higher scores denote greater symptoms burden;					
*variables from SCAN, higher scores denote greater symptoms burden.					

396 Supplementary Table 2

397

398