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Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment

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Abstract

Major depressive disorder (MDD) often occurs during pegylated IFN- α 2 (IFN- α) treatment. Identifying who is at risk for MDD in this population is essential, and epidemiological studies suggest that sleep may be related to depression risk. Controlling for pre-existing depression symptoms, we therefore examined whether sleep quality prior to IFN- α treatment would predict subsequent MDD incidence during IFN- α treatment. Adults with hepatitis C but without current clinical MDD ($n=86$) were evaluated prior to IFN- α treatment and then prospectively monitored during treatment using self-report measures of sleep quality (PSQI), depression (BDI), and anger and irritability (AIAQ), as well as with Structured Clinical Interviews for DSM-IV Axis I Disorders (SCID-I). During IFN- α treatment, 19% developed MDD, 19% developed subsyndromal depression with irritability, and one developed mania. Controlling for baseline depression symptoms and past history of depression, patients with worse sleep quality (PSQI ≥ 10) prior to treatment had shorter time until developing MDD (Hazard ratio = 10.6; 95% Confidence Interval = 3.4–32.2; log-rank $\chi^2=33.83$, $P<0.0001$) or any severe psychiatric problem (Hazard ratio = 6.2; 95% Confidence Interval=2.9–13.1; log-rank $\chi^2=36.86$, $P<0.0001$). These findings may have important implications for understanding, predicting, and possibly preventing depression, particularly in individuals treated with IFN- α .

Keywords

Insomnia; Survival Analysis

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1. Introduction

Sleep disturbances are a hallmark of major depressive disorder (MDD) (Hamilton, 1989), with a likely bidirectional relationship. Longitudinal studies over follow-up intervals of 1–35 years have consistently identified insomnia as a risk factor for the later development of both new onset and recurrent depression episodes (Ford and Kamerow, 1989; Eaton et al., 1995; Breslau et al., 1996; Chang et al., 1997; Riemann and Voderholzer, 2003; Perlis et al., 2006; Buysse et al., 2008). These prospective, epidemiological data suggest that insomnia could represent a vulnerability factor for the later development of depression. However, it is also possible that poor sleep is simply a surrogate marker for elevated subsyndromal depression, a possibility difficult to address in these epidemiologic trials. One recent study has attempted to control for baseline subsyndromal symptoms in assessing risk for depression recurrence in a large late-life cohort followed for two years (Cho et al., 2008).

In patients starting interferon- α (IFN- α) therapy, the development of MDD in the first few months of treatment has been a common finding (Trask et al., 2000; Schaefer et al., 2002; Loftis and Hauser, 2004; Raison et al., 2005b). IFN- α is an immune modulatory cytokine with antiviral and antiproliferative effects used to treat several cancers and viral infections, including hepatitis C. Over 2% of the U.S. population have been exposed to hepatitis C, with most developing chronic infection. Currently, IFN- α based treatments are the primary interventions for this illness, and the incidence of IFN- α -induced MDD in hepatitis C patients ranges from 15%–45% in most prospective studies (Asnis and De La Garza, 2006). This high incidence and rapid rate of development makes this population very amenable to prospective examination.

It is plausible that poor sleep quality could enhance vulnerability to developing MDD in patients who are started on IFN- α . A preliminary study of 32 cancer patients receiving interleukin-2 and/or IFN- α assessed sleep with a visual analog scale and found a correlation between poor sleep and increases on the Montgomery-Asberg Depression Rating Scale after 4 weeks of treatment (Capuron et al., 2004), consistent with our own preliminary observations that poor sleep may predict depression (Lotrich et al., 2008). However, multiple studies have regularly noted that elevated depression symptoms at baseline predict MDD during IFN- α treatment (Capuron and Ravaut, 1999; Scalori et al., 2000; Raison et al., 2005a; Raison et al., 2005b; Lotrich et al., 2007). It is possible that patients with mild or subsyndromal depressive symptoms (i) over-estimate their sleep problems; (ii) would be more likely to have sleep problems; and (iii) are more likely to have other co-occurring depression vulnerabilities. To specifically examine the predictive role of poor sleep, it is therefore critical to control for the confounding role of any coexisting subsyndromal depression symptoms.

With this in mind, we prospectively investigated whether poor sleep quality at baseline would predict the subsequent incidence of MDD in patients receiving IFN- α , particularly when controlling for the presence of any other depression symptoms or past history of depression. In addition to MDD as an outcome, irritability, agitation, anger, and mixed manic states may occur during IFN- α treatment (Kraus et al., 2003; Constant et al., 2005; Raison et al., 2005b; Lotrich et al., 2007; Lotrich et al., 2008). As the neuropsychiatric syndrome(s) seen during IFN- α treatment remains under debate, we therefore assessed both the incidence of categorical MDD as well as any type of diagnosed mood disorder or severe mood disturbance. If sleep is a critical predictor of depression vulnerability as has been suggested (Ford and Kamerow, 1989), this may offer a target for designing and targeting prophylactic interventions for depression and mood disorders, and in particular, for depression secondary to IFN- α .

2. Methods

2.1 Participants

We report data on 86 euthymic patients with hepatitis C (Table 1) started on combination pegylated-IFN- α 2 and oral ribavirin treatment and followed up to four months as part of a study examining genetic risk for depression, wherein an overlapping set of these patients have been previously described in a study of the serotonin transporter polymorphism (Lotrich et al., 2008). The sample was drawn from a University of Pittsburgh Medical Center clinic specializing in liver diseases. Patients whose hepatologist recommended IFN- α treatment were approached by study staff to participate in a research study investigating the association of IFN- α and depression. Interested eligible (see below) participants signed informed consent forms which, along with the study procedures, were approved by the University of Pittsburgh Institutional Review Board.

Patients were excluded from this study if they had an active Axis-I disorder (e.g., mood, anxiety, psychotic, impulse control, or drug/alcohol use disorders) within six months prior to starting IFN- α , as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1995). Individuals with a history of prior depressive episodes were eligible as long as they were in remission for at least 6 months ($n=33$). Eleven participants were taking stable doses of antidepressants. Most participants had typical medical co-morbidities of individuals in their 40s but were otherwise generally healthy as reflected by low Cumulative Illness Rating Scale-Geriatric (Miller et al., 1992) scores (Table 1). For ethical reasons, patients who developed a major mood disorder during IFN- α treatment were provided a psychiatric intervention that typically consisted of beginning an antidepressant or “mood stabilizing” medication.

2.2 Measures

The SCID-I was administered at baseline, and then used to diagnose MDD during IFN- α treatment. The Beck Depression Inventory-II (BDI) was the primary measure of self-reported depression symptoms (Beck et al., 1996). To avoid confounding depression symptoms and sleep ratings, we used BDI minus the sleep item (BDI-s). Irritability and anger severity was measured with the Anger Irritability and Aggression Questionnaire (AIAQ) (Coccaro et al., 1991). Self-reported sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). This validated 19-item questionnaire consists of 7 components (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over a 1-month time interval) which are summed to yield a global score (0–21; higher numbers indicate more sleep disturbance/poorer sleep quality).

2.3 Procedure

The BDI, AIAQ, and PSQI were administered prior to IFN- α (pre-treatment baseline), and at weeks 2, 4, 8, 12, and 16 during treatment. If participants developed significant mood concerns (reflected by a BDI >15 and/or spontaneously reported by the participant and/or their hepatologist), an abbreviated SCID-I was administered as soon as possible to determine the presence of a DSM-IV mood disorder. During this study, a number of patients developed severe mood problems but did not meet DSM-IV criteria for MDD. These patients were notable for severe irritability and significant concerns about hostility, for example, “road-rage” or violent outbursts at home. Although these individuals did not meet criteria for MDD or bipolar disorder, psychiatric intervention to prevent potentially injurious behavior was deemed necessary and therefore instituted. Our provisional term for this group is subsyndromal depression (SD) with irritability. The two primary endpoints for our analyses

were therefore (i) the time until categorical MDD or (ii) the time until any-cause psychiatric morbidity (i.e., when psychiatric intervention was required) through week 16.

2.4 Data analysis

Demographics and other baseline characteristics (i.e., CIRS-G, past history of depressive disorders, and pre-treatment PSQI, BDI-s, and AIAQ scales) were compared with Fisher's exact tests or independent sample t-tests for participants who did and did not require psychiatric intervention through week 16 of IFN- α treatment. The BDI-s was the only variable deemed to not have a normal distribution based on a Kolmogorov-Smirnov test, and therefore was compared with the Mann-Whitney test.

The upper quartile of baseline PSQI scores was 9, and the distribution of scores in the right tail suggested a high severity group at scores ≥ 10 . This score also coincides with published studies of primary insomnia patients that generally show mean values of 10 and greater (Backhaus et al., 2002). For Kaplan-Meier survival analyses using the Mantel-Cox log-rank test, we therefore dichotomized individuals into those with moderate to severe sleep problems (PSQI ≥ 10) and those with less severe complaints (PSQI < 10).

We first conducted a set of survival analyses specifically focusing on the development of MDD, censoring other types of psychiatric morbidity (i.e., individuals initiating treatment for mania or SD with irritability) or who those who discontinued or withheld IFN- α treatment (9 for neutropenia, 2 developed acute liver failure, 1 died, 4 discontinued for severe fatigue and somatic side effects, and 3 were noncompliant or stopped injections on their own). Because baseline PSQI was moderately correlated with baseline BDI-s ($r=.38$), and having a past history of depressive disorder ($r=.31$), Cox proportional hazards models were then conducted while controlling for these potentially confounding variables. The proportionality assumption was tested by assessing the risk at each event time, which was not significant. Next, we conducted similar survival analyses where the diagnostic endpoint was the time until all-cause psychiatric morbidity, where about 38% of the individuals required psychiatric intervention at some point in these first 16 weeks. Because baseline AIAQ scores were moderately correlated with baseline PSQI ($r=.18$), AIAQ was included as an additional control variable in these Cox proportional hazards models.

To further validate our findings, we conducted several sensitivity analyses. First, we excluded the 11 participants who were taking stable doses of antidepressants at baseline. Second, we used lower PSQI cut-off values (PSQI ≥ 9 or ≥ 8) as grouping factors. This was to examine whether our findings were an artifact of dichotomizing the sample at PSQI ≥ 10 . Third, we explored the relationship of the seven individual PSQI subscales with MDD incidence.

ANOVAs, with post-hoc analyses using the Least Significant Difference, were used to compare psychiatric symptoms (BDI-s, AIAQ, and PSQI) in those who developed MDD, SD with irritability, or no psychiatric diagnosis. We analyzed the last measurement prior to either psychiatric intervention or discontinuation of IFN- α , or end of the study.

3. Results

During the 16-week study period, psychiatric intervention was required in 33/86 (38%) participants: 16 (19%) developed categorical MDD, 16 (19%) required treatment for SD with clinically worrisome irritability/hostility, and one developed frank mania (1%). As previously noted (Lotrich et al., 2008), patients labeled with "SD and irritability" did not have grandiosity, racing thoughts, elevated mood, increased goal-directed activities, decreased need for sleep, or increased talkativeness. Pre-treatment global PSQI, AIAQ, and

BDI scores were all significantly higher for participants requiring psychiatric intervention during INF- α treatment, but the groups did not differ in age, gender, race, CIRS-G scores (Table 1). A past history of depressive disorders was evident in a significantly larger percentage of those requiring psychiatric intervention (55%) than in those not requiring psychiatric intervention (28%).

The average pre-treatment PSQI was 6.7 ± 4.1 , typical for populations with chronic illness such as lupus, rheumatoid arthritis, and multiple sclerosis (Cakirbay et al., 2004; Lobentanz et al., 2004; Costa et al., 2005). Moderate to severe pre-treatment sleep disturbance (PSQI ≥ 10) was reported by 18/86. Of these, 15/18 (83%) experienced psychiatric deterioration and required subsequent psychiatric intervention for MDD, SD with irritability, or mania. Of those reporting baseline PSQI < 10 , only 18/68 (26%) required psychiatric intervention.

Categorical DSM-IV MDD was significantly predicted by pre-treatment PSQI ≥ 10 in a Kaplan-Meier analysis (log-rank $\chi^2_{(1)} = 33.83$, $P < 0.0001$) (Figure 1). In Cox proportional hazards models, the association of pre-treatment PSQI with subsequent MDD remained statistically reliable when entered together with past history of depressive disorder and baseline BDI-s (Table 2). Controlling for these variables, participants with baseline PSQI ≥ 10 were over 10 times more likely to develop MDD than those with lower baseline PSQI scores (hazard ratio = 10.58, 95% CI = 3.43–32.63). In this model, past history of MDD was no longer predictive, however, baseline BDI-s remained a significant predictor of MDD incidence (hazard ratio = 1.10, which corresponds to a 10% increase in risk for each unit increase in BDI-s; as an exemplar, a BDI-s score of 10 would be equal to a hazard ratio of 2.59).

Similarly, psychiatric interventions for any reason occurred significantly faster in patients with PSQI ≥ 10 (log-rank $\chi^2_{(1)} = 36.86$, $P < 0.0001$). Again, using Cox proportional hazards models, the impact of pre-treatment PSQI remained statistically reliable when it was entered together with past history of depression, baseline BDI-s and AIAQ (Table 2); those with baseline PSQI ≥ 10 were over six times more likely to require psychiatric intervention than those with lower PSQI baseline scores (hazard ratio = 6.20, 95% CI = 2.93–13.09). None of the control variables were significant predictors when baseline PSQI was included in the model (Table 3).

We compared symptom increases during IFN- α treatment in those who did not require any psychiatric intervention, those who developed MDD, and those who developed SD with irritability (Table 4). BDI-s elevations were greater in those meeting criteria for MDD compared to those not requiring psychiatric intervention ($P = 0.010$), but only non-significantly greater than those in the SD group ($P = 0.220$). BDI-s increases in those with SD were greater than those who did not require psychiatric intervention ($P = 0.040$). Conversely, total AIAQ and irritability subscale scores increased the most in those with SD, significantly greater compared to those who did not require intervention ($P = 0.011$ and $P = 0.026$ for AIAQ total and irritability scores, respectively), but only non-significantly higher than those with MDD ($P = 0.307$ and $P = 0.530$, respectively). The modest increases in PSQI were similar across all three groups ($P = 0.526$).

3.1 Sensitivity analyses

Excluding the 11 participants taking stable doses of antidepressants at baseline had minimal impact on the Cox proportional hazards models. PSQI ≥ 10 continued to predict categorical MDD incidence (hazard ratio = 7.11, 95% CI = 1.96–25.82) or the requirement for all-cause psychiatric intervention (hazard ratio = 6.28, 95% CI = 2.69–14.67).

PSQI ≥ 9 significantly predicted the development of categorical MDD (hazard ratio = 5.71, 95% CI = 1.93–16.89), as well as requiring psychiatric intervention for any reason (hazard ratio = 2.90, 95% CI = 1.44–5.84). PSQI ≥ 8 also significantly predicted the development of categorical MDD (hazard ratio = 5.04, 95% CI = 1.68–15.11), as well as requiring psychiatric intervention for any reason (hazard ratio = 2.60, 95% CI = 1.29–5.23). Thus, our observation that elevated baseline PSQI scores predicted the development of psychiatric consequences during IFN- α does not appear to be an artificial property of our initial dichotomization. However, determining the most useful cut-off criteria will require ROC analyses with a larger sample size.

We next explored whether any of the individual seven PSQI subscales were driving the relationship between sleep quality and MDD incidence. Using Cox proportional hazard models with the same control variables, sleep efficiency, duration, latency, and quality were all similarly significant predictors of categorical MDD (hazard ratios ranging from 1.88 to 2.56) or the requirement of psychiatric intervention for any reason (hazard ratios ranging from 1.54 to 1.93). Notably, daytime dysfunction and the other two subscales (use of sleep medication and sleep disturbances) were not significant predictors.

4. Discussion

Individuals reporting poor sleep quality prior to IFN- α were more likely to subsequently develop either MDD and/or require psychiatric intervention for any mood disorder early in IFN- α treatment. Crucially, the ability of elevated PSQI scores to predict subsequent MDD was not mitigated when baseline depression symptoms and history of depression were included in the model. Thus, baseline PSQI scores do not appear to be a proxy for pre-existing subclinical depressive symptoms. Consistent with prior reports (Capuron and Ravaud, 1999; Scalori et al., 2000; Raison et al., 2005a; Raison et al., 2005b; Lotrich et al., 2007), symptoms of baseline depression were higher in participants who developed MDD during IFN- α , and continued to be a significant predictor for developing MDD even when co-entered with sleep quality. Regardless, the role of sleep remained the largest predictor. Unfortunately, insomnia often goes unrecognized and untreated (Jindal et al., 2004; Rosenberg, 2006).

In designing this prospective study, we did not exclude subjects with primary sleep disorders or other sources of insomnia other than depression. It is possible that differences in the prevalence and rate of depression development between studies may be related to differences in this important variable. Moreover, for ethical reasons, we attempted to be very resolute in identifying and treating those who developed mood disorders. This may be another reason that 38% of the subjects were started on a psychiatric medication, a percentage that is higher than other some other studies. Many other studies find that the majority of depression occurs within the first 12 weeks of IFN- α (Hauser et al., 2002; Dieperink et al., 2003; Schaefer et al., 2004; Reichenberg et al., 2005; Castera et al., 2006), but it is possible that occasional cases of later-onset depression occurring after our final 16-week follow up period were missed—although this is not something that we typically observe.

Regardless, our findings are consistent with epidemiologic data, where insomnia symptoms are a vulnerability factor for idiopathic depression (Ford and Kamerow, 1989; Eaton et al., 1995; Breslau et al., 1996; Chang et al., 1997; Riemann and Voderholzer, 2003; Perlis et al., 2006; Buysse et al., 2008). Importantly, we used a psychometrically well-validated measure of sleep quality, the PSQI (Buysse et al., 1989). We were also able to confidently control for the confounding relationship of higher BDI scores in those with poor sleep. Moreover, because this is a comparatively homogenous cohort studied over 16 weeks or less, it is

unlikely that there were other variables that could confound the relationship between poor sleep and vulnerability. Also, it is yet unknown the extent to which these preliminary results can be generalized to other populations of patients with hepatitis C (e.g., those with active substance abuse and/or active depression), other illness populations treated with IFN- α (e.g. melanoma), or other medically ill populations at risk for depression.

The distribution of baseline PSQI scores in our population suggested a higher severity group (≥ 10) just above the upper quartile, which we exploited for survival analyses. Ten is the average score for individuals with categorically diagnosed insomnia (Buysse et al., 1989; Backhaus et al., 2002). Nonetheless, although both PSQI ≥ 9 and ≥ 8 significantly predicted the development of depression, a larger study will be required to more confidently determine an appropriate clinical cut-off value using receiver operating curve analyses. Because the PSQI is a subjective self-report measure, it may be confounded by other variables. Future refinements to our findings will require a more objective measure of sleep quality such as polysomnography or actigraphy.

The relationship of poor sleep quality was strongest with risk for MDD, but it was also associated more broadly with the development of any mood disorder. Increases in hostility scores during IFN- α treatment have been documented by our group and others (Kraus et al., 2003; Kraus et al., 2005), with up to 24.5% developing clinically relevant anger/hostility (Kraus et al., 2003). Some have suggested that irritability is part of a mixed depressive state comprised of irritable mood, distractibility, agitation, and insomnia (Constant et al., 2005). In one prospective study, almost 20% met the criteria for MDD with some “mixed hypomanic” symptoms, predominantly irritability (Castera et al., 2006). In larger clinical efficacy studies where formal measures of irritability were not made but adverse effects were documented, “irritability” rates were between 19% and 35% (McHutchison et al., 1998; Manns et al., 2001; Fried et al., 2002). Thus, irritability could be (i) part of a severe but subsyndromal form of agitated depression, (ii) a distinct psychiatric entity, or (iii) a form of mixed mood disorder. We have provisionally labeled these patients as having a type of “subsyndromal depression” based on their clinical presentation, as well as BDI and AIAQ scores (non-significant trends towards lower BDI and non-significant trends towards higher AIAQ). The lack of standardized and accepted diagnostic criteria is a clear limitation for generalizing to other clinics and studies. Regardless, our findings regarding sleep quality are consistent whether risk for MDD is assessed independently or in conjunction with the less-defined SD. Further work will be necessary to further delineate the development of ‘mixed’ or ‘subsyndromal’ forms of depression and/or severe irritability during IFN- α treatment. For now, results of the analyses including SD and irritability should be taken as very preliminary.

A plausible mechanistic implication of our findings is that poor sleep quality causally enhances vulnerability for depression. Converging evidence suggests that inflammatory cytokines, sleep, and depression are highly interrelated (Irwin, 2001). Recent evidence indicates the involvement of proinflammatory cytokines in the etiology of both MDD (Zorrilla et al., 2001; Capuron and Dantzer, 2003) and sleep disturbances such as sleep apnea, insomnia, and sleep restriction (Vgontzas and Chrousos, 2002; Vgontzas et al., 2004). Sleep disturbances triggered by cytokines could also hypothetically increase vulnerability for depression (Benca, 2000). In this study, PSQI scores did slightly worsen during the combined IFN- α /ribavirin treatment. However, PSQI scores slightly increased in participants receiving IFN- α , whether they developed depression or not. This argues against the possibility, but does not prove, that the IFN- α -induced sleep disturbance caused the depression in our participants.

Nonetheless, we could not exclude the possibility that poor sleep quality at baseline is merely a marker for another entity that is causally involved in vulnerability to depression. We have recently found that genetic variability in the serotonin transporter is associated with both risk for MDD and elevated PSQI scores (Lotrich et al., 2008). There may be other potential biological or genetic factors that may be involved in the relationship between sleep quality and depression risk within the context of IFN- α .

Beyond these mechanistic implications however, these findings may have immediate clinical implications for predicting and possibly preventing depression in individuals treated with IFN- α . The psychiatric syndrome triggered by IFN- α is both prevalent and severe (Trask et al., 2000; Schaefer et al., 2002; Loftis and Hauser, 2004; Raison et al., 2005b; Asnis and De La Garza, 2006). Prophylactic use of SSRIs prevented IFN- α -induced depression in one small study (Musselman et al., 2001), but this has not been universally replicated (Morasco et al., 2007). Moreover, antidepressants are not without risks in this population (Asnis and De La Garza, 2006). Identifying pre-treatment factors that predict vulnerability to IFN- α -induced depression could help target prophylactic treatments appropriately. Sleep may be one such factor. Sleep disturbances such as insomnia and sleep deprivation are associated with mood symptoms and mood dysregulation (Pilcher and Huffcutt, 1996; Buysse et al., 2007). Moreover, insomnia impacts the trajectory of idiopathic depression, leading to greater episode severity, increased suicidality, and lower rates of remission (Agargun et al., 1997; Lustberg and Reynolds, 2000; Franzen and Buysse, in press). Recent evidence suggests that hypnotic medications in combination with SSRIs may favorably impact depression trajectory in patients who meet criteria for insomnia and idiopathic MDD (Fava et al., 2006); however, there has been little study on preventing depression by targeting sleep quality. Further clinical trials will be necessary to determine whether behavioral (e.g., Bootzin and Perlis, 1992) and/or pharmacological sleep-focused interventions can lower the incidence and severity of psychiatric consequences of IFN- α .

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Figure 1.

Kaplan-Meier analysis of the proportion of patients with baseline global PSQI ≥ 10 (poor sleep) and < 10 (good sleep) who required intervention for categorical MDD during the first 16 weeks of combination pegylated-IFN- $\alpha 2$ and ribavirin treatment. 'o' denotes cases censored for discontinuing or withholding IFN- α treatment for any medical or psychiatric reason other than MDD.

Table 1

Participant Demographic and Clinical Characteristics at Study Enrollment.

	Total Sample (n=86)	Status during IFN- α ^a			P value ^b
		MDD (n=16)	SD (n=16)	No Intervention (n=53)	
Age, y Mean (SD)	47.4 (12.4)	48.8 (6.5)	45.7 (12.0)	47.6 (14.0)	0.804
Gender, % male	66	56	81	64	0.645
Race, % white	88	75	86	92	0.173
CIRS-G total, mean (SD)	3.9 (1.7)	4.5 (1.5)	3.7 (2.0)	3.8 (1.7)	0.597
Past history of depressive disorder, %	38	69	44	28	0.022
On antidepressants at baseline, %	13	31	0	11	0.742
BDI, mean (SD)	7.5 (6.5)	12.0 (6.9)	6.9 (4.3)	6.2 (6.3)	0.007
BDI-s, mean (SD)	6.7 (6.0)	10.9 (6.4)	5.9 (3.6)	5.6 (5.9)	0.007
AIAG total, mean (SD)	33.6 (16.2)	38.0 (13.5)	37.5 (18.1)	30.8 (16.2)	0.044
Global PSQI score					
Mean (SD)	6.7 (4.1)	10.5 (4.5)	6.9 (4.5)	5.4 (3.1)	0.001
□□ % Scoring ≥ 10	21	63	25	6	<0.0001

^aFor status during the first 16 weeks of IFN- α treatment, MDD refers to those who developed major depressive disorder, SD refers to those who developed subsyndromal depression with severe irritability, and intervention refers to all individuals who developed psychiatric deterioration and required psychiatric intervention for any reason (i.e., all-cause psychiatric morbidity), and includes individuals who developed categorical MDD, SD, and mania.

^bComparing intervention vs. no intervention

Cox regression models: Hazard of poor sleep quality for categorical MDD during IFN- α accounting for past history of depression, and baseline self-reported depression and irritability.

Table 2

	β	Wald χ^2 (df=1)	P	Hazard Ratio	95% CI
Past history of depressive disorder	0.680	1.43	0.232	1.97	0.65–6.01
Baseline BDI-s	0.095	4.92	0.027	1.10	1.01–1.20
Baseline PSQI ≥ 10	2.359	16.84	< 0.0001	10.58	3.43–32.63

β refers to the unstandardized regression coefficient estimate.

Cox regression models: Hazard of poor sleep quality for psychiatric deterioration requiring intervention during IFN- α accounting for having a past history of depression, and baseline self-reported depression and irritability.

Table 3

	β	Wald χ^2 (df=1)	P	Hazard Ratio	95% CI
Past history of depressive disorder	0.309	0.65	0.419	1.36	0.64–2.88
Baseline BDI-s	0.046	1.80	0.180	1.05	0.98–1.12
Baseline AIAQ	0.002	0.02	0.889	1.00	0.98–1.03
Baseline PSQI ≥ 10	1.824	22.84	< 0.0001	6.20	2.93–13.09

β refers to the unstandardized regression coefficient estimate.

Table 4

The mean (standard deviation) increase in symptoms during the first 16 weeks of interferon treatment (the last observation prior to psychiatric intervention minus the baseline score). Group means with the same superscript did not significantly differ ($P > 0.05$). Test statistics were performed either with the Kruskal Wallis Test (BDI-s) or an ANOVA (all others). Note that the degrees of freedom differ as a result of missing or incomplete follow up data for several participants.

Measure	Status during IFN- α			Test statistic
	Major Depression	Subsyndromal Depression	No Intervention	
BDI-s	7.9 (8.8) ^a	4.1 (5.7) ^a	1.1 (5.8) ^b	$\chi^2 (2)=9.14, P=0.010$
AIAQ Total	3.8 (15.6) ^{a, b}	8.7 (15.2) ^a	-1.5 (11.9) ^b	$F(2,78)=3.68 P=0.030$
AIAQ Irritability	2.4 (4.5) ^{a, b}	3.3 (4.5) ^a	0.5 (4.0) ^b	$F(2,79)=3.13 P=0.049$
PSQI	2.4 (4.4) ^a	0.9 (3.6) ^a	1.5 (3.6) ^a	$F(2,79)=0.63 P=0.536$

The superscripts ^a and ^b indicate group means that did not significantly differ.