The implications of hypersomnia in the context of major depression: Results from a large, international, observational study

Running title: *Correlates of hypersomnia in depression*

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Abstract: (243/250 words)

According to the DSM-5, “reduction in the need for sleep” is the only sleep-related criteria for mixed features in depressive episodes. We aimed at studying the prevalence, clinical correlates and the role of hypersomnia in a sample of acutely depressed patients. Secondarily, we factors significantly increasing the odds of hypersomnia were studied. We conducted a post-hoc analysis of the BRIDGE-II-Mix study. Variables were compared between patients with hypersomnia (SLEEP+) and with insomnia (SLEEP-) with standard bivariate tests. A stepwise backward logistic regression model was performed with SLEEP+ as dependent variable. A total of 2514 subjects were dichotomized into SLEEP+ (n=423, 16.8%) and SLEEP- (n=2091, 83.2%). SLEEP+ had significant higher rates of obese BMI (p<0.001), BD diagnosis (p=0.027), severe BD (p<0.001), lifetime suicide attempts (p<0.001), lower age at first depression (p=0.004) than SLEEP-. Also, SLEEP+ had significantly poorer response to antidepressants (AD) such as (hypo)manic switches, AD resistance, affective lability, or irritability (all 0<0.005). Moreover, SLEEP+ had significantly higher rates of mixed-state specifiers than SLEEP- (all 0<0.006). A significant contribution to hypersomnia in our regression model was driven by metabolic-related features, such as “current bulimia” (OR=4.21) and “overweight/obese BMI (OR=1.42)”. Globally, hypersomnia is associated with poor outcome in acute depression. Hypersomnia is strongly associated with mixed features and bipolarity. Metabolic aspects could influence the expression of hypersomnia, worsening the overall clinical outcome. Along with commonly used screening tools, detection of hypersomnia has potential, costless discriminative validity in the differential diagnosis unipolar and bipolar depression.

Keywords: major depression, bipolar depression, mixed features, hypersomnia, comorbidity, screening-

Introduction

Sleep disturbances are highly prevalent in affective disorders (Asaad et al., 2016; Bradley et al., 2017). In bipolar disorder (BD) they may occur in 30-60% of patients, but reported rates vary from 10% to 80% depending on definition and management of potential confounding factors such as pharmacological treatments (M. Steinan et al., 2016; M. K. Steinan et al., 2016). Sleep disturbances have been increasingly recognized as important predictors of relapse in both major depressive disorder (MDD) and BD (Bao et al., 2017; Bromberger et al., 2016; Craig et al., 2000; Gershon et al., 2017; Sakurai et al., 2017). Most descriptive studies on depressed or BD subjects with sleep alterations have focused on insomnia or decreased need to sleep, while fewer studies explored the presence of hypersomnia and its associated clinical features, despite its reported prevalence in 17-78% of patients with BD depression (Steinan et al., 2016).

Recent data on theoretical models of BD supported the hypothesis that sleep disturbances may be a marker of underlying global circadian dysregulation (Kapczinski et al., 2011; Rosa et al., 2013), including unfavorable rapid cycling course or mood instability (Mosolov, 1996; Strejilevich et al., 2013) and involving other parameters like the body mass index (BMI) (Samalin et al., 2017; M. Steinan et al., 2016). Specifically, a Delayed Sleep Phase (DSP), defined as sleep onset insomnia and/or morning sleepiness that may extend for 3-6 hours, was present in 10% of a sample of 404 BD patients and associated to a higher mean BMI (Steinan et al., 2016b). In a cross-sectional study higher BMI in BD but not healthy controls significantly correlated with lower sleep efficiency, shorter total sleep time, longer sleep onset latency, higher fragmentation index, higher inter-day variability (Boudebesse et al., 2015).

A relationship between depression, especially with atypical features, and obesity has been widely demonstrated (Chou and Yu, 2013; de Wit et al., 2010; Lasserre et al., 2014; Luppino et al., 2010) but the nature of this association still remains unclear. Atypical symptoms, which include hypersomnia, in depressed patients have been associated with both obesity and bipolarity (Forty et al., 2008; Łojko et al., 2015). Likewise, excess bodyweight and obesity are highly prevalent in individuals with BD and this association is considered as one of many comorbidities generating concern

in BD populations due to important health implications (Liu et al., 2013). Unfortunately, the direction of this association is not clear. In fact, obese patients show a higher risk of developing major MDD and BD (Simon et al., 2006), but the course of bipolar depression is also frequently affected by the development of overweigh and obesity, possibly related to the effects of psychotropic medications or to comorbid diagnoses with eating disorders, such as binge eating disorder (BED). Notwithstanding, this association underpins genetic and neurobiological liability (McElroy et al., 2018, 2013, 2011; McElroy and Keck, 2014). In BD, obesity is directly associated with a worse illness course and outcome, including increased suicidality and decreased cognitive performance (Fagiolini et al., 2004; Yim et al., 2012). Metabolic comorbidity in BD may also act as a "mood destabilizer", increasing depressive symptom severity and recurrence (Liu et al., 2013). A recent post-hoc analysis of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE-II-MIX) naturalistic study (Perugi et al., 2016, 2015; Popovic et al., 2015) assessed the association between obesity and the presence of bipolar features, concluding that higher BMI in patients with major depression (MDE) seems to be associated with a lifetime diagnosis of BD and with a poorer illness outcome and suggesting that obesity in patients with MDE could be considered a possible marker of bipolarity (Petri et al., 2017).

The objective of the present post-hoc analysis was to assess possible diagnostic and clinical correlates of insomnia (SLEEP-) or hypersomnia (SLEEP+) in the population recruited for the BRIDGE-II-Mix study. Secondarily, a statistical model predicting the likelihood of hypersomnia was performed, as well as a statistical model to understand whether the presence of combined hypersomnia and overweight/obesity phenotype could define a subgroup of patients with specific clinical features.

Methods

Study population recruitment

This study is a post-hoc analysis of the BRIDGE-II-Mix study (Perugi et al., 2015). The primary objective of BRIDGE-II-MIX naturalistic study was to provide a reliable estimate of the frequency of mixed states in a large international sample of patients

diagnosed with MDE according to several sets of criteria. The BRIDGE-II-Mix Study was a multisite, international, non-interventional, cross-sectional study. The recruitment procedure and the inclusion criteria have been described in a previous study (Popovic et al., 2015). From an initial pool of 2811 patients with MDE, sleep disturbances were detected in 2514 patients who were thus included in the present post-hoc analysis.

Data collection

In a single consultation the participating psychiatrists completed a case report form for each patient, incorporating inclusion criteria, socio-demographic variables (age, gender, marital status), biometrics values (height, weight), in- or out- patient status, history of psychiatric symptoms (mood symptoms, suicide attempts) and previous psychiatric hospitalizations. Features of the MDE, including bipolar symptoms listed in the DSM-IV-TR diagnostic criteria for BD, known risk factors for BD (e.g. family history of BD, early onset depression), previous response to ADs, psychiatric comorbidity, current treatment and functional status determined by the investigator using the Global Assessment of Functioning (GAF) were assessed (Endicott et al., 1976).

The evaluation packet was explicitly structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of an acutely ill patient. No rating scales requiring calibration with a standard were incorporated. Raters were instructed to follow their usual practice, as training might have altered these practices and might be seen as a biasing factor.

The primary objective of the BRIDGE-II-MIX study was to establish the frequency of depressive mixed states by analyzing all the relevant symptoms of either pole. After the publication of DSM-5, this was post-hoc defined as 1) the proportion of patients fulfilling DSM-5 criteria for MDE with mixed features (American Psychiatric Association, 2013), and 2) research based diagnostic criteria for mixed states (RDC). RDC are defined by the presence of MDE plus 3 out of the following 14 hypomanic symptoms for at least a week: irritable mood, affective lability, distractibility, psychomotor agitation, impulsivity, aggression (verbal or physical), racing thoughts,

more talkative/pressure to keep talking, hyperactivity, increased energy, risky behavior, grandiosity, elation, hyper-sexuality. The proportion of patients fulfilling criteria for BD according to the DSM-IV-TR and bipolarity specifier proposed by Angst et al. (Angst et al., 2013, 2011, 2005) was also identified. The bipolarity specifier attributes a diagnosis of BD to patients who experienced an episode of elevated mood or irritable mood or increased activity with at least three of the symptoms listed under Criterion B of the DSM-IV-TR, associated with at least one of the three following consequences: (i) unequivocal and observable change in functioning uncharacteristic of the person's usual behavior, (ii) marked impairment in social or occupational functioning observable by others or (iii) requiring hospitalization or outpatient treatment. No minimum duration was required and no exclusion criteria were applied.

Ethical aspects

In each participating Country, the study protocol was approved by the local ethics committee, in accordance with the Declaration of Helsinki. Each patient provided written informed consent in order to participate.

Statistical analyses

The sample was dichotomized into patients reporting reduced sleep (SLEEP-) and increased sleep (SLEEP+). Variables were compared between the 2 study subgroups with Chi-square (categorical variables) and Student's t-test (continuous variables). A stepwise backward logistic regression model was then used to identify the likelihood of selected variables in predicting insomnia versus hypersomnia. The stepwise modeling procedure started with the full model and consisted, for each step, in eliminating the least statistically significant variable from the model and re-computing the revised model, until all remaining variables were at $p<0.1$. Statistical analyses were performed using the Statistical Package for Social Sciences (Statistical Package for Social Science-SPSS, 23.0 version for Windows Inc., Chicago, IL, USA). All p values were two-tailed and statistical significance was set at $p<0.05$.

RESULTS

A total of 2514 depressed individuals were derived from the original BRIDGE-II-MIX sample and considered in the present post-hoc analysis. The sample was dichotomized into SLEEP- (n=2091, 83.2%) and SLEEP+ (n=423, 16.8%) subgroups, based on the presentation of objective reduction of sleep or hypersomnia respectively.

When considering sociodemographic and lifestyle characteristics of the sample, SLEEP+ patients showed significant higher rates of single marital status (29.3% vs. 22.9%, p=0.006) and obese BMI (23.0% vs. 15.4%, p<0.001), significant less normal BMI (47.1 % vs. 37.1%, p<0.001) than SLEEP-. No differences were found in sex distribution or age at evaluation (see Tab. 1).

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When considering characteristics related to current diagnosis and possible past course of illness, SLEEP+ subgroup showed significant higher rates of BD diagnosis (20.6% vs. 16.0%, p=0.027), a more severe course of BD illness measured with CGI (2.80±1.72 vs. 2.26±1.68, p<0.001), higher rates of atypical features (32.2% vs. 1.8%, p<0.001) and lifetime suicide attempts (29.3% vs. 21.0%, p<0.001), significant lower rates of MDD (79.4% vs. 84.0, p<0.001), also at first episode (18.0% vs. 26.0, p=0.027) than SLEEP-. SLEEP+ also showed significant lower age at first psychiatric symptoms (29.14±12.19 vs. 33.38±12.93, p=0.012) and age at first depression onset (32.55± 11.75 vs. 35.93±12.68, p=0.004) than SLEEP-. When considering past episodes, SLEEP+ patients showed a significantly higher number of depressions (5.71±6.99 vs. 4.48±5.78, p<0.001) and suicide attempts (1.52±3.01 vs. 0.41±3.98, p=0.031), last year's overall number of mood episodes (2.99±6.66 vs. 2.12±3.94, p<0.001), total days spent depressed (120.00±96.00 vs. 107.94±96.14, p=0.016) and total days spent (hypo)manic 20.21±43.57 vs. 12.24±39.94, p<0.001) than SLEEP- patients (See Tab.2).

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SLEEP+ patients presented significantly higher rates of mixed-state according to RDC (32.9% vs. 27.6%, p=0.029), but not to DSM-5 specifier (5.0% vs. 8.3%, p=0.021). When considering each RDC mixed symptom, SLEEP+ presented more frequently racing thoughts, (15.1% vs. 10.6%, p=0.007), affective lability (37.6% vs. 27.5%, p<0.001), distractibility (29.6% vs. 23.4%, p=0.007), impulsivity (16.8% vs. 13.2%, p=0.048), hypersexuality (4.0% vs. 2.3%, p=0.042) than SLEEP-, and significantly less risky behavior (5.0% vs. 7.8% , p=0.041).

Past treatments with antidepressants (AD) were statistically more frequent in SLEEP+ patients (85.3% vs. 79.5%, p=0.006), and this subgroup of patients also presented significant higher rates in all variables related to poor response to AD, such as reporting (hypo)manic switches (24.1% vs. 15.3%, p<0.001), resistance to AD treatment (34.3% vs. 27.1%, p=0.003), affective lability (41.6% vs. 26.7%, p=0.001) or irritability (33.1% vs. 24.8%, p<0.001) (See Tab.3).

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SLEEP+ patients presented frequent comorbidities with other psychiatric conditions, statistically significant compared to SLEEP- for obsessive-compulsive disorder (OCD, 7.6% vs. 4.2%, p=0.002), social phobia (13.5% vs. 6.4%, p<0.001), generalized anxiety disorder (GAD, 23.2% vs. 17.2%, p=0.003), binge eating syndrome (13.7% vs. 6.0%, p<0.001), bulimia (6.1% vs. 1.0%,p<0.001), night eating syndrome (5.5% vs. 2.2%, p<=.001). Atypical antipsychotics (34.0% vs. 22.1%, p<0.001) and mood stabilizers (40.0% vs. 26.0, p<0.001) were significantly more frequently used in SLEEP+ group (See Tab.4).

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Stepwise backward logistic regression was performed to assess the impact of 25 factors on the likelihood that patients would report a problem of hypersomnia.

The full model as a whole was significant, χ^2 (12, N= 2461)=153.392, p<0.001. A total of 11 independent variables made a unique statistically significant contribution to the model, here presented in order of strength in predicting hypersomnia: “current

bulimia" (OR=4.21), "current social phobia" (OR=1.77), "overweight/obese BMI (OR=1.42)", "affective lability with previous AD treatment" (OR=1.37), "affective lability" (OR=1.37), "treatment with atypical antipsychotics (OR=1.36), "treatment with mood stabilizers" (OR=1.33), "lifetime suicide attempts (OR=1.31), "number of days depressed in the last year" (OR=1.00), "age at first depression" (OR=0.98)"risky behavior symptoms" (OR=0.32) (See Tab.5).

We decided to consider dichotomized BMIs subgroups, by dividing the sample in "patients with BMI above normal and "patients with BMI of normal value or below". Sleep subgroups still differed statistically, as SLEEP+ (241, 57.0%) were more frequently overweight/obese than SLEEP- (1002, 47.9%, χ2 11.539, p=0.001). Given the consistent contribution of metabolic-related variables in predicting the model of hypersomnia, we conducted a secondary analysis on the patients with both hypersomnia and BMI above normal in order to define this more extreme, "atypical" phenotype. These patients presented themselves as a more extreme phenotype with respect to the SLEEP+ subgroup (See Supplementary Material Table S1). A similar comparison between this atypical profile and the opposite phenotype (sleep reduction/BMI below normal) showed again the clinical distance between these clinical phenotypes (See Supplementary Material Table S2). The stepwise backward logistic regression conducted on the extreme phenotype was also overall significant (7, N= 2478, χ^2= 98.868, p<0.0005), with significant contribution made by current bulimia (OR=3.99), current binge eating (OR=2.30), current social phobia (OR=1.65), current treatment with mood stabilizers (OR=1.50), current treatment with atypical antipsychotics (OR=1.48), affective lability with previous AD treatments (OR=1.44), current affective lability (OR=1.38) (See Supplementary Material Table S2).

DISCUSSION

In the present post-hoc analysis on a large sample of acutely depressed patients recruited from a large multi-site study, hypersomnia showed a strong association with mixed features.

Sleep alterations in depression positively relate to a worse course of illness (Takaesu et al., 2017) and an increase in suicidality (Littlewood et al., 2018). More, sleep alterations are amongst the top warning signs of suicide (Rebecca A Bernert et al., 2017). While insomnia symptoms have been commonly described in mood disorders and BD, hypersomnia is a significant but underexplored problem (Vieta et al., 2018a) (Vieta et al, 2018). Recently, a positive association between hypersomnia and suicidal behaviors has been reported (Michaels et al., 2017). In our sample of depressed subjects, as expected, sleep disturbances were mostly prevalent (N=2514 of 2811, 89,4%). Among them, 83.2% presented insomnia during the index episode SLEEP-, while 16.8% was experiencing hypersomnia SLEEP+. SLEEP- patients were more frequently at their first affective onset or were diagnosed with unipolar depression, compared with SLEEP+. Similar findings of high rates of insomnia have been found in major unipolar depression (approximately 90%), indicative of initial diagnosis of depression and higher severity of symptoms (Baglioni and Riemann, 2012). On the contrary, a diagnosis of BD was significantly more frequent in the SLEEP+ group, supporting previous data on the frequent occurrence of atypical features in bipolar depression, previously described especially in BD type II (Thase, 2007). Notably, in our sample we did not find differences in BD subtypes among the SLEEP+ patients, in line with recent finding pointing on the prevalence of hypersomnia in BD type I (Kaplan and Williams, 2017). According to the primary aim of the study, we focused on the SLEEP+ subgroup and we found an overall higher severity of BD, higher number of mood episodes, depressions, and higher numbers of days spent depressed and/or (hypo)manic compared with the SLEEP- group. The last finding is an unexpected result since hypersomnia is not contemplated as a manic or hypomanic symptom (American Psychiatric Association, 2013). Specifically, our SLEEP+ group positively related with past mood elation, which in turn is traditionally associated with insomnia or decreased need for sleep (American Psychiatric Association, 2013, 2000). Our results, when confirmed prospectively using a longitudinal design, could support the hypothesis that insomnia and hypersomnia may and do occur within the same illness course (Kaplan and Williams, 2017).

Several other findings from the present study seem to support the association between hypersomnia and bipolar diathesis, such as younger age at the first psychiatric symptoms and younger age at first depressive episode in the SLEEP+ group. These are among the most relevant clinical indicators of unrecognized bipolarity in depressed patients (Angst et al., 2012, 2010; Tondo et al., 2014). Also, the higher frequency of both DSM-5 and RDC mixed specifier during the index depressive episode in the SLEEP+ group points towards an association with bipolarity (Iwanami et al., 2015; McIntyre et al., 2015; Solé et al., 2017; Takeshima and Oka, 2015). Yet, the DSM-5 specifier fails to consider the possibility of an increased duration of sleep as possible symptom of mixicity, potentially leaving aside patients that could very well fit into the group (Pacchiarotti et al., 2011; Popovic et al., 2016).

With respect to treatment regimens, SLEEP+ presented significantly higher frequencies of mood stabilizers and atypical antipsychotics use, coherently with the higher BD prevalence Also, SLEEP+ patients reported, in the past, higher rates of antidepressant use, resistance, associated (hypo)manic switches, and worsening of depression (with affective lability, aggressiveness, chronicity), all these factors being associated with bipolarity in our same sample (Barbuti et al., 2017; Mazzarini et al., 2018; Verdolini et al., 2017). This converges with past observations on the association between hypersomnia and worse response to AD treatment that call for specific therapeutic strategies (Kaplan and Williams, 2017; Verdolini et al., 2018).

From a prognostic standpoint, SLEEP+ group had a significant poorer outcome correlates expressed by higher rates of comorbidities, especially with bulimia, OCD, social phobia and GAD, higher rates of suicide ideation, compared to SLEEP- and in line with previous studies (Rebecca A Bernert et al., 2017; Rebecca A. Bernert et al., 2017; Michaels et al., 2017; ten Have et al., 2018; van Krugten et al., 2018). Hence, hypersomnia is a relevant target for early intervention strategies (Vieta et al., 2018b).

In our results, different significant findings in SLEEP+ patients pointed at metabolic and weight-related features, such as higher rates of comorbid eating disorders (i.e. binge eating disorders, night eating and bulimia), and BMI from overweight to obese. This significance persisted after logistic regression, as bulimia and BMI above normal significantly contributed as unique factors to the likelihood of hypersomnia. These

associations, together with the finding of a bipolar diathesis in the SLEEP+ group, outline a possible shared susceptibility to BD and metabolic disturbances manifested as obesity/weight gain, in line with previous data (Boudebesse et al., 2015). For these reasons, we specifically studied the extreme phenotype of hypersomnia and overweight/obese (BMI>25, above normal) patients. Indeed, this subgroup presented a clear overlap with the whole SLEEP+ population, presenting an even stronger association with mixicity and BD-related clinical and prognostic features, such as the use of BD treatments, poor response to antidepressants and presence of affective lability.

Last, in our study, the cumulative effects of risk factors for obesity and hypersomnia outlined a significant role of medications such as atypical antipsychotics and mood-stabilizers. The effect of these treatments on both increased sleep and appetite is well known (Yatham et al., 2018), even though in our study is not preponderant.

5. Limitations

Although this study tried to provide clinical and prognostic information on the associations between hypersomnia, obesity and BD on a large sample of MDE patients, several limitations can be highlighted. First, the cross-sectional design of both the primary study and this post-hoc analysis does not allow for causal inferences. Second, a confounding effect is the greater use of medications strongly related with weight-gain and sedation such as atypical antipsychotics and mood stabilizers, both in SLEEP+ and hypersomnia/overweight groups. Third, the sample of acutely depressed patients does not present an evaluation of euthymic phases, neither in unipolar, nor in BD patients. Moreover, we relied on the definition of sleep problems on the basis of the absence/presence of the symptom, but we did not assessed total sleep hours, daytime sleepiness or delay phase of sleep, that would have. Similarly, we did not employ specific sleep questionnaires or objective instrumental sleep measurements, such as actigraphy and polysomnography. Yet, the very definitions of insomnia and hypersomnia provide a univocal and objective, albeit clinical, esteem of increased and decreased sleep, commonly observed from the perspective of daily clinical practice.

6. Conclusions

The findings in the present post-hoc analysis outline the important of hypersomnia as a negative factor in a major depressive episode. Moreover, its strong link with bipolar diathesis calls for its potential discriminative validity in the differential diagnosis between unipolar and bipolar depression. Along with commonly used screeners for bipolarity, excessive duration of night sleep represents an effective, costless clinical feature to be taken into account in the diagnostic assessment of an acute depressive episode.

The co-occurrence of hypersomnia and overweight/obesity might represent a more extreme clinical phenotype of bipolarity complicated by treatment-related adverse effects. BD patients presenting hypersomnia and obese/overweight could benefit from an integrated approach aimed at reducing the impact of these risk factors through the improvement of dietary habits, physical activity, sleep hygiene, lifestyle behaviors, along with tolerable pharmacological treatments, in order to ameliorate their illness course and outcome.

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Tab. 1. *Sociodemographic and lifestyle characteristics of the included sample (n=2514).*

	Sleep- (n=2091)		Sleep+ (n= 423)			
Variables (YES)	**n**	**%**	**n**	**%**	χ^2	**p**
Sex (female)	1430	68.4	305	72.1	2.271	0.132
Marital status						
Married	1153	55.1	220	52.0	1.392	0.238
Divorced	336	16.1	63	14.9	0.364	0.546
Single	479	22.9	124	29.3	7.891	**0.006**
Current smoker	725	34.7	158	37.4	1.109	0.292
BMI						
Underweight	77	3.8	22	5.3	2.145	0.143
Normal	961	47.1	155	37.1	12.369	**<0.001**
Overweight	688	33.7	145	34.7	0.301	0.610
Obese	314	15.4	96	23.0	15.197	**<0.001**
Variable	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**
Age	43.96	13.80	41.08	13.03	3.953	**<0.001**

Notes: BMI = *Body Mass Index, underweight (<18.5), normal (18.5 to 25), Overweight (25 to 30), Obese (>30*.
SD = *Standard Deviation*.

Tab. 2. *Diagnostic and past course of illness characteristics of the included sample.*

	Sleep- (n=2091)		Sleep+ (n= 423)			
Variables (YES)	**n**	**%**	**n**	**%**	χ^2	**p**
Diagnosis						
BD Diagnosis						
Total	334	16.0	87	20.6	5.326	**0.027**
BD type I	206	9.9	54	12.8	3.222	0.080
BD type II	128	6.1	33	7.8	1.657	0.198
UMD	1757	84.0	336	79.4	5.326	**0.027**
First Episode	543	26.0	76	18.0	12.137	**<0.001**
Clinical features						
Presence of fatigue/energy loss	1960	93.9	412	97.4	8.381	**0.004**
Atypical features	37	1.8	136	32.2	506.803	**<0.001**
Lifetime suicide	439	21.0	124	29.3	14.012	**<0.001**
Illness onset	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**
Age at 1st symptoms	33.38	12.93	29.14	12.19	6.192	**<0.001**
Age at 1st depression	35.93	12.68	32.55	11.75	5.041	**<0.001**
Current Episode						
Duration	93.43	123.85	98.01	139.85	0.457	0.499
Duration of (hypo)manic symptoms	12.19	46.59	11.15	22.63	0.073	0.788
N of (hypo)manic symptoms	1.80	2.69	2.08	2.75	3.72	0.054
Severity of mania	1.32	0.82	1.32	0.84	2.082	0.149
Severity of depression	4.50	0.98	4.53	0.89	0.208	0.648
Severity of BD	2.26	1.68	2.80	1.72	33.140	**<0.001**
Past Episodes						
N of depressions	4.48	5.78	5.71	6.99	14.607	**<0.001**
Tot suicidal attempts	0.41	1.54	0.58	1.21	4.676	**0.031**
Tot hospitalizations	1.72	3.98	1.52	3.01	0.962	0.327
Past Year						
N of mood episodes	2.12	3.94	2.99	6.66	13.130	**<0.001**
Tot days depressed	107.94	96.14	120	96.00	5.854	**0.016**
Tot days (hypo)manic	12.24	39.94	20.21	43.57	13.573	**<0.001**

Notes: BD = *Bipolar Disorder*; **UMD** = *Unipolar Major Depression*; **N** = *Number*; **Tot** = *Total*; **SD** = *Standard Deviation*.

Tab. 3. *Mixed specifiers and BD-related characteristics of the included sample.*

	Sleep- (n=2091)		Sleep+ (n= 423)			
Variables (YES)	**n**	**%**	**n**	**%**	χ^2	**p**
DSM-5 Mixed specifier	173	8.3	21	5.0	5.410	**0.021**
RDC Mixed specifier	577	27.6	139	32.9	4.790	**0.029**
RDC Mixed symptoms						
Psychomotor agitation	342	16.4	58	13.7	1.839	0.175
Irritable mood	667	31.9	151	35.7	2.313	0.128
Racing thoughts	221	10.6	64	15.1	7.281	**0.007**
Affective lability	576	27.5	159	37.6	17.149	**<0.001**
More talkative/pressure to keep talking	236	11.3	52	12.3	0.351	0.553
Distractibility	489	23.4	125	29.6	7.244	**0.007**
Increased energy	139	6.6	27	6.4	0.040	0.842
Aggression (verbal or physical)	286	13.7	62	14.7	0.283	0.595
Hyperactivity	168	8.0	34	8.0	0.000	0.998
Grandiosity	69	3.3	19	4.5	1.480	0.224
Mood elation	91	4.4	20	4.7	0.118	0.731
Impulsivity	275	13.2	71	16.8	3.913	**0.048**
Risky behavior	163	7.8	21	5.0	4.156	**0.041**
Hypersexuality	48	2.3	17	4.0	4.149	**0.042**
Past treatments with ADs						
Past use of ADs	1662	79.5	361	85.3	7.685	**0.006**
(Hypo)manic switches	319	15.3	102	24.1	19.799	**<0.001**
Resistance to treatment	566	27.1	145	34.3	9.018	**0.003**
Mood lability	559	26.7	176	41.6	37.623	**0.001**
Irritability	518	24.8	140	33.1	12.616	**<0.001**
Response unknown	151	7.2	31	7.3	0.006	0.938

Notes: AD = *Antidepressants*. **RDC** = *Research Diagnostic Criteria*.

Tab. 4

Variables (YES)	Sleep- (n=2091) n	Sleep- (n=2091) %	Sleep+ (n= 423) n	Sleep+ (n= 423) %	χ^2	p
Comorbidities						
Panic disorder	222	10.6	49	11.6	0.349	0.548
OCD	87	4.2	32	7.6	9.072	**0.002**
Social phobia	134	6.4	57	13.5	24.929	**<0.001**
GAD	358	17.2	98	23.2	8.667	**0.003**
Eating disorders	124	6.0	57	13.7	30.9555	**<0.001**
Binge eating syndrome	40	1.9	25	6.0	22.721	**<0.001**
Anorexia	99	4.8	29	7.0	3.441	0.068
Bulimia	20	1.0	25	6.1	49.939	**<0.001**
Night eating syndrome	46	2.2	23	5.5	14.099	**<0.001**
ADHD	45	2.2	12	2.9	0.776	0.378
Borderline personality	136	6.5	27	6.4	0.009	1.000
Alcohol abuse						
Use resulting in failure	104	5.0	17	4.0	0.706	0.401
In hazardous situations	54	2.6	11	2.6	<0.001	0.985
Legal problems	21	1.0	3	0.7	0.327	0.568
Continuous	48	2.3	13	3.1	0.890	0.345
Never dependence	1330	63.8	253	60.0	2.220	0.150
Substance abuse						
Use resulting in failure	33	1.6	4	0.9	0.975	0.504
In hazardous situations	20	1.0	3	0.7	0.239	0.785
Legal problems	6	0.3	3	0.7	1.755	0.185
Continuous	43	2.1	8	1.9	0.047	1.000
Never dependence	1326	63.6	262	62.2	0.281	0.596
Treatments						
No treatment	234	11.2	43	10.2	0.377	0.609
BZDs	978	46.8	190	44.9	0.486	0.485
Other anxiolytics	85	4.1	15	3.5	0.248	0.618
SSRIs	942	45.1	190	44.9	0.003	0.960
SNRIs	388	18.6	79	18.7	0.003	0.954
TCAs	386	18.5	72	17.0	0.489	0.484
Other antidepressants	216	10.3	55	13.0	2.613	0.106
Typical antipsychotics	216	10.3	51	12,1	1.105	0.293
Atypical antipsychotics	463	22.1	144	34.0	27.203	**<0.001**
Mood stabilizers	544	26.0	169	40.0	33.633	**<0.001**
ECT	39	1.9	6	1.4	0.399	0.527

Notes: OCD = *Obsessive-Compulsive Disorder*; **GAD** = *Generalized Anxiety Disorder*; **ADHD** = *Attention Deficit Hyperactivity Disorder*; **BZD** = *Benzodiazepine*; **SSRI** *Selective Serotonin Re-Uptake Inhibitor*; **SNRI** =*Serotonin and norepinephrine reuptake inhibitors*; **TCA** = *Tricyclic Antidepressant*; **ECT** = *Electro-Convulsive Treatment*.

Tab. 5. *Final variables in the stepwise backward logistic regression model*

							95% C.I.for EXP(B)	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Overweight-obese BMI	0.348	0.116	8.953	1	0.003	1.417	1.128	1.780
Tot days DEP /last year	0.001	0.001	5.367	1	0.021	1.001	1.000	1.002
Age at 1st DEP	-0.018	0.005	12.510	1	0.000	0.983	0.973	0.992
Lifetimes suicide attempts	0.266	0.131	4.151	1	0.042	1.305	1.010	1.686
Current OCD	0.426	0.230	3.433	1	0.064	1.531	0.976	2.403
Current social phobia	0.572	0.184	9.641	1	0.002	1.772	1.235	2.543
Current bulimia	1.437	0.330	19.013	1	0.000	4.210	2.206	8.033
Affective lability (past AD)	0.316	0.129	6.056	1	0.014	1.372	1.067	1.766
Affective lability (current)	0.311	0.128	5.940	1	0.015	1.365	1.063	1.752
Risky behaviors symptom	-1.133	0.264	18.423	1	0.000	0.322	0.192	0.540
Currently on AAP	0.306	0.130	5.582	1	0.018	1.359	1.054	1.752
Currently on MS	0.288	0.132	4.786	1	0.029	1.334	1.030	1.726

Notes. C.I. = *Confidence Intervals.* **AAP** = *Atypical Antipsychotics*; **AD** = *Antidepressants*; **BMI** = *Body-Mass Index*; **DEP** = *Depression*; **MS** = *Mood Stabilizers*; **OCD** = *Obsessive-Compulsive Disorder*.

Supplementary Tab S1. Bivariate statistics on "Atypical Phenotype" vs. the rest of the sample.

	Others (n=2277)		Sleep+ / Weight+ (n= 241)			
Variables (YES, significant)	**n**	**%**	**n**	**%**	**X2**	**p**
BD	366	16.1	55	22.8	7.057	**0.008**
BD type I	221	9.7	39	16.2	9.806	**0.002**
UMD	1907	83.9	186	77.2	7.057	**0.008**
First depressive episode	584	25.7	35	14.5	14.649	**<0.001**
Suicide attempts	488	21.5	75	31.1	11.678	**0.001**
RDC mixed specifier	630	27.7	86	35.7	6.792	**0.009**
Previous AD treatment	1804	79.4	219	90.9	18.351	**<0.001**
(Hypo)Manic switches	354	15.6	67	27.8	23.364	**<0.001**
Resistance to AD	618	27.2	93	38.6	13.962	**<0.001**
Affective lability	626	27.5	109	45.2	32.950	**<0.001**
Irritability	568	25.0	90	37.3	17.214	**<0.001**
Current OCD	101	4.5	18	7.5	4.393	**0.036**
Current social phobia	157	6.9	34	14.1	16.033	**<0.001**
Current GAD	400	17.6	56	23.2	4.579	**0.032**
Current binge eating	45	2.0	20	8.4	34.875	**<0.001**
Current night eating	52	2.3	17	7.2	18.741	**<0.001**
Bulimia	25	1.1	20	8.4	64.505	**<0.001**
On atypical antipsychotics	518	22.8	89	36.9	23.788	**<0.001**
On mood stabilizers	605	26.6	108	44.8	35.510	**<0.001**
Variable	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**
Age of first symptoms	32.88	12.99	30.74	11.90	4.734	**0.030**
Age of first depression	35.50	12.710	34.16	11.39	7.111	**0.008**
N past depressions	4.59	6.05	5.66	5.651	6.935	**0.009**
N mood ep. last 365 days	2.16	4.03	3.27	7.71	13.278	**<0.001**
Tot days (hypo)mania /last 365 days	12.64	39.57	22.45	46.92	12.750	**<0.001**
Severity of mania	1.31	0.81	1.49	0.95	9.242	**0.002**
Severity of BD	2.29	1.69	2.90	1.68	27.292	**<0.001**
Tot (hypo)manic symptoms	1.80	2.67	2.33	2.92	8.539	**0.004**

Notes: AD = *Antidepressants;* **BD** = *Bipolar disorder*; **UMD** = *Unipolar Major Depression*; **N** = *Number*; **Ep** = *Episodes*; **Tot** = *Total*.

Supplementary Tab S2. Bivariate statistics on "Extreme Phenotypes"

	Sleep-/weight- (n=77)		Sleep+ / Weight+ (n= 241)			
Variables (YES, significant)	**n**	**%**	**n**	**%**	**X2**	**p**
BD	7	9.1	55	22.8	7.009	**0.008**
BD type I	3	3.9	39	16.2	7.685	**0.004**
UMD	70	90.9	186	77.2	7.009	**0.008**
First depressive episode	34	44.2	35	14.5	30.160	**<0.0001**
Suicide attempts	18	23.4	75	31.1	1.691	0.193
Previous AD treatment	50	64.9	219	90.9	30.116	**<0.0001**
(Hypo)Manic switches	9	11.7	67	27.8	8.330	**0.04**
Resistance to AD	21	27.3	93	38.6	3.250	0.071
Affective lability	16	20.8	109	45.2	14.621	**<0.0001**
Irritability	14	18.2	90	37.3	9.736	**0.002**
Current OCD	0	0.0	18	7.5	6.096	**0.014**
Current social phobia	7	9.1	34	14.1	1.308	0.253
Current GAD	12	15.6	56	23.2	2.033	0.154
Current binge eating	2	2.6	20	8.4	2.970	0.085
Current night eating	2	2.6	17	7.2	2.082	0.149
Anorexia	16	21.1	18	7.6	10.764	**0.001**
Bulimia	2	2.6	20	8.4	2.970	0.085
On atypical antipsychotics	12	15.6	89	36.9	12.267	**<0.0001**
On mood stabilizers	14	18.2	108	44.8	17.503	**<0.0001**
Variable	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**
Age of first symptoms	29.47	13.29	30.74	11.90	2.064	0.152
Age of first depression	31.71	12.70	34.16	11.39	1.835	0.165
N past depressions	3.48	4.88	5.66	5.651	9.244	**0.003**
N mood ep. last 365 days	2.24	4.77	3.27	7.71	1.224	0.269
Tot days (hypo)mania /last 365 days	11.84	28.18	22.45	46.92	3.482	0.063
Severity of mania	1.21	0.60	1.49	0.95	5.553	**0.019**
Severity of BD	2.00	1.65	2.90	1.68	15.980	**<0.0001**
Tot (hypo)manic symptoms	1.86	2.74	2.33	2.92	1.587	0.209

Notes: AD = *Antidepressants;* **BD** = *Bipolar disorder*; **UMD** = *Unipolar Major Depression*; **N** = *Number*; **Ep** = *Episodes*; **Tot** = *Total*.

Supplementary Tab. S3: results from the stepwise logistic regression for "Extreme Phenotype"

							95% C.I.for EXP(B)	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Current social phobia	0.504	0.220	5,259	1	0.022	1.655	1.076	2.546
Current binge eating	0.834	0.328	6,467	1	0.011	2.303	1.211	4.380
Current bulimia	1.384	0.352	15,428	1	0.000	3.990	2.000	7.959
Current OCD	0.321	0.154	4,335	1	0.037	1.379	1.019	1.866
Affective lability (past AD)	0.362	0.158	5,233	1	0.022	1.436	1.053	1.958
Currently on AAP	0.390	0.157	6,187	1	0.013	1.476	1.086	2.007
Currently on MS	0.405	0.158	6,621	1	0.010	1.500	1.101	2.042

Notes. C.I. = *Confidence Intervals.* **AAP** = *Atypical Antipsychotics*; **AD** = *Antidepressants*; **MS** = *Mood Stabilizers*; **OCD** = *Obsessive-Compulsive Disorder*.