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CIRCADIAN RHYTHMS DISRUPTIONS AND EATING DISORDERS: CLINICAL IMPACT AND POSSIBLE PSYCHOPATHOLOGICAL CORRELATES

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SUMMARY

Background: *A link between abnormalities in circadian rhythms and the development of eating disorders was extensively hypothesized, mainly in consideration of the influence of the circadian clock on eating behavior. The present review is aimed at summarizing the evidence about biological rhythms disruptions in eating disorders, possibly clarifying their impact on the psychopathological profile of such patients.*

Methods: *Electronic database MEDLINE/PubMed/Index Medicus was systematically searched for original articles examining the prevalence of circadian rhythms disruptions in eating disorders (anorexia nervosa, bulimia nervosa, binge eating disorder).*

Results: *Studies included in the review confirmed the hypothesis of a high prevalence of circadian disruptions in eating disorders. The analyzed research mainly focused on sleep-wake cycle, rest-activity abnormalities and hormonal secretion, whilst literature about other circadian rhythms was scanty. Altered biological rhythms presented higher association with specific psychopathological features, but such relationship was assessed in few studies.*

Conclusions: *Circadian rhythms disruptions were confirmed to be relevant aspects in the context of eating disorders. Further research is needed in order to clarify the role of biological rhythms in such illnesses, in the attempt to address adjunctive treatment strategies with the possible focus of circadian abnormalities.*

Key words: *circadian rhythms - biological rhythms - eating disorders - anorexia nervosa - bulimia nervosa - binge eating disorder*

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INTRODUCTION

Eating disorders (EDs) are complex psychiatric conditions that involve patients' global functioning and present a complex etiopathogenesis, encompassing both psychological and biological aspects (American Psychiatric Association 2013). Over the last decade, several studies focused on circadian rhythms and their alterations in patients suffering from EDs. Circadian rhythms disruptions already demonstrated to play a significant role in several psychiatric disorders, possibly being correlated to their pathophysiology (Cretu et al. 2016, Allega et al. 2018). The hypothesis of a possible disruption in biological rhythms also in EDs arises from the fact that the circadian pacemaker is connected with metabolic and hedonic centers, controlling both feeding and other activities (Mendoza 2018). Subsequently, all circadian rhythms, i.e. sleep-wake rhythm, activity levels, social patterns, hormonal secretion, and not only those related to eating behaviors, can potentially be altered in patients affected by EDs. It was hypothesized that patients with abnormalities in eating attitudes display predominantly phase-delayed circadian rhythms of various behavioral and neuroendocrine factors, and that the timing of key rhythms involved in food intake and metabolism would be altered (Goel et al. 2009). This was already demonstrated in animal models, where changes in food intake resulted in a fragmentation of sleep and a reduction of slow wave sleep (Lauer & Krieg 2004). In addition, circadian dysruptions may represent not only relevant symptomatological features in EDs, but also possible modulators of some clinical aspects of such disorders, which could be i.e. demonstrated by the link between insomnia and poorer treatment outcomes (Allison et al. 2016). Notwithstanding the potential interest of circadian dysruptions in EDs, an extensive assessment of their impact on this complex group of disorders is still lacking. Subsequently, the aim of the present review is to summarize the evidence about circadian abnormalities in the main EDs, focusing on their prevalence and possible influence on clinical and psychopathological features.

METHODS

We conducted a systematic search of the electronic database MEDLINE/PubMed/Index Medicus using the following search string: ((((anorexia nervosa) OR bulimia nervosa) OR binge eating) OR eating disorders) AND (((circadian rhythms) OR biological rhythms) OR sleep-wake cycle). Two independent investigators (GM and FB) performed the literature search, title/abstract screening and full text screening. The reference list of selected articles underwent further screening in order to search for additional literature. We included in the present review original studies reporting data about the prevalence and the possible clinical impact of circadian rhythms disruption in the main EDs, namely anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED). Only research conducted in the past 15 years was considered for inclusion (screening period: 1st January 2004 - 31st May 2019). Articles presenting

hypotheses without empirical investigation, reviews, letters to the editor, case reports and studies concerning animal models were excluded. No language restriction was applied.

RESULTS

Literature search results

The database search initially yielded 672 records. Among these, 21 were selected after performing title-abstract screening. Further evaluation led to the exclusion of 3 articles. Two more papers were deemed eligible for inclusion in the review after hand-screening of relevant references. Subsequently, the full text examination identified 20 papers which were included in the present review.

Content results

Hormonal circadian patterns

Patterns of circadian hormone secretion in patients with EDs were evaluated in ten of the included studies, with the measurement of blood and salivary levels at different times of the day (Misra et al. 2005, Germain et al. 2007, dos Santos et al. 2007, Germain et al. 2009, Germain et al. 2010, Monteleone et al. 2011, Galusca et al. 2012, Ostrowska et al. 2013, Galusca et al. 2015, Germain et al. 2016). Thirteen hormones were taken into account in the selected articles (see Table 1), mainly regulating food intake and appetite. The circadian rhythm of such molecules was significantly decreased/absent or dysregulated in subgroups of patients affected by EDs, with frequent abnormalities in their daily mean blood/salivary concentration. An exception was demonstrated for orexigenic neuropeptide 26RFa, which showed a circadian profile similar in BN and controls, whilst it was significantly decreased in all-type AN (Galusca et al. 2012). A similar result was found for obestatin and ghrelin, which showed abnormalities only in AN patients but not in BN (Germain et al. 2010). Studies considering also constitutional thinness demonstrated that some abnormalities were detectable as well in these subgroups for the analyzed hormones (Germain et al. 2007, Germain et al. 2009, Germain et al. 2016).

Sleep-wake rhythm

Sleep-wake disruptions in EDs were examined in eight of the included studies, by analyzing sleep architecture (Tzichinsky & Latzer 2006, Sauchelli et al. 2015, Tanahashi et al. 2017, Asaad Abdou et al. 2018, Kandeger et al. 2018, Roveda et al. 2018) and sleep quality (Lundgren et al. 2008, Sauchelli et al. 2015, Tromp et a. 2016, Tanahashi et al. 2017). Different measures of assessment were used, including objective (i.e., actigraphy and polisomnography) and subjective (i.e., self-administered questionnaires) instruments. Sleep abnormalities appeared to be significantly more frequent in patients with EDs (Lundgren et al. 2008, Sauchelli et al. 2015, Tromp et al. 2016, Asaad Abdou et al. 2018). Studies considering obese patients with and without BED showed that patients with BED did not present sleep architecture abnormalities when compared to obese subjects (Roveda et al. 2018), with the whole obese group showing more significant sleep disturbances. Despite this, in another study the BED subgroup demonstrated abnormalities in specific parameters, such as minutes of wakefulness during sleep (Tzischinsky & Latzer 2016). One study, using a structured questionnaire and polisomnography, also demonstrated higher rates of parasomnias and daytime hypersomnia in AN and BN, as well as abnormalities in indexes such as sleep latency, sleep efficiency and arousal (Asaad Abdou et al. 2018). When comparing different AN subtypes, binge eating-purging type presented with worse sleep quality, abnormal sleep duration and more disrupted circadian rhythm (Sauchelli et al. 2015, Tanahashi et al. 2017). Furthermore, insomnia and sleep parameters abnormalities were linked to a higher severity of depressive symptoms in EDs (Asaad Abdou et al. 2018) and presented an indirect influence on disordered eating attitudes (Kandeger et al. 2018).

Chronotype/circadian preference

Four of the selected studies analyzed patterns of activities in EDs, with a particular focus on circadian preferences (Natale et al. 2008, Harb et al. 2012, Roveda et al. 2018, Kandeger et al. 2018). Studies assessing chronotype found a significant association with eveningness, both when the sample was composed of patients with all-type EDs (Natale et al. 2008) and only with diagnosis of BED (Harb et al. 2012). In this subgroup of patients, levels of daytime activity also resulted to be reduced (Roveda et al. 2018). On the other side, a study assessing eating patterns and diurnal preference in a sample of students did not find any significant correlation between chronotype and disordered eating attitudes (Kandeger et al. 2018).

Other circadian rhythms

One study assessed circadian eating patterns and mood variations among patients with diagnosis of BN, by means of self-administered instruments (Lundgren et al. 2008). Dysregulated eating behaviors presented a significant circadian component, with the prevalence of night-time eating and morning anorexia. Similarly, mood variations across the day were strongly prevalent, with a higher rate of depression during the evening/night.

DISCUSSION

The results of the present review, as expected, demonstrated high rates of biological rhythms dysregulation in patients with EDs, when considering sleep/wake cycle, activity patterns/chronotype and hormone secretion. Abnormalities in the circadian concentrations of the studied hormones, especially molecules controlling food intake (i.e. NYY, GLP-1, leptin, ghrelin, obestatin,

Table 1. Summary of the included studies assessing circadian rhythms in EDs

References	Study Design	Sample	Analyzed circadian rhythm	Circadian rhythm assessment measure(s)
Asaad Abdou et al. 2018	Observational, prospective, cross-sectional study	23 females with AN or BN (age 18-45) 20 controls matched for age and sex	Sleep architecture	Structured Sleep Disorder Questionnaire PSG
Kandeger et al. 2018	Observational prospective study	383 students (60.1% females), mean age 21.1 (±0.1), who were screened for disordered eating attitudes (4.2% met the criteria)	Chronotype/circadian preference, sleep architecture	MEQ, Insomnia severity index
Roveda et al. 2018	Observational, prospective, cross-sectional study	8 obese females 8 obese females with BED	Rest-activity circadian rhythm and sleep architecture	Actigraphy and Actiwatch Sleep Analysis Software
Tanahashi et al. 2017	Observational, prospective, cross-sectional study	12 AN binge eating-purging type 8 AN restricting type	Sleep quality and sleep architecture	PSQI
Germain et al. 2016	Observational, prospective, cross-sectional study	10 restrictive type AN women 5 binge-purgeing type AN women 15 recovered restrictive type AN women 4 BN women 10 constitutional thinness women 7 healthy obese women 10 normal weight women	Plasmatic IL-7 rhythm	24-hour sampling of IL-7 (12 measurements), leptin and cortisol (6 measurements)
Tromp et al. 2016	Observational prospective study	574 young adults, 12% with EDs (screened positive at ESP)	Sleep quality and daytime functioning	SLEEP-50 questionnaire subscales for sleep apnea, insomnia, circadian rhythm disorder and daytime functioning
Galusca et al. 2015	Observational, prospective, cross-sectional study	23 AN young women 22 CT young women 14 normal weight age-matched controls	Plasmatic NPY and αMSH rhythm	24-hour sampling of NPY, αMSH (12 measurements), leptin, GH and cortisol (6 measurements)
Sauchelli et al. 2015	Observational, prospective, cross-sectional study	48 AN patients 98 healthy weight controls	Sleep quality, sleep architecture	PSQI
Ostrowska et al. 2013	Observational, prospective, coss-sectional study	86 females (13-18 years) with AN and 21 healthy subjects (13-17 years)	Melatonin rhythm	Melatonin blood samples (2 measurements)
Galusca et al. 2012	Cross-sectional study	19 restrictive AN women 10 binge-purging AN women 14 CT women 10 bulimic women 10 normal-weight age-matched controls	Orexigenic neuropeptide 26RFa rhythm	24-hour sampling of 26RFa (12 measurements), leptin, GH, cortisol (6 measurements)
Harb et al. 2012	Cross-sectional study	100 subjects (77% females), mean age 39.5 (±11.7) years, 66% overweight. 43% presented binge eating, 27% abnormal eating attitudes/behaviors, 18% night eating behavior.	Chronotype/circadian preference	MEQ

Notes: αMSH = Melanocyte stimulating hormone type α; AM = Anti-meridian; AN = Anorexia nervosa; BDI = Beck Depression Inventory; BED = Binge Eating Disorder; BN = Bulimia nervosa; CT = constitutional thinness; EDs = Eating disorders; ESP = Eating Disorder Screen for Primary Care; GH = Growth hormone; GLP-1 = Glucagone-like peptide 1; IGF-1 = Insulin-like growth factor-1; IL-7 = Interleukin-7; EAT = Eating Attitude Test; EDI-2 = Eating Disorders Inventory-2; MEQ = Morningness/eveningness questionnaire, reduced version; MEQr = Morningness/eveningness questionnaire; NEQ = Night eating questionnaire; NPY = Neuropeptide Y; PM = Post-meridian; PSG = Polisomnography; PSQI = Pittsburgh Sleep Quality Index; PYY = Peptide YY

Table 1. Continues

References	Study Design	Sample	Analyzed circadian rhythm	Circadian rhythm assessment measure(s)
Monteleone et al. 2011	Cross-sectional study	8 AN females 8 age-matched controls	α-amylase and cortisol salivary levels	Salivary samples 15, 30, 60 min from awakening and at 10 AM, 12 AM (before lunch), 4 PM, 6 PM, 7 PM and 8 PM (before dinner)
Germain et al. 2010	Cross-sectional study	22 restrictive type AN women 10 binge-purgeing type AN women 16 normal-weight BN women 9 age-matched control subjects	Plasmatic ghrelin, obestatin, and PYY rhythm	24-hour sampling of leptin, GH, cortisol, obestatin, total and acylated ghrelin, and PYY (12 measurements)
Germain et al. 2009	Cross-sectional study	15 restrictive type AN young women 9 young women restored from AN 10 CT 9 control subjects	Plasmatic obestatin and ghrelin rhythm	24-hour sampling of leptin, GH, cortisol, obestatin, total and acylated ghrelin (6 measurements)
Lundgren et al. 2008	Observational prospective study	31 females, diagnosis of BN	Eating behavior (nighttime patterns and morning anorexia) Sleep quality Circadian mood variations	NEQ, EDI-2, BDI
Natale et al. 2008	Observational, prospective, cross-sectional study	270 females:146 recruited in a EDs treatment centre, 240 controls	Chronotype/circadian preference	MEQr
Dos Santos et al. 2007	Prospective transversal controlled study	12 female patients with diagnosis of AN (10 restrictive type, 2 bulimic type, age: 15-35) 13 age-matched healthy and ovulatory females	24-hour salivary cortisol rhythm	Multiple salivary cortisol determinations (9 AM, 5 PM, 11 PM)
Germain et al. 2007	Observational, prospective, cross-sectional study	12 AN young women 10 age-matched CT 7 age-matched normal weight	Plasmatic PYY, GLP-1, ghrelin, leptin and GH rhythm	24-hour sampling of PYY, GLP-1, ghrelin, leptin GH, cortisol (every 4 hours measurements)
Tzischinsky & Latzer 2006	Observational, prospective, cross-sectional study	36 obese patients (divided in obeses with and without BED) 25 normal weight controls	Sleep architecture	Mini actigraphs, self-reported questionnaires (Mini-Sleep Questionnaire, Standard Technion Clinical Sleep Questionnaire) and sleep diary
Misra et al. 2005	Observational, prospective, cross-sectional study	22 AN females (12-18 years) 18 age-matched healthy controls	Plasmatic ghrelin, GH, cortisol rhythm	Blood samples every half hour for 12h at night

Notes: αMSH = Melanocyte stimulating hormone type α; AM = Anti-meridian; AN = Anorexia nervosa; BDI = Beck Depression Inventory; BED = Binge Eating Disorder; BN = Bulimia nervosa; CT = constitutional thinness; EDs = Eating disorders; ESP = Eating Disorder Screen for Primary Care; GH = Growth hormone; GLP-1 = Glucagone-like peptide 1; IGF-1 = Insulin-like growth factor-1; IL-7 = Interleukin-7; EAT = Eating Attitude Test; EDI-2 = Eating Disorders Inventory-2; MEQ = Morningness/eveningness questionnaire, reduced version; MEQr = Morningness/eveningness questionnaire; NEQ = Night eating questionnaire; NPY = Neuropeptide Y; PM = Post-meridian; PSG = Polisomnography; PSQI = Pittsburgh Sleep Quality Index; PYY = Peptide YY

orexigenic neuropeptides), were shown in a relevant number of the considered studies, confirming the hypothesis of a significant biological load in the etiopathogenesis of EDs, which should thus be considered psychoneuroendocrine diseases as historically defined (Brambilla et al. 2001). The differences in circadian hormone profiles shown between AN restrictive and binge-purgeing subtype could present possible implications in the differential diagnosis of such subgroups (Germain et al. 2010). Moreover, the distinct profile that some studies demonstrated for AN when compared to constitutionally thin patients (Germain et al. 2007, Germain et al. 2009, Germain et al. 2016) suggests a possible link between specific psychopathological features and hormone secretion abnormalities, which should be further clarified in future studies. This could be evaluated also in consideration of the direct effect that some of the abnormally secreted hormones,

i.e. somatotropic axis hormones, might play on specific symptomatological features, such as mood and anxiety (Brambilla et al. 2018). The presence of sleep disorders and diurnal preference variations in patients with EDs was as well expected, in consideration of the influence that such biological features show on eating attitudes and on their implication on general health status (Kandeger et al. 2018). Furthermore, the relationship between altered sleep and eating features was already demonstrated by the characterization of forms of disordered eating and sleeping, i.e. the night eating syndrome (NES) (American Psychiatric Association 2013). Sleep disorders were demonstrated to be prevalent in all-type EDs, which could also suggest that sleep/wake cycle dysregulation could represent a common risk factor for such illnesses (Allison et al. 2016). Noteworthy, few studies further investigated the possible influence of altered sleep and diurnal preference on distinct psychopathological features (Lundgren et al. 2008, Asaad Abdou et al. 2018, Kandeger et al. 2018). Evening chronotype, which was frequently showed by patients with EDs, was associated in previous studies with specific disturbances of mood, alertness and, more recently, with dissociative experiences (Selvi et al. 2017), which could represent one of the psychopathological underpinnings of altered eating behaviors (Castellini et al. 2019). Further research on the symptomatological correlates of circadian disorders in EDs could help identifying core features, which could be at the basis of behavioral disturbances in this complex group of illnesses connecting them to specific biological correlates, as already demonstrated for emotional dysregulation, disturbances of body image and vulnerability to interpersonal stress (Anderson et al. 2018, Monteleone et al. 2018, McLean & Paxton 2019). Moreover, widening the research interest to further biological rhythms, i.e. social activity patterns, as already demonstrated for mood disorders, where extensive interviews were developed at this aim (Allega et al. 2018) could add significant evidence to the impact of circadian disruptions in EDs and provide new possible therapeutic targets. This review presents limitations. First, the small sample sizes of the included studies contributed to a possible risk of bias in most of the considered research. In addition, the heterogeneity of the measures used for the assessment of circadian rhythms abnormalities, particularly for what concerns sleep, for which subjective instruments were mainly used, might represent a major flaw of previous literature. Furthermore, the present review did not take into account nor other possible manifestations of EDs, such as NES, which could present relevant implications in terms of connection with biological rhythms alterations (Allison et al. 2016), neither studies which did not assess hormones in their circadian profile, possibly excluding further literature of interest (Brambilla et al. 2018).

CONCLUSIONS

Circadian disruptions were confirmed to be prevalent features in eating disorders, but the literature on the topic is still scanty, focusing only on specific biological rhythms. Further research is needed in order to clarify the psychopathological correlates of such abnormalities, their implication on differential diagnosis and their role as possible risk factors, also in the attempt to address adjunctive treatment strategies.

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Contribution of individual authors:

Giulia Menculini, Francesca Brufani, Valentina Del Bello & Patrizia Moretti conceived and designed the review.

Giulia Menculini & Francesca Brufani performed the literature search.

Francesca Brufani wrote substantial part of the introduction.

Giulia Menculini wrote substantial part of methods.

Giulia Menculini & Valentina Del Bello wrote substantial part of results.

Giulia Menculini discussed results.

Patrizia Moretti & Alfonso Tortorella corrected the first draft of the manuscript.

Alfonso Tortorella supervised all phases of the study design and writing of the manuscript.

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