INTRODUCTION

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The Night Eating Syndrome (NES)

General background

The escalating worldwide prevalence of obesity has drawn attention to the association between abnormal eating patterns or eating disorders, weight gain and obesity.[1] Researches had been inconsistent regarding whether obesity leads to eating disorders or vice versa, as some studies showed that obese individuals presenting for weight loss programs report abnormal eating patterns. Also, atypical eating patterns may result in poor treatment outcomes.[2]

The Night Eating Syndrome (NES) is one of these eating disorders. It was first described in 1955 by Stunkard as a disorder consisting of morning anorexia, evening hyperphagia, and insomnia. The presence of nocturnal ingestions (awakening to eat) was added to these criteria later.[3]

Only few papers have been published about night eating in the past several years after a hiatus of over 40 years since the original description by Stunkard et al. [4] The reported prevalence of NES varies and this variability might be a result of the variable diagnostic criteria, different and small clinical samples. [5,6] But as a whole, it seems to increase with severity of obesity. The prevalence of NES was 0.4%-1.5%[7-9] of normal weight individuals,[10] 8.9% and 10% of obese outpatients,[3] 13.7% and 15% of obese individuals in two samples,[3] and 7.9% and 15% in morbidly obese surgical patients in some studies.[11,12] while in others 15-25%.[7- 9] Two other studies of severely obese, treatment refractory participants had much higher rates of 51% and 64%.[3,7]

NES has been associated with life stress,[3] psychoneurotocism,[10] depression,[10,12] low mood,[4] and adverse reactions to weight loss.[3] Past studies used epidemiological instruments[10, 12] or analogue scales[4] which are not diagnostic in nature.

The relation between NES and BMI has been differed among studies. [13-16]Several reports have shown positive associations between NES and BMI. [4,14,17,18] In contrast, others found no associations between NES and BMI.[13,19]

The typical behavioral characteristics of the night eating syndrome have been described as morning anorexia, evening hyperphagia and insomnia. The causes for this disturbed and delayed circadian pattern of food intake are not clear; however the neuroendocrine differences between individuals with NES and controls seem to be consequences rather than causes of altered pattern and timing of food intake. [20,21] These neuroendocrine changes have been described as changes in the circadian rhythm by an attenuation in the nocturnal rise of the plasma concentrations of melatonin and leptin and an increased circadian secretion of cortisol. The night eaters also have an overexpressed hypothalamic-pituitary-adrenal axis with an attenuated response to stress.

In conclusion, the mechanisms behind the increased CRH stimulation may involve alterations in the neurotransmitter systems, causing increased nocturnal appetite and disruption in the sleep pattern. This may, to some extent, explain the disturbances in the circadian secretions of melatonin and leptin and the behavioral characteristics of the night eating syndrome.[19]

Historical background and definitions

Night eating syndrome (NES)

It was first described by Stunkard in 1955[4] as a syndrome characterized by morning anorexia, evening hyperphagia and insomnia either initial or at the middle of night by awakening frequently accompanied by eating. Only few papers have been published about this syndrome for decades since the original description by Stunkard et al. [4,10]

In 1990, another term was described by the American Sleep Disorders Association in the International Classification of Sleep Disorders which is (Nocturnal eating syndrome). This syndrome was defined as: frequent and recurrent awakenings to eat and normal sleep onset following ingestion of the desired food.[22] Some studies suggest that there is little difference in the occurrence of the two syndromes. These differences were not clear in the literature. In some articles both terms are used synonymously.[18, 23, 24] For example, In the International Classification of Sleep Disorders, night eating is given as synonymous with nocturnal eating. Recent studies suggest that there is more to unite the two syndromes than there are differences between them.[12]

Morning anorexia

Various definitions had been given in different studies as no appetite for breakfast.[3] Negligible food intake.[4] Skipping breakfast altogether.[25] Or not starting to eat until later in the day or delay in the onset of appetite in the morning.[3] or delay of eating for several hours after awakening.[9] Clearly the literature does not adequately define morning anorexia as regards to morning time and the frequency needed for diagnosis. Only one set a frequency threshold by requiring that breakfast must be skipped at least four times a week.[13]

Evening hyperphagia

It's definition vary in terms of the amount of food consumed, the time frame is involved and whether the evening meal "dinner" is included[3] when defining the amount of food consumed after the specified time of the day.[3] The criteria for the amount of food consumed vary from as low as 25% of daily caloric intake[4] to as high as 50% or more.[3] Other definitions do not rely on the percentage of daily caloric intake but requires that the largest food intake occurs after 7 PM.[9]

Evening time is defined in some studies as after 7 PM[13] however, due to the cultural variations regarding the timing of dinner, the definitions focus on caloric consumption after dinner.[26]

Evolution of diagnostic criteria

Developments in the conceptualization of NES have been hindered over time by the adoption of differing diagnostic criteria by researchers from various disciplines as summarized in Table1. Thirty years after the originally proposed criteria of ‘morning anorexia’, ‘hyperphagia until midnight on 50% of nights’ and ‘sleep onset insomnia’, the emotional component of ‘eating with tension’ and ‘without enjoyment’ was added, then removed again when Stunkard revisited the syndrome in 1996.[3] Refinements to the original criteria at that time included no appetite for breakfast, 50% or more of food intake after 7 PM and trouble getting to sleep and/or staying asleep, as well as nocturnal awakenings to eat. Further refinements in 2003 sought to differentiate NES from other EDs, emphasize the nocturnal eating and account for cultural differences by removing the

time restriction.[27] By 2008 these criteria were acknowledged as too restrictive and were broadened again to include 'at least 25% of food intake consumed after the evening meal and/or at least two episodes of nocturnal eating per week'. The emotional component of distress also reappeared as a core criterion.[28]

Table (1): Evolution Of Diagnostic Criteria Of NES.

Author	Year	Criteria
Stunkard [4]	1955	Morning anorexia, nocturnal hyperphagia until midnight on 50% of nights, sleep onset insomnia.
Kuldau [7]	1986	Morning anorexia, eating later in day, on and off evening eating without enjoyment, sleep onset insomnia, evening tension.
Rand [8]	1993	Morning anorexia, excessive evening eating, evening tension and/or feeling upset, insomnia
Stunkard [3]	1996	No appetite for breakfast, 50% or more of food intake after 1900 hours, trouble getting to sleep and/or staying asleep
Birketvedt[10]	1999	Morning anorexia evening overeating (including at least 50% of food intake after 1800 hours) insomnia.
Powers [29]	1999	More than 25% of total energy intake after evening meal, trouble sleeping, trouble appetite in the morning.
Ceru-Bjork [30]	2001	As per Stunkard[7] and waking up at night and getting out of bed to eat and/or after having gone to bed, getting out of bed to eat or eating in bed.
Napolitano[31]	2001	Morning anorexia, evening hyperphagia, emotional distress, sleep difficulties.
Adami [26]	2002	Morning anorexia, more than 25% of total energy intake after evening meal, trouble falling and/or staying asleep most nights.
Stunkard [27]	2003	Morning anorexia, even if subject eats breakfast, evening hyperphagia. At least 50% of the daily caloric intake is consumed in snacks after the last evening meal, awakenings at least once a night, at least 3 nights a week, consumption of high-calorie snacks during the awakenings on frequent occasions, the pattern occurs for a period of at least 3 months, absence of other eating disorders.

NES is now considered as a dysfunction of circadian rhythm with a disassociation between eating and sleeping, characterized by a phase onset delay of morning appetite and continuation of evening eating.[32,33] Current diagnostic criteria proposed by the International NES Working Group in 2008 at the First International Night Eating Symposium are listed below.

2010 Criteria for NES (all of A–F need to be met).

A	Core criterion: Daily pattern of eating demonstrates a significantly increased intake in the evening and/or night time, as manifested by one or both of the following:	1. At least 25% of food intake is consumed after the evening meal. 2. At least two episodes of nocturnal eating per week.
B	Core criterion: Awareness and recall of evening and nocturnal episodes are present	
C	Core descriptors: The clinical picture is characterised by at least three of the following features:	1. Lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week. 2. Presence of a strong urge to eat between dinner and sleep onset and/or during the night. 3. Presence of a belief that one must eat to initiate or return to sleep. 4. Sleep onset and or/sleep maintenance insomnia are present four or more nights per week. 5. Mood is frequently depressed and/or mood worsens in the evening.
D	Core criterion: The disorder associated with significant distress and/or impairment in functioning	
E	Core criterion: The disordered pattern of eating has been maintained for at least 3 months	
F	Core criterion: The disorder is not secondary to substance abuse or dependence, medical disorder, medication or another psychiatric disorder.	

The DSM-5 diagnostic criteria for NES are as follows:[34]

- Repeated occurrences of night eating, demonstrated by eating after waking from sleep or by an excess in food intake after the evening meal.
- The individual is aware of and can recall the eating.
- Other influences such as changes in the individual's sleep-wake cycle or social norms cannot better explain the night eating.
- Significant distress and/or impairment in functioning results from the night eating.
- The disordered pattern of eating is not caused by binge-eating disorder, a mental disorder, a medical disorder, or the effect of medication.

Epidemiology

The prevalence of NES is estimated at 1.5% in the general population,[35] 6%[30] to 14% in obesity clinics and 8% to 42% in pre-operative bariatric surgery obese patients in the US. Such a wide range of estimates is most certainly influenced by varying assessment methods (e.g. survey vs. interview) and diagnostic criteria. However, in general, these results suggest that NES is more prevalent with increasing adiposity. Because NES occurs commonly among the obese and has been reported to interfere with weight loss attempts, [13] it may be useful target for treatment in a subgroup of the overweight/obese population. NES also occurs in persons with normal weight (body mass index [BMI] = 18.5-25 kg/m2).[10,36] Marshall et al (2004) indicated that half of the overweight persons presenting with NES reported being normal weight before the onset of night eating, suggesting that NES may be a pathway to excess weight and obesity.[36]

Besides, the prevalence of NES is estimated between 3.8 and 9.7% according to various studies in patients with diabetes of any type. The presence of NES in diabetics is an important predictor of change in glycosylated haemoglobin (HbA1c > 7), obesity, depressed mood and two or more complications of diabetes and also of poor adherence to diet, exercise physical and control of blood glucose.[37,38]

Regarding the distribution between the sexes, NES is much more common in females than in males. Grilo *et al*[39] examined the frequency of nighttime eating and its correlation in men and women with binge eating disorder .A sample of consecutively evaluated adults (45 men and 162 women) with binge eating disorder were assessed with semi-structured interviews and a battery of behavioral and psychological measures. Overall, 28% (n = 58) of the participants reported nighttime eating. A significantly higher proportion of men (42%) than women (24%) reported nighttime eating. Overall, participants who reported nighttime eating had a significantly higher body mass index, but otherwise differed little from those who did not report nighttime eating. Men and women without nighttime eating differed little on behavioral and psychological measures, whereas women with nighttime eating had significantly higher levels of eating, weight and body-shape concerns than men with nighttime eating. [39]

NES begins during early adulthood, with the age of onset ranging from the late teens to late twenties and appears to be long-lasting [31,36] with periods of remission and exacerbation that may coincide with life event stress[4,23] NES also appears to run in families. Compared with controls, patients with NES are 4.9 times more likely to have a first degree relative with NES.[40]

Lundgreen et al. (2010)[41] assessed the prevalence of NES and binge eating disorder among overweight, obese, weight-loss-seeking individuals with serious mental illness. Sixty-eight consecutive overweight (body-mass index (BMI > 25kg/m2) and obese (BMI > 30

kg/m2) individuals with serious mental illness (mean age = 43.9 years; mean BMI = 37.2 kg/m2; 67.6 % Caucasian, 60.3% female) who were enrolled in a group behavioral weight-loss treatment program were assessed at baseline for NES and binge eating disorder with clinician-administered diagnostic interviews. Using conservative criteria, 25.0% met the criteria for NES, 5.9% met the criteria for binge eating disorder, and only one participant met the criteria for both NES and binge eating disorder. They concluded that obese individuals with serious mental illness, compared with previously studied populations, are at significantly greater risk for NES, but are not at greater risk for binge eating disorder. Stress, sleep patterns and medication use might account for the high prevalence of NES found in this population. This study confirmed the findings of a previous study, also performed by Lundgreen et al (2006)[42] assessing the prevalence of NES and its comorbid psychopathology in a psychiatric population. The NEQ was administered to 399 patients in two psychiatric outpatient clinics. Those scoring above 20 on the questionnaire (n = 205) were assessed for NES with a semi-structured telephone interview. Chart reviews of all participants were performed to determine their psychiatric diagnoses and medications. Forty-nine participants (12.3%) met the criteria for NES.

Greater rates of substance use disorders were found among patients diagnosed with NES than among those without the syndrome. Obese patients were more likely than non- obese patients to manifest NES. This study showed that NES is prevalent among psychiatric clinic outpatients and is likely to co-occur with substance use disorders and obesity.[34]

A recent study in two centers in the US (at the University of Minnesota and the University of Pennget sylvania) reported quite a high prevalence rate of NES in a general outpatient psychiatric clinic population, with 16.5% meeting criteria based on questionnaire and interview data, thus further supporting the link between NES and psychiatric co-morbidity.[43] The average BMI in the NES-positive group was 33.0 ± (9.3) compared with 27.4 ± (6.9) in the psychiatric clinic outpatients without NES, suggesting that overweight and obese patients in that setting may be at quite a high risk of having NES.

Etiology and risk factors

Biological perspective

In 1999 Birketvedt et al,[10] reported that nighttime awakenings were far more common among night eaters than among controls, and more than one-half of these awakenings were associated with food intake. The typical neuroendocrine characteristics were an attenuation of nocturnal rises in secretions of melatonin and leptin and increased diurnal secretion of Cortisol. Cortisol, melatonin, and leptin are regulatory hormones with typical circadian rhythms that regulate various physiological and metabolic functions.[44,45]

Another main regulator is the hypothalamic-pituitary-adrenal (HPA) axis, which orchestrates several biological functions. The circadian rhythms represent the biological endocrine clock, whereas the HPA axis represents the stress-induced biological response. However, the interplay between these two main regulators of biological functions was not well understood. One study reported that subjects suffering from night-eating episodes had signs of disturbances in the HPA axis with an attenuated ACTH and Cortisol response to CRH. The mechanisms behind the increased CRH stimulation may involve alterations in the neurotransmitter systems, causing increased nocturnal appetite and disruption in the sleep pattern. This may, to some extent, explain the disturbances in the circadian secretions of melatonin and leptin and the behavioral characteristics of the night eating syndrome.[46]

Also, previous studies have shown that NES involves a delay in the timing of food intake.[20,21] Goel et al (2009)[32] extend these findings by showing that NES may be a disorder of circadian rhythm dysregulation[32] with accompanying nighttime sleep disturbances[33] Prolonged eating, possibly a result of an earlier ghrelin acrophase, may phase delay the putative peripheral oscillator for leptin and concurrently may phase delay the central oscillator controlling circadian signals for melatonin and Cortisol. Thus, they theorize that patients with NES may show a dysregulation between peripheral oscillators that provide signals for the regulation of food intake and also may show a phase delay in the central oscillator. Their physiological findings may have clinical utility: they point to potential therapeutic chronobiologic options for treating NES, including bright light therapy.[32] Such therapeutic options could be adjuvants or alternatives to previously proposed treatments including cognitive behavioral therapy, which focuses on stimulus control (e.g., restriction of access to food), regulation of circadian food intake, and sleep hygiene.[21]

Psychological perspective

Persons with NES may have a general vulnerability to stress, perceiving life event stress as less controllable and/or predictable. As NES tends to occur during periods of life event stress and the ingestion of food may be a learned as an aspect of mood regulation. Perhaps NES involves a genetic or hormonal predisposition, triggered by life event stress that results in a de-synchronization of the sleep/wake and eating cycles amongst vulnerable individuals. There is evidence that NES may involve a genetic component,[42,47,48] but to date, no studies have focused on specific genes involved in this syndrome. Genetic studies would greatly enhance our understanding of NES. Identifying individuals at risk for the development of NES as well as the mechanisms by which NES develops and is maintained remain important goals for future research.[49]

Clinical picture and assessment tools

Basically, NES is not the same as binge eating disorder, although individuals with NES are often binge eaters. People with binge eating disorder eat large amounts of food at different times of day, while those with NES eat the majority of their food at night, but do not always binge. Individuals with NES feel like they have no control over their eating patterns and often feel shame and guilt over their condition. NES affects an estimated 1.5% of the population and is equally common in men and women, according to the National Institute of Mental Health.[50]

NES, also called the ‘nocturnal eating syndrome’, is a very specific disorder in which the affected individual wakes up several times during the night and is unable to fall back to sleep unless they eat something. Another characteristic of this disorder is that foods eaten during these waking episodes are often highly caloric in content and unhealthy. These eating episodes usually occur in secret and any evidence is often hidden from others.[50] The night eating behaviour seems totally beyond the affected individual's control. For these individuals, 35% or more of their calories are eaten after dinner time.[51]

Eating disorder specialists use the term ‘night eating syndrome’, coined in 1955 by Stunkard et al.,[4] for patients exhibiting nighttime eating. The criteria for NES include the consumption of 50% or more of daily calories after the evening meal, eating after waking from sleep and morning anorexia.[4] Furthermore, Stunkard and colleagues in 1996 revisited this definition to specify over 50% of input energy occurs after 1900 h, accompanied by initial insomnia or sleep disturbance and permanent daytime anorexia.[3]

Also NES is associated with a greater incidence of anxiety, depression, low self-esteem and a strong sense of guilt for the loss of control associated with compulsive over ingestion of food during the night. For a diagnosis of NES it is necessary that the symptoms are present for at least three consecutive months.[3]

Subsequently other controlled studies added other NES criteria.[10] Such studies revealed a surprising coherence of the behavioral and neuroendocrine patterns of persons selected on the basis of morning anorexia, evening hyperphagia and insomnia. Persons selected on the basis of these minimal criteria were found to manifest not only sleep-onset insomnia but also, quite unexpectedly, nighttime awakenings during half of which food was ingested. This distinctive circadian pattern of behaviour was associated with a similarly distinctive pattern of mood disturbance. Contrary to the usual pattern found in depression, the mood of the night eaters fell during the evening.

Allison *et al*. in 2010 [52] proposed new criteria for diagnosis of NES. This research established two core criteria: (1) the consumption of at least 25% of daily caloric intake after the evening meal and/or (2) evening awakenings with ingestions at least twice per week. Five descriptors have been added to the core criteria, three of which are required for the diagnosis of NES. Additionally, persons must be aware of their nocturnal ingestions, they must experience distress or impairment in functioning and they must have experienced the signs and symptoms for the past three months. These criteria help standardize the definition of NES. Additional aspects of the nosology of NES yet to be fully elaborated include its relationship to other eating and sleep disorders. Assessment and analytical tools are needed to assess these new criteria more accurately. These nosographical criteria for NES were proposed for inclusion in the diagnosis of axis I of DSM V edition of the American Psychiatric Association and they have been further confirmed in several studies using self-report, structured interviews and rating scales.[53]

In this way the NES can be clearly distinguished from other related diseases such as binge eating disorder or sleep-related eating disorder (SRED). The authors conclude that a clearer connotation nosographic allows a better definition for the prevalence, association with obesity, assessment of the frequent comorbidity and a more effective determination of the underlying biological implications.[52] Therefore, NES appears to be a combination of an eating disorder, a sleeping disorder and a mood disorder.[54,55]

O'Reardon et al. in 2004 [20] compared the eating and sleep–wake patterns of persons with NES with those of matched control subjects. The pattern of cumulative energy intake of the night eaters suggests a phase delay in energy consumption relative to sleep–wake times. NES may involve a dissociation of the circadian control of eating relative to sleep.

For possible confirmation of diagnosis, other assessment tools have proved profitable. The purpose of the first study was to evaluate the Night Eating Questionnaire (NEQ) as a measure of severity of the NES.[56] The 14-item NEQ assesses the behavioral and psychological symptoms of NES.

The original unpublished 9-item version Night Eating Questionnaire (NEQ) with a 4 likert scale which measured evening hyperphagia, morning anorexia, insomnia, nocturnal ingestions, and mood, was developed by Stunkard and colleagues. The items were subsequently converted to a 5 point scale and the questionnaire was lengthened.[57]

As research continued to expand, a 13-item version, also known as the Night Eating Syndrome Questionnaire (NESQ) was published in the Weight and Lifestyle Inventory

(WALI) in 2001,[58] and psychometrically evaluated by Vander Wal et al in 2005.[59] One item on this scale has two parts and the final item, pertaining to duration, is not scored.

Another 13-item version was published which does not assess duration, but does contain a question pertaining to control over the night eating episodes. [36] A 12-item version of the NEQ, called the Night Eating Symptom Scale, was developed to assess seven day symptom presentation and response to treatment. [60] Unlike the previous two versions, the level of awareness during the night eating episodes is not ascertained. Like the Marshall version, control over night eating is assessed; however, duration is not.[36]

The latest and most comprehensive 14-item version of the NEQ was published in 2008 by Allison and colleagues.[56] This version assesses awareness and has two questions pertaining to control rather than a single question as was the case in previous versions.

The reason for getting up in the night (other than to use the bathroom) is also specified. The Allison version also allows persons who do not engage in night eating to skip questions pertaining to night eating episodes. Duration is again assessed via a supplemental item. The Allison version has four factors: nocturnal ingestions, evening hyperphagia, morning anorexia, and mood/sleep, as well as a higher order factor score. It has acceptable internal consistency reliability and correlates with the percent of calories consumed in the evening, the number of nocturnal ingestions, morning hunger, disturbed eating attitudes and behaviors, sleep quality, mood, and perceived stress. The positive predictive value (PPV; i.e., the likelihood that someone has NES) of a score of 25 or greater is 40.7%; the PPV of a score of 30 or greater is 72.7%.[56]

An alternative self-report questionnaire, the Night Eating Diagnostic Questionnaire (NEDQ), was originally designed to assess the NES criteria specified by Stunkard et al. (1996)[3] and was recently modified to include questions that allow for the diagnosis of NES on the basis of the 2008 consensus criteria.[61] The NEDQ has 21 items and takes about 15 min to complete. The NEDQ assesses both morning anorexia as well as consumption of breakfast as some persons with NES will eat a light breakfast out of a sense of obligation or attempt to alter their habits despite having no appetite. The NEDQ also contains questions assessing both the amount eaten after 7 pm as well as after the evening meal, allowing for comparison of the old and new diagnostic criteria. Further, detailed questions about sleep quality, timing, and duration are included.[49]

The Night Eating Syndrome History and Inventory (NESHI), a semi-structured interview by which to diagnose NES includes questions pertaining to the schedule and amount of food eaten per day, history of NES symptoms, sleeping routine, mood symptoms, life stressors, weight and diet history, and previous treatment. The current 14-item version of the NEQ is embedded within the NESHI albeit in an interview format.[49]

The NEQ appears to be an efficient, valid measure of severity for NES.[56] The second study took the form of a semi-structured interview, the NES and Inventory (night eating syndrome history and inventory), characterized by an assessment of food intake for 24 h, including the recall of food and snacks and sleep patterns.[37] This second study showed that among obese adults with type 2 diabetes, NES was reported more frequently than binge eating disorder, which, in turn, was less common than expected.[37]

Differential Diagnosis

- **Bulimia nervosa and binge eating disorder**

The presence of episodes of nocturnal feeding is not a peculiarity of NES, but can also occur in other abnormal eating behavior, such as bulimia nervosa or binge eating disorder, though rarely, however, without day anorexia. NES differs from binge eating disorder and bulimia nervosa in that the food is not consumed in large quantities and is not accompanied by typical compensatory behavior.[31,39] NES is more a change in the timing of food intake, which disrupts the regularity of sleep, rather than a large quantity of food being consumed at a single time.[54]

- **Sleep related eating disorder (SRED)**

Identifying abnormal nocturnal eating is critically important for patient care and public health. Obesity is a global pandemic and a leading cause of preventable mortality in the USA, with more than 100 000 deaths annually. Normally, nighttime energy homoeostasis is maintained, despite an absence of food intake, through appetite suppression and alterations in glucose metabolism that result in stable energy stores. Two conditions break this nighttime fast and are associated with weight gain as well as medical and neuropsychiatric comorbidities. SRED is characterized by isolated nocturnal eating, whereas NES is a circadian delay in meal timing leading to evening hyperphagia, nocturnal eating and morning anorexia (Table 2).[62]

Table (2): Differences between NES and SRED.

	NES	SRED
Nocturnal ingestion	+	+
Morning anorexia	+	+
Alterations level of consciousness	−	+
Amnesia of nocturnal event	−	+
Possible ingestion of harmful or toxic substances	−	+
Frequent association with sleepwalkers	−	+
Frequent comorbidity with PLMD, RLS or OSA	−	+

SRED is a little-described syndrome combining features of sleep disorders and eating disorders. The behaviour consists of partial arousals from sleep followed by rapid ingestion of food, commonly with at least partial amnesia surrounding the episode the following day. A study provided an estimate of the prevalence of SRED and revealed that SRED is more common than is generally recognized, especially in those with a daytime eating disorder. Sleep disorder symptoms are often associated with SRED, as are depression and dissociation. Evaluation of individuals with eating disorders should include assessment for sleep-related eating.[63]

Patients with SRED, during episodes of nocturnal feeding, may swallow unconsciously, not only foods high in calories, but also compounds or liquids that are inedible or even toxic.[64] SRED is often associated with other sleep disorders such as the periodic leg movement disorder, restless legs syndrome or obstructive sleep apnea.

The most prominent cited distinction between NES and SRED is the level of consciousness during nighttime eating episodes. Whereas those with NES eat after attaining full awareness, those with SRED often report that they are 'half asleep, half awake' or even fully asleep during nocturnal episodes and may have impaired recollection of the event the following morning.[65]

The difference between NES and SRED may be that patients with the latter are sleep-walkers who happen to eat, whereas patients with NES are those with binge eating disorder who happen to eat at night. On the other hand, many of those patients with alterations in level of consciousness during nocturnal eating (and thus diagnosed with SRED) may also have night eating with full alertness, either during other episodes in the same night or at other periods during the course of the nocturnal eating disorder. In this way, rather than being two distinct disorders, pure SRED and NES may reflect opposite ends of a continuum of impairment of consciousness during nocturnal eating.[66] Although these diagnostic issues remain unresolved on clinical and scientific bases, the recent revision of the International Classification of Sleep Disorders (ICSD) has effectively eliminated the distinction between the two disorders.

Definition and diagnostic criteria for sleep-related eating disorders from The International Classification of Sleep Disorders:[62]

A. Recurrent episodes of involuntary eating and drinking occur during the main sleep period.

B. One or more of the following must be present with the recurrent episodes of involuntary eating and drinking:

1. Consumption of peculiar forms or combinations of food or inedible or toxic substances.
2. Insomnia related to sleep disruption from repeated episodes of eating, with a complaint non restorative sleep, daytime fatigue, or somnolence.
3. Sleep-related injury.
4. Dangerous behaviour performed while in pursuit of food or while cooking food.
5. Morning anorexia.
6. Adverse health consequences from recurrent binge eating of high caloric food.

C. The disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use or substance use disorder (hypoglycaemic states, peptic ulcer disease, reflux oesophagitis, Kleine–Levin syndrome, Kluver–Bucy syndrome, and nighttime extension of daytime anorexia nervosa (binge/purge subtype), bulimia nervosa and binge eating disorder).

Treatment

Pharmacological treatment

Studies have suggested that central nervous system (CNS) serotonin modulation may lead to an effective treatment of NES. In 1994 an investigation reported that all 6 patients treated with D-fenfluramine, over a 6-15 month follow-up period, had a pronounced reduction in the number of nighttime eating episodes and caloric intake.[23] Another report described complete eradication of symptoms in 4 night eating subjects as early as 2weeks after initiation of SSRI medication.[67] Based on the relatively rapid effect in NES, it has been suggested that SSRIs act through a direct serotonergic effect in the hypothalamus which controls circadian

rhythms and feeding behavior.[54] Also, it has been suggested that the high carbohydrate food typically consumed in night eaters may be related to CNS serotonin modulation. In particular, a high carbohydrate-to-protein ratio facilitates the availability of tryptophan which is then converted into CNS serotonin that promotes the initiation of sleep and reversal of sleep disruption.[10] One open-label, un-blinded study investigated the effect of sertraline on NES.[60] After 12 weeks the patients who completed the study reported less caloric intake at night, less nocturnal ingestions, and fewer awakenings. Another study assessed the effectiveness of sertraline in a group of 41 tele- medicine patients, after 8 weeks the subjects demonstrated decreased evening hyperphagia and the mean body weight of the overweight and obese subjects fell by 3 kg.[68]

Recently, a double-blinded, placebo controlled randomized study assessed the efficacy of sertraline in the treatment of NES. The largest decrease in symptoms occurred by the second week, indicating an early effect. It is not known whether or not this is a specific sertraline effect or a more general SSRI effect.[69]

Early studies have suggested that topiramate, an anti-seizure agent with anorexic effects, may be an effective treatment in relieving the abnormal feeding patterns of NES.[70]

Sedating agents have not been proven to be effective in treating NES and in many cases are associated with exacerbating night eating. In a review of 23 patients enrolled in a clinical trial for NES, there were 16 reported exposures to sedating agents (primarily Zolpidem). None of the exposures were considered effective[60] Importantly, Zolpidem has been associated with triggering amnestic nocturnal eating in patients with and without NES.[71]

Non pharmacological

Bright light therapy

Bright light is an effective intervention for phase advancing the circadian rhythm, the timing and duration of the light stimulus as well as the brightness and wave-length of light affects the magnitude of phase shift. The human phase response curve to light suggests a phase advance of the circadian rhythm is achieved when the light stimulus is presented immediately after CT min .Given a possible serotonergic basis to NES, bright light therapy was tried in two case studies. Friedman et al(2002)[72] report the successful treatment of a 51-year-old obese woman with NES and comorbid major depressive disorder. Despite two years of maintenance treatment of paroxetine, (40 mg/day), the depression continued to worsen. The depression and NES responded to a dose of 14 morning sessions of 10,000 lx light (the equivalent of full daylight); one month later, the NES returned, but was successfully treated with an additional 12 sessions. In a second study, a 46-year-old normal weight man with co-morbid major depressive disorder in partial remission responded to 14 consecutive morning sessions of 10,000 lx light.[73] Together, these results support the use of bright light therapy for the treatment of comorbid NES and major depressive disorder. Further study of bright light therapy is warranted.

Psychological treatment

Several studies have been done to examine the effect of psychological treatment on NES and the results were variable. Allison et al. (2010)[74] present a cognitive behavioral self-help book for NES based on their clinical experience in treating the disorder which addresses seven basic areas. First, education about NES, healthy eating, and sleep is

provided in accord with each area of intervention. Second, patients are instructed to keep a food diary with the goals of implementing a regular eating schedule with greater food intake during the day and reduced intake at night. The amount of food eaten after dinner is gradually reduced to a single structured post-dinner snack and the amount of food eaten during night time awakenings is reduced to the minimum necessary to re-attain sleep. Improvements in nutrition, food choices, and portion size are recommended. Self-monitoring, structured meals and snacks, stimulus control, exposure and response intervention to craved foods and imagery are strategies used to achieve these goals. Third, relaxation strategies, including deep breathing and progressive muscle relaxation, are prescribed to reduce the stress associated with reduced caloric intake as well as to unwind at the end of the day. Fourth, patients are instructed in sleep hygiene, such as the limitation of alcohol, caffeine, and water prior to sleep, the use of nighttime rituals, and regular sleep times. Fifth, cognitive restructuring is used to address beliefs regarding the need to eat, insomnia, and co-morbid depressive symptomatology. Sixth, physical activity is recommended as important component of physical and mental well-being. Finally, patients are instructed to solicit both emotional and instrumental support from loved ones and medication consultation is recommended as needed.[49]

A clinician-delivered version of the treatment was tested among 25 patients with NES in an uncontrolled trial consisting of 10 sessions spaced across 12 weeks,[61] only 14 patients attended 8 of the 10 sessions, they showed favorable improvements in caloric intake after dinner, nocturnal ingestions, and NEQ scores, number of awakenings per week, depressed mood, and quality of life.

Relaxation may produce beneficial effects via the reduction of CRF, subsequent reduction in cortisol release, and resulting increase in melatonin. Physical activity may be beneficial for the treatment of NES via its effects on sleep, including decreases in REM latency, increases in slow wave sleep, and increases in total sleep duration[75,76] or its effects on mood.[77] Finally, the bright light therapy, and CBT as well as the possible necessity and utility of combining therapies may be assessed.[49]

Depression

General background

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and sense of well-being.[78] Depressed people feel sad, anxious, empty, hopeless, worried, helpless, worthless, guilty, irritable, hurt, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details, or making decisions, and may contemplate, attempt, or commit suicide. Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains, or digestive problems may also be present.[79]

Depressed mood is not always a psychiatric disorder. It may also be a normal reaction to certain life events, a symptom of some medical conditions, or a side effect of some drugs or medical treatments. Depressed mood is also a primary or associated feature of certain psychiatric syndromes such as clinical depression.

Types of depression

Major depressive episode: Criteria for the diagnosis of major depressive episode are laid out in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).

A major depressive episode is defined as a syndrome in which at least 5 of the following symptoms have been present during the same 2-week period:[80]

a. Depressed mood (for children and adolescents, this can also be an irritable mood).
b. Diminished interest or loss of pleasure in almost all activities (anhedonia)
c. Significant weight change or appetite disturbance (for children, this can be failure to achieve expected weight gain).
d. Sleep disturbance (insomnia or hypersomnia).
e. Psychomotor agitation or retardation.
f. Fatigue or loss of energy.
g. Feelings of worthlessness.
h. Diminished ability to think or concentrate; indecisiveness.
i. Recurrent thoughts of death, suicidal.
j. A pattern of long-standing interpersonal rejection ideation, suicide attempt, or specific plan for suicide.

Further stipulations are as follows:

a. At least 1 of the symptoms must be diminished interest/pleasure or depressed mood.
b. The symptoms must cause significant distress or impairment of functioning in social, occupational, or other important areas.
c. Depression should not have been precipitated by the direct action of a substance or a general medical condition.
d. Symptoms should not meet criteria for a mixed episode (ie, for both manic and depressive episode).
e. Symptoms are not better accounted for by bereavement (ie, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation).

f. A major depressive episode should not be superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or a psychotic disorder not otherwise specified (NOS).

g. In older adults, rigorously applying the DSM-IV-TR criteria for major depressive disorder has been argued to result in missing a large portion of patients with depressive symptoms and associated functional impairment.

Depressive disorders can be rated as mild, moderate, or severe. The disorder can also occur with or without psychotic symptoms, which can be mood congruent or incongruent. Depressive disorders can be determined to be in full or partial remission. When an episode lasts longer than 2 consecutive years, the depression should be diagnosed as chronic.

The DSM-5 removed the current system of axes used to class diagnoses into broad groups. It had restructured diagnostic groups to bring disorders that are similar in underlying vulnerabilities and symptom characteristics under the same headings.[81]

A. Five (or more) of the following symptoms have been present during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

Further specifications are as follows

1. **Depression with melancholic features:** In depression with melancholic features, either a loss of pleasure in almost all activities or a lack of reactivity to usually

pleasurable stimuli is present. Additionally, at least 3 of the following are required:

a. A depressed mood that is distinctly different from the kind that is felt when a loved one is deceased.
b. Depression that is worse in the morning.
c. Waking up 2 hours earlier than usual.
d. Observable psychomotor retardation or agitation.
e. Significant weight loss or anorexia.
f. Excessive or inappropriate guilt.

2. **Depression with catatonic features:** Diagnosis of depressive episodes with catatonic features requires at least 2 of the following, according to the DSM-IV-TR:
   a. Motoric immobility in the form of catalepsy or stupor.
   b. Motor over-activity that seems purposeless and not in response to external stimuli.
   c. Extreme negativism or mutism.
   d. Voluntary movement peculiarities such as posturing, grimacing, stereotypy, and mannerisms.
   e. Echolalia or echopraxia.
3. **Atypical depression:** An episode of depression may be identified as having atypical features. Characteristics of this subtype are mood reactivity and exclusion of melancholic and catatonic subtypes in addition to 2 or more of the following for a period of at least 2 weeks:
   a. Increased appetite or significant weight gain.
   b. Increased sleep.
   c. Feelings of heaviness in arms or sensitivities of the legs that extend far beyond the mood disturbance episodes and result in significant impairment in social or occupational functioning.
   d. Reversed diurnal mood change (ie, severity worse in the evening than the morning).

   This type is important due to its relation to excessive eating and therefore, may be related to NES.
4. **Postpartum depression:** Depression in the postpartum period is a common and potentially very serious problem; up to 85% of women can develop mood disturbances during this period. For most women, symptoms are transient and relatively mild (ie, "postpartum blues"); however, 10-15% of women experience a more disabling and persistent form of depression, with an onset later than the postpartum blues, and 0.1-0.2% of women experience postpartum psychosis.[82-85]

Postpartum psychiatric illness was initially conceptualized as a group of disorders specifically linked to pregnancy and childbirth and thus was considered diagnostically distinct from other types of psychiatric illness. However, evidence within the past decade suggests that postpartum psychiatric illness is virtually indistinguishable from psychiatric disorders that occur at other times during a woman's life.[86-88] However, the likelihood of a bipolar outcome is substantially higher in postpartum psychosis.

Rapidly fluctuating mood, tearfulness, irritability, and anxiety are common symptoms of postpartum blues.[89-92] Symptoms peak on the fourth or fifth day after delivery and last for several days, but they are generally time-limited and spontaneously remit within the first 2 postpartum weeks.[89] Symptoms do not interfere with a mother's ability to function and to care for her child.

Women with more severe symptoms or symptoms persisting longer than 2 weeks

should be screened for postpartum depression.[87,88] Typically, postpartum depression develops insidiously over the first 3 postpartum months,[93] although the disorder may have a more acute onset. Postpartum depression is more persistent and debilitating than postpartum blues.

Signs and symptoms of postpartum depression are clinically indistinguishable from major depression that occurs in women at other times. In the postpartum period, depression is characterized as intense sadness, anxiety, or despair. These symptoms interfere with the mother's ability to function, with risk of self-harm or harm to the infant.[93]

The American Academy of Pediatrics (AAP) states that more than 400,000 infants are born each year to mothers who are depressed. The AAP encourages pediatric practices to create a system to better identify postpartum depression to ensure a healthier parent-child relationship.[94]

Although effective non-pharmacologic and pharmacologic treatments are available, both patients and their caregivers frequently overlook postpartum depression.[87] Untreated postpartum affective illness places both the mother and infant at risk and is associated with significant long-term effects on child development and behavior;[86,88,93] therefore, appropriate screening, prompt recognition, and treatment of depression are essential for both maternal and infant well-being and can improve outcomes.[95]

5. **Seasonal affective disorder:** About 70% of depressed people feel worse during the winter and better during the summer. To meet the diagnostic criteria for seasonal mood disorder, depression should be present only at a specific time of year. An individual should demonstrate at least 2 episodes of depressive disturbance in the previous 2 years, and seasonal episodes should substantially outnumber non seasonal episodes. Patients with seasonal affective disorder are more likely to report atypical symptoms, such as hypersomnia and increased appetite.

Diagnosing seasonal affective disorder in children is difficult because they experience the recurrent universal stressor of beginning school every autumn. Also, a young child might present with apparent seasonal affective disorder but not yet have had previous episodes.

6. **Major depressive disorder with psychotic features:** The presentation of severe major depressive disorder may include psychotic features. Psychotic features include delusions and hallucination and may be mood congruent or mood incongruent. Mood-congruent psychoses are often consistent with classic depressive themes, such as personal inadequacy, guilt, disease, or deserved punishment. Mood-incongruent psychoses are not consistent with these typical themes but may also occur in depression.

Major depressive disorder with psychotic features is considered a psychiatric emergency. Patients may require psychiatric hospitalization.

7. **Depressive disorders not otherwise specified:** The *DSM-IV-TR* includes a category of disorders with features of depression that do not meet criteria for a specific mood disorder or adjustment disorder with depressed mood. Examples include the following:
   a. A depressive episode superimposed on residual schizophrenia
   b. Recurrent depression lasting less than 2 weeks
   c. A non-recurrent mild depressive disturbance that does not meet criteria for dysthymia
   d. Non–stress-related episodes that do not meet the criteria for a major depressive episode.

The relations between NES, obesity, depression and antidepressants

This study was suggesting a relation between depression, antidepressants, obesity and night eating syndrome and this chapter will discuss these several relations between them. So, we will discuss comorbid obesity and depression as obesity might be a complication of NES, NES may me a sign or associated manifestation of depression. Also, NES may be improved or induced by the use of certain antidepressants.

I. Associated pathophysiology of depression, obesity and NES

There is an evidence of a biological link between obesity, NES and depression which remains complex. It seems relevant to stress, the hypothalamic pituitary adrenal axis dysregulation.

Stress is a challenge to the natural homeostasis of an organism [(96)]. The stress response is characterized by acute behavioral and physical adaptations, including increased cognition, analgesia, gluconeogenesis, lipolysis, and inhibition of reproduction [(97)]. There are two major components of the stress response: the autonomic nervous system (ANS), which encompasses the sympathetic and parasympathetic nervous system, and the HPA axis. These systems work centrally and peripherally to produce several responses. The 'fight or flight response' is an active reaction to either confront the stressor or escape confrontation. The 'defeat response' is when the individual does not engage in either the fight or flight response and ultimately 'loses' the confrontation; this is the primary stress response in modern society and is associated with HPA axis changes.[(98)]

Although an acute short-term stress response is necessary for homeostasis recovery, chronic or prolonged stress responses can be harmful and may cause several disease states[(96)] and may lead to hyperactivity of the HPA axis.

Hypothalamic–pituitary–adrenal axis

The HPA axis is one of two major neuroendocrine systems associated with the stress response. Corticotropin-releasing hormone (CRH), secreted from the para-ventricular nucleus (PVN) of the hypothalamus, stimulates the synthesis of adrenocorticotropin (ACTH) from the anterior pituitary gland. ACTH stimulates cortisol production from the adrenal cortex. Cortisol is transported in circulation bound to corticosteroid-binding globulin (CBG) and directed to peripheral target tissues, where its availability is dependent on the activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme. The 11β-HSD1 isoform converts the inactive cortisone into active cortisol, and the 11β-HSD2 isoform converts cortisol to the inactive cortisone.[(99)]

a) Hypothalamic–pituitary–adrenal axis dysregulation in obesity

Studies in the field of obesity research in the past 10 years have demonstrated that obesity and metabolic syndrome are characterized by chronic inflammation.[(100)] Pro-inflammatory cytokines can stimulate the HPA axis; conversely, cortisol decreases the production of cytokines and other inflammatory mediators.[(101,102)] Therefore, it is evident that there exists some crosstalk between the HPA axis and the inflammatory response; this may relate to the role of HPA axis alterations in the development of obesity.

b) Hypothalamic–pituitary–adrenal axis dysregulation in depression

Hyperactivity of the HPA axis is one of the best-replicated findings in the neurobiology of depression, CRF neurons are present in the hypothalamus (paraventricular nucleus) and extrahypothalamic regions, both of which exhibit alterations in depressed patients.

Hypothalamic CRF changes

Research suggests that the primary hypothalamic perturbation in the HPA axis in depression might consist of increased numbers of CRF-containing neurons and CRF mRNA in the paraventricular nucleus, which leads to hypersecretion of hypothalamic CRF.[103] Presumably, the increased CRF synthesis and secretion lead to a chain of events, starting from enlargement of the pituitary gland with increased ACTH secretion, and leading to enlargement of the adrenal cortex with increased baseline cortisol levels.[104] This hypercortisolemia is assumed to result in alterations in the glucocorticoid receptors, which become less functional, or downregulated, or "glucocorticoid resistant," in some depressed patients. However, researchers have also hypothesized that the glucocorticoid resistance could be a primary defect in depression leading to hypercortisolemia secondary to the absence of feedback inhibition of glucocorticoid on the pituitary and hypothalamus.[105]

Results from 2 well-studied endocrinologic tests that reflect the function of the HPA axis have been found to be abnormal in many depressed patients. Fifty percent of depressed patients exhibit nonsuppression of cortisol secretion after administration of the dexamethasone suppression test (DST). Dexamethasone, a synthetic glucocorticoid, is believed to bind to the glucocorticoid receptors located in the anterior pituitary, thereby reducing ACTH secretion, and ultimately cortisol production. However, in depression, glucocorticoid receptors may become dysfunctional, as mentioned earlier. In another test, the CRF stimulation test, intravenous administration of exogenous CRF causes depressed patients to exhibit a blunted ACTH response compared with that in healthy subjects. This blunted response is likely due in part to downregulation of CRF receptors in the pituitary that is secondary to persistent increased CRF secretion. Another explanation for the blunted ACTH response to CRF is the increased feedback inhibition of ACTH by basal hypercortisolemia.[106]

How may these alterations in the HPA axis produce depression? It has been hypothesized that changes in the glucocorticoid receptors in certain regions of the brain (eg, the hippocampus) might contribute to the depressive symptoms. The hippocampus normally exhibits an inhibitory effect on the HPA axis. However, when glucocorticoid receptors are altered secondary to hypercortisolemia, this inhibitory effect may become impaired and lead to a feed-forward effect on the HPA axis with ultimate persistent secretion of cortisol. Also, as mentioned earlier, hypercortisolemia is associated with neurotoxicity as well as reduced neurogenesis in the hippocampus, and a dysfunctional hippocampus may underlie some of the depressive symptoms. Interestingly, studies have documented reduced hippocampal volume in some depressed patients. Researchers have postulated that this reduced hippocampal volume might reflect glucocorticoid-induced neuronal atrophy; however, postmortem examination of hippocampal neurons is needed to confirm this hypothesis.[107]

Support for the theory of glucocorticoid resistance-mediated depression is derived from laboratory animal studies showing that antidepressants and electroconvulsive therapy

(ECT) alter glucocorticoid receptors, enhancing the binding of glucocorticoids to these receptors. Interestingly, this effect of antidepressants on glucocorticoid receptors takes 2 weeks, about the same duration of time needed for antidepressants to begin improving depressive symptoms.[106]

Extrahypothalamic CRF system

There is considerable evidence that depression, at least in some patients, is associated with hyperactivity of extrahypothalamic CRF neurons. This hypothesis is supported by:

1. Elevated CSF CRF concentrations (which reflect extrahypothalamic CRF) in some depressed patients as compared with healthy controls, patients with schizophrenia and those with senile dementia.[108]
2. Downregulation of the postsynaptic frontal cortical CRF receptors in depressed suicide victims.[109]
3. Depressive/anxiety like behavior after administration of CRF directly into the cerebral ventricles and/or specific sites of the CNS.[110]

c) Hypothalamic–pituitary–adrenal axis dysregulation in NES

Subjects suffering from night-eating episodes had signs of disturbances in the HPA axis with an attenuated ACTH and Cortisol response to CRH. The mechanisms behind the increased CRH stimulation may involve alterations in the neurotransmitter systems, causing increased nocturnal appetite and disruption in the sleep pattern. This may, to some extent, explain the disturbances in the circadian secretions of melatonin and leptin and the behavioral characteristics of the night eating syndrome.[46]

II. Comorbid depression and obesity

There is a bidirectional association between depression and obesity: obese persons had a 55% increased risk of developing depression over time, whereas depressed persons had a 58% increased risk of becoming obese.

Although evidence of a biological link between overweight, obesity, and depression remains complex and not definitive,[111-114] it seems relevant to highlight the most current lines of reasoning within the possibility of a biological pathway. First, we will discuss the direction of obesity exposure on depression outcome. Obesity can be seen as an inflammatory state, as weight gain has been shown to activate inflammatory pathways[115,116] and inflammation in turn has been associated with depression.[117-119] Because inflammation plays a role in both obesity and depression, inflammation could be the mediator of the association. Also, the hypothalamic-pituitary-adrenal axis (HPA axis) might play a role, because obesity might involve HPA-axis dysregulation[120,121] and HPA-axis dysregulation is well known to be involved in depression.[122,123] Through HPA-axis dysregulation, obesity might cause development of depression. Finally, obesity involves increased risks of diabetes mellitus and increased insulin resistance,[124] which could induce alterations in the brain[125] and increase the risk of depression.[126] In addition to biological mechanisms, psychological pathways should be mentioned. Being overweight and the perception of overweight increases psychological distress.[127,128] Obesity may increase body dissatisfaction and decrease self-esteem, which are risk factors for depression.[129] Disturbed eating patterns and eating disorders, as well as experiencing physical pain as a direct consequence of obesity, are also known to increase the risk of depression.[130,131]

Also, obesity affects the course of depression when they become comorbid with each other, as it has an effect on severity, frequency of the attacks as well as the resistance to treatment in the presence of obesity.[132,133]

The fact that depression causes an increase of weight over time may also be caused by neuroendocrine disturbances. Björntorp in 2001[134] argued that depression induces (abdominal) obesity through long-term activation of the HPA axis. Cortisol, in the presence of insulin, inhibits lipid-mobilizing enzymes, a process mediated by glucocorticoid receptors that are found in fat depots and especially in intra-abdominal visceral fat.[135] Another important mechanism is the adoption of an unhealthy lifestyle, such as insufficient physical exercise and unhealthy dietary preferences, possibly leading to obesity.

Depression treatment and management

Approach Considerations

The combination of medication and psychotherapy generally provides the quickest and most sustained response. Combination therapy has also been associated with significantly higher rates of improvement in depressive symptoms; increased quality of life; and better treatment compliance, especially when treatment is needed for longer than 3 months.[136,137]

Usually, 2-12 weeks at a therapeutic dose, with assumed adherence to the regimen, are needed for a clinical response to become evident. The choice of medication should be guided by anticipated safety and tolerability, which aid in compliance; physician familiarity, which aids in patient education and anticipation of adverse effects; and history of previous treatments. Often, treatment failures are caused by medication noncompliance, inadequate duration of therapy, or inadequate dosing.

According to the 2008 American College of Physicians guideline on using second-generation antidepressants to treat depressive disorders, patient preferences should be given serious consideration when choosing the best course of pharmacotherapy for patients with depressive disorders. The patient may want to avoid use of a particular antidepressant if he or she had a previous negative experience with the drug.[138]

The 2008 ACP guideline advises that treatment for major depressive disorder should be altered if the patient does not have an adequate response to pharmacotherapy within 6-8 weeks. Once satisfactory response is achieved, treatment should be continued for 4-9 months in patients with a first episode of major depression that was not associated with significant suicidality or catastrophic outcomes. In those who have had 2 or more episodes of depression, a longer course of maintenance treatment may prove beneficial.[138]

In 2011, the American Psychiatric Association (APA) updated its Practice Guideline for the Treatment of Patients with Major Depressive Disorder.[139] The 2011 APA guideline emphasizes the need to customize a treatment plan for each patient based on a careful assessment of symptoms, including rating scale measurements administered by a clinician or the patient, as well as an analysis of therapeutic benefits and side effects.

Treatment should maximize patient function within specific and realistic goals. The initial modality should be chosen on the basis of the following:[139]

1. Clinical assessment.
2. Presence of other disorders.

3. Stressors.
4. Patient preference.
5. Reactions to previous treatment.

Pharmacologic therapy for depression

Drugs used for treatment of depression include the following:

1. Selective serotonin reuptake inhibitors (SSRIs).
2. Serotonin/norepinephrine reuptake inhibitors (SNRIs).
3. Atypical antidepressants.
4. Tricyclic antidepressants (TCAs).
5. Monoamine oxidase inhibitors (MAOIs).
6. St. John's wort.

III. Relation of antidepressants to weight gain and obesity

There are a variety of ways through which psychotropic medications can cause weight gain as an unwanted side effect. These medications interfere with neuromodulators involved in the process of energy balance. Some medications decrease the resting metabolic rate. Others cause an increase in fasting glucose and lipids or increase cravings for sweets. Interestingly, overweight patients who take psychotropic medications gain more weight than lean patients, women gain more weight than men and the degree of weight gain correlates with the degree of improvement of patients' psychiatric symptoms.

As there are few researches studying the association of antidepressants and NES through its effect on weight gain, so, this study tried to explore this form of association.

Different types of antidepressants and there relation to weight gain

Monoamine oxidase inhibitors (MAOI) cause weight gain in most patients while some patients can actually experience weight loss. Phenelzine causes a degree of weight gain similar to tricyclic antidepressants. Reversible MAOI such as moclobemide may be less likely to cause weight gain.[140]

There are various hypotheses that can explain why patients gain weight when they take **tricyclic antidepressants (TCA)**. One is an increased carbohydrate craving, which is attributed to their strong antihistaminergic effect. Another postulated mechanism for weight gain is neurotransmitter modulation at the hypothalamic level, which changes the regulation of body fat stores and increases energy efficiency. Weight gain can happen even after short courses of treatment like one month. A review by Garland et al[141] reported a weight gain of 0.37 to 1.37 kg/month of therapy. A study by Berken et al [142] reported a weight gain of 1.3 to 2.9 lbs per months over 6 months of treatment. This suggests that there is a cumulative risk of weight gain proportional to the duration of treatment. Patients who take TCAs have a 5% to 24% decrease in resting metabolic rate.[143] Amitriptyline causes more weight gain than imipramine and despiramine.[141] Interestingly, not all patients gain weight: Frank et al[144] reported a 13.3% incidence of more than 10% body weight increase in patients treated for an average of 33 weeks.

Selective serotonin reuptake inhibitors (SSRI) are the most commonly used antidepressants. They exhibit an anorectic effect in the early treatment phase, sometimes due to side effects like nausea. Some SSRIs can cause weight gain with long-term use. This was first described soon after fluoxetine was introduced in the United States[145] and

then reported in subsequent clinical trials. The possible mechanism for SSRI-induced weight gain could be related to recovery from depression, thus improved appetite,[146] overall appetite stimulation and increase in carbohydrate cravings[147] and changes in the serotonin 5-HT 2c receptor activity.[148] Different SSRIs were studied against each other in a 6-month trial,[149] which suggested that fluoxetine leads to a modest weight loss over 6 months, paroxetine causes a significant weight gain (defined as >7% increase in body weight and over 6 months), and sertaline causes modest weight gain. The rate of weight gain was 22.5% for paroxetine, 6.8% for fluoxetine and 4.2% for sertaline. There was no placebo arm of the study. There are also reports of increased carbohydrate craving and subsequent weight gain with citalopram.[150]

Mirtazapine is a tetracyclic antidepressant, which causes a significant increase in appetite and carbohydrate craving, possibly due to its histamine H1 blocking effect. The weight gain effect happens early in the course of treatment (2.4 kg weight gain in 4 weeks) and tends to be more pronounced in females.[151] It seems to be less common (13%) than with amitriptyline (22%) over a 20-week trial.[152]

Venlafaxine is weight neutral during short-term treatment. A 12-week trial of venlafaxine versus fluoxetine showed no significant weight gain for either agent.[153] There are not enough data regarding long term effects.

Bupropion causes weight loss, documented in many clinical trials.[154-157] It can be used as an aid for smoking cessation and weight loss in non-depressed individuals. Because of its weight loss effect, it can be tried as a first-line agent in obese patients with major depression who do not have contraindications. It can also be used in combination with other antidepressants allowing a dose decrease of an agent that causes weight gain.

Nefazodone causes minimal weight gain. In a 36week study, 7.6% patients reported weight gain versus 8.6% of placebo.[158] Another study looked at comparing nefazodone with SSRIs and the weight gain occurred in 8.8% of nefazodone-treated patients versus 17.9% of the SSRI-treated patients.[159]

IV. Relation of antidepressants to NES

Studies have suggested that central nervous system (CNS) serotonin modulation may lead to an effective treatment of NES. In 1994 an investigation reported that all 6 patients treated with D-fenfluramine, over a 6-15 month follow-up period, had a pronounced reduction in the number of nighttime eating episodes and caloric intake.[23] Another report described complete eradication of symptoms in 4 night eating subjects as early as 2weeks after initiation of SSRI medication.[67] Based on the relatively rapid effect in NES, it has been suggested that SSRIs act through a direct serotonergic effect in the hypothalamus which controls circadian rhythms and feeding behavior.[54]

One open-label, un-blinded study investigated the effect of sertraline on NES.[60] After 12 weeks the patients who completed the study reported less caloric intake at night, less nocturnal ingestions, and fewer awakenings. Another study assessed the effectiveness of sertraline in a group of 41 tele- medicine patients.[68] After 8 weeks the subjects demonstrated decreased evening hyperphagia and the mean body weight of the overweight and obese subjects fell by 3 kg.

Recently, a double-blinded, placebo controlled randomized study assessed the efficacy of sertraline in the treatment of NES.[69] The largest decrease in symptoms occurred by the second week, indicating an early effect. It is not known whether or not this is a specific sertraline effect or a more general SSRI effect.

From the two afore-mentioned relations it is not clear whether antidepressants can be a cause of inducing NES as the only clear and direct association between antidepressants and NES was in its use for treatment of NES.

So, our thesis suggested that by the evident relation between antidepressants and weight gain, and the other relation between weight gain and NES. Therefore, we tried to find a relation between antidepressants and NES (in the form of causing NES).

Regarding NES relation with depression, it is not clear whether depression is a cause, an association or both are comorbid disorders with a common pathophysiology.

Although, many studies were made among the relation between NES and depression most of them were from NES perspective. There are presently few studies regarding the rate of NES in depressed patients and the relation to antidepressants.

In such a context, this descriptive study was conducted to fill these research gaps and comparing the NES in patients diagnosed as major depression with and without antidepressants.