clinical and translational neuroscience

MDPI

Review

Is Sleep-Related Eating Disorder (SRED) a NREM Parasomnia or a Heterogenous Disease?

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Abstract: Sleep-related eating disorder (SRED) is a relatively rare but probably underestimated disorder, where affected patients exhibit nocturnal eating episodes with impaired consciousness and subsequent amnesia. SRED has originally been classified as NREM (non-rapid eye movement) parasomnia, with an obviously high number of concomitant sleep disorders. We suggest that SRED may represent a heterogenous disease, based on accumulating data in recent studies. Some SRED patients may be better classified as sleep-related movement disorders with an underlying dopaminergic dysfunction. Hypnotic drugs may play a crucial role in triggering amnestic SRED in both parasomnic and sleep-related movement-disordered SRED.

Keywords: sleep-related eating disorder; epidemiology; parasomnia; nocturnal eating syndrome

Citation: Zobrist, N.; Zhang, Z.; Khatami, R. Is Sleep-Related Eating Disorder (SRED) a NREM Parasomnia or a Heterogenous Disease? *Clin. Transl. Neurosci.* **2024**, *8*, 1. https://doi.org/10.3390/ctn8010001

Academic Editor: Karl-Olof Lovblad

Received: 3 October 2023
Revised: 7 December 2023
Accepted: 12 December 2023
Published: 19 December 2023

1. Introduction

Sleep-related eating disorder (SRED) has been recently described as a new entity, and added to the section of NREM parasomnias in group of disorders of arousal (e.g., sleepwalking, confusional arousals and sleep terror) in international classification of sleep disorders-third edition (ICSD-3) [1]. As is typical for disorders of arousal, SRED is defined by abnormal behaviors occurring during NREM-sleep. These are characterized by episodes of eating and drinking, accompanied by incomplete or partial awareness of the episodes. Recently, new data have raised doubt on the parasomnic etiology of SRED, and researchers have proposed a more heterogenous nature for SRED. In this comprehensive exploration, the epidemiology, including comorbidities of SRED, the variety and commonalities of clinical features, and the differences between SRED and the nocturnal eating syndrome (NES), possible causes and triggers of the disease, a diagnosis strategy and management of the condition, including pharmacological and non-pharmacological treatment are reviewed. All these aspects will be discussed in arguing for the alternative hypothesis, that SRED is a heterogenous disease.

2. Difference between SRED and NES

It is important to distinguish sleep-related eating disorder (SRED) from nocturnal eating syndrome (NES), for reasons of neurobiology and personalized management. The difference has been best described by coining NES as an eating disorder with associated insomnia, whereas SRED is described as a type of parasomnia [2]. NES was introduced into the literature by Stunkard [3] in 1955, by describing 25 patients with refractory obesity, most of them female, with sleep onset insomnia, who ingested 25% of their calories after the evening meal during conscious nocturnal eating. SRED was described later, in 1991, by Carlos Schenck [4], in adult patients who had partial or complete amnesia in relation to their eating episodes and a strong association with other sleep disorders. In a subsequent study, Schenck [5] investigated most of the patients using PSG, and found a high number

of arousals from deep slow-wave sleep in these patients, leading the authors to consider it as a variant of non-rapid eye movement (NREM) arousal disorder parasomnia.

Until now, the most important difference between NES and SRED is that NES patients are usually aware of their nocturnal eating episodes, and recall them the next morning. There are, however, overlapping features and common comorbidities. Patients with SRED, for example, may also have conscious eating behavior which will be defined as NES. In other words, some night-time episodes with full awareness will not exclude the diagnosis of SRED. Indeed, there are data showing that amnestic SRED is especially common in patients taking benzodiazepine receptor agonists, and is thus attributed to hypnotic medications, rather than SRED itself [4,6,7]. Both SRED and NES may share common triggers, e.g., sleep deprivation, stress and sedative medication.

3. Epidemiology

Population-level epidemiological data on sleep-related eating disorder are scarce. Based on the available data, SRED can be considered a relatively rare but underestimated condition. Prevalence of SRED varies from 1% up to 4.6% [8–13]. The highest prevalence of 4.6% has been reported in a college student group (69% female, mean age 26.7 years) [13]. With this prevalence data above coming from different sources, such as telephone-interviews or healthy control groups, it is difficult to compare and infer these data with respect to the real prevalence. Further epidemiological data are needed, consistent with a well-known long diagnostic delay of 8.3 ± 8.8 years [14]. We trace this delay back to patients' health-care behavior and the general unfamiliarity of practitioners with the disease. Both might be explained by the variety of perceived severity of the illness. Patients with SRED are typically female [5,14,15], originally described as young adults with symptom onset in adolescence or early adulthood [5,15]. However, SRED can occur at any stage, including children (see below).

The low number of patients with prior eating disorders as originally described by Schenck (1993) [5] has not been confirmed in a subsequent case series, in which prevalence was up to 35% [15]. Higher prevalence rates of SRED have been reported in various patient groups, such as in patients with psychiatric disorders [13] or in other sleep disorders such as restless legs syndrome (RLS) (odds ratio of lifetime SRED compared to healthy controls: 48.8 (confidence interval, CI = 6.5–365.2)) [10] or in narcolepsy type 1 (NT1) (7.9% in patients vs. 1% in a control group) [8]. SRED is often accompanied by other comorbid sleep disorders (see also Table 1), including obstructive sleep apnea syndrome (OSA) (26% reported in Santin et al.) [5,14], up to 73.3% prevalence of insomnia [16], almost 80% of patients reporting a history of parasomnia [15], and high rates of affective disorders, with a depression prevalence of 38.2% [14]. Many patients were taking psychotropic medication or had a history of substance abuse (up to 24%) [5]. Patients with SRED tend to be overweight, with reported mean BMIs between 25.5 and 27.4 [5,14–16].

Table 1. Comorbidities reported in SRED patients.

Comorbidity	Santin et al., 2014 [14]	Brion et al., 2012 [16]	Winkelman et al., 1998 [15]	Schenck et al., 1993 [5], Data from Cumulative Series
Sleep disorders				
History of parasomnia			78.3% (18)	
Insomnia	58.8% (20)	73.3%		
OSA	26% (9) (PSG-documented)			10.5% (4) *
RLS	47% (16)	28.6%		13.2% (5) as RLS/PLM *
Sleepwalking (SW)	11.7% (4)	Current/past sleepwalking/sleep terrors: 66%; childhood sleepwalking/sleep terror: 53.3%; current sleepwalking: 46.7%		60.5% (23) *; SW combined states 7.9% (3) *
Bruxism	17.6% (6)			
Psychiatric		61.5%		47.4% (18)

Table 1. *Cont.*

Comorbidity	Santin et al., 2014 [14]	Brion et al., 2012 [16]	Winkelman et al., 1998 [15]	Schenck et al., 1993 [5], Data from Cumulative Series
Depression	38.2% (13)	Depression score: /24 = 6.1 ± 4.4 vs. 3.2 ± 2.9 (healthy controls), significant		Major depression, *n* = 8, *n* = 4, active. All mood disorders, incl. major depression, bipolar disorder, etc.: 36.8% (14)
Anxiety disorders		Anxiety score: /24 = 10.5 ± 3.7 vs 5.6 ± 3.7 (healthy controls), significant		18.4% (7)
Eating disorders		History of eating disorders: 60%	Daytime eating disorders (total): 34.8% (8); bulimia nervosa: 13.0% (3); anorexia nervosa 13.0% (3); binge-eating disorder: 8.7% (2)	5.3% (2) Anorexia nervosa, nocturnal bulimia (nervosa?) *; eating disorders: 10.5% (4)
Alcohol-substance abuse				23.7% (9), including alcohol (in remission), amphetamine (in remission), cocaine and opiates (in remission) and Triazolam (active)
Other Conditions				
Gastroenterological				18.4% (7)
Neurological (such as narcolepsy, migraines, etc.)				28.9% (11)

Data in % (*n* =). Data sources in table header. Empty fields = no data available or may be categorized differently. * classification of the sleep-related eating disorders at time of publication. OSA is obstructive sleep apnea syndrome, PSG is polysomnography, RLS is restless legs syndrome, PLM is periodic limb movement.

4. Clinical Features

Patients with SRED present, with the following key symptoms:

4.1. Complex Eating or Drinking Behavior Arising from NREM Sleep

Nocturnal eating in SRED patients usually arises from deep NREM sleep stages within the first 1–3 h after sleep onset. In one study, >95% of all eating episodes arose from NREM sleep. Although SRED patients eat in the absence of hunger or thirst, eating behavior is described as binge-like rapid ingestion, abnormal pruning or feeding frenzies, resulting in high amounts of ingested food or drinks. The majority (>65% of the patients) may eat inappropriate food [5]. Uncooked/raw foods, such as unboiled rice or uncooked pasta, or even non-ingestible/non-food items like soaps, are reported. Ingestible food may be eaten improperly prepared, like hot boiled eggs with eggshells, and may lead to severe burns or other injuries in approximately one-third of the patients [5]. Some of these patients require medical care, even intensive-care management. Some patients also have preferences for high caloric food or sweets, in particular for sugar-containing drinks, and eat higher carbohydrates and fats, compared to their daytime eating [17]. Nearly half of the patients attribute their overweight exclusively to their nocturnal eating behavior [2]. Some SRED patients also smoke during or after eating episodes [18], which has been interpreted as an indicator for impulsive behavior as a common possible pathophysiology.

4.2. Partial Awakening

The patients are not fully awake at a clinical and at an electrophysiological level. Clinically partial awakening is indicated by a reduced responsiveness of the patient during the episodes. They also lapse back into automatic behavior when left undisturbed. As with other NREM-parasomnias, SRED episodes usually arise from deep-NREM sleep stages, typically N3 sleep. Polysomnographic recordings are consistent with incomplete awakening from NREM sleep, showing a slow mixed-frequency activity in EEG in 50–70% of the eating episodes [5,15]. Similar to episodes of somnambulism, a high number of abrupt arousals are evident during NREM sleep stages, in particular during slow-wave sleep [16]. The nature of partial awakening is not fully understood, but may reflect a dissociated state. Partial awakening is thought to be the reason for the two other key features, partial consciousness and incomplete recall.

4.3. Partial Consciousness and Incomplete Recall

During their SRED episodes, the vast majority of 80% of the patients are not at all, or only partially, aware of their eating behaviors [5,15]. They may appear in an awake state, due to their obvious eating or drinking behavior or because they are engaged in preparing the food, such as chopping vegetables, roasting meat, or cooking with hot water. The level of consciousness may vary, depending on the case series [17], and even in the same patient, from episode to episode. It may also depend on concurrent medication, in particular whether patients are taking benzodiazepins or Z-drugs. Many patients describe themselves as "semi"-awake, performing automated activity. The person may react when directly approached by turning their heads towards the voice, or may reply with incomprehensible, mumbled answers. Clinically, the precise level of consciousness is often hard to estimate from pure history taking, because recall of episodes is also impaired. If not told about it by their partners sharing their bed, patients may recognize indirect signs of their nocturnal behavior the next morning. They may find a mess in the kitchen from preparing the meals, or an empty fridge. For diagnostic purposes, it is therefore recommended that video-polysomnography (V-PSG) should be performed in the sleep lab, and the lab staff should be instructed on how to assess the level of consciousness and how to test the patient's recollection of the episodes immediately after morning awakening. For many patients, amnesia with respect to the nocturnal activities is embarrassing, and it is one of major burdens of the disease. Both partial consciousness and partial awakening are the major reasons for risk of harm to the patient, together with the environment, because they are not aware of ingesting non-palatable food and are unable to control food preparation. This semiautomated behavior may result in dangerous food preparation using the stovetops, and increases the risk of fires [7,19,20].

5. Causes and Triggers of SRED

As in other NREM parasomnias, several factors may contribute to its manifestation and severity; the most important ones are sleep deprivation, concomitant medication, anxiety and stress.

Sleep Deprivation is a well-known triggering factor for all NREM-parasomnias: a lack of sleep and irregular sleep–wake patterns increase the likelihood of eating episodes. The exact mechanism is not yet clear, but intensifying deep-NREM sleep by the higher power of slow–wave sleep may contribute to the inability to wake up completely.

Concomitant medications: sedative-hypnotics and some antidepressants have been associated with the occurrence of SRED, in particular, benzodiazepines and Z-drugs; zolpidem, for example, has been found to increase the risk of SRED [2]. Previous studies have shown that zolpidem may cause or augment SRED, at least in patients with RLS, and the discontinuation of zolpidem and effective treatment of RLS can also resolve SRED [7].

Stress and Anxiety: emotional stress and anxiety are frequently discussed triggers for parasomnias, including SRED. It remains unclear whether emotional stress and anxiety act directly or via sleep problems, and whether they are specifically mediated by difficulties of sleep initiation or sleep maintenance, leading to sleep deprivation.

Genetics: similar to other disorders of arousal, an increased number of affected family members have been described, although the reported percentage of 5–26% [5,15,16] is lower compared to sleep walking and sleep terror, which are 47–52% and 32%, respectively [16,21]. In rare cases, SRED can run in families [5,15], and one affected twin pair [22] has been described. So far, specific causative genes or gene loci have not yet been identified. HLA-DQB1 genes have been linked with an elevated risk of sleep walking [23]. It is therefore likely that other susceptibility genes may be found for SRED, in the future.

6. Special Aspects of SRED

6.1. SRED in Children and Adolescents

Scarce data indicate that SRED also exists in children and young adolescents. Symptom onset has been described in three patients before the age of 10 [15]. A case report documents

a 9-year-old boy with only partial responsiveness during the period, probably triggered by a paradoxical effect of clonazepam [24]. Another case report identified risperidone in a 16-year old adolescent girl as potential cause of SRED, associated with a sleep-related injury to "her finger with a knife while she was trying to cut an apple" [25]. If SRED is suspected in children, early recognition is crucial to achieve proper diagnosis and to implement appropriate early treatment intervention of causative or triggering factors, including associated sleep disorders.

6.2. SRED and RLS

Some researchers have pointed to striking commonalities between restless legs syndrome (RLS) and SRED, raising the idea that nocturnal eating may represent an additional symptom of RLS in some cases [26]. Similarities have been found at different levels, including epidemiology, clinical features, associated triggers, electrophysiology and course of diseases, including treatment response. A high frequency of SRED (13–47%) [4,6,10,14,16] and NES (up to 61%) [6,10] has been reported in RLS patients. Nocturnal eating/SRED may precede the typical RLS motor restlessness, while SRED onset concomitant with or after RLS manifestation seems to be more frequent [10], indicating that nocturnal eating is not a necessary pre-stage of RLS. In both RLS and SRED, female patients are overrepresented. At a symptom level, the way of food ingestion has been described as "restless eating", and Irfan et al. [26] emphasized that expression of both eating and motor symptoms frequently fluctuate in parallel. Two electrophysiological markers, periodic limb movements (PLM) and rhythmic masticatory muscle activity (RMMA), are frequently seen in polysomnographic recordings in both patient groups [16,17]. Finally, RLS patients, when incorrectly treated with benzodiazepine receptor agonists, may be predisposed to develop SRED [6].

7. Diagnosis of SRED

The diagnosis criteria of SRED according to ICSD-3 are shown in Table 2. Diagnosis is based on careful history taking, including a third-party anamnesis. Detailed description of the eating episodes should include the time, frequency, and duration, as well as the type of ingested food. If applicable, a third party should provide information on the perceived state of awareness of the patient. Due to a patient's complete or partially impaired consciousness and reduced recall of the episodes, questions such as opened food packages, untidy kitchens, or other indications of the symptoms of SRED may be necessary. It is important to assess triggers for the episodes and cues for other underlying sleep disorders carefully.

Table 2. Diagnostic criteria according to ICSD-3 [1].

	Criteria A–D Must Be Met
A.	Recurrent episodes of dysfunctional eating that occur after an arousal, during the main sleep period.
B.	The presence of at least one of the following, in association with the recurrent episodes of involuntary eating: 1. Consumption of peculiar forms or combinations of food or inedible or toxic substances. 2. Sleep-related injurious or potentially injurious behaviors performed while in pursuit of food or while cooking food. 3. Adverse health consequences from recurrent nocturnal eating.
C.	There is partial or complete loss of conscious awareness during the eating episode, with subsequent impaired recall.
D.	The disturbance is not better explained by another sleep disorder, mental disorder, medical disorder, medication, or substance use.

A complete medication anamnesis with special regard for possible pharmacological triggers of SRED should be performed subsequently. Home-video recording is a useful tool to document the episodes. Repeated recording may help to estimate the frequency and

severity, by capturing potentially dangerous nocturnal behavior. In-lab V-PSG should be considered to differentiate SRED from other entities and to assess other suspected sleep disorders as an underlying cause (see list of potential differential diagnoses, below). The probability of recording an informative episode in a single V-PSG recording is relatively high. In one study, 60% of the patients presented with at least one episode, and single patients had multiple episodes [16]. Note that diagnosis can be made on positive anamnesis alone, even in the absence of episodes in V-PSG [14]. Winkelman et al. described abnormal PSG results in patients with SRED, i.e., in general patients had significant sleep disruption but sleep efficacy remained normal [15]. Brion et al. reported a similar general pattern of disturbed sleep between an SRED and a sleepwalking group. Eating episodes were reported after arousals from N2 and N3 sleep stages, showing "a diffuse alpha rhythm [. . .] and no evidence of mixed or slow local EEG frequencies" [16]. The latency from sleep onset until the first chewing movement may be an interesting parameter [16], although its sensitivity and specificity is not known yet. Hypersynchronous EEG delta activity is rare in SRED (personal observation by the authors). As in other NREM parasomnias, sleep deprivation combined with forced awakening should theoretically increase the likelihood of provoking an eating episode during PSG recording, but the extent of this intervention is not documented in the literature. In general, it remains rather unclear which criteria should be used to diagnose SRED using V-PSG as a single diagnostic tool.

An evaluation of daytime sleepiness, if applicable, should include a multiple-sleep latency test (MSLT). Blood analysis and imaging is not recommended if it is not needed to rule out other clinical conditions or potential differential diagnoses.

Important differential diagnoses for SRED and triggering factors should be considered during the whole diagnostic process:

- Nocturnal eating syndrome (NES): differentiation as described above;
- Bulimia nervosa, and other eating-disorders, according to DSM-V;
- Kleine–Levin syndrome;
- Epileptic disorders;
- Psychiatric conditions;
- Other medical disorders (which could have an impact on sleep–wake control, consciousness or nutrition);
- Triggering and promoting factors;
- Pharmaceutical triggers, as noted above;
- Other sleep disorders as underlying causes, such as other parasomnias, insomnia, RLS, OSA, etc.;
- Sleep deprivation;
- Fever.

8. Pathomechanism

8.1. Is SRED a Neuroendocrine Disorder?

There is evidence to suggest that neuroendocrine factors, including hormones like melatonin, cortisol, leptin, growth hormone and ghrelin, may play a role in NES [27–29]. Leptin, known as a satiation hormone, is one hormone that regulates appetite and energy balance. It signals to the brain when people have had enough to eat and should stop eating. Leptin has a physiological nocturnal rise that correlates with sleep onset [30]. Conversely, low leptin levels lead to increased hunger and a tendency to eat during the night. Previous studies have found that people with NES have lower leptin levels but a higher level of cortisol, compared to controls, during the night [27]. As a counterpart, ghrelin is a hormone produced in the stomach, which stimulates hunger. Ghrelin levels typically rise before meals and decrease after eating. The abnormal regulation of ghrelin could lead to increased hunger and night-time eating [28]. Orexins are hypothalamic neurotransmitters that play a key role in regulating the sleep–wake cycle, energy balance and appetite. They are lacking in patients with narcolepsy type 1 (NT1). The fact that SRED is frequent in NT1 [31] indicates that orexin may also play a role in SRED. It needs to be emphasized that most

previous studies were carried out in NES but not in patients with SRED, because of the lack of clear distinction between the two disorders [2]. Many cases that were formerly characterized as NES in previous studies investigating neuroendocrine factors may now be characterized as SRED [2]. Therefore, more data directly from SRED are needed to better understand the neuroendocrine basis of SRED in the future.

8.2. Is SRED a Specific form of NREM Parasomnia, as Currently Classified?

As mentioned above, SRED is currently classified as NREM arousal disorder parasomnia, based on (1) the presence of typical clinical symptoms, such as automatic behavior, complete or partial awareness, and unresponsiveness to external stimuli and amnesia regarding the event, (2) polysomnographic features of arousal disorders (episodes arising from NREM sleep, mostly deep slow-wave sleep, frequent abrupt arousal in deep-NREM sleep), and (3) the high prevalence of sleep walking in SRED. Within this framework, many clinical features can be conceptualized using a sleep–wake boundary dyscontrol. Impaired state boundaries will allow wake and sleep components to co-occur at the same time, resulting in a dissociation of otherwise well-separated vigilance states.

In NREM parasomnias, two principal factors lead to shifts in the balance of sleep–wake boundary control. Firstly, any factor that deepens NREM sleep (e.g., by sleep deprivation or medication) will enhance sleep inertia and override an otherwise normal arousal system. Under physiological conditions, complete wakefulness and full gain of consciousness is realized within seconds, after awakening from NREM sleep. In parasomnias, partial awakening and incomplete awareness is best explained by incomplete awakening, due to increased NREM sleep inertia. Additional impairment of the arousal system by hypnotic medication will further enhance the dysbalance of sleep–wake systems, and contribute to the failure of the brain to fully transit into complete wakefulness. Secondly, any increase in arousal frequency will raise the probability of the brain shifting to incomplete awakening. Therefore, any unspecific sleep fragmentation, e.g., by comorbid sleep disorders like RLS and OSA, or orexin deficiency in narcolepsy (which induces arousal instability), represents a potential source of manifest parasomnic episodes. Incomplete awakenings, in turn, lead to dissociation of brain functions. Imaging and electrophysiological data indicate that automated behavior results from a dissociation due to the wake-induced activation of motor pathways and sleep-induced deactivated frontal lobes [32,33]. A similar mechanism may underly amnesia, in that frontal association cortical areas are disengaged from hippocampal cortices [34].

Although these results are conclusive for NREM parasomnias, and it is tempting to adapt the same mechanisms for SRED, some questions remain unanswered; e.g., whether parasomnia is a necessary precondition of SRED. In fact, a recent review study [35] showed that in nine in-lab PSG studies that successfully recorded eating episodes in patients with SRED, only 30% of these episodes occurred during deep-NREM sleep, and three studies reported episodes occurring in REM sleep [5,15,17]. The partial or complete loss of awareness of eating is one of the criteria for the diagnosis of SRED. However, several studies [15,17] reported that their patients diagnosed with SRED were fully aware of their eating at night. Therefore, in some SRED cases, the hypothesis that amnesia is related to a parasomnic mechanism such as the dissociation of sleep–wake systems cannot be applied [34].

8.3. Is SRED a Movement Disorder Related to Dopaminergic Dysfunction, Similar to RLS?

Based on commonalities of SRED and RLS (see section above) a common pathophysiology involving dopaminergic pathways has been proposed. Previously, nocturnal eating has been considered as a compensatory behavior for prolonged wake periods. This would resemble the “killing time” strategy of insomnia patients, in response to prolonged wake time, rather than reflecting an underlying dopaminergic RLS-related dysfunction. However, a study comparing insomnia patients with RLS patients found more frequent SRED episodes in RLS patients, although prolonged nocturnal wake time was higher in insomnia

patients [5]. This suggests that nocturnal eating in RLS is not simply a passing-time behavior. The occurrence of PLM and RMMA in SRED patients is another link to a common dopaminergic dysfunction in both disorders, since both PLM and RMMA movement are mediated by dopaminergic mechanism. In polysomnographic studies, Vetrugno et al. found RMMA in most of the SRED patients (29 out of 35) [16], and Brion et al. observed a short latency to the first chewing movement in patients with SRED, compared to patients who had sleep walking [16]. Indeed, most chewing movements occurred within 1 min after sleep onset in patients with SRED.

As dopamine is known to mediate impulsive behavior, one could consider SRED and RLS as impulse-control disorders. The urge to move their legs reported by RLS patients resembles the urge to eat in SRED. Also, the co-occurrence of compulsive eating and compulsive nocturnal smoking in some patients would support this idea [36]. Dopaminergic dysfunction for the reward system has already been shown in patients with adiposity and overeating. PET imaging studies have demonstrated low striatal D2-receptor availability and a compensatory increase in nigrostriatal and mesolimbic dopaminergic (ML-DA) activity, accompanied by reduced frontal inhibition [37,38]. Reward-related circuits are not only active during wakefulness, but also during normal sleep, as demonstrated by direct recording from reward-related neurons in animals and by functional imaging in humans [39–42]. Sleep boosts neural representations of rewarded events compared to non-rewarded events, by giving a higher priority to reactivation during sleep [42]. In a case report, two SRED patients showed elevated scores for reward sensitivity and novelty seeking in specific psychometric inventories that have been associated with increased mesolimbic dopaminergic sensitivity [43]. However, systematic assessment of other key symptoms of impulse-control disorders, such as lack of premeditation, lack of perseverance, sensation seeking and urgency, have not been carried out yet in SRED patients with RLS. More research is needed to substantiate the role of the reward system in SRED.

It has even been discussed whether dopaminergic drugs themselves cause SRED in RLS patients [44]. Some of these drugs are prone to induce a severe dopamine dysregulation syndrome, leading to compulsive gambling, shopping, punding or hypersexuality [45]. Studies with dopaminergic drugs in SRED patients have shown inconsistent therapeutic effects [5,46], but did not report on aggravation of nocturnal eating or induction of a dopamine dysregulation syndrome. The therapeutic role of dopamine antagonists is not yet clear, since they have been shown to either increase or reduce food intake in animals [47], depending on the receptor subtype.

8.4. Is Amnestic SRED Caused by Medication?

It is well-accepted that medication, in particular benzodiazepine and Z-drugs, contributes to amnestic SRED. This has raised the question whether unspecific sedation, rather than SRED-related mechanisms themselves, cause amnesia. Irfan et al. argued that some patients already predisposed to nocturnal eating (such as RLS patients) will develop amnestic SRED when exposed to agents that suppress memory, as well as executive function [26]. Other studies reported that the clinical features of drug-induced SRED and primary SRED (i.e., patients without any comorbid sleep disorders or any possible causative medication) are different [48]. Patients with drug-induced SRED usually start SRED at an older age, with a significantly higher rate of total amnesia during most of their SRED episodes, a significantly lower rate of comorbidity of NES, and a significantly lower rate of history of other parasomnias such as sleepwalking, compared to patients with primary SRED. Therefore, hypnotic drug-induced SRED may be partially independent from the parasomnic mechanisms leading to primary SRED. Primary SRED definitely exists, but probably as a rare disorder. Komada et al. collected a case series of 30 primary-SRED patients without any other sleep disorders and without drug-induced SRED, across a relatively long period of 8 consecutive years, from 2003 to 2011 [48]. More objective pathophysiological measures are needed to better distinguish the differences between drug-induced SRED and primary SRED, in addition to the clinical features.

9. Management and Treatment

Treatment goals should be prioritized, together with the patients, taking the following aspects into account:

9.1. Initial Management Should Aim at Avoiding Harm to the Patient

Patients should be advised to create environmental safety, with simple measures. These includes reliably locking the kitchen or refrigerator door, and the use of time switches for stoves. Patients should remove knives and other potentially hazardous kitchen tools, and prevent access to food. More complicated are counter measures for avoiding injuries by ingesting non-palatable food.

9.2. Non-Pharmacological and Pharmacological Approaches

Pharmacological treatment recommendations for SRED are primarily based on a few small controlled trials, case series and case reports. In addition, analyzing the effect of medication on SRED remains rather difficult, due to comorbid disorders and incoherent targeted outcome measures (e.g., reducing the number of eating episodes, improving sleep continuity and daytime sleepiness, or achieving a loss in weight gain). Winkelman et al., in 2020 [49], published a placebo-controlled randomized clinical trial for the efficacy of topiramate, showing that "topiramate is an effective treatment of sleep-related eating in patients with SRED, predominantly in those with greater levels of impaired awareness and reduced memory for nocturnal eating." Limitations are the small study sample and the high drop-out rate. Side-effects were paresthesia, cognitive dysfunction and dysgeusia, and daytime sleepiness. Pharmacological studies in RLS patients using dopaminergic drugs have shown beneficial effect in a small case series (mostly with L-Dopa/Carbidopa plus codeine), with immediate and sustained effects on nocturnal eating [4]. A pilot study (n = 11) using low-dose pramipexole in a randomized, double-blind, placebo-controlled crossover study, failed to control nocturnal eating, although nocturnal activity monitored via actigraphy improved [46]. Whereas a randomized control trial shows sertraline to be useful as a treatment for NES, only a case study (n = 2) suggests low-dose sertraline to be successful in SRED [50,51]. Also, case reports using a combination of clonazepam and pramipexole (with triazolam dosage adjustments) or the use of ramelteon (results can be confounded, due to dosage adjustments and the inclusion of NES) were published [52,53]. Further studies on the treatment of SRED, targeting other sleep and metabolic systems, would be beneficial.

9.3. Treatment of Comorbidities and Reduction in Body Weight

Similarly important is the management of treatable underlying conditions such as other sleep disorders, eating disorders and psychiatric disorders. The psychosocial aspects of SRED should also be part of a comprehensive treatment plan: patient education, addressing the fear of not being in control of these nocturnal episodes, addressing fears of not being able to lose weight, showing the possibilities for weight reduction, a discussion of possible effects of the episodes on daytime performance, and other topics emerging from the patient. We identify a research gap in the treatment of SRED using non-pharmacological approaches, as there is no convincing evidence, such as studies with a randomized controlled trial design, in existence at the moment.

10. Conclusions

Sleep-related eating disorder is a relatively rare sleep condition, showing a multifactorial etiology, which needs careful clinical work-up of the underlying mechanisms. SRED is characterized by food ingestions during the sleep period, often with reduced consciousness and amnesia, showing features of a parasomnia. The differentiation of NES and SRED need to be evaluated in an interdisciplinary way. Diagnosis as currently defined according to ICSD-3 criteria carries the risk that SRED is considered as a homogenous disease. Clinicians should be aware that SRED is probably more heterogenous than previously thought.

SRED may represent a spectrum of diseases, ranging from primary SRED (without any recognizable comorbidity), to parasomnic SRED, SRED with prevailing comorbid sleep disorders, amnestic SRED induced by hypnotic drugs, and RLS-related SRED with a presumed dopaminergic dysfunction. Therapeutic management needs to be individualized, depending on the specific entity. Due to the potential implications of SRED on a patient's quality of life, further research and the development of valuable treatment options for all patient groups are warranted.

Author Contributions: Conceptualization, methodology, writing—original draft preparation, writing—review and editing, carried out by all three authors (N.Z., Z.Z. and R.K.); supervision by R.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created.

Acknowledgments: This study was supported by the Clinic Barmelweid Research Foundation.

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

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