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# Restless Nocturnal Eating: A Common Feature of Willis-Ekbom Syndrome (RLS)

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SCIENTIFIC INVESTIGATIONS

**Study Objectives:** To determine the frequency of nocturnal eating (NE) and sleep related eating disorder (SRED) in restless legs syndrome (RLS) versus psychophysiological insomnia (INS), and the relationship of these conditions with dopaminergic and sedative-hypnotic medications.

**Design:** Prospective case series.

**Setting:** Sleep disorders center.

**Patients:** Newly diagnosed RLS or INS.

**Intervention:** RLS or INS pharmacotherapy with systematic follow up interview for NE/SRED.

**Measurements and Results:** Patients presenting with RLS (n = 88) or INS (n = 42) were queried for the presence of NE and SRED. RLS patients described nocturnal eating (61%) and SRED (36%) more frequently than INS patients (12% and 0%; both p < 0.0001). These findings were not due to arousal frequency, as INS patients were more likely to have prolonged nightly awakenings (93%) than RLS patients (64%; p = 0.003). Among patients on sedative-hypnotics, amnestic SRED and sleepwalking were more common in the setting of RLS (80%) than INS (8%; p < 0.0001). Further, NE and SRED in RLS were not secondary to dopaminergic therapy, as RLS patients demonstrated a substantial drop (68% to 34%; p = 0.0026) in the frequency of NE after dopamine agents were initiated, and there were no cases of dopaminergic agents inducing novel NE or SRED.

**Conclusion:** NE is common in RLS and not due to frequent nocturnal awakenings or dopaminergic agents. Amnestic SRED occurs predominantly in the setting of RLS mistreatment with sedating agents. In light of previous reports, these findings suggest that nocturnal eating is a non-motor manifestation of RLS with several clinical implications discussed here.

**Keywords:** Nocturnal eating, sleep related eating disorder, restless legs syndrome, Willis-Ekbom Syndrome, psychophysiological insomnia, dopaminergic therapy, sedative-hypnotics, benzodiazepines/benzodiazepine receptor agonists

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Restless legs syndrome, or Willis-Ekbom Syndrome (labeled RLS), is characterized by an underlying discomfort, primarily in the lower extremities that compels the afflicted to move. These symptoms are relieved, although only momentarily, with movement and may interfere with sleep initiation or maintenance.[1]

RLS has been associated with non-motor phenomena. In particular, patients with RLS often describe other comorbidities such as mood and anxiety disorders,[2] as well as other nocturnal compulsions such as nocturnal smoking that interfere with sleep.[3] Further, patients with these non-motor manifestations of RLS have more severe motor restlessness as measured by the International RLS Rating Scale.[3]

Recently, an investigation demonstrated a high frequency of dysfunctional nocturnal eating (SRED) in patients with RLS. This community-based case-control study found that 33 of 100 RLS patients met criteria for SRED compared to only 1% of normal population controls.[4] The authors pondered whether SRED was related to underlying RLS brain pathology or whether it was merely "killing time" during prolonged nocturnal awakenings, as previously suggested.[5] Conversely it has been suggested SRED in RLS may be due to anti-RLS dopaminergic agents.[6,7]

Most investigations of nocturnal eating (NE; eating after an arousal from sleep, prior to terminal awakening) have focused upon SRED. However, we have noticed subtler non-dysfunctional forms of NE, commonly in the setting of RLS. Also, we have noted that many cases of zolpidem-induced SRED had been originally misdiagnosed as having psychophysiological insomnia (INS), a condition for which a benzodiazepine receptor agonist was prescribed, but later noted to have underlying motor restlessness as the cause of their sleep difficulties.

To establish whether NE is common in RLS and whether NE is a product of frequent nocturnal awakenings, we compared the frequency of NE as well as SRED among patients presenting with RLS and INS, a distinct condition of cognitive hypervigilance that manifests with frequent nocturnal awaken-

**BRIEF SUMMARY**

**Current Knowledge/Study Rationale:** This study compared the prevalence of NE and SRED in RLS to INS, a disorder with similar sleep disruption to determine whether nocturnal feeding behavior in RLS is merely "killing time." We then prospectively determined therapeutic response with dopaminergic and sedative medications.

**Study Impact:** TThis study expands the clinical manifestation of RLS to include restless eating and proves that NE and SRED can be relieved by dopaminergic therapy. Further this study suggests that other parasomnias (such as sleepwalking) may frequently be due to the mistreatment of RLS with sedative agents.

**Table 1**—RLS versus psychophysiological insomnia

| | RLS | INS | p value |
|---|---|---|---|
| Total patients | 88 | 42 | |
| Gender (F/M) | 63/25 | 23/19 | 0.075[1] |
| Age (mean) | 56.1 (CI = 2.67) | 52.9 (CI = 4.35) | 0.10[2] |
| BMI (mean) | 32.4 (CI = 1.67) | 28.2 (CI = 1.82) | 0.003[2] |
| # NE[3] | 54 (61%) | 5 (12%) | < 0.0001[1] |
| # SRED | 32 (36%) | 0 (0%) | < 0.0001[1] |
| # Pts who average at least one prolonged (> 5 min) nightly awakening | 56 (64%) | 39 (93%) | 0.0003[1] |

[1]Fisher exact test (2-sided). [2]Type 2 T-Test with 2 tails. [3]NE: both non-dysfunctional nocturnal eating and SRED.

**Table 2**—Prior sedative exposure

| | RLS | INS | |
|---|---|---|---|
| # Pts with exposure to benzodiazepine or BRA[1] | 15 | 25 | |
| # Pts with amnestic SRED or Sleepwalking on benzodiazepine or BRA | 12/15 (80%) | 2/25 (8%) | p < 0.0001[2] |

[1]Benzodiazepine receptor agonist. [2]Fisher exact test (two-sided).

**Table 3**—Amnestic NE and sedative[1] exposure

| | RLS NE+ | INS NE+ |
|---|---|---|
| # Of NE patients with recall data | 41 | 4 |
| # Of pts with complete or partial amnesia | 23 (56%) | 0 (0%) |
| Partial amnesia | 7 | 0 |
| # On sedative (%) | 2/7 (29%) | N/A |
| Complete amnesia | 16 | 0 |
| # On sedative (%) | 13/16 (81%) | N/A |
| # Without any amnesia | 18 (44%) | 4 (100%) |
| # On sedative (%) | 1/18 (6%) | 2/4 (50%) |

[1]Benzodiazepine or BRA (only one RLS patient was exposed to a benzodiazepine alone without a BRA).

ings. Moreover, we reviewed prior sedative-hypnotic exposure, either benzodiazepines or benzodiazepine receptor agonists, to determine whether RLS patients were more likely to manifest amnestic SRED or other sleepwalking behaviors than patients with INS. Finally, we followed RLS patients prospectively to evaluate the effect of dopaminergic agents on NE and SRED.

## METHODS

Consecutive adult patients who presented to the University of Minnesota Medical Center, Sleep Disorders Center or the Minnesota Regional Sleep Disorders Center with a complaint of difficulty sleeping were screened for either RLS or INS. All patients completed a 9-page comprehensive sleep questionnaire that evaluated sleep and circadian rhythm phenomena, in addition to surveying for medical comorbidities and neuropsychiatric disease. Current and past medications were documented. One investigator (MJH) performed all clinical evaluations, using a structured interview and examination. ICSD-2 criteria were used to diagnose both RLS and INS.[1] Patients were excluded if they met criteria for both syndromes or if they had other causes of sleep initiation or maintenance failure. The most common disorder of exclusion was Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type.

Once diagnosed with either RLS or INS, using a structured 1-page nocturnal eating questionnaire, patients were queried about the frequency and characterization of both nocturnal arousals and nocturnal eating. A prolonged nocturnal arousal was defined as lasting > 5 minutes. Previous exposure to dopaminergic or sedative-hypnotic medication was specifically asked and documented.

A patient was considered to have NE if they admitted to nocturnal eating at least once a month; inquiries were subsequently made into whether the feeding behavior was dysfunctional. SRED was diagnosed if recurrent nocturnal eating was present with one or more of the following criteria: (1) ingestion of unusual or inedible substances, (2) difficulty falling back asleep or nonrestorative sleep, (3) sleep related injury or potentially injurious behaviors, (4) morning anorexia, (5) or adverse health consequences.[1]

If NE was present, the food types and subjective nature of the feeding episodes were documented. In particular, the patient's hunger, memory, and control of NE were all quantified. Bed partner report, if available, was also gathered. Further, RLS NE patients were asked whether they had restlessness symptoms at the time of the NE.

Both RLS and INS patients were then treated in a standardized fashion and followed prospectively. The patients sleep initiation and maintenance symptoms, restlessness, as well as NE and SRED were serially evaluated with a structured follow-up interview.

## RESULTS

RLS patients were overwhelmingly more likely to demonstrate NE and SRED than patients with INS, despite being less likely to have prolonged nocturnal awakenings (**Table 1**). Further, patients with RLS were far more likely to have amnestic SRED or sleepwalking when exposed to sedative-hypnotics than patients with INS (**Tables 2, 3**). Examples of other parasomnia behaviors among RLS but not INS patients on sedating agents included amnestic sexual behavior and smoking.

Of the 12 RLS patients with sedative-induced SRED or sleepwalking, all had previously been misdiagnosed and treated as having insomnia. Eleven of the 12 discontinued BRA once the diagnosis of RLS was made. All 11 patients described a cessation of amnestic nocturnal events after stopping the BRA, with complete elimination of NE in 3 patients, while the remaining 8 patients had persisting wakeful NE that was subsequently responsive to dopaminergic therapy (see dopaminergic treatment below). Conversely, in most patients with INS, treatment (either CBT-I or sedative-hypnotic) was well tolerated. Only 2 INS patients had a report of BRA induced amnestic behavior, both isolated to one event, and are still on sedative-hypnotics.

Hunger data were available on 35 RLS patients with NE. Only 31% of these patients described hunger prior to the nocturnal feeding behaviors. Patients often described that they had

an urge to eat that prevented them from falling asleep, but once food was ingested, sleep was reinitiated. Conversely, of the 3 INS patients for whom hunger data were available, 2 described hunger as a predominant driver for NE.

Among the RLS patients, gender was evenly distributed between NE+ and NE- patients, and there were non-statistically significant differences in age, BMI, and ferritin levels. RLS patients who were NE were more likely to report prolonged nightly awakenings than RLS patients who were not NE (**Table 4**).

Prospective therapy data indicates that NE is reduced by correction of RLS with dopaminergic agents (**Tables 5, 6**). Several different classes of RLS therapies were used, including gabaergics and opiods, but dopaminergic treatment data were available on 44 patients. A striking reduction of both NE (30/44 to 15/44; p = 0.0026) and SRED (18/44 to 9/44; p = 0.063) was noted, and only one patient had a worsening of NE. Among RLS patients without NE there were no reports of *de novo* NE once dopaminergics were started. Among INS patients, 1 of the 2 patients with NE continued to have nondysfunctional NE after treatment with zolpidem. There were no *de novo* reports of NE among INS patients once pharmacotherapy was started.

Among RLS patients who had resolution of motor symptoms, all NE ceased as well. Only patients who continued to have motor symptoms also continued to have NE. Several of the patients (6/9) who described no improvement in NE were unable to tolerate dopaminergic therapy. Nausea and impulsive (non-eating) behaviors such as online shopping and excessive ethanol ingestion were cited as reasons dopaminergic treatment was discontinued.

## DISCUSSION

*"They often have to get up and walk, 'like a caged bear,' to quote one of my patients, or they go into the kitchen and get something to eat."*—Karl-Axel Ekbom, *Neurology*, 1960

This study augments previous reports, including Ekbom's seminal 1960 publication,[8] that NE is pervasive among patients with RLS (see quote above). Further, we have demonstrated that NE is not merely "killing time" as previously suggested,[5] because patients with INS were more likely to have prolonged nightly awakenings than patients with RLS but less likely to have NE. As expected, amnestic SRED was common in the setting of sedative-hypnotic use among RLS patients but not INS patients. Finally, our prospective data demonstrate that contrary to previous speculation, dopaminergic agents improve NE and SRED in RLS.

This study and a critical review of the literature suggest an intimate relationship between NE and RLS. Here the evidence and implications of such a relationship is presented.

### Epidemiology of NE/SRED and RLS

RLS is a disorder affecting approximately 8% to 10% of the population and thus a common cause of sleep initiation and maintenance failure.[1,9,10] Both RLS and SRED are more common in women.[1,9,11,12]

While our study demonstrated the high frequency of NE in RLS, RLS has been commonly noted among patients with SRED.[13-15] This finding has been particularly profound among patients with medication-induced SRED.[16-21] In fact, even among SRED cases where RLS frequency was not addressed, there is a peculiar incidence of conditions frequently comorbid with RLS, such as Parkinson disease[22] and narcolepsy.[23]

Like nondysfunctional nocturnal eating (a non-pathological variation of SRED), RLS may be mild or only minimally interfering with sleep onset. Further, RLS sensations are often difficult for patients to define, and current symptomatic criteria are not easily translated between languages. Moreover, the pervasive use of opioid and gabaergic agents may intermittently mask symptoms, and thus RLS may go unrecognized during routine clinical evaluation.[24] While these drugs suppress motor symptoms, they may be taken without the ideal timing or dosing needed to optimize sleep maintenance, allowing for breakthrough nocturnal phenomena such as NE. Thus, the actual prevalence of the RLS clinical spectrum is likely larger than current estimates. These findings bear special significance for the obesity pandemic since according to this study and others,[4] the majority of RLS patients have NE, and more than a third have SRED.

**Table 4**—RLS NE+ versus RLS NE-

| | NE+ | NE- | p value |
|---|---|---|---|
| Total Patients | 54 | 34 | |
| Gender (F/M) | 39/15 | 24/10 | 1.00[1] |
| Age (mean) | 55.1 (CI = 2.85) | 57.5 (CI = 5.24) | 0.40[2] |
| BMI (mean) | 33.1 (CI = 2.33) | 31.3 (CI = 2.23) | 0.30[2] |
| Ferritin (mean) | 94.9 (CI = 30.2) | 68.8 (CI = 32) | 0.37[2] |
| # Pts who average at least one prolonged (> 5 min) nightly awakening | 39 (72%) | 17 (50%) | 0.043[1] |

[1]Fisher exact test (2-sided). [2]Type 2 T-Test with 2 tails.

**Table 5**—Targeted pharmacology data

| | RLS | | | INS | | |
|---|---|---|---|---|---|---|
| # Of pts with pharmacological treatment data | 44 | | | 25 | | |
| Pharmacotherapy | Dopaminergics[1] | | | Benzodiazepines or BRA[2] | | |
| Average duration of follow-up | 11.8 months | | | 6 months | | |
| | Pre Rx | Post Rx | p value | Pre Rx | Post Rx | p Value |
| # (%) Pt with NE[1] | 30 (68%) | 15 (34%) | 0.0026 | 2 (8%) | 1 (4%) | 1.000 |
| # (%) pt with SRED | 18 (41%) | 9 (20%) | 0.063 | 0 (0%) | 0 (0%) | NA |

[1]Pramipexole, ropinirole, or carbidopa/levodopa. [2]Benzodiazepine receptor agonists: either zolpidem or eszopiclone. [3]NE: Defined as nocturnal eating > than once a month.

**Table 6**—Dopaminergic treatment and NE

| | |
|---|---|
| Total # of RLS Pt with dopaminergic treatment data | 44 |
| PRE-TREATMENT | |
| # NE | 30 (68%) |
| # SRED | 18 (41%) |
| # of Non-NE | 14 (32%) |
| POST-TREATMENT | |
| NE RLS Pts | |
| # with 100% resolved NE | 15 (50%) |
| # with 75%-99% reduction NE frequency | 5 (17%) |
| # with < 75% reduction or no change in NE frequency | 9 (30%) |
| # with exacerbation of NE | 1 (3%) |
| SRED RLS Pts | |
| # with 100% resolved SRED | 9 (50%) |
| # with 75%-99% reduction NE frequency | 3 (17%) |
| # with < 75% reduction or no change in NE frequency | 5 (28%) |
| # with exacerbation of NE | 1 (6%) |
| Non-NE RLS Pts | |
| # who developed NE on treatment | 0 (0%) |

## Similarities in Clinical Course

Intriguingly, the compulsive nature of NE strikingly resembles the underlying RLS feeling (often poorly described) of discomfort in the lower extremities that compels movement. Motor activity relieves the discomfort, and sleep is unable to be reinitiated until this urge is addressed.[1] Several of our patients described a premonition that eating would assist in the promotion of sleep. One compelling example was a 73-year-old female with a longstanding history of RLS who noticed that eating cookies would allow for sleep to be reinitiated. Interestingly, this behavior was noted in her mother who also suffered from RLS.

Previous reports of SRED noted that patients described a compulsion to eat, without hunger, which interfered with sleep maintenance. Once food was ingested, the feeling abated and sleep was able to be reinitiated.[1,4,13] A more recent case noted a 74-year-old woman who originally presented 20 years prior with uncontrollable RLS and SRED. Both the nocturnal eating and RLS were well controlled with various combinations of opioids and dopaminergics. Then with the eruption of a right lower extremity zoster, the patient had a relapse of both RLS (bilateral motor symptoms) as well as distressful nocturnal eating leading to weight gain. Compellingly, the RLS and SRED resolved in parallel with the resolution of skin lesions. Medications were not adjusted in the period immediately prior to, during, or after the zoster event.[20]

## Amnestic SRED is Predominantly Mistreatment of RLS as INS

The majority of patients in the original SRED series, where NE behaviors were predominantly amnestic, were taking sedative-hypnotic medication.[13] Conversely, in a later series of 26 patients with full consciousness during nocturnal eating, all were sedative free,[15] prompting the suggestion that amnesia in SRED is predominantly medication induced.[25] Our investigation helps confirm that amnestic SRED is unusual in the absence of sedative-hypnotic medication (**Table 3**).

Further, our study demonstrates that among RLS patients NE is pervasive (61%). Conceptually, if RLS patients are predisposed for NE, then amnestic SRED would be the expected result when treated with agents that suppress memory as well as executive function. Thus it was not a surprise that 80% of our RLS patients who had previously been exposed to sedative-hypnotics had a history of amnestic SRED or other sleepwalking behavior (**Table 2**).

Nearly all of the sedative exposures that induced amnestic NE were from BRA. Only one RLS patient, who also incidentally had fully conscious NE without sedation, had fully amnestic NE induced by a benzodiazepine (clonazepam). These findings are of particular relevance, as benzodiazepines are occasionally prescribed for the treatment of RLS. Further investigations are needed to evaluate the frequency by which benzodiazepines may induce amnestic NE among patients with RLS.

While RLS is a condition distinct from INS, it can be easily misdiagnosed and thus mistreated as INS. In 2002, the first case series of 5 patients with zolpidem-induced amnestic SRED was reported. Incidentally, all 5 patients were noted to have RLS.[16] Others have commented that RLS appears to be ubiquitous in the setting of zolpidem-induced SRED.[21] In fact, we are unaware of any zolpidem-induced SRED report where RLS was explicitly considered and subsequently not discovered.[16-21]

Tellingly, NE (both conscious and amnestic) among our INS patients was rare (**Table 3**). Among our 25 INS patients treated with either a benzodiazepine or benzodiazepine receptor agonist, only 2 reported amnestic behavior. One patient described a prolonged SW event during which she left her home and vandalized an apartment complex with spray paint. Another patient described one episode of amnestic nocturnal eating 5 years prior. Both patients claimed that the events never recurred and are still on sedating medications. Prospectively, there have been no reports of amnestic behaviors among INS patients treated with sedative-hypnotics after an average treatment follow-up of 6 months.

These findings are consistent with previous reports where SRED, sleepwalking, and other complex sleep behaviors are rare (1% or less) in zolpidem-treated INS patients when RLS has been carefully excluded.[26] Thus we conclude that in the absence of motor restlessness, sedative-hypnotics are safe agents for INS.

Intriguingly, among the 5 NE positive INS patients in this study, 2 reported a history consistent with atypical RLS. One patient described a family history of RLS as well as her own remote history of motor restlessness from several years prior. The other INS patient reported a need to ambulate around the bedroom in order to "cool off" from the heat of his cancer-related night sweats.

## Other Non-Motor Compulsions in RLS

Compulsive nocturnal eating is not unexpected as investigators have described other non-motor nocturnal urges. Among 6 patients with NE and nocturnal smoking, 5 were noted to have RLS. These patients claimed that they would wake up and be unable to return to sleep without eating and/or smoking.[27] In a follow-up study looking for sleep-related smoking among RLS patients there was a six-fold higher prevalence than among matched controls (12% versus 2%). Interestingly, among RLS patients with nocturnal smoking, SRED was common (83%), and both phenomena began simultaneously. In our study, consistent with these findings, pa-

tients with NE often described that NE developed in concert with motor restlessness.

Non-motor manifestations of RLS have more severe motor restlessness as measured by the International RLS Rating Scale.[3] We noted that RLS patients with NE were more likely to have more frequent awakenings than RLS patients without NE (**Table 4**), consistent with the suggestion that non-motor manifestations of RLS are markers of more severe disease.

While we did not formally survey for nocturnal smoking, 3 RLS patients (all with NE or SRED) volunteered that they smoked on a nightly basis after an arousal from sleep. All 3 stated that the urge to smoke was different from daytime smoking urges in that they felt a profound sense the smoking was necessary to reinitiate sleep. This is not unexpected as cigarette smoking results in modulation of CNS dopamine activity,[28] and thus may be therapeutic in RLS. None of our patients with INS reported nocturnal smoking behaviors.

Intriguingly 2 of our patients with RLS and NE described other nocturnal compulsive behaviors. The first patient reported that in parallel to her RLS symptoms, she had the peculiar urge to pick off her toenail polish; the second needed to look up bits of geographic trivia on the internet. These behaviors were not present during the daytime and occurred in parallel to motor restlessness. After several minutes of toenail polish picking or, for example, identifying the location of an island off the coast of Texas, they were able to fall back asleep. The first patient had noticed that all nocturnal compulsions abated with opioid therapy and the second with dopaminergics. We suspect that more thorough investigations of RLS patients will reveal other nocturnal compulsive behaviors.

## NE/SRED in RLS Is Relieved by and Not Caused by Dopaminergic Agents

Similar to RLS,[1] NE and SRED are related to dysfunction in the CNS dopamine circuits. Dopamine mediates behaviors such as motor restlessness, smoking, and binge eating.[1,29] A polysomnography (PSG) study of 35 SRED patients demonstrated that 77% had PSG confirmation of wakeful RLS and periodic limb movements (PLM) during sleep.[15] Further, rhythmic masticatory muscle activity (RMMA) and bruxism are dopaminergic phenomena[15,30] associated with RLS[31] and commonly seen in SRED.[13,15]

It has been suggested that nocturnal eating in RLS patients may be caused by dopaminergic agents as these agents are known to trigger impulsive behaviors such as gambling.[6,7] Conversely, dopamine agents suppress feeding behavior in animal models.[32]

This report, following up previous investigations, provides strong evidence that dopaminergic agents help treat, and are not the cause of NE. A review of the original SRED series noted that dopaminergic therapy resolved the dysfunctional eating in 7 of 8 patients in whom the treatment was attempted.[13] Later, 2 cases of SRED were noted to resolve with levodopa (in combination with buproprion and trazodone).[33] In a separate survey of patients with both SRED and RLS, 10 reported that NE emerged prior to or concomitant with motor restlessness, and none reported that nocturnal eating emerged after the start of dopaminergic therapy. Also, RLS patients with SRED were not significantly more likely to use dopaminergic drugs than RLS patients without SRED. In fact, subjects whose nocturnal eating symptoms were under control were more likely to be on these agents than subjects who continued to have nocturnal eating.[4] Further, a double-blind treatment trial of pramipexole for SRED demonstrated improved sleep and reduced nighttime activity, although, admittedly, nocturnal eating ingestions were not reduced in this small study.[34]

In the series published here, we monitored therapy outcome in 44 RLS patients previously unexposed to dopaminergics with and without NE. In this population, the frequency of both NE (68% to 34%; $p = 0.0026$) and SRED (41% to 20%; $p = 0.063$) diminished by half with dopaminergics. Further, only one patient reported an exacerbation of NE after dopamine agents were initiated, and there were no cases of dopaminergics inducing *de novo* NE (**Tables 5, 6**).

Tellingly, our patients frequently noted a resolution of NE in parallel to resolution of RLS motor symptoms. One example was of a 63-year-old male who described a 10-year history of motor restlessness along with compulsive nocturnal eating that had resulted in weight gain. Both phenomena interfered with sleep onset and maintenance, and both had responded to 0.5 mg of pramipexole; however, augmentation became a problem, and dosages were increased to 3 mg. During periods of breakthrough motor symptomatology, he noted a greater frequency of nocturnal eating with subsequent weight gain. Gabapentin was added but provided only modest additional benefit, and he eventually failed both pramipexole and ropinerole due to augmentation and what he described as distressing sexual urges. He was subsequently treated with methadone 10 mg, which he states permanently resolved the motor restlessness and nocturnal eating.

Importantly, no patients with resolution of motor symptoms on dopaminergic agents had a persistence of NE.

Finally, treatment with dopaminergic agents appears to improve other non-motor manifestations of RLS. In a previous report, all RLS patients who had resolved nocturnal smoking had been treated with dopaminergic agonists.[3] One of our RLS patients with nocturnal smoking was started on dopaminergics and reported a resolution of nocturnal, although not daytime smoking (the other 2 nocturnal smoking patients noted above were lost to follow-up).

## Is RLS a Link between SRED and the Night Eating Syndrome (NES)?

A statement is necessary regarding the potential implication that these findings have to either unify or further distinguish the two major conditions of dysfunctional eating during the main sleep period. There are notable similarities and distinctions between NES (not to be confused with NE) and SRED. Both share a chronic course, familial associations, comorbid neuropsychiatric disease, and are frequently associated with weight gain and obesity.[35] Investigations have suggested that NES is a circadian delay in meal timing resulting in evening hyperphagia, with or without nocturnal eating, and morning anorexia. NES is currently diagnosed if 25% of food intake is consumed after the evening meal (evening hyperphagia) and/or there are at least 2 episodes of nocturnal eating per week with clinical consequences.[36]

SRED has historically been distinguished from NES by amnestic eating alone without evening hyperphagia. However, changes in the definition of SRED[1] expanded SRED to include non-amnestic eating increasing the overlap between these 2 conditions. Thus at this point, the only feeding behavior that is

**Table 7**—The relationship between NE/SRED and RLS

1. Nocturnal eating is pervasive among patients with RLS
   - Noted in Ekbom's 1960 description.
   - Not merely "killing time" as patients with other causes of fragmented sleep rarely break the nocturnal fast.
2. Dysfunctional nocturnal eating (SRED) is common in patients with RLS.
3. RLS is nearly ubiquitous in cases of SRED.
   - Every SRED report in which RLS was explicitly considered, RLS was found
4. In most cases of sedative induced SRED the underlying disorder for which the sedative was originally prescribed was not INS, but instead RLS, a condition that is easily confused with INS.
   - Based on the findings of frequent NE in RLS, sedative-hypnotic medications, which suppress memory and executive function, would be expected to disinhibit amnestic SRED.
   - The rise of amnestic SRED reports parallels the widespread use of benzodiazepine receptor agonist use.
   - SRED is rarely noted when patients with underlying motor restlessness excluded from benzodiazepine receptor agonist treatment.
5. The compulsive nature of NE is similar in character to the motor manifestations of RLS, as they frequently arise, intensify, and subside in parallel.
   - Non-motor manifestations of RLS such as NE indicate more severe disease.
6. Polysomnographic studies demonstrate PLMs, RMMA, and bruxism in SRED. These phenomena are frequently noted in RLS and like RLS are associated with dopaminergic dysfunction.
7. Dopaminergic treatments for RLS improve, rather than exacerbate nocturnal eating and SRED.

**Table 8**—The implications of a NE as a non-motor manifestation of RLS

1. Diagnostic implications
   a. Helps distinguish RLS from other similar conditions of sleep initiation and maintenance failure.
      - Improves diagnosis across languages:
        - Subjective motor urges are often difficult to translate. Conversely, "Do you get up and eat at night?" is relatively simple.
   b. Suggests that cases of sedative-hypnotic induced complex behaviors (not only nocturnal eating) should be carefully scrutinized for RLS.
2. Therapeutic Implications
   a. The presence of NE with RLS should be an indication, not contraindication for dopaminergic treatment.
   b. RLS with NE indicates more severe disease and suggests the need for expedited treatment.
   c. In the setting of INS the risk of sedative-hypnotic induced complex behavior is low.
3. Considering the widespread prevalence of RLS these findings suggest that NE/SRED may be a pervasive but reversible cause of weight gain.
4. Further support for a change in RLS nomenclature to Willis-Ekbom Syndrome. A goal of the International Restless Legs Syndrome Study Group and RLS patient groups.

undisputably labelled SRED by eating disorder investigators is unconscious or partially conscious nocturnal eating, which as we have demonstrated, appears to predominantly occur in the setting of sedative-hypnotic medications prescribed for RLS. Thus it is plausible that the most *"pure SRED"* cases are in fact related to adverse events from medication misapplications. This hypothesis can be tested in prospective studies.

The purported pathophysiological mechanisms of both NES and SRED are similar and complementary. NES is attributed to an abnormality in the circadian timing of caloric intake relative to sleep, while SRED has been characterized as a breakdown in nocturnal fasting mechanisms.[35,36] Of course, these explanations are not mutually exclusive, and in this regard the high frequency of NE in RLS may, in fact, explain the circadian hypothesis of NES. RLS symptoms, both motor and non-motor, have circadian fluctuations, which reach a symptomatic crescendo during the late evening in parallel with the abnormal nighttime feeding in NES.[24,37] Only one study has looked into the incidence of both conditions among RLS patients and noted that compared to SRED (33%), NES was rare (3%).[4] However, this study utilized a now outdated definition of NES, excluding many NES patients under the revised criteria, particularly those whose predominant feature would be nocturnal eating.[38] One notable study[39] investigated NES patients with PSG and demonstrated an increased number of awakenings and reduced sleep duration, suggesting an underlying sleep disrupting process. No comment was made regarding the presence or absence of RLS or periodic limb movements.

While we did not specifically survey for NES (i.e., did not systematically question about or quantitate evening hyperphagia), several of our RLS patients described evening hyperphagia, suggesting that these patients could also be given the diagnosis of NES. In fact, many of our RLS patients who reported evening hyperphagia did not have NE. Persuasively, these patients were more likely to have RLS symptoms limited to the evening, interfering with sleep initiation but not sleep maintenance.

Clearly further investigations of are needed in patients with abnormal nocturnal eating. Ecological momentary assessment (EMA), a method where a portable electronic device periodicially surveys appetite, food intake, sleep perception, and other symptoms, is an elegant method of evaluating circadian phenomena. EMA has been used by NES investigators[40] and would be ideal for considering whether patients with SRED have evening hyperphagia and morning anorexia or whether NES patients have motor restlessness of RLS.

We speculate that NES and SRED may, in fact, be a unitary disorder, with restless nighttime eating existing on a spectrum and being interpreted differently by separate clinical fields. Regardless, collaborative investigations between sleep and eating disorder specialists will either unify these currently disparate disorders or with greater insight demonstrate fundamentally distinct pathologies. Engagement between collaborators will help reach the ultimate goal of identifying proper diagnoses and effective therapy for all patients.

## Limitations and Future Directions

Clinical investigations of disorders with symptomatic criteria such as RLS and INS are heavily dependent upon self-report. In the future more objective measurements such as with polysomnography for periodic limb movements, or EMA for diurnal variations in motor and non-motor phenomena, are needed to further define the relationship between RLS and nocturnal eating.

RLS is a common, diverse disorder with many associations such as renal disease, iron deficiency, neuropathy, and pregnancy. RLS may be further subtyped according to age of onset,

family history, and treatment response. This study was not large enough to distinguish the prevalence of NE or SRED among these various subgroups. Future investigations are needed to help distinguish which RLS patients are at the highest risk for NE and SRED. These discoveries would be of particular therapeutic relevance, as benzodiazepines, which could potentially induce amnestic SRED, are often used in the treatment of RLS.

## CONCLUSION

The evidence listed in **Table 7** suggests that NE is often a non-motor manifestation of RLS and that mistreatment of RLS as INS is a crucial step in the pathogenesis of drug-induced SRED cases. The implications of establishing NE as a RLS symptom are then listed in **Table 8**.

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## DISCLOSURE STATEMENT

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