Restless Legs Syndrome: A Review from Causation to Cure

By

Mustafizur Rahman
19146023

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

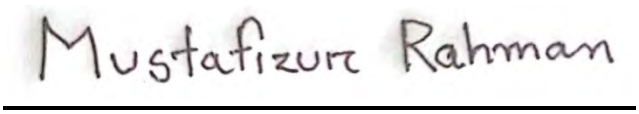
School of Pharmacy
BRAC University

February 2023

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.



Mustafizur Rahman
19146023

Approval

The thesis/project titled “Restless Legs Syndrome: A Review from Causation to Cure” submitted by Mustafizur Rahman (19146023) of Spring 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Faruque Azam

Lecturer

School of Pharmacy

BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin

Program Director and Assistant Dean

School of Pharmacy

BRAC University

Dean:

Professor Dr. Eva Rahman Kabir

Dean

School of Pharmacy

BRAC University

Ethics Statement

This study comprises no human or animal trial.

Abstract

Restless legs Syndrome (RLS) is a common neurological disorder which manifests as an urge to move the legs when at rest. The disease is often misdiagnosed due to its low recognition and patient's difficulty to explain their symptoms. The exact mechanism in which the disease develops is still unknown and the pathogenesis is based on different hypothesis. A universal treatment plan for this disease is also unknown and every patient needs individualized treatment depending on their condition. Different conditions have been proved to be associated with this disease such as, Iron Deficiency Anemia, Diabetes Mellitus and End Stage Renal Disease. This review article emphasizes on the pathogenesis of the disease based on different hypothesis. It also establishes connection between this disease and other conditions. Lastly, it provides individualized treatment plans for each category of patients based on evidence.

Keywords: Restless Legs Syndrome, Pathogenesis, Treatment

Dedication

This review article is dedicated to my beloved parents.

Acknowledgement

All praises to Almighty Allah for giving me the ability and power to accomplish this project.

I would like to thank my honorable thesis supervisor, Faruque Azam, Lecturer, School of Pharmacy without whom I would not be able to accomplish this project. His guidance and support have helped to come up with new ideas to fulfill this project and I am forever grateful to him.

My respect and gratitude to the Honorary Dean of the School of Pharmacy, Professor Dr. Eva Rahman Kabir as well as the Honorary Program Director of the School of Pharmacy, Professor Dr. Hasina Yasmin who has supported me throughout the entire journey to an undergraduate degree.

Lastly, I am thankful to my parents who has raised me up with their utmost care and love.

Table of Contents

List of Tables

List of Acronyms

RLS	Restless Legs Syndrome
HRQOL	Health Related Quality of Life
DA	Dopamine Agonists
PD	Parkinson's Disease
CKD	Chronic Kidney Disease
BMI	Body Mass Index
ESRD	End Stage Renal Disease
CSF	Cerebrospinal Fluid
AASM	American Academy of Sleep Medicine
IRLSSG	International Restless Legs Syndrome Study Group
DAT	Dopamine Transporter
SPCET	Single-Photon Emission Computerized Tomography
PET	Positron Emission Tomography
PLMS	Periodic Leg Movements in Sleep
EDS	Excessive Day Time Sleepiness
MRI	Magnetic Resonance Imaging

Chapter 1

Introduction

1.1 Background

The symptoms of RLS include an urge to move in order to alleviate the painful feelings, most often while sitting or while trying to sleep. This urge may be relieved by walking, stretching or even just shifting position slightly. The patients always describe the unpleasant sensations as creeping, crawling, tingling, pulling or painful deep inside the limbs (Trenkwalder et al., 2005). These unpleasant sensations can occur unilaterally or bilaterally with the knees, the ankles, or even the whole lower limbs (Trenkwalder et al., 2005). The patient's ability to sleep is often disrupted as a result. When a patient has RLS and seeks consultation in clinical practice, the most frequent complaint they have is that they cannot sleep (Mohri et al., 2008). It has a pronounced circadian rhythm, which manifests as a worsening of symptoms in the evening and a brief remission in the morning shortly after waking up (C. Kushida et al., 2007). If the condition is allowed to progress for a longer period of time, it is more probable that the symptoms may spread to other parts of the body such as, the arms, rather than only the legs. It is not unheard of for individuals to acquire arm restless syndrome in conjunction with the progression of illness (Freedom & Merchut, 2003). Movements such as, walking, stretching or bending the legs provides at least temporary and partial relief from the soreness (Trenkwalder et al., 2005).

The degree to which Health Related Quality of Life (HRQOL) is negatively impacted by RLS is directly proportional to the severity of the patient's symptoms. The 36-Item Short Form Health Survey (SF-36), which measures HRQOL, is a survey that has 36 questions and is used to generate eight scales related to physical and mental health as well as health transition (Guo et al., 2017). The majority of patients present with fairly moderate symptoms; only 11.9% of those individuals seek

medical attention and only around 3.4% of all patients need medication therapy (W. Hening, 2004). The most significant morbidities, apart from intense pain, were a loss of sleep and a disruption of routine activities (Trenkwalder et al., 2005). Patients who presented with mild or moderate symptoms reported experiencing pain less often, with a lower intensity, and with the symptoms having less of an impact on their ability to sleep. When compared to the general population, individuals who reported having severe or very severe RLS symptoms invariably indicated obvious deficiencies in various parameters (Trenkwalder et al., 2005). Patients who are seriously impacted may complain of having problems with their everyday lives, including their employment and their social activities. This might be because they are not getting enough sleep at night (C. A. Kushida, 2007). The quantity and quality of sleep as well as daytime alertness may all play a role in the development of sadness and anxiety (Stevens, 2015).

Patients with primary RLS are those who do not have any underlying ailment that may explain the reported symptoms. This kind of RLS is the most frequent form of the condition (Symvoulakis et al., 2010). This shows that there is a genetic tendency for RLS, since around 6 out of every 10 of these individuals have a family history of the condition (Montplaisir et al., 1997). Once it begins, it is often a disorder that lasts a person's whole life but may progress clinically in a variety of ways (Allen et al., 2003; Rodrigues et al., 2009). Those who are afflicted by RLS at a younger age are more likely to have a history of the illness in their families than those who are affected at an older age (Winkelmann et al., 2000).

The term secondary form of RLS refers to RLS that is caused by certain medical circumstances. RLS may first manifest itself during pregnancy or may become more severe as a result of this condition (Symvoulakis et al., 2010). In research that included 500 pregnant women, 19% of the women had

this disease (Chapman et al., 1988). This is a very harmless type of RLS, which often reaches its worst symptoms during the third trimester of pregnancy and has a propensity to go away following delivery (Manconi et al., 2004). RLS has been linked to inadequate iron storage on many occasions (Symvoulakis et al., 2010). According to the findings of certain studies, a serum ferritin level that is lower than 50 mcg/l may be associated with a more severe manifestation of RLS symptoms. The symptoms show signs of improvement after treatment with iron replacement therapy (Aul et al., 1998; Sun et al., 1998). In addition, people with renal disease are often afflicted by this condition (Gigli et al., 2004; Goffredo Filho et al., 2003; Winkelman et al., 1996). It has been found that the prevalence of RLS in this group of patients varies anywhere from 20% to 57% (Symvoulakis et al., 2010). RLS may go into remission in some patients after they get a kidney donation (Yasuda et al., 1986). Researchers discovered that roughly 30% of the individuals in their cohort who had polyneuropathy also suffered from RLS. The majority of the RLS patients presented with a condition known as small fiber sensory neuropathy (Gemignani et al., 2006). There is evidence that some drugs, such as, tricyclic antidepressants, selective serotonin reuptake inhibitors, lithium, dopamine antagonists and caffeine may make RLS symptoms worse or cause them for the first time (Symvoulakis et al., 2010).

1.2 Epidemiology

The prevalence of RLS has been estimated to fall anywhere between 5% and 10% among populations of Caucasians, particularly those of European and North American descent, although the frequency is lower in Asian nations. However, if only clinically significant RLS is included (i.e., occurring one to two times per week and causing moderate to severe discomfort), a prevalence of 2% to 3% is recorded. Notable fact is that the prevalence of the disease is twice as high in women as it is in men, and that older individuals are more likely to be affected by the disease than children and adults: the

prevalence of the disease grows up to 60–70 years of age (Allen et al., 2005; Ito & Inoue, 2015).

Although children are less likely to be affected, RLS does occur in children, and its frequency is believed to be somewhere around 2% in the pediatric population. It might be difficult to describe the symptoms of RLS in younger children, which can lead to the condition being underreported. RLS is more common in school-aged children and teenagers (2–4)%, who are more likely to display clinically severe RLS. As a result, RLS is most prevalent in this age group (Ito & Inoue, 2015; Picchietti & Stevens, 2008).

RLS may be divided into two categories: early-onset, which occurs in patients less than 45 years old and late-onset, which occurs in patients older than 45 years old. The symptoms of early-onset RLS tend to develop slowly and are more likely to run in families,while the symptoms of late-onset RLS may proceed more quickly and are more likely to be linked with concomitant conditions, most notably an iron deficiency (Wijemanne & Ondo, 2017).

1.3 Impact on Health

The effect on one's quality of life that is caused by RLS is comparable to that which is caused by type 2 diabetes and osteoarthritis (Allen et al., 2005; Happe et al., 2009). There is a correlation between increased symptom intensity and severe psychological impairment across a number of different psychological areas (Leschziner & Gringras, 2012). Patients who have the condition have longer adjusted sleep latencies and a higher arousal index compared to controls (Winkelman et al., 2009) and they report having difficulties starting sleep, difficulty sustaining sleep and unrefreshing sleep two to three times more frequently than controls do (Ohayon et al., 2012).

In addition, there is mounting evidence that RLS is linked to metabolic dysregulation, autonomic dysfunction and an increased risk of cardiovascular disease (Leschziner & Gringras, 2012). A

recent in-depth systematic analysis of 629 sources came to the conclusion that the condition is significantly associated cardiovascular diseases, probably associated with diabetes and impaired glucose tolerance and may be only moderately associated with body mass index and dyslipidemia (Innes et al., 2012). It is possible that RLS contributes to an increased risk for these disorders, possibly through chronic activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis; alternatively, these conditions may contribute to an increased risk for the syndrome; or RLS may be linked to these disorders through shared risk factors (Leschziner & Gringras, 2012).

1.4 Associated Characteristics

Insomnia: At least 14 research investigations involving sleep clinic, primary care and community-based populations corroborated the clinical observation that insomnia is a major and uncomfortable consequence of untreated RLS. Varying research populations (clinic vs community) as well as different criteria for the diagnosis of RLS and sleep-related symptoms, are likely to account for differences in the findings of the various studies. However, research that use questionnaires and interviews, both uncontrolled and controlled, consistently reveal that between 50% and 85% of RLS patients suffer from a form of insomnia that is both troublesome and affects both the onset and maintenance of sleep. The prevalence of insomnia complaints in patients with RLS is much greater than in controls based on research that was conducted in community-based controlled trials. Sleep problems have also been established by polysomnographic studies. To summarize, insomnia is a substantial contributor to the morbidity that individuals with RLS experience (Earley & Silber, 2010).

Anxiety disorders: When compared to the general population, the percentage of those suffering

with RLS who also have anxiety problems is much higher (Mackie & Winkelman, 2015). One research compared more than 2000 members of the general population who suffered from various ailments with 130 patients who were diagnosed with RLS after undergoing a standardized diagnostic interview and found that patients diagnosed with RLS were shown to have a significantly higher frequency of anxiety disorders. RLS was associated with panic disorder and generalized anxiety disorder most significantly (Winkelmann et al., 2005).

The cause-and-effect relationship of RLS and anxiety disorders is probably not straightforward. The etiologic processes are not fully known. It is possible that people are predisposed to both illnesses due to a similar neurobiological and genetic substrate, or it is also possible that one condition plays a causative role in the onset of the other disorder. Patients with RLS stated that the beginning of their RLS symptoms happened prior to the mental condition. Although there are other conceivable reasons, this shows that the mental disease may be induced by RLS in at least some individuals. This is despite the fact that there are other possible causes (Mackie & Winkelman, 2015).

There are many possible processes that may be at play when RLS is the cause of or a contributing factor in anxiety disorders. Patients who suffer RLS commonly have anticipatory anxiety about the pain of their symptoms and loss of sleep. This anticipatory anxiety may aggravate a propensity to an anxiety disorder (Mackie & Winkelman, 2015). In normal volunteers, losing sleep raises sympathetic tone and heightens the overall mood of anxiety (Baum et al., 2014; Klumpers et al., 2015). Patients who already have panic disorder are more likely to develop panic attacks when they experience severe sleep loss (Roy Byrne et al., 1986). Insufficient sleep may also play a role in the development of panic disorder in some RLS patients who are predisposed toward panic attacks (Mackie & Winkelman, 2015).

Neuropathies: There has been a link established between RLS and neuropathies. On the other hand, the link is convoluted and the extent to which neuropathy and RLS are associated is unknown. Neuropathy is more common in those who do not have a family history of RLS; it might entail sensory complaints and it manifests in adulthood rather than childhood (Allen & Earley, 2001). A study used skin biopsies to diagnose small-fiber neuropathy in RLS patients complaining of sensory dysesthesias found that 80% of those patients who had abnormal skin biopsies had a late age of symptom development, compared to just 18% of those patients who had normal skin biopsies (Polydefkis et al., 2000). There are additional case reports that relate RLS to other illnesses that present with neuropathy. In addition, it seems that people who have RLS are more likely to have the neuropathy that is linked with rheumatoid arthritis and diabetes (Allen & Earley, 2001).

1.5 Research Gap

Two research gaps that have been found regarding the topic of this project:

- The pathogenesis of this disease is still unknown.
- An optimum treatment plan is a clinical unmet need.

1.6 Objectives of the Study

The main objectives behind this review paper are:

- To discuss the pathogenesis of this disease based on different hypothesis.
- To establish the relationship of different conditions to the pathogenesis of this disease.
- To identify treatment plan for each category of patients based on evidence.

1.7 Significance of the Study

Major significance of the review paper is:

- Role of iron and dopamine to the pathogenesis of the disease.
- Evidence that different drugs can induce this disease.
- Evidence that different conditions can contribute to the pathogenesis of the disease.
- Treatment for general patients.
- Treatment for children and pregnant woman with the disease.
- Probable reasons behind treatment failure of this disease.

Chapter 2

Methodology

PubMed Database was searched for studies related to ‘‘restless legs syndrome’’. The term “restless legs syndrome” was crossed with, “pathogenesis”, “treatment” and “prevalence”. Any studies which were based on other languages rather than English were excluded. Any studies which had outdated information as well as any studies without peer-review were also excluded.

Chapter 3

Pathogenesis

3.1 Iron Hypothesis

Iron deficiency is the single most important and well-defined key environment factor associated with RLS. The pioneering RLS experiments conducted by Ekbom and Nordlander made note of this inadequacy in the data (Allen, 2015). The extent of RLS rises with a reduction in peripheral iron (Sun et al., 1998), and the frequency of this condition is about nine times higher in iron deficiency anemia than in normal populations (Allen et al., 2013). All disorder that lower iron level is proved to be linked to a greater danger for RLS and waking early in the night. In addition, in some instances, effective management of the iron shortage might lessen the extent of RLS symptoms (Allen, 2015). However, the vast majority of RLS patients have usual levels of serum ferritin and there is no evidence to suggest that their peripheral iron reserves are aberrant. It seems that the iron status in the central nervous system is more important to the pathophysiology than the peripheral iron levels (Earley et al., 2000; Mizuno et al., 2005).

Iron deficiency in the brain is the single most well-documented biochemical anomaly associated with RLS (Allen, 2015). Based on initial reports and Magnetic Resonance Imaging (MRI) of the substantia nigra and red nucleus, there was a reduction in the amount of iron found in the brain (Allen et al., 2001). At this point, a lack of iron in the brain as a cause of RLS has been shown in six separate investigations, each of which used a unique methodology and was conducted in a separate laboratory (Allen et al., 2001; Earley et al., 2006; Godau et al., 2008; Moon et al., 2014; Rizzo et al., 2013; Schmidauer et al., 2005). The substantia nigra is the region of the brain that display lower iron most consistently. The putamen and the caudate also show iron deficiency to a lesser degree (Allen, 2015).

Recent research using more sophisticated measurement techniques has shown evidence of reduced iron status in the thalamus (Rizzo et al., 2013). The iron deficit is thought to be mostly regional and the impacted regions involve not just iron excessive regions like the substantia nigra but also iron deficient places, notably the thalamus. Some iron-excessive regions have not showed a consistent reduction in iron for RLS (e.g., cerebellar dentate nucleus). In light of this, it would seem that the pathogenesis involves a regional brain iron deficiency, which is present in the majority of RLS patients despite their usual iron level (Allen, 2015).

The transformation in iron regulatory proteins that were observed in RLS autopsy investigations indicate a relationship that is unexpectedly complex. L-ferritin is found in higher levels in the brains of people with RLS than H-ferritin. More so than L-ferritin, H-ferritin is responsible for the transportation and accommodation of iron (Allen, 2015). In neuromelanin cells of the substantia nigra, the level of transferrin receptor is lowered, which is the opposite of the reaction that would normally be anticipated in response to reduced iron status (Connor et al., 2004). The process by which iron is transported into the brain provides a more comprehensive picture rather (Allen, 2015). The evaluation of the micro vessels in the motor cortex by autopsy revealed a decrease in the activity of iron regulatory protein-1, which was associated with a decrease in the iron intake/storage proteins of transferrin receptor, transferrin and H-ferritin. However, there was no change in the amount of ferroportin, which is the protein responsible for iron export. Therefore, a consistent pattern of decreased iron transport into the brain and more specifically, into the neuromelanin cells of the substantia nigra has been identified (Connor, Ponnuru, Wang, et al., 2011). Iron transport was also impaired in the choroid plexus. The epithelial cells had lower levels of iron and H-ferritin, which is consistent with having an iron deficiency. However, these cells had higher levels of mitochondrial ferritin, which indicates greater iron uptake by the mitochondria. The iron regulating proteins in the choroid plexus are upregulated, which results in an increase in both cellular iron intake (through the

transferrin receptor and transferrin) and iron export (ferroportin) (Connor, Ponnuru, Wang, et al., 2011). These cells have a design that is compatible with a faster yield of iron, which would feed an enhanced mitochondrial iron level (Allen, 2015). In the cells of the substantia nigra, an elevated level of mitochondrial ferritin was also discovered, although this was not the case in the putamen (Snyder et al., 2009). It seemed that there were more mitochondria in these cells, which resulted in an increased requirement for iron. Therefore, it would seem that the mitochondria have obtained their iron excess at the price of cytosolic iron and a total cytosolic cellular iron shortfall (Allen, 2015).

To conclude, Brain iron deficiency in RLS patient is characterized by a malfunction to deliver enough iron transport across the blood brain barrier, which is then accompanied by a regional malfunction to intake enough iron inside the neuromelanin of the substantia nigra. The intriguing and potentially significant discovery of greater mitochondrial ferritin and iron yield in the choroid plexus and maybe the substantia nigra may indicate a basic component of the iron hypothesis that needs additional research (Allen, 2015).

Hypoxia and myelin loss are the two primary predicted pathophysiologic outcomes of brain iron shortage, and they have both been observed. The ability to transport oxygen is dependent on iron, therefore a reduction in iron should be interpreted as a possible warning sign of hypoxia.It has been discovered that there is an elevation of the hypoxia inducible factor 1-alpha in the substantia nigra of RLS patients. In the microvessels, there was an increase in the levels of both the hypoxia inducible factor 2-alpha and the vascular endothelial growth factor (Snyder et al., 2009). In spite of the fact that there was no clear evidence of true hypoxia, these variations were nevertheless seen (Allen, 2015).

In two separate trials, individuals with RLS had hypoxia in their leg muscles, which could not be explained by their activity levels. It's possible that these are the after effects of a more widespread

iron management issue (Wåhlin Larsson et al., 2007; Wåhlin-Larsson et al., 2009). Recent research has shown to an increased disparity in blood flow in the morning and blood flow in the evening in RLS patients (Oskarsson et al., 2014) as well as relative hypoxia in the leg muscles of these patients (Salminen et al., 2014). It is possible that hypoxia or the activation of hypoxic pathways is one of the pathways that leads to RLS symptoms (Allen, 2015). This discovery may explain why there is such a high frequency of RLS in those who have chronic obstructive pulmonary disease (Benediktsdottir et al., 2010; Kaplan et al., 2008; lo Coco et al., 2009).

The formation of myelin is dependent on iron, and a lack of brain iron in animals results in a reduction in the amount of myelin proteins, lipids and cholesterol (Ortiz et al., 2004; Yu et al., 1986). It is reasonable to anticipate that the brain iron deficiency associated with RLS will result in a little but considerable reduction in myelin. Imaging studies showed substantial reductions in the amount of white matter in the corpus callosum, anterior cingulum, and precentral gyrus, which supported this theory (Allen, 2015). In addition, postmortem examinations revealed a reduction (25%) in myelin proteins (Connor, Ponnuru, Lee, et al., 2011). This extent of myelin deficiency might be a contributing factor in RLS symptoms (Allen, 2015).

Table 1: Prevalence of RLS in Iron Deficiency Anemia.

Reference	**Country**	**Method**	**Age (Years)**	**RLS % (Sample size)**
(Telarović & Čondić, 2019)	Croatia	Interview	34 (Mean age)	29% (231)
(Kolukisa et al., 2016)	Turkey	Interview	38.3 for RLS and 38.8 for non RLS (Mean age)	41.1% (51)

(Rangarajan & D'Souza, 2007)	India	Interview	18+	34.3% (64)
(Bae et al., 2021)	Korea	Interview	54.02 for RLS & 47.22 for non RLS (Mean age)	40.3% (124)
(Allen, Auerbach, et al., 2013)	USA	Interview	45.6 (Mean age)	31.5% (251)
(Akyol et al., 2003)	Turkey	Interview	24-66 for RLS and 21-58 for non RLS	41.1% (34)

3.2 Dopamine Hypothesis

Dopaminergic medications, more specifically selective D3 receptor agonists, are very useful in the treatment of RLS. These medicines serve both as supporting criteria for the diagnosis and as first-line therapy with quick effectiveness. On the other hand, neuroleptics, which are dopamine antagonists, may either initiate or exacerbate RLS. Based on these data, it seems that the dopaminergic system plays a significant part in the pathophysiology of RLS. Dopamine availability may be affected by iron deficiency, since iron is a cofactor for the enzyme tyrosine hydroxylase, whose activity is the rate-limiting step in the conversion of levodopa to dopamine. On the other hand, a primary dopaminergic deficiency in RLS patients has never been satisfactorily shown (Dauvilliers & Winkelmann, 2013).

The results of previous neuroimaging investigations using either Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) scans have indicated unreliable modifications in the basal ganglia's dopamine receptor D2 or D3 binding. These findings include statements of declines and inclines. Though, a more recent investigation found considerably

decreased dopamine transporter (DAT) attachment with unaltered overall cellular DAT in the putamen and caudate, but not in the ventral striatum (Earley et al., 2011). Cerebrospinal fluid (CSF) investigations on dopamine metabolites are similarly unreliable in RLS; however, one study revealed magnificent rise in 3-ortho-methyldopa and homovanillic acid, which stimulates dopaminergic system in severe RLS patients (Allen et al., 2009). Other CSF studies on dopamine metabolites in RLS have also been inconsistent. A recent neuropathological study showed some dopaminergic abnormalities in the brain tissue of people with RLS. Specifically, there was a significant decrease in D2 receptors in the putamen, which correlated with the severity of RLS. However, there were no changes in receptor 1 or dopamine transporters (Dauvilliers & Winkelmann, 2013). Tissues taken from people with RLS in their brains revealed large elevations in the enzyme tyrosine hydroxylase in the substantia nigra, but not in the putamen (Connor et al., 2009). These fascinating results, which reflect an abnormally engaged dopaminergic pathway, have also been described in both animal and cell models of iron deficiency. As a result, they provide more support for the notion that RLS is a primary iron deficiency disease (Dauvilliers & Winkelmann, 2013).

Recent research has shown that individuals with RLS have an increased glutamate/glutamine level in their thalamus, which correlates with sleep-wake pattern disruption (Allen, Barker, et al., 2013). These findings point to the engagement of non-dopaminergic neurons, more especially glutamatergic system ones, in the underlying disturbances in sleep-wake patterns that are associated with RLS. According to these findings, it seems that dopaminergic system causes a more supporting part in the motor components of RLS, whereas non-dopaminergic neurons, notably the glutamatergic system ones, may be involved in the underlying sleep-wake pattern disruptions (Dauvilliers & Winkelmann, 2013).

If RLS is caused by a hyperdopaminergic condition, then the apparent issue that arises is why therapy

with dopamine agonists or L-DOPA may reduce the symptoms of RLS (Khan et al., 2017). RLS is characterized by an increase in the overall amount of dopaminergic activity, which in turn leads to a downregulation of dopamine receptors. In RLS, there is a circadian system of dopamine action that shows stimulation at the time of sunrise and throughout the day, then relative inhibition after sunset. This occurs despite the fact that total dopamine activity is likely increased. RLS symptoms may be caused by a condition of dopamine insufficiency that develops during the evening hours as a result of the combination of dopamine receptor downregulation and reduced dopamine activity throughout the night. As a result, supplying extra dopamine activity, whether by dopamine agonism or enhanced L-DOPA, assists in alleviating the signs of RLS (Allen, 2015; Earley et al., 2014).

3.3 Drug Induced RLS

The side effects of antipsychotic, antidepressant and Antiepileptic medications are similar to the symptoms of RLS (Perez-Lloret et al., 2012). Therefore, several medications have the potential to cause RLS symptoms in persons who are already predisposed to developing them. This is because these treatments have the potential to cause RLS symptoms to become more severe. Treatment for each person must be individualized, one-of-a-kind, and maybe collaborative amongst many fields (psychiatric, neurological, somnology). Furthermore, a close eye should be kept on patients with pharmacoresistant RLS who also have mental comorbidities that need psychotropic medication (Chenini et al., 2018).

Antidepressants: RLS is a condition that may be caused by some antidepressants with serotonergic action or made worse by RLS that was already present (Hoque & Chesson, 2010; Rottach et al., 2008). The tetracyclic antidepressants are the potent triggers of RLS: nearly 28% of subjects on mirtazapine obtain or see an aggravation. whereas RLS only impacts around 9% of individuals overall

who are taking antidepressants (Rottach et al., 2008). Some medications such as, tricyclics, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors are also capable of causing RLS. Regarding monoamine oxidase inhibitors, there is no dependable evidence available (Hoque & Chesson, 2010). Even though bupropion has been suspected of triggering Periodic limb movements in sleep, it is not known to cause RLS (Bayard et al., 2011).

Neuroleptics: RLS may be made worse or induced by using any neuroleptic, with the exemption of aripiprazole, which is a partial dopamine agonist. They are also capable of causing akathisia, which may produce symptoms similar to those of RLS, but without the evening worsening or improvement brought on by activity that is typical of RLS. With the exception of domperidone, the vast majority of antiemetics as well as some tranquilizers are also obtained after neuroleptics (Chenini et al., 2018).

It is vital to make the anesthetist aware that a patient with RLS is contraindicated to droperidol (Karroum et al., 2010; Raux et al., 2010). The use of droperidol to reduce nausea and constipation is common in perioperative anesthesia and when initiating a morphine pump (Chenini et al., 2018).

Sodium oxybate: Oxybate sodium therapy, which is approved for the treatment of narcolepsy, may sometimes elicit RLS and periodic leg movements in sleep (Abril et al., 2007).

Lithium: Treatment with lithium has been linked to the development of RLS in certain patients, most likely in those who were already susceptible (Terao et al., 1991).

Tramadol hydrochloride: Tramadol hydrochloride, which is often used to treat RLS and the occasional aggravation of RLS, has been proven to make RLS symptoms worse (Hoque & Chesson, 2010; Perez-Lloret et al., 2012). However, a number of the doctors prescribe it on a daily basis and find that it is effective in treating persistent RLS. It is important not to rule out the possibility of using it as a treatment for pharmacoresistant RLS, particularly in individuals who cannot take other

morphinics or derivatives of them due to medical conditions (Chenini et al., 2018).

Antihistamines: Because hypnotic antihistamines are phenothiazines, which are derivatives of neuroleptics, using them might make RLS worse (Chenini et al., 2018).

Table 2: Antipsychotic induced case reports.

Reference	**Drug**	**Dose /Frequency**	**Age /Sex**	**Concurrent Disease**	**Comments**
(Aggarwal et al., 2010)	Olanzapine	10 mg/d increased to 15 mg/d	36/M	Paranoid schizophrenia	Olanzapine got replaced by aripiprazole without relapse of RLS symptoms.
(Aggarwal et al., 2010)	Olanzapine	15 mg/d	29/M	Schizophrenia	Patient got relief from RLS after olanzapine was replaced by risperidone.
(Bolaños-Vergaray et al., 2011)	Aripiprazole	5 mg/d, increased to 15 mg/d	45/F	Major depressive disorder, schizophrenia	RLS alleviated after stopping the drug.
(Kang et al., 2009)	Olanzapine	5 mg/d increased to 20 mg/d	36/F	Schizophrenia	Olanzapine was replaced by clozapine.
(Aggarwal et al., 2010)	Olanzapine	2.5 mg/d	62/F	Bipolar disorder type II	Patient got relief from RLS after olanzapine was replaced by quetiapine.
(Kang et al., 2009)	Olanzapine	5 mg/d increased to 20 mg/d	34/M	Paranoid schizophrenia	RLS symptoms were alleviated after dose reduction.
(Kang et al., 2009)	Olanzapine	10 mg/d	55/M	Hypomanic episodes	RLS symptoms alleviated after stopping olanzapine.

(Kang et al., 2009)	Olanzapine	5 mg/d increased to 20 mg/d	59/M	Bipolar I disorder	RLS symptoms alleviated after stopping olanzapine.
(Kang et al., 2009)	Olanzapine	Dose titrated to 20 mg/d	28/F	Paranoid schizophrenia	Dose reduction alleviated RLS symptoms.
(Khalid et al., 2009)	Olanzapine	20 mg/d	54/F	Bipolar disorder	RLS symptoms alleviated after olanzapine was replaced by aripiprazole.
(Kraus et al., 1999)	Olanzapine	10 mg/d increased to 20 mg/d	41/M	Schizophrenia	Low alleviation of RLS symptoms after the dose was reduced.
(Basu et al., 2014)	Olanzapine	10 mg/d increased to 15 mg/d	38/F	Schizophrenia	Olanzapine was replaced by risperidone and RLS symptoms got alleviated.
(Zhao et al., 2014)	Olanzapine	2.5 mg/d increased to 5 mg/d	59/F	Generalized anxiety disorder	RLS symptoms got alleviated after stopping olanzapine.
(Zhao et al., 2014)	Olanzapine	2.5 mg/d	51/M	Insomnia	RLS symptoms got alleviated after stopping olanzapine.
(Kumar et al., 2014)	Olanzapine	10 mg/d	56/F	Delusional disorder	RLS symptoms got alleviated after adding gabapentin.
(Duggal & Mendhekar, 2007)	Clozapine	25 mg/d increased to 50 mg/d	26/F	Bipolar disorder	Clozapine replaced by olanzapine and RLS symptoms resolved.
(Chathanchirayil, 2011)	Clozapine	325 mg/d increased to 500 mg/d	29/F	Treatment resistant paranoid schizophrenia	RLS symptoms persisted with clozapine use.

(Raveendranathan et al., 2013)	Clozapine	Dose increased up to 300 mg/d	34/F	Treatment resistant paranoid schizophrenia	Aripiprazole was added with clozapine and RLS symptoms resolved.
(John et al., 2014)	Clozapine	Dose increased to 300 mg/d	28/F	Major depressive disorder	RLS symptoms resolved after adding pramipexol with clozapine.
(Chou et al., 2010)	Quetiapine and Paroxetine	200 mg and 12.5 mg/d respectively	47/M	Antidepressant induced mania/depression	RLS symptoms resolved after stopping quetiapine.
(Pinninti et al., 2005)	Quetiapine	100 mg/d increased to 200 mg/d	68/F	Insomnia	RLS symptoms resolved after reducing dose.
(Rittmannsberger & Werl, 2013)	Quetiapine	50 mg/d increased to 200 mg/d	65/M	Major depressive disorder	RLS symptoms after resolved after stopping quetiapine.
(Rittmannsberger & Werl, 2013)	Quetiapine	25 mg/d	41/F	Bipolar disorder type II	RLS symptoms resolved after stopping quetiapine.
(Rittmannsberger & Werl, 2013)	Quetiapine	50 mg/d increased to 100 mg/d	54/F	Major depression	RLS symptoms resolved after stopping quetiapine.
(Rittmannsberger & Werl, 2013)	Quetiapine	50 mg/d	66/F	Major depression	RLS symptoms resolved after stopping quetiapine.
(Rittmannsberger & Werl, 2013)	Quetiapine	50 mg increased to 75 mg/d	33/F	Borderline personality disorder	RLS symptom resolved after adding pramipexole with quetiapine.
(Rittmannsberger & Werl, 2013)	Quetiapine	100 mg/d increased to 200 mg/d	49/F	Major depression	RLS symptoms resolved after stopping quetiapine.

(Rittmannsberger & Werl, 2013)	Quetiapine	Dose increased up to 150 mg/d	61/M	Major depression	RLS symptoms resolved after dose was reduced.
(Urbano & Ware, 2008)	Quetiapine	Dose increased up to 600 mg/d	53/F	Bipolar disorder type II	RLS symptoms resolved after adding ropinirole with quetiapine.
(Webb, 2012)	Quetiapine	Dose increased up to 600 mg/d	44/M	Bipolar disorder type II	RLS symptoms resolved after stopping quetiapine.
(Michopoulos et al., 2014)	Quetiapine and Venlafaxine	Quetiapine 150 mg/d and Venlafaxine 600 mg/d	44/M	Bipolar disorder type 1	RLS symptoms resolved after stopping quetiapine.
(Vohra, 2015)	Quetiapine	Dose not reported	40/F	Schizoaffective disorder	RLS symptoms resolved after stopping quetiapine.
(Vohra, 2015)	Quetiapine	300 mg/d	43/F	Bipolar affective disorder	RLS symptoms resolved after stopping quetiapine.
(Vohra, 2015)	Quetiapine	Dose increased to 250 mg/d	39/F	Recurrent depression	RLS symptoms resolved after stopping quetiapine.
(Vohra, 2015)	Quetiapine	Dose increased to 300 mg/d	38/F	Recurrent depression	RLS symptoms resolved after adding ropinirole with quetiapine.
(P. H. Chen, 2016)	Quetiapine	100 mg/d increased to 150 mg/d	46/M	Bipolar disorder type II	RLS symptoms resolved after stopping quetiapine.

(Z. Soyata et al., 2015)	Quetiapine	100 mg/d	39/F	Depression	RLS symptoms resolved after adding pramipexol with quetiapine.
(Wetter et al., 2022)	Risperidone	4 mg/d	31/F	Schizoaffective disorder	RLS symptoms resolved after replacing risperidone with quetiapine.
(McCall et al., 2014)	Asenapine	5 mg/d	60/F	Major depression	RLS symptoms resolved after stopping asenapine.
(Ghori et al., 2016)	Lurasidone	40 mg/d	71/F	Bipolar disorder type I	RLS symptoms resolved after stopping lurasidone.
(Horiguchi et al., 1999)	Haloperidol	3 mg/d	51/F	Schizophrenia	RLS symptoms resolved after adding clonazepam with haloperidol.

Table 3: Antidepressant induced case reports.

Reference	**Drug**	**Dose**	**Age /Sex**	**Concurrent Disease**	**Comments**
(Chopra et al., 2011)	Mirtazapine	15 mg daily	85/M	Mild depression	Mirtazapine stopped and replaced by low dose gabapentin.
(Ağargün et al., 2002)	Mirtazapine	15 mg/d increased to 30 mg/d	45/M	Major depressive disorder	Clonazepam improved RLS symptoms and insomnia.
(Chang et al., 2006)	Mirtazapine	30 mg increased 60 mg/d	32/M	Major depressive episode	Clonazepam treatment failed; mirtazapine was substituted by cirzodone which improved RLS symptoms.
(Bahk et al., 2002)	Mirtazapine	15 mg/d	56/F	Major depressive disorder	Clonazepam aggravated RLS symptoms and got replaced by

					paroxetine which eliminated RLS symptoms completely.
(Pae et al., 2004)	Mirtazapine	15 mg/d increased to 30 mg/d	58/F	Major depressive disorder	Mirtazapine was replaced by tianeptine and clonazepam which aggravated depression. But readministration of mirtazapine didn't bring back RLS symptoms.
(Bonin et al., 2000)	Mirtazapine	15 mg/d	33/F	Depression	RLS symptoms resolved after substituting mirtazapine with fluvoxamine.
(Prospero-Garcia et al., 2006)	Mirtazapine and Fluoxetine	15 mg/d and 20 mg/d respectively	63/F, 50/F, 41/M	Depression	RLS symptoms resolved after mirtazapine was stopped.
(Park et al., 2009)	Mirtazapine	15 mg/d increased to 45 mg/d	64/F	Depression	RLS symptoms resolved after mirtazapine was replaced by bupropion.
(Makiguchi et al., 2015)	Mirtazapine	7.5 mg/d increased to 45 mg/d	80/F	Depression	RLS symptoms resolved after adding pramipexole.
(Nader et al., 2007)	Citalopram	20 mg/d increased to 60 mg/d	48/F	Major depressive disorder	Citalopram was substituted by bupropion and sertraline and RLS symptoms disappeared completely.
(Hargrave & Beckley, 1998)	Sertraline	25 mg/d	71/M	Dysphoric mood, irritability and tearfulness	RLS symptoms resolved after sertraline was replaced by lorazepam.

(Sanz-Fuentenebro et al., 1996)	Paroxetine	20 mg/d	33/M	Adjustment disorder and depressed mood	Paroxetine discontinued and RLS symptoms resolved.
(Öztürk et al., 2006)	Paroxetine	40 mg/d increased to 60 mg/d	36/M	Obsessive-compulsive disorder	RLS symptoms resolved after adding oxcarbazepine.
(Page et al., 2008)	Escitalopram	10 mg/d increased to 20 mg/d	34/F	Depression	RLS recurred after retrial with reduced dose. Thus, non-pharmacological treatment was chosen.
(Bakshi, 1996)	Fluoxetine	20 mg/d increased to 60 mg/d	22/F	Depression	RLS symptoms resolved after stopping fluoxetine.
(Simpson, 1996)	Nefadozone	100 mg/d increased to 600 mg/d	43/M	Depressive disorder	Carbidopa/levodopa controlled release and clonazepam were added at bedtime without worsening RLS.
(Nikolaou et al., 2015)	Duloxetine	60 mg/d	52/F	Major depression	RLS symptoms resolved after stopping duloxetine.
(Heiman & Christie, 1986)	Lithium	Increased up to 1800 mg/d	48/F	Manic episodes	RLS recurred after retrial with lithium. Thus, lithium was stopped and RLS symptoms resolved.
(Terao et al., 1991)	Lithium	800 mg/d increased to 1000 mg/d	18/M	Obsessive-compulsive disorder	RLS symptoms resolved after reducing dose.

Table 4: Antiepileptics induced case reports.

Reference	Drug	Dose	Age/ Sex	Concurrent disease	Comments
(J. T. Chen et al., 2003)	Zonisamide	100 mg/d increased to 400 mg/d	27/F	Epilepsy	Zonisamide was continued for epilepsy management despite having RLS.
(Velasco et al., 2007)	Zonisamide	100 mg/d increased to 200 mg/d	50/F	Chronic migraine	Zonisamide treatment was stopped.
(Bermejo, 2009)	Topiramate	100 mg/d	32/F	Chronic migraine	RLS symptoms resolved after stopping zonisamide.
(Bermejo, 2009)	Topiramate	150 mg/d	36/F	Severe migraine	RLS symptoms resolved after stopping topiramate.
(Romigi et al., 2007)	Topiramate	100 mg/d	26/F	Post traumatic epilepsy	Topiramate was switched to carbamazepine.
(Romigi et al., 2007)	Topiramate	200 mg/d	52/F	Symptomatic epilepsy	Cabergoline reduced RLS symptoms.

3.4 RLS in Pregnancy

The fact that RLS is more common in women who are not pregnant than in those who are pregnant lends credence to the theory that hormone exposure plays a part in the pathogenesis of the condition. It is still not understood which hormone is responsible for the most important part of the endocrinologic storm that occurs during pregnancy. Progesterone and estrogens, both of which function as neurosteroids, exert a complicated and mostly unexplained regulation on the central nervous system (Prosperetti & Manconi, 2015). Research on epilepsy shown that estrogens have a

function that is proconvulsive and that progesterone has a role that is protective against seizures (Alam et al., 2013). When RLS occurs outside of pregnancy, it has been shown that women who use treatments based on estrogen are more likely to acquire the condition than women who do not use estrogen (Budhiraja et al., 2012). There may be a correlation between the estrogenic hypothesis and the high occurrence of symptoms experienced during the 3rd trimester, which is also the time of pregnancy in which plasmatic levels are at their peak (Prosperetti & Manconi, 2015).

The enzyme tyrosine hydroxylase requires iron and tetrahydrobiopterin as co-factors in order to produce dopamine. Folate, on the other hand, is necessary for the regeneration of tetrahydrobiopterin. Because of this, there is a possibility that dopamine synthesis may decrease if levels of iron or folate are low (Bottiglieri et al., 1992; Kaufman, 1991). Folate, iron and other iron markers in the serum, such as, ferritin and hemoglobin, are all seen in lower concentrations during pregnancy compared to when the woman is not pregnant. Two potential causes for this phenomenon are an increase in total blood volume, which results in a dilution effect, and the consumption of iron and folate by the developing fetus. An early start to fetal iron and folate use, which leads to a fast reduction in iron reserves and decreasing serum ferritin, occurs early in pregnancy (Srivanitchapoom et al., 2014). In addition, if the mother's iron reserves are insufficient at the start of the pregnancy, this procedure might be exceedingly stressful for the mother (Fenton et al., 1977). It has been observed that having a low serum ferritin before or during the early stages of pregnancy is a predictor of RLS developing throughout the pregnancy (Tunç et al., 2007). The symptoms of RLS, on the other hand, improve dramatically after delivery and this improvement is not reliant on the levels of iron or folate, which will take a longer period of time to regain their previous levels. As a result, one should not consider this mechanism to be a significant contribution to the pathophysiology of RLS seen during pregnancy (Srivanitchapoom et al., 2014).

RLS symptoms may be made worse during pregnancy by a number of psychological problems, including anxiety, stress, tension, insomnia and fatigue (Manconi, Govoni, de Vito, Tiberio Economou, et al., 2004). The symptoms of RLS might be brought on by neuropathy or radiculopathy. The expanding growth of the fetus creates a pressure on the lumbosacral nerve roots producing RLS symptoms which diminish during birth (Srivanitchapoom et al., 2014). However,one research indicated that there was no significant difference in the newborn anthropometric values between the RLS group and the non-RLS group (Manconi, Govoni, de Vito, Economou, et al., 2004).

Table 5: Prevalence of RLS in pregnant woman.

Reference	**Method**	**Prevalence in Pregnancy (Sample Size)**
(Suzuki et al., 2003)	Self-administered questionnaires	19.9% (16528) in all months of pregnancy
(Manconi, Govoni, de Vito, Economou, et al., 2004)	Clinical interviews	26.6% (642) in all months of pregnancy
(Tunç et al., 2007)	Clinical interviews	26.02% (146) in all months of pregnancy
(Harano et al., 2008)	Self-administered questionnaires	2.9% in all months of pregnancy, 1.6% in 1st trimester, 2.3% in 2nd trimester and 3.5% in 3rd trimester (19441)
(Sikandar et al., 2009)	Clinical interviews	30% (271) in all months of pregnancy
(Balendran et al., 2011)	Self-administered questionnaires	22.5% (211) in 3rd trimester
(Uglane et al., 2011)	Self-administered questionnaires	34% (251) in all months of pregnancy
(S. J. Chen et al., 2018)	Self-administered questionnaires	10.4% (461) in all months of pregnancy
(Wesström et al., 2014)	Web-based surveys	18.5% (142) in all months of pregnancy
(Mindell et al., 2015)	Web based surveys	24% (1214) in all months of pregnancy

(Meharaban et al., 2015)	Self-administered questionnaires	43.7% (231) in all months of pregnancy
(Plancoulaine et al., 2017)	Self-administered questionnaires	12% in 1st trimester, 20% in 2nd trimester and 32.5% in 3rd trimester (200)

3.5 RLS in Kidney Disease

It is believed that an iron deficiency is involved in the processes that lead to an increased risk of RLS developing in individuals who have renal disease, especially in those who are already receiving dialysis (Earley, Allen, et al., 2000; Molnar et al., 2006). Patients with RLS who were undergoing dialysis were shown to have considerably lower blood hemoglobin levels and a greater frequency of iron deficit when compared with controls in a cross-sectional study that included 992 patients who had kidney transplantation (Molnar et al., 2005). It is essential to point out, however, that an association between the existence of RLS in patients who are undergoing dialysis and indicators of iron shortage such as, low serum ferritin level, hemoglobin level or hematocrit has not been established (Collado-Seidel et al., 1998; Unruh et al., 2004). Under-dialysis and hypoparathyroidism are two other conditions that have been linked to an increased risk of RLS in people undergoing dialysis (Collado-Seidel et al., 1998; Unruh et al., 2004).

The fluctuation in the incidence of RLS among patients who are undergoing renal transplantation lends credence to the hypothesis that kidney failure or dialysis is responsible for the emergence of RLS symptoms (Molnar et al., 2005; Molnar, Novak, et al., 2007; Winkelmann et al., 2002). The incidence of RLS raised with the extent of renal disease in individuals who were waiting for kidney transplantation and in patients who were undergoing dialysis (Molnar et al., 2005). The prevalence of RLS is lower in individuals who have had a kidney transplant as compared to patients with severe

renal disease who are on dialysis (4.8% vs 23.5%, respectively) (Molnar et al., 2005). On the other hand, there are not enough big prospective trials that describe changes in RLS and the severity of symptoms following transplant (Novak et al., 2015).

Table 6: Prevalence of RLS in Chronic Kidney Disease (CKD) patients.

Reference	**Country**	**Method**	**Stage**	**Mean Age**	**RLS/Total**
(Loewen et al., 2009)	Canada	Questionnaire	5	58	7/12
(Stefanidis et al., 2013)	Greece	Interview	5	65	154/579
(Hui et al., 2002)	Hong Kong	Questionnaire	5	49.5	30/43
(Hui et al., 2000)	Hong Kong	Questionnaire	5	56.7	124/201
(Telarović et al., 2007)	Croatia	Interview	5	Not reported	49/82
(Molnar, Novak, et al., 2007)	Hungary	Questionnaire	Transplant	49	35/785
(Szentkiralyi et al., 2009)	Hungary	Questionnaire	Mix	48	55/949
(Razeghi et al., 2012)	Iran	Questionnaire	5	56	35/108
(Molnar, Szentkiralyi, et al., 2007)	Hungary	Questionnaire	Transplant	49	38/804
(Mucsi et al., 2005)	Hungary	Questionnaire	5	54	45/333
(Chrastina et al., 2015)	Slovakia	Interview	Transplant	51.14	30/75

(Rijsman et al., 2004)	Netherlands	Interview	5	55	28/48
(Gigli et al., 2004)	Italy	Questionnaire	5	64	127/601

3.6 RLS in Diabetes Mellitus

The prevalence of RLS was much greater in different cohorts of people with type 2 diabetes, ranging from 25% to 27 %, which is significantly higher than the occurrence of 10% to 15 % in the general population (Lopes et al., 2005; Merlino et al., 2010; Phillips et al., 2006; Skomro et al., 2001). Intuitively, it seems sense to consider the possibility that diabetic polyneuropathy could be the only factor explaining the symptoms (Ioja et al., 2012). Nevertheless, findings from a research reveal that diabetic polyneuropathy is an independent risk factor for developing RLS; this does not mean that diabetic polyneuropathy is the sole cause for RLS. Type 2 diabetes mellitus is found to be an independent risk factor for developing RLS, even after adjusting for age, hemoglobin level, iron level, Hemoglobin A1C level, creatinine level, body mass index (BMI) and polyneuropathy. The research has been criticized for not examining the possibility of small-fiber neuropathy, which might have acted as a confounding factor (Merlino et al., 2007). It's probable that this is due to the fact that type 2 diabetes is associated with malfunction in the central nervous system. According to the findings of a research, the amount of dopamine in diabetic rats was reduced in certain regions of the central nervous system, including the striatum and the midbrain, both of which play a crucial role in RLS (Gallego et al., 2003). Only lately have researchers begun looking into the effects RLS might have on diabetic patients. Patients with type 2 diabetes who participated in case-control research in the United States found that RLS was linked with poor sleep quality, Excessive Daytime Sleepiness

(EDS), a deterioration in quality of life and higher anxiety and depression. However, the influence on glycemic outcome (a worse Hemoglobin A1C level) was only significant in the subgroup that reported EDS, which opened the door to a potential pathogenetic relationship between RLS, proinflammatory state, and glycemic management (Cuellar & Ratcliffe, 2008).

Table 7: Prevalence of RLS in Diabetes Mellitus patients.

Reference	**Mean Age (Years)**	**Method**	**DM(M/F)**	**RLS (+)/RLS (-)**	**Prevalence in Diabetes Mellitus (%)**
(Arosemena Coronel et al., 2017)	64.08	Questionnaire	290(207/283)	134/156	46.2%
(Castillo-Torres et al., 2018)	47.85	Interview	59	11/48	18.6%
(Cuellar & Ratcliffe, 2008)	59.5	Not available	121	54/67	44.6%
(Modarresnia et al., 2018)	54.89	Questionnaire	210 (83/127)	41/169	19.5%
(Tuo et al., 2019)	65.0	Questionnaire	90	9/81	10.0%
(Akın et al., 2019)	60.9	Interview	318 (126/192)	90/228	28.3%
(Bhagawati et al., 2019)	46.55	Questionnaire	72	21/51	29.2%
(Rafie et al., 2016)	53.8	Interview	44	22/22	50.0%
(Sunwoo et al., 2019)	44.5	Questionnaire	135	7/128	5.2%
(Pinheiro et al., 2020)	56.0	Not available	210 (139/71)	17/193	8.0%

Chapter 4

Treatment

4.1 Treatment for General Patients

4.1.1 Iron therapy: The only treatment that has shown any promise in treating RLS in patients with iron insufficiency is supplementation with iron. It is recommended that the patient take between 50 and 65 mg of elemental iron with each dosage. Iron may be given anywhere from one to three times each day, depending on how severe of a deficit the patient has. Iron should be taken on an empty stomach with 200 mg of vitamin C in order to achieve optimal absorption. The most prevalent adverse effect is constipation. Patients who may be at risk should get prophylactic administration of motility medications. Every three months, a patient should have an iron panel, which measures the saturation percentage of ferritin. The target ferritin concentration should be between 50 and 60 mcg/l. Iron replenishment should not be given to anybody who has a saturation level of 45% or more in order to prevent the underlying hemochromatosis from becoming worse (Gamaldo & Earley, 2006).

Administering iron intravenously to a patient should be considered who has a severe iron shortage (ferritin level less than 10 mcg/l) and an intolerance to oral iron supplementation. There have been no reports of anaphylaxis associated with Intravenous iron formulations, which include sodium ferric gluconate complex and iron sucrose. In general, giving an intravenous dose of 100 mg of iron will result in an increase of 10 mcg/l in the serum ferritin level. Infusions ranging from 100 to 125 mg may be given at intervals of at least two days in order to obtain the desired ferritin level of 60 mcg/l (Gamaldo & Earley, 2006).

4.1.2 Dopaminergic drugs: Dopamine agonists have been used promptly in the treatment of RLS

(Akpinar, 1982). The efficacy of these medications in reducing the severity of RLS symptoms has been shown by a significant number of clinical studies (Manconi et al., 2021). Because it takes these medicines around an hour to start working and because they primarily target the Dopamine receptor D3, they may be used whenever they are needed (Manconi et al., 2011).

Dopamine agonists including pramipexole, ropinirole and rotigotine are used in the treatment of RLS. Orthostatic hypotension, headaches, nausea and lower-limb oedema are the side effects of pramipexole that occur most often among patients who take the medication (Manconi et al., 2021). Patients who have a history of compulsive or impulsive behaviors should avoid using these kinds of medicines because, despite their rarity, they have the potential to set off compulsive and impulsive behaviors (S. Bayard et al., 2013). Daytime sleep episodes have also been recorded with dopamine agonists, although they are more often associated with the treatment of Parkinson's disease. Although these attacks are rare, they may have potentially life-threatening repercussions for those who drive. This effect, however, is very uncommon in RLS patients since the daily dosage of dopamine agonists is far less than what is given to Parkinson's disease sufferers (Möller et al., 2000). Ropinirole has a very similar efficacy and adverse effect profile to that of pramipexole, which means that they are almost interchangeable (Zintzaras et al., 2010). Symptoms of RLS were also alleviated by using rotigotine, which was administered in the form of a transdermal patch that allowed for continuous release. Despite this, over half of the patients required to terminate therapy due to side effects, augmentation and ineffectiveness (Oertel et al., 2011). Because of the distinctive manner in which it is administered, rotigotine may be of particular use to patients who have daytime symptoms, who have issues swallowing and who are scheduled to undergo surgery. The dosage of dopamine agonists should be maintained at minimum level in all individuals diagnosed with RLS and the dose should never be increased to a level that is higher than the

maximum dose that is indicated (Manconi et al., 2021).

4.1.3 Antiepileptics: The antiepileptic drug gabapentin, which is physically linked to the inhibitory central nervous system (CNS) neurotransmitter Gama Amino Butyric Acid (GABA), has showed promise as a potential therapy for RLS. Studies conducted on animals have shown that the medication offers protection against seizures that are brought on by GABA antagonists or GABA production inhibitors. When treating individuals who have renal impairment, the dosage levels of gabapentin as well as the frequency with which it is given should be changed according to the degree of impairment. It would seem that people with mild to severe RLS symptoms who are also dealing with genuine pain benefit the most from treatment with gabapentin (Satija & Ondo, 2008).

Gabapentin enacarbil is a medication that is similar to gabapentin but has been changed for increased absorption in the stomach. Significant success in the treatment of RLS has been proven in a number of larger, multicenter, placebo-controlled studies, with just moderate side effects (Satija & Ondo, 2008).

Carbamazepine was the first antiepileptic that was looked at in relation to RLS, and further investigations led to its incorporation into the treatment recommendations in the American Academy of Sleep Medicine (AASM) standards report. Carbamazepine is used to treat epilepsy, however the precise mechanism by which it achieves this effect is not fully known. It is well known that carbamazepine inhibits post-tetanic potentiation of synaptic transmission and blocks use-dependent sodium channels to prevent recurrent firing of neuron. The majority of doctors believe that the effectiveness of carbamazepine is low in comparison to that of other therapies; nonetheless, there are very little comparative data available (Satija & Ondo, 2008).

Other antiepileptic drugs, such as, valproate or lamotrigine, should be examined as potential

alternatives, despite the fact that controlled clinical trials have not shown any of these treatments to be effective in reducing RLS symptoms (Satija & Ondo, 2008).

Medications used to treat epilepsy should be taken with meals whenever possible to reduce the risk of gastrotoxicity. There have been isolated cases of people developing severe rashes and Stevens-Johnson syndrome after taking lamotrigine. These have mostly occurred in individuals who have been subjected to fast dosing while also getting treatment from other medications that inhibit the drug's metabolism (such as, valproate) (Satija & Ondo, 2008).

4.1.4 Opioids: It is used when patient suffers from augmentation or when there is an associated severe pain disorder that requires drugs. Although there is widespread agreement on the positive benefits of modest doses of opioids on RLS symptoms, there have been very few clinical studies that were adequately performed. Notably, modest doses of methadone and oxycodone have shown to be useful in the treatment of RLS (Silber et al., 2018; Silver et al., 2011). Sedation, constipation, depression, anxiety and altered awareness are some of the negative symptoms that might occur. It is important to note that these medicines may also raise the risk for opioid-induced respiratory depression (Silber et al., 2018). A practitioner who has obtained sufficient expertise in the treatment with these medications should be the one to write a prescription for opioids. It is necessary to do close surveillance on patients who are getting opioids (Manconi et al., 2021).

4.1.5 Benzodiazepines: In order to treat the symptoms of RLS, benzodiazepines and notably clonazepam, have been utilized extensively. They act on the receptor for gamma aminobutyric acid (GABA), which results in a slowing down of activity throughout the central nervous system (Rinaldi et al., 2016). In addition, benzodiazepines are known to lessen the anxiety that is typically associated with RLS (Brand et al., 2013). When administering these medications, consideration must be given to the possibility that the patient would acquire a tolerance to the medicine &

becoming dependent on it. This is especially important for treatments that last for an extended period of time (Zucconi et al., 2018).

In spite of how often they are used, the American Academy of Sleep Medicine (AASM) clinical practice guideline advises against using benzodiazepines as first-line medicines. However, the guideline acknowledges that they might be used as part of a combination treatment (Aurora et al., 2012).

4.1.6 Emerging treatments: Alternative nondopaminergic therapy approaches based on glutamatergic and adenosinergic processes are now in the process of being developed and give intriguing therapeutic options (Ferré et al., 2017). Based on these notions, two novel medications are being obtained: perampanel and dipyridamole (Romero-Peralta et al., 2020).

Perampanel, an Alpha-amino-3-hydroxy-Methyl-4-isoxazole Propionic Acid (AMPA) receptor antagonist, was tested in 22 individuals with RLS during the course of a therapy that lasted for eight weeks. Both of these drugs improved RLS symptoms significantly (Garcia-Borreguero et al., 2017).

The administration of dipyridamole, a medication that inhibits Equilibrative Nucleoside Transporter 1 (ENT-1) reuptake mechanisms and as a consequence, raises extracellular adenosine levels, led to a reduction in the extent of RLS symptoms as well (Garcia-Borreguero et al., 2018).

Several research have been conducted to explore the efficacy of nonpharmacological therapies that are alternative and complimentary (Romero-Peralta et al., 2020). Altering the excitability of the cortex is one of the goals of the noninvasive therapy known as Repetitive transcranial magnetic stimulation (RTMS). Patients diagnosed with RLS may find that RTMS significantly improves their motor system symptoms as well as their anxiety and this improvement may last for at least two months (Lin et al., 2015). Randomized controlled trials are required in order to determine

whether or not a new medication or nonpharmacological therapy is successful (Romero-Peralta et al., 2020).

Sleep hygiene: Maintaining good sleep hygiene entails engaging in a variety of activities and routines that work to improve one's capacity for rest. The most important piece of advice is to establish a schedule for oneself, so that one may make an effort to go to sleep at the same time every night. Following an extended period of exercise, at the same time each day. Before going to bed, taking a warm bath or engaging in some other light exercise for a few minutes. Patients who suffer RLS should make every effort to avoid situations in which they are sleep deprived since this might make their symptoms worse. Therefore, the purpose of sleep hygiene is to make it possible for a person who has RLS to receive the recommended amount of sleep (W. A. Hening, 2007).

Lifestyle modification: Only anecdotal accounts and clinical impressions may serve as evidence for the efficacy of making changes to one’s lifestyle. It would suggest that coffee and nicotine are able to make RLS symptoms worse. Alcohol, particularly when drank in the evening, is known to exacerbate the symptoms of RLS. Patients should be made aware of the potential side effects of popular stimulants and sedatives, since avoiding or lowering consumption of these substances may result in reduced symptoms of RLS. People should also be encouraged to integrate a reasonable amount of physical activity into their everyday routines. A number of epidemiologic studies have suggested that a lack of any exercise is positively associated with exacerbation of RLS symptoms. This is contrary to the experience of many patients, who report an increase in symptoms later in the evening after engaging in strenuous exercise during the day. Patients diagnosed with RLS should give serious consideration to adopting a healthy lifestyle, which includes regular, but not too strenuous physical activity and adherence to dietary guidelines designed to lower the risk of cardiovascular and metabolic disorders (W. A. Hening, 2007).

4.2 Treatment in Pregnancy

4.2.1 Dopaminergic drugs: Dopaminergic agent supplementation could be the most effective treatment option in pregnancy (Srivanitchapoom et al., 2014). In addition, American Academy of Sleep Medicine (AASM) advocate dopaminergic drugs as the medicine of choice for the first stage of treatment of RLS (Aurora et al., 2012; Garcia-Borreguero et al., 2012). There are compounds that are not derived from ergot, such as, pramipexole, rotigotine, and ropinirole. Ergot derivatives include bromocriptine and carbergoline. The majority of research on dopaminergic drugs has been conducted on patients with Parkinson's disease and endocrine problems. However, neither the effectiveness nor the safety of these medications have been definitively demonstrated as a means of treating RLS in pregnant women (Srivanitchapoom et al., 2014). The findings pertaining to pramipexole and rotigotine originated from a recent case series gathered information about dopaminergic drugs that are utilized in RLS treatment while pregnant. There was a total of 9 instances in which pramipexole was used during pregnancy and 2 cases in which rotigotine was used and all of the women gave birth to infants who were born without any congenital abnormalities (Dostal et al., 2013). In the case of ropinirole, a woman who was pregnant and had a family history of Parkinson's disease caused by a mutation in the Parkin gene and who took ropinirole for a total of five weeks while she was pregnant was able to give birth to healthy twins (Serikawa et al., 2011). The findings on the safety of levodopa in pregnant women originate from a large number of Parkinson's disease cases that have been documented (Allain et al., 1989; Cook & Klawans, 1985; Hagell et al., 1998). Only 3 out of 42 infants delivered to women who took levodopa during pregnancy were found to have minor birth defects (Dostal et al., 2013). In conclusion, further research has to be done to determine the effectiveness and safety of dopaminergic medications in the treatment of RLS during pregnancy (Srivanitchapoom et al.,

2014).

4.2.2 Iron therapy: It has been established that all pregnant women, regardless of their hemoglobin levels, should get additional oral iron (Gupta et al., 2016). On the other hand, pregnant women with pre-existing RLS may benefit from the iron treatment that is administered intravenously. Even in the absence of pregnancy, women who had low serum ferritin status (<50 mcg/l) benefited from intravenous iron therapy by experiencing a significant alleviation or total disappearance of RLS symptoms (Vadasz et al., 2013). In addition, pregnancies in which women who had RLS before to becoming pregnant were treated with intravenous iron therapy did not result in the development of RLS symptoms until the latter stages of the pregnancy (Picchietti et al., 2012). There are a variety of different formulations of injectable iron available. Comparative research on the effects of intravenous iron carboxymaltose and intravenous iron sucrose was conducted on pregnant women who were anemic. The results showed that both intravenous iron preparations were well tolerated and caused a least amount of side events. However, it has been found that iron carboxymaltose provides a larger amount of iron and hence the medicine of quality for intravenous iron therapy, particularly in the late stages of the second or third trimester (Christoph et al., 2012). Patients who are not pregnant and who have RLS have shown that intravenous iron carboxymaltose is an effective treatment for treating RLS symptoms when used alone as a monotherapy (Allen et al., 2011). It has been discovered that another version of intravenous iron called iron dextran is beneficial in curing RLS; however, greater chance of anaphylactic shock is there (Ondo, 2010).

4.2.3 Antiepileptic drug: In the treatment of RLS, carbamazepine was the first anticonvulsant to be assessed in controlled double-blind research (Telstad et al., 1984). Carbamazepine is a fair alternative for the therapy of RLS in pregnancy as there is a considerable body of information

on the likely security of its usage both for the mother and the baby (Gupta et al., 2016). Carbamazepine was shown to be related with the least danger for birth defect, according to the findings of the Epilepsy and Pregnancy Register in the United Kingdom (Morrow et al., 2006). It has also been shown that gabapentin is a very effective treatment for RLS. Although there are only a few studies available, it seems that gabapentin is safe for both the mother and the developing baby (Montouris, 2003). In a recent meta-analysis of randomized controlled trials for the treatment of RLS, gabapentin and pregabalin were shown to be beneficial in the non-dopaminergic medication category (Hornyak et al., 2014). However, the International Restless Legs Syndrome Study Group consensus guideline discourage its usage during pregnancy (Garcia-Borreguero et al., 2013).

4.2.4 Opioids: According to the guidelines of the American Academy of Sleep Medicine (AASM), opioids including oxycodone, propoxyphene, tramadol and methadone have the potential to be utilized as a treatment for the symptoms of RLS in patients who are not pregnant (Aurora et al., 2012). However, it has not been determined whether or if these medicines are effective in treating RLS in pregnant women (Srivanitchapoom et al., 2014). Recent comprehensive case-controlled research demonstrated a link between early pregnancy maternal opioid analgesic treatment and certain birth defects (Broussard et al., 2011). However, some studies have documented probable examples of newborns who had long-term exposure to tramadol intra-uterine developing neonatal abstinence syndrome. This disease is characterized by withdrawal symptoms in the newborn after the mother stops using the drug (Hartenstein et al., 2010; Meyer et al., 1997; O'Mara et al., 2010; Willaschek et al., 2009). In conclusion, opioids should be avoided as much as possible for the treatment of RLS symptoms during pregnancy (Srivanitchapoom et al., 2014).

4.2.5 Benzodiazepines: There is another option available in the form of benzodiazepines for the treatment of RLS in pregnant women; however, the data supporting their safety in pregnancy is limited. There is an increased risk of cleft palate when benzodiazepines are taken during the first trimester. One meta-analysis, on the other hand, found no relationship between prenatal exposure to benzodiazepines and the likelihood of significant abnormalities or mouth cleft based on the findings of previous research (Dolovich et al., 1998; Enato et al., 2011). On the other hand, when the data from case-control studies were combined, it was shown that there was a considerable elevated risk for serious abnormalities or mouth cleft alone (Dolovich et al., 1998; Enato et al., 2011). Only very few cases of the newborn withdrawal syndrome have been described (Gillberg, 1977). Clonazepam is the benzodiazepine that has been researched and used for RLS the most and it has been proved to be safe and successful in treating the condition. However, temazepam and triazolam have also been demonstrated to be useful in treating the condition (Saletu et al., 2001). Clonazepam was not recommended as a first-line therapy for RLS by the American Academy of Sleep Medicine or the International Restless Legs Syndrome Study Group due to a lack of evidence (Aurora et al., 2012; Garcia-Borreguero et al., 2013).

4.3 Treatment of RLS with Depression

In the recent past, population- and clinic-based epidemiological research have shown an increased incidence of depressive disorders in individuals with RLS (Hornyak et al., 2006). It is still unknown what causes RLS sufferers to also experience symptoms of depression. Recent research demonstrated that sleep disruptions and the negative effects they have are significant variables that contribute to depressed symptoms in RLS patients (Hornyak et al., 2006). Insomnia symptoms, in general, have been shown in the past to have predictive value for the development of depression at a later point (Riemann & Voderholzer, 2003).

The scientists suggested bupropion as a first-choice treatment, but they also suggested noradrenergic antidepressants such reboxetine as an alternate treatment option. In cases where these medications did not provide the desired results, serotonergic antidepressants were used. Some people with RLS may take bupropion or reboxetine, but not all of them can and some of the adverse effects, such as, severe and unacceptable agitation, can occur even at modest doses. The clinical history of the patient seems to be another component that is further essential to the therapy of depression in RLS (Hornyak et al., 2006). If the depressive illness appeared later or in conjunction with severe RLS symptoms, dopamine agonists, which are the first-line therapy for RLS, often not only eliminate RLS but also relieve the symptoms of the underlying depressive condition (W. A. Hening et al., 2004). An extra course of therapy with antidepressants is often required for individuals who were already suffering from a depressive condition prior to the onset of RLS (Hornyak et al., 2006).

4.4 Treatment in Children

Iron reserves are smaller in teenagers than they are in adults because of rise in red cell mass throughout growth phases in both male and female. Therefore, the concentration of serum ferritin in adolescents is often lower than that of adults (Silber et al., 2021). Even if the ideal values have not been determined, one should seriously consider taking iron supplements if the concentration of serum ferritin is lower than 50 mcg/l (Kotagal & Silber, 2004). Oral ferrous sulfate in the amount of 3 to 5 mg/kg should be provided once day before breakfast. The route of administration might be tablet or liquid. Constipation and pain in the stomach region are potential side effects. The concentration of serum ferritin should be measured again after three months to verify that it has increased to a level more than 50 mcg/l (Silber et al., 2021).

Consideration may be given to the use of intravenous iron delivery in the event that oral iron treatment is not well tolerated or is not accompanied by an increase in serum ferritin concentration that is deemed to be sufficient (Silber et al., 2021). In a case series, it was shown that administering iron sucrose at a dose of 5 mg/kg up to a maximum of 200 mg over the course of 2 hours was successful (Grim et al., 2013). Another option is to utilize ferric carboxymaltose at a dose of 10 mg/kg up to a maximum of 1000 mg over the course of one hour (Silber et al., 2021). When iron is administered intravenously, there is a possibility that the patient may have subcutaneous extravasation, which results in a brownish coloring of the skin, gastrointestinal pain and hypersensitivity responses (Silber et al., 2021).

There have been no extensive controlled studies of pharmacologic medicines conducted on children, and the Food and Drug Administration has not given its approval to any medications for the treatment of RLS in children (Silber et al., 2021). The suggestions that are provided below are grounded in a combination of individual experiences and case studies (DelRosso & Bruni, 2019; Rulong et al., 2018). If iron is not required or is ineffective, the first-line drugs that are used include gabapentin (5-15 mg/kg) and pregabalin (2-3 mg/kg). Clonazepam, at dosages ranging from 0.1 to 1 mg, is an example of a second-line agent. Sedation and paradoxical hyperactivity are both potential side effects of this medication. Dopamine agonists such as, pramipexole (0.0625-0.25 mg), ropinirole (0.25-0.5 mg), and the rotigotine patch (1-3 mg) are administered to children. If treatment over a prolonged period of time is being considered, there is a substantial risk of augmentation; hence, it is essential to carefully monitor patients for impulse control disorders. In children, who also have an anxiety disorder or attention deficit hyperactivity disorder, clonidine, which is an alpha-2-adrenergic agonist, is a treatment option that might be examined (0.05-0.4 mg). Sedation, irritability, depression and orthostatic hypotension are among of the potentially harmful side effects that might restrict its use (DelRosso & Bruni, 2019; Rulong et al., 2018).

Chapter 5: Conclusion

5.1 Conclusion

This study has been able to identify the key aspects of the mechanisms of the disease. Studies conducted till now conclude that RLS patients has a dopaminergic dysfunction in the brain and the central nervous system has an iron deficit. Although studies on RLS have clarified the functions of the dopamine and iron systems, it is still unknown what causes either an excess of dopamine or a deficit of iron. The limitations of this study are very minimal yet very crucial. These limitations are related to the study design of those observational studies which are included in this review article. The study design did not match with one another which might have caused variations in the result. Some studies did not diagnose the disease according to International Restless Legs Syndrome Study Group diagnostic criteria which might have led to false positive diagnosis of the patient. To clarify the mechanisms underlying RLS, it will likely take a great deal of human and animal research and it is likely that the true pathophysiologic story of RLS is much more complicated than involvement of one or two biologic systems.

5.2 Future Recommendations

More awareness should be created to recognize this disease among general practitioners. Furthermore, extensive research should be carried on to establish the pathogenesis of the disease from which a universal treatment plan can be achieved. At last, clinical trials should be carried on based on different drug combinations to find drugs which can be beneficial in the long-term treatment of the disease.

Reference

Abril, B., Carlander, B., Touchon, J., & Dauvilliers, Y. (2007). Restless legs syndrome in narcolepsy: A side effect of sodium oxybate? *Sleep Medicine* https://doi.org/10.1016/j.sleep.2006.06.003.

Ağargün, M. Y., Kara, H., Özbek, H., Tombul, T., & Ozer, O. A. (2002). Restless legs syndrome induced by mirtazapine [1]. In *Journal of Clinical Psychiatry* (Vol. 63, Issue 12). https://doi.org/10.4088/JCP.v63n1214a

Aggarwal, S., Dodd, S., & Berk, M. (2010). Restless Leg Syndrome Associated with Olanzapine: A Case Series. In *Current Drug Safety* (Vol. 5).

Akın, S., Bölük, C., Türk Börü, Ü., Taşdemir, M., Gezer, T., Şahbaz, F. G., & Keskin, Ö. (2019). Restless legs syndrome in type 2 diabetes mellitus. *Primary Care Diabetes*, *13*(1). https://doi.org/10.1016/j.pcd.2018.08.006

Akpinar, S. (1982). Treatment of Restless Legs Syndrome With Levodopa Plus Benserazide. In *Archives of Neurology* https://doi.org/10.1001/archneur.1982.00510230065027

Akyol, A., Kiylioglu, N., Kadikoylu, G., Bolaman, A. Z., & Ozgel, N. (2003). Iron deficiency anemia and restless legs syndrome: Is there an electrophysiological abnormality? *Clinical Neurology and Neurosurgery*, *106*(1). https://doi.org/10.1016/j.clineuro.2003.07.004

Alam, M. N., Ahmad, A., Al-Abbasi, F. A., & Ahmad, A. (2013). Female ovarian steroids in epilepsy: A cause or remedy. In *Pharmacological Reports* (Vol. 65, Issue 4). https://doi.org/10.1016/S1734-1140(13)71061-2

Allain, H., Bentue-Ferrer, D., Milon, D., Moran, P., Jacquemard, F., & Defawe, G. (1989). Pregnancy and parkinsonism. A case report without problem. *Clinical Neuropharmacology*, *12*(3). https://doi.org/10.1097/00002826-198906000-00006

Allen, R. P. (2015). Restless Leg Syndrome/Willis-Ekbom Disease Pathophysiology. In *Sleep Medicine Clinics* (Vol. 10, Issue 3, pp. 207–214). W.B. Saunders. https://doi.org/10.1016/j.jsmc.2015.05.022

Allen, R. P., Adler, C. H., Du, W., Butcher, A., Bregman, D. B., & Earley, C. J. (2011). Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial. *Sleep Medicine*, *12*(9), 906–913. https://doi.org/10.1016/j.sleep.2011.06.009

Allen, R. P., Auerbach, S., Bahrain, H., Auerbach, M., & Earley, C. J. (2013a). The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *American Journal of Hematology*, *88*(4). https://doi.org/10.1002/ajh.23397

Allen, R. P., Auerbach, S., Bahrain, H., Auerbach, M., & Earley, C. J. (2013b). The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *American Journal of Hematology*, *88*(4), 261–264. https://doi.org/10.1002/ajh.23397

Allen, R. P., Barker, P. B., Horska, A., & Earley, C. J. (2013). Thalamic glutamate/glutamine in restless legs syndrome increased and related to disturbed sleep. *Neurology*, *80*(22). https://doi.org/10.1212/WNL.0b013e318294b3f6

Allen, R. P., Barker, P. B., Wehrl, F., Song, H. K., & Earley, C. J. (2001). MRI measurement of brain iron in patients with restless legs syndrome. *Neurology*, *56*(2). https://doi.org/10.1212/WNL.56.2.263

Allen, R. P., Connor, J. R., Hyland, K., & Earley, C. J. (2009). Abnormally increased CSF 3-Ortho-methyldopa (3-OMD) in untreated restless legs syndrome (RLS) patients indicates more severe disease and possibly abnormally increased dopamine synthesis. *Sleep Medicine*, *10*(1). https://doi.org/10.1016/j.sleep.2007.11.012

Allen, R. P., & Earley, C. J. (2001). Restless legs syndrome: A review of clinical and pathophysiologic features. In *Journal of Clinical Neurophysiology* (Vol. 18, Issue 2). https://doi.org/10.1097/00004691-200103000-00004

Allen, R. P., Picchietti, D., Hening, W. A., Trenkwalder, C., Walters, A. S., Montplaisi, J., Bara-Jimenez, W., Becker, P., Bell, G., Berger, K., Bliwise, D. L., Brooks, D., Consens, F., Earley, C. J., Ehrenberg, B. L., Foley, D., Murray, C. F., Garcia-Borreguero, D., Hallett, M., … Zucconi, M. (2003). Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine*, *4*(2). https://doi.org/10.1016/S1389-9457(03)00010-8

Allen, R. P., Walters, A. S., Montplaisir, J., Hening, W., Myers, A., Bell, T. J., & Ferini-Strambi, L. (2005a). Restless Legs Syndrome Prevalence and Impact. *Archives of Internal Medicine*, *165*(11). https://doi.org/10.1001/archinte.165.11.1286

Allen, R. P., Walters, A. S., Montplaisir, J., Hening, W., Myers, A., Bell, T. J., & Ferini-Strambi, L. (2005b). Restless legs syndrome prevalence and impact: REST general population study. *Archives of Internal Medicine*, *165*(11). https://doi.org/10.1001/archinte.165.11.1286

Arosemena Coronel, M., Sánchez Armijos, J., Tettamanti Miranda, D., Vásquez Cedeño, D., Mariani Carrera, R., Navarro Chávez, M., & Castillo, P. R. (2017). Excessive daytime somnolence is

associated with hypoglycemia in adult Latinos with type 2 diabetes mellitus. *Sleep Medicine*, *36*. https://doi.org/10.1016/j.sleep.2017.04.012

Aul, E. A., Davis, B. J., & Rodnitzky, R. L. (1998). The importance of formal serum iron studies in the assessment of restless legs syndrome. *Neurology*, *51*(3). https://doi.org/10.1212/WNL.51.3.912

Aurora, R. N., Kristo, D. A., Bista, S. R., Rowley, J. A., Zak, R. S., Casey, K. R., Lamm, C. I., Tracy, S. L., & Rosenberg, R. S. (2012). The treatment of restless legs syndrome and periodic limb movement disorder in adults - An update for 2012: Practice parameters with an evidence-based systematic review and meta-analyses. In *Sleep* (Vol. 35, Issue 8, pp. 1039–1062). https://doi.org/10.5665/sleep.1988

Bae, H., Kim, K. T., Heo, M. H., Do, Y. R., & Cho, Y. W. (2021). The prevalence and clinical characteristics of restless legs syndrome in patients with iron deficiency anemia in Korea. *Journal of Clinical Sleep Medicine*, *17*(7). https://doi.org/10.5664/jcsm.9230

Bahk, W. M., Pae, C. U., Chae, J. H., Jun, T. Y., & Kim, K. S. (2002). Mirtazapine may have the propensity for developing a restless legs syndrome? A case report [2]. In *Psychiatry and Clinical Neurosciences* (Vol. 56, Issue 2). https://doi.org/10.1046/j.1440-1819.2002.00955.x

Bakshi, R. (1996). Fluoxetine and restless legs syndrome. *Journal of the Neurological Sciences*, *142*(1–2). https://doi.org/10.1016/0022-510X(96)00180-3

Balendran, J., Champion, D., Jaaniste, T., & Welsh, A. (2011). A common sleep disorder in pregnancy: Restless legs syndrome and its predictors. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *51*(3). https://doi.org/10.1111/j.1479-828X.2011.01294.x

Basu, A., Kundu, S., & Khurana, H. (2014). Olanzapine-induced restless leg syndrome: A case report and review of literature. *Indian Journal of Pharmacology*, *46*(4). https://doi.org/10.4103/0253-7613.135965

Baum, K. T., Desai, A., Field, J., Miller, L. E., Rausch, J., & Beebe, D. W. (2014). Sleep restriction worsens mood and emotion regulation in adolescents. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *55*(2). https://doi.org/10.1111/jcpp.12125

Bayard, M., Bailey, B., Acharya, D., Ambreen, F., Duggal, S., Kaur, T., Rahman, Z. U., Roller, K., & Tudiver, F. (2011). Bupropion and restless legs syndrome: A randomized controlled trial. *Journal of the American Board of Family Medicine*, *24*(4). https://doi.org/10.3122/jabfm.2011.04.100173

Bayard, S., Langenier, M. C., & Dauvilliers, Y. (2013). Decision-making, reward-seeking behaviors and dopamine agonist therapy in restless legs syndrome. *Sleep*, *36*(10). https://doi.org/10.5665/sleep.3044

Benediktsdottir, B., Janson, C., Lindberg, E., Arnardóttir, E. S., Olafsson, I., Cook, E., Thorarinsdottir, E. H., & Gislason, T. (2010). Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep Medicine*, *11*(10). https://doi.org/10.1016/j.sleep.2010.08.006

Bermejo, P. E. (2009). Restless legs syndrome induced by topiramate: Two more cases. In *Journal of Neurology* (Vol. 256, Issue 4). https://doi.org/10.1007/s00415-009-0073-5

Bhagawati, J., Kumar, S., Agrawal, A., Acharya, S., Wanjari, A., & Kamble, T. (2019). Impact of different stages of chronic kidney disease on the severity of Willis–Ekbom disease. *Journal of Family Medicine and Primary Care*, *8*(2). https://doi.org/10.4103/jfmpc.jfmpc_418_18

Bolaños-Vergaray, J., Obaya, J. C., Gonzalez, R., Echeverri, C., & Piquer, P. (2011). Restless legs syndrome due to aripiprazole. In *European Journal of Clinical Pharmacology* (Vol. 67, Issue 5). https://doi.org/10.1007/s00228-010-0952-9

Bonin, B., Vandel, P., & Kantelip, J. P. (2000). Mirtazapine and restless leg syndrome: A case report [4]. In *Therapie* (Vol. 55, Issue 5).

Bottiglieri, T., Hyland, K., Laundy, M., Godfrey, P., Carney, M. W. P., & Toone, B. K. (1992). Folate deficiency, biopterin and monoamine metabolism in depression. *Psychological Medicine*, *22*(4). https://doi.org/10.1017/S0033291700038447

Brand, S., Beck, J., Hatzinger, M., & Holsboer-Trachsler, E. (2013). Patients suffering from restless legs syndrome have low internal locus of control and poor psychological functioning compared to healthy controls. *Neuropsychobiology*, *68*(1). https://doi.org/10.1159/000350957

Broussard, C. S., Rasmussen, S. A., Reefhuis, J., Friedman, J. M., Jann, M. W., Riehle-Colarusso, T., & Honein, M. A. (2011). Maternal treatment with opioid analgesics and risk for birth defects. *American Journal of Obstetrics and Gynecology*, *204*(4), 314.e1-314.e11. https://doi.org/10.1016/j.ajog.2010.12.039

Budhiraja, P., Budhiraja, R., Goodwin, J. L., Allen, R. P., Newman, A. B., Koo, B. B., & Quan, S. F. (2012). Incidence of restless legs syndrome and its correlates. *Journal of Clinical Sleep Medicine*, *8*(2). https://doi.org/10.5664/jcsm.1756

Castillo-Torres, S. A., Ibarra-Sifuentes, H. R., Sánchez-Terán, H., Sánchez-Martínez, C., Chávez-Luévanos, B., & Estrada-Bellmann, I. (2018). Restless legs syndrome in end-stage renal disease patients undergoing hemodialysis. *Arquivos de Neuro-Psiquiatria*, *76*(12), 827–830. https://doi.org/10.1590/0004-282x20180133

Chang, C. C., Shiah, I. S., Chang, H. A., & Mao, W. C. (2006). Does domperidone potentiate mirtazapine-associated restless legs syndrome? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(2). https://doi.org/10.1016/j.pnpbp.2005.10.001

Chapman, P. J. C., Wilkinson, P. R., & Davidson, R. N. (1988). *Restless leg syndrome in pregnancy*.

Chathanchirayil, S. J. (2011). Restless Legs Syndrome Probably due to Clozapine. *Australian & New Zealand Journal of Psychiatry*, *45*(11). https://doi.org/10.3109/00048674.2011.594949

Chen, J. T., Garcia, P. A., & Alldredge, B. K. (2003). Zonisamide-induced restless legs syndrome. *Neurology*, *60*(1). https://doi.org/10.1212/WNL.60.1.147

Chen, P. H. (2016). Restless leg syndrome induced by escitalopram and lithium combined with quetiapine treatment in bipolar II disorder: A case report. In *Clinical Neuropharmacology* (Vol. 39, Issue 2). https://doi.org/10.1097/WNF.0000000000000135

Chen, S. J., Shi, L., Bao, Y. P., Sun, Y. K., Lin, X., Que, J. Y., Vitiello, M. v., Zhou, Y. X., Wang, Y. Q., & Lu, L. (2018). Prevalence of restless legs syndrome during pregnancy: A systematic review and meta-analysis. In *Sleep Medicine Reviews* (Vol. 40, pp. 43–54). W.B. Saunders Ltd. https://doi.org/10.1016/j.smrv.2017.10.003

Chenini, S., Arnulf, I., Monaca, C. C., & Ghorayeb, I. (2018). French consensus: Pharmacoresistant restless legs syndrome. In *Revue Neurologique* (Vol. 174, Issues 7–8, pp. 522–531). Elsevier Masson SAS. https://doi.org/10.1016/j.neurol.2018.06.003

Chopra, A., Pendergrass, D. S., & Michael Bostwick, J. (2011). Mirtazapine-induced worsening of restless legs syndrome (RLS) and ropinirole-induced psychosis: Challenges in management of depression in RLS. *Psychosomatics*, *52*(1). https://doi.org/10.1016/j.psym.2010.11.009

Chou, K. J., Chen, P. Y., & Huang, M. C. (2010). Restless legs syndrome following the combined use of quetiapine and paroxetine. In *Progress in Neuro-Psychopharmacology and Biological Psychiatry* (Vol. 34, Issue 6). https://doi.org/10.1016/j.pnpbp.2010.05.009

Chrastina, M., Martinková, J., Minar, M., Zilinska, Z., Valkovic, P., & Breza, J. (2015). Impact of kidney transplantation on restless legs syndrome. *Bratislava Medical Journal*, *116*(7). https://doi.org/10.4149/BLL_2015_077

Christoph, P., Schuller, C., Studer, H., Irion, O., de Tejada, B. M., & Surbek, D. (2012). Intravenous iron treatment in pregnancy: Comparison of high-dose ferric carboxymaltose vs. iron sucrose. *Journal of Perinatal Medicine*, *40*(5). https://doi.org/10.1515/jpm-2011-0231

Collado-Seidel, V., Kohnen, R., Samtleben, W., Hillebrand, G. F., Oertel, W. H., & Trenkwalder, C. (1998). Clinical and biochemical findings in uremic patients with and without restless legs syndrome. *American Journal of Kidney Diseases*, *31*(2). https://doi.org/10.1053/ajkd.1998.v31.pm9469505

Connor, J. R., Ponnuru, P., Lee, B. Y., Podskalny, G. D., Alam, S., Allen, R. P., Earley, C. J., & Yang, Q. X. (2011). Postmortem and imaging based analyses reveal CNS decreased myelination in restless legs syndrome. *Sleep Medicine*, *12*(6). https://doi.org/10.1016/j.sleep.2010.10.009

Connor, J. R., Ponnuru, P., Wang, X. S., Patton, S. M., Allen, R. P., & Earley, C. J. (2011). Profile of altered brain iron acquisition in restless legs syndrome. *Brain*, *134*(4). https://doi.org/10.1093/brain/awr012

Connor, J. R., Wang, X. S., Allen, R. P., Beard, J. L., Wiesinger, J. A., Felt, B. T., & Earley, C. J. (2009). Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain*, *132*(9). https://doi.org/10.1093/brain/awp125

Connor, J. R., Wang, X. S., Patton, S. M., Menzies, S. L., Troncoso, J. C., Earley, C. J., & Allen, R. P. (2004). Decreased transferrin receptor expression by neuromelanin cells in restless legs syndrome. *Neurology*, *62*(9). https://doi.org/10.1212/01.WNL.0000123251.60485.AC

Cook, D. G., & Klawans, H. L. (1985). *Levodopa during pregnancy*.

Cuellar, N. G., & Ratcliffe, S. J. (2008a). A comparison of glycemic control, sleep, fatigue, and depression in type 2 diabetes with and without restless legs syndrome. *Journal of Clinical Sleep Medicine*, *4*(1). https://doi.org/10.5664/jcsm.27079

Cuellar, N. G., & Ratcliffe, S. J. (2008b). Restless legs syndrome in type 2 diabetes implications to diabetes educators. *Diabetes Educator*, *34*(2), 218–234. https://doi.org/10.1177/0145721708314180

Dauvilliers, Y., & Winkelmann, J. (2013). Restless legs syndrome: Update on pathogenesis. In *Current Opinion in Pulmonary Medicine* (Vol. 19, Issue 6, pp. 594–600). https://doi.org/10.1097/MCP.0b013e328365ab07

DelRosso, L., & Bruni, O. (2019). Treatment of pediatric restless legs syndrome. In *Advances in Pharmacology* (Vol. 84). https://doi.org/10.1016/bs.apha.2018.11.001

Dolovich, L. R., Addis, A., Vaillancourt, J. M. R., Power, J. D. B., Koren, G., & Einarson, T. R. (1998). Benzodiazepine use in pregnancy and major malformations or oral cleft: Meta-analysis of cohort and case-control studies. *British Medical Journal*, *317*(7162). https://doi.org/10.1136/bmj.317.7162.839

Dostal, M., Weber-Schoendorfer, C., Sobesky, J., & Schaefer, C. (2013). Pregnancy outcome following use of levodopa, pramipexole, ropinirole, and rotigotine for restless legs syndrome

during pregnancy: A case series. *European Journal of Neurology*, *20*(9), 1241–1246. https://doi.org/10.1111/ene.12001

Duggal, H. S., & Mendhekar, D. N. (2007). Clozapine-associated restless legs syndrome [1]. In *Journal of Clinical Psychopharmacology* (Vol. 27, Issue 1). https://doi.org/10.1097/JCP.0b013e31802e7587

Earley, C. J., Allen, R. P., Beard, J. L., & Connor, J. R. (2000). Insight into the pathophysiology of restless legs syndrome. In *Journal of Neuroscience Research* (Vol. 62, Issue 5). https://doi.org/10.1002/1097-4547(20001201)62:5<623::AID-JNR1>3.0.CO;2-H

Earley, C. J., B. Barker, P., Horská, A., & Allen, R. P. (2006). MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. *Sleep Medicine*, *7*(5). https://doi.org/10.1016/j.sleep.2005.11.009

Earley, C. J., Connor, J., Garcia-Borreguero, D., Jenner, P., Winkelman, J., Zee, P. C., & Allen, R. (2014). Altered Brain iron homeostasis and dopaminergic function in Restless Legs Syndrome (Willis-Ekbom Disease). In *Sleep Medicine* (Vol. 15, Issue 11). https://doi.org/10.1016/j.sleep.2014.05.009

Earley, C. J., Connor, J. R., Beard, J. L., Malecki, E. A., Epstein, D. K., & Allen, R. P. (2000). Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology*, *54*(8). https://doi.org/10.1212/WNL.54.8.1698

Earley, C. J., Kuwabara, H., Wong, D. F., Gamaldo, C., Salas, R., Brasic, J., Ravert, H. T., Dannals, R. F., & Allen, R. P. (2011). The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. *Sleep*, *34*(3). https://doi.org/10.1093/sleep/34.3.341

Earley, C. J., & Silber, M. H. (2010). Restless legs syndrome: Understanding its consequences and the need for better treatment. In *Sleep Medicine* (Vol. 11, Issue 9, pp. 807–815). https://doi.org/10.1016/j.sleep.2010.07.007

Enato, E., Moretti, M., & Koren, G. (2011). Motherisk Rounds: The Fetal Safety of Benzodiazepines: An Updated Meta-analysis. *Journal of Obstetrics and Gynaecology Canada*, *33*(1). https://doi.org/10.1016/S1701-2163(16)34772-7

Fenton, V., Cavill, I., & Fisher, J. (1977). Iron Stores in Pregnancy. *British Journal of Haematology*, *37*(1). https://doi.org/10.1111/j.1365-2141.1977.tb08819.x

Ferré, S., Earley, C., Gulyani, S., & Garcia-Borreguero, D. (2017). In search of alternatives to dopaminergic ligands for the treatment of restless legs syndrome: iron, glutamate, and adenosine. In *Sleep Medicine* (Vol. 31). https://doi.org/10.1016/j.sleep.2016.08.019

Freedom, T., & Merchut, M. P. (2003). *Arm Restlessness as the Initial Symptom in Restless Legs Syndrome*. http://archneur.jamanetwork.com/

Gallego, M., Setién, R., Izquierdo, M. J., Casis, O., & Casis, E. (2003). Diabetes-Induced Biochemical Changes in Central and Peripheral Catecholaminergic Systems. *Physiological Research*, *52*(6).

Gamaldo, C. E., & Earley, C. J. (2006). Restless legs syndrome: A clinical update. *Chest*, *130*(5), 1596–1604. https://doi.org/10.1378/chest.130.5.1596

Garcia-Borreguero, D., Cano, I., & Granizo, J. J. (2017). Treatment of restless legs syndrome with the selective AMPA receptor antagonist perampanel. *Sleep Medicine*, *34*. https://doi.org/10.1016/j.sleep.2017.03.012

Garcia-Borreguero, D., Ferini-Strambi, L., Kohnen, R., O'Keeffe, S., Trenkwalder, C., Högl, B., Benes, H., Jennum, P., Partinen, M., Fer, D., Montagna, P., Bassetti, C. L., Iranzo, A., Sonka, K., & Williams, A. M. (2012). European guidelines on management of restless legs syndrome: Report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *European Journal of Neurology*, *19*(11). https://doi.org/10.1111/j.1468-1331.2012.03853.x

Garcia-Borreguero, D., Guitart, X., Garcia Malo, C., Cano-Pumarega, I., Granizo, J. J., & Ferré, S. (2018). Treatment of restless legs syndrome/Willis-Ekbom disease with the non-selective ENT1/ENT2 inhibitor dipyridamole: testing the adenosine hypothesis. *Sleep Medicine, 45*. https://doi.org/10.1016/j.sleep.2018.02.002

Garcia-Borreguero, D., Kohnen, R., Silber, M. H., Winkelman, J. W., Earley, C. J., Högl, B., Manconi, M., Montplaisir, J., Inoue, Y., & Allen, R. P. (2013). The long-term treatment of restless legs syndrome/Willis-Ekbom disease: Evidence-based guidelines and clinical consensus best practice guidance: A report from the International Restless Legs Syndrome Study Group. *Sleep Medicine*, *14*(7). https://doi.org/10.1016/j.sleep.2013.05.016

Gemignani, F., Brindani, F., Negrotti, A., Vitetta, F., Alfieri, S., & Marbini, A. (2006). Restless legs syndrome and polyneuropathy. *Movement Disorders*, *21*(8). https://doi.org/10.1002/mds.20928

Ghori, A. K., Sajatovic, M., & Tampi, R. R. (2016). A case of emergent restless legs syndrome with lurasidone therapy. In *Journal of Clinical Psychopharmacology* (Vol. 36, Issue 3). https://doi.org/10.1097/JCP.0000000000000496

Gigli, G. L., Adorati, M., Dolso, P., Piani, A., Valente, M., Brotini, S., & Budai, R. (2004a). Restless legs syndrome in end-stage renal disease. *Sleep Medicine*, *5*(3), 309–315. https://doi.org/10.1016/j.sleep.2004.01.014

Gigli, G. L., Adorati, M., Dolso, P., Piani, A., Valente, M., Brotini, S., & Budai, R. (2004b). Restless legs syndrome in end-stage renal disease. *Sleep Medicine*, *5*(3), 309–315. https://doi.org/10.1016/j.sleep.2004.01.014

Gillberg, C. (1977). *"Floppy infant syndrome" and maternal diazepam*.

Godau, J., Klose, U., di Santo, A., Schweitzer, K., & Berg, D. (2008). Multiregional brain iron deficiency in restless legs syndrome. *Movement Disorders*, *23*(8). https://doi.org/10.1002/mds.22070

Goffredo Filho, G. S., Gorini, C. C., Purysko, A. S., Silva, H. C., & Elias, I. E. F. (2003). RESTLESS LEGS SYNDROME IN PATIENTS ON CHRONIC HEMODIALYSIS IN A BRAZILIAN CITY Frequency, biochemical findings and comorbidities. In *Arq Neuropsiquiatr* (Vol. 61, Issue B).

Grim, K., Lee, B., Sung, A. Y., & Kotagal, S. (2013). Treatment of childhood-onset restless legs syndrome and periodic limb movement disorder using intravenous iron sucrose. *Sleep Medicine*, *14*(11). https://doi.org/10.1016/j.sleep.2013.06.006

Guo, S., Huang, J., Jiang, H., Han, C., Li, J., Xu, X., Zhang, G., Lin, Z., Xiong, N., & Wang, T. (2017). Restless legs syndrome: From pathophysiology to clinical diagnosis and management. In *Frontiers in Aging Neuroscience* (Vol. 9, Issue JUN). Frontiers Media S.A. https://doi.org/10.3389/fnagi.2017.00171

Gupta, R., Dhyani, M., Kendzerska, T., Pandi-Perumal, S. R., Bahammam, A. S., Srivanitchapoom, P., Pandey, S., & Hallett, M. (2016). Restless legs syndrome and pregnancy: Prevalence, possible pathophysiological mechanisms and treatment. In *Acta Neurologica Scandinavica* (Vol. 133, Issue 5, pp. 320–329). Blackwell Publishing Ltd. https://doi.org/10.1111/ane.12520

Hagell, P., Odin, P., & Vinge, E. (1998). Pregnancy in Parkinson's disease: A review of the literature and a case report. *Movement Disorders*, *13*(1). https://doi.org/10.1002/mds.870130110

Happe, S., Reese, J. P., Stiasny-Kolster, K., Peglau, I., Mayer, G., Klotsche, J., Giani, G., Geraedts, M., Trenkwalder, C., & Dodel, R. (2009). Assessing health-related quality of life in patients with restless legs syndrome. *Sleep Medicine*, *10*(3). https://doi.org/10.1016/j.sleep.2008.01.002

Harano, S., Ohida, T., Kaneita, Y., Yokoyama, E., Tamaki, T., Takemura, S., Osaki, Y., & Hayashi, K. (2008). Prevalence of restless legs syndrome with pregnancy and the relationship with sleep disorders in the Japanese large population. *Sleep and Biological Rhythms*, *6*(2). https://doi.org/10.1111/j.1479-8425.2008.00343.x

Hargrave, R., & Beckley, D. J. (1998). Restless leg syndrome exacerbated by sertraline [2]. In *Psychosomatics* (Vol. 39, Issue 2). https://doi.org/10.1016/S0033-3182(98)71370-2

Hartenstein, S., Proquitte, H., Bauer, S., Bamberg, C., & Roehr, C. C. (2010). Neonatal abstinence syndrome (NAS) after intrauterine exposure to tramadol. In *Journal of Perinatal Medicine* (Vol. 38, Issue 6, pp. 695–696). https://doi.org/10.1515/JPM.2010.102

Heiman, E. M., & Christie, M. (1986). Lithium-aggravated nocturnal myoclonus and restless legs syndrome. In *The American journal of psychiatry* (Vol. 143, Issue 9). https://doi.org/10.1176/ajp.143.9.1191b

Hening, W. (2004). The clinical neurophysiology of the restless legs syndrome and periodic limb movements. Part I: Diagnosis, assessment, and characterization. In *Clinical Neurophysiology* (Vol. 115, Issue 9, pp. 1965–1974). https://doi.org/10.1016/j.clinph.2004.03.032

Hening, W. A. (2007). Current Guidelines and Standards of Practice for Restless Legs Syndrome. *American Journal of Medicine*, *120*(1 SUPPL. 1). https://doi.org/10.1016/j.amjmed.2006.11.004

Hening, W. A., Allen, R. P., Earley, C. J., Picchietti, D. L., & Silber, M. H. (2004). An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. In *Sleep* (Vol. 27, Issue 3). https://doi.org/10.1093/sleep/27.3.560

Hoque, R., & Chesson, A. L. (2010). Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: Literature review, qualitative scoring, and comparative analysis. In *Journal of Clinical Sleep Medicine* (Vol. 6, Issue 1). https://doi.org/10.5664/jcsm.27716

Horiguchi, J., Yamashita, H., Mizuno, S., Kuramoto, Y., Kagaya, A., Yamawaki, S., & Inami, Y. (1999). Nocturnal eating/drinking syndrome and neuroleptic-induced restless legs syndrome. *International Clinical Psychopharmacology*, *14*(1).

Hornyak, M., Scholz, H., Kohnen, R., Bengel, J., Kassubek, J., & Trenkwalder, C. (2014). What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. In *Sleep Medicine Reviews* (Vol. 18, Issue 2). https://doi.org/10.1016/j.smrv.2013.03.004

Hornyak, M., Voderholzer, U., & Riemann, D. (2006). Treatment of depression in patients with restless legs syndrome: What is evidence-based? In *Sleep Medicine* (Vol. 7, Issue 3, pp. 301–302). https://doi.org/10.1016/j.sleep.2005.12.008

Hui, D. S. C., Wong, T. Y. H., Ko, F. W. S., Li, T. S. T., Choy, D. K. L., Wong, K. K., Szeto, C. C., Lui, S. F., & Li, P. K. T. (2000). Prevalence of sleep disturbances in Chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. *American Journal of Kidney Diseases*, *36*(4). https://doi.org/10.1053/ajkd.2000.17664

Hui, D. S. C., Wong, T. Y. H., Li, T. S. T., Ko, F. W. S., Choy, D. K. L., Szeto, C. C., Lui, S. F., & Li, P. K. T. (2002). Prevalence of sleep disturbances in Chinese patients with end stage renal failure on maintenance hemodialysis. *Medical Science Monitor*, *8*(5).

Innes, K. E., Selfe, T. K., & Agarwal, P. (2012). Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: A systematic review. In *Sleep Medicine Reviews* (Vol. 16, Issue 4). https://doi.org/10.1016/j.smrv.2011.04.001

Ioja, S., Weir, I. D., & Rennert, N. J. (2012). Relationship between sleep disorders and the risk for developing type 2 diabetes mellitus. *Postgraduate Medicine*, *124*(4), 119–129. https://doi.org/10.3810/pgm.2012.07.2573

Ito, E., & Inoue, Y. (2015). The International Classification of Sleep Disorders, third edition. American Academy of Sleep Medicine. Includes bibliographies and index. In *Nihon rinsho. Japanese journal of clinical medicine* (Vol. 73, Issue 6).

John, A. P., Adriana, S., Anne La'Brooy, J., & Piepiorka-Sokolowska, D. (2014). Successful treatment of clozapine-associated restless leg syndrome with pramipexole. In *Journal of*

Clinical Psychopharmacology (Vol. 34, Issue 6). https://doi.org/10.1097/JCP.0000000000000225

Kang, S. G., Lee, H. J., & Kim, L. (2009). Restless legs syndrome and periodic limb movements during sleep probably associated with olanzapine. *Journal of Psychopharmacology*, *23*(5). https://doi.org/10.1177/0269881108091876

Kaplan, Y., Inonu, H., Yilmaz, A., & Ocal, S. (2008). Restless legs syndrome in patients with chronic obstructive pulmonary disease. *Canadian Journal of Neurological Sciences*, *35*(3). https://doi.org/10.1017/S0317167100008957

Karroum, E. G., Raux, M., Riou, B., & Arnulf, I. (2010). Implications anesthésiques du syndrome des jambes sans repos: observations cliniques et recommandations pratiques. *Annales Francaises d'Anesthesie et de Reanimation*, *29*(12). https://doi.org/10.1016/j.annfar.2010.09.002

Kaufman, S. (1991). Some metabolic relationships between biopterin and folate: Implications for the "methyl trap hypothesis." *Neurochemical Research*, *16*(9). https://doi.org/10.1007/BF00965847

Khalid, I., Rana, L., Khalid, T. J., & Roehrs, T. (2009). Refractory restless legs syndrome likely caused by olanzapine. *Journal of Clinical Sleep Medicine*, *5*(1). https://doi.org/10.5664/jcsm.27396

Khan, F. H., Ahlberg, C. D., Chow, C. A., Shah, D. R., & Koo, B. B. (2017). Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. In *Journal of Neurology* (Vol. 264, Issue 8, pp. 1634–1641). Dr. Dietrich Steinkopff Verlag GmbH and Co. KG. https://doi.org/10.1007/s00415-017-8431-1

Klumpers, U. M. H., Veltman, D. J., van Tol, M. J., Kloet, R. W., Boellaard, R., Lammertsma, A. A., & Hoogendijk, W. J. G. (2015). Neurophysiological effects of sleep deprivation in healthy adults, a pilot study. *PLoS ONE*, *10*(1). https://doi.org/10.1371/journal.pone.0116906

Kolukisa, M., Soysal, P., Gültekin, T. Ö., Karatoprak, C., Bilgen, H. R., & Gürsoy, A. E. (2016). Restless Leg Syndrome/Willis-Ekbom disease in women with iron deficiency anemia, A nyugtalan láb szindróma / Willis-Ekbom-betegség vashiányos anaemiás nők körében. *Ideggyógyászati Szemle*, *69*(9–10). https://doi.org/10.18071/isz.69.0356

Kotagal, S., & Silber, M. H. (2004). Childhood-onset restless legs syndrome. *Annals of Neurology*, *56*(6). https://doi.org/10.1002/ana.20292

Kraus, T., Schuld, A., & Pollmacher, T. (1999). Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine [5]. In *Journal of Clinical Psychopharmacology* (Vol. 19, Issue 5). https://doi.org/10.1097/00004714-199910000-00017

Kumar, V., Ambekar, N., Singh, A., & Venkatasubramanian, G. (2014). Successful treatment of antipsychotic-induced restless legs syndrome with gabapentin. In *Asian Journal of Psychiatry* (Vol. 9). https://doi.org/10.1016/j.ajp.2014.01.010

Kushida, C. A. (2007). Clinical Presentation, Diagnosis, and Quality of Life Issues in Restless Legs Syndrome. *American Journal of Medicine*, *120*(1 SUPPL. 1). https://doi.org/10.1016/j.amjmed.2006.11.002

Kushida, C., Martin, M., Nikam, P., Blaisdell, B., Wallenstein, G., Ferini-Strambi, L., & Ware, J. E. (2007). Burden of restless legs syndrome on health-related quality of life. *Quality of Life Research*, *16*(4), 617–624. https://doi.org/10.1007/s11136-006-9142-8

Leschziner, G., & Gringras, P. (2012). Restless legs syndrome. In *BMJ (Online)* (Vol. 344, Issue 7858). https://doi.org/10.1136/bmj.e3056

Lin, Y. C., Feng, Y., Zhan, S. Q., Li, N., Ding, Y., Hou, Y., Wang, L., Lin, H., Sun, Y., Huang, Z. Y., Xue, Q., & Wang, Y. P. (2015). Repetitive transcranial magnetic stimulation for the treatment of restless legs syndrome. *Chinese Medical Journal*, *128*(13). https://doi.org/10.4103/0366-6999.159344

lo Coco, D., Mattaliano, A., Coco, A. lo, & Randisi, B. (2009). Increased frequency of restless legs syndrome in chronic obstructive pulmonary disease patients. *Sleep Medicine*, *10*(5). https://doi.org/10.1016/j.sleep.2008.04.014

Loewen, A., Siemens, A. D., & Hanly, P. (2009). Sleep disruption in patients with sleep apnea and end-stage renal disease. *Journal of Clinical Sleep Medicine*, *5*(4). https://doi.org/10.5664/jcsm.27542

Lopes, L. A., Lins, C. D. M. M., Adeodato, V. G., Quental, D. P., de Bruin, P. F. C., Montenegro, R. M., & de Bruin, V. M. S. (2005). Restless legs syndrome and quality of sleep in type 2 diabetes. *Diabetes Care*, *28*(11). https://doi.org/10.2337/diacare.28.11.2633

Mackie, S., & Winkelman, J. W. (2015). Restless Legs Syndrome and Psychiatric Disorders. In *Sleep Medicine Clinics* (Vol. 10, Issue 3, pp. 351–357). W.B. Saunders. https://doi.org/10.1016/j.jsmc.2015.05.009

Makiguchi, A., Nishida, M., Shioda, K., Suda, S., Nisijima, K., & Kato, S. (2015). Mirtazapine-induced restless legs syndrome treated with pramipexole. In *Journal of Neuropsychiatry and Clinical Neurosciences* (Vol. 27, Issue 1). https://doi.org/10.1176/appi.neuropsych.13120357

Manconi, M., Ferri, R., Zucconi, M., Clemens, S., Giarolli, L., Bottasini, V., & Ferini-Strambi, L. (2011). Preferential D2 or preferential D3 dopamine agonists in restless legs syndrome. *Neurology*, *77*(2). https://doi.org/10.1212/WNL.0b013e3182242d91

Manconi, M., Garcia-Borreguero, D., Schormair, B., Videnovic, A., Berger, K., Ferri, R., & Dauvilliers, Y. (2021). Restless legs syndrome. In *Nature Reviews Disease Primers* (Vol. 7, Issue 1). Nature Research. https://doi.org/10.1038/s41572-021-00311-z

Manconi, M., Govoni, V., de Vito, A., Economou, N. T., Cesnik, E., Casetta, I., Mollica, G., Ferini-Strambi, L., & Granieri, E. (2004a). Restless legs syndrome and pregnancy. *Neurology*, *63*(6), 1065–1069. https://doi.org/10.1212/01.WNL.0000138427.83574.A6

Manconi, M., Govoni, V., de Vito, A., Economou, N. T., Cesnik, E., Casetta, I., Mollica, G., Ferini-Strambi, L., & Granieri, E. (2004b). Restless legs syndrome and pregnancy. *Neurology*, *63*(6), 1065–1069. https://doi.org/10.1212/01.WNL.0000138427.83574.A6

Manconi, M., Govoni, V., de Vito, A., Tiberio Economou, N., Cesnik, E., Mollica, G., & Granieri, E. (2004). Pregnancy as a risk factor for restless legs syndrome. *Sleep Medicine*, *5*(3). https://doi.org/10.1016/j.sleep.2004.01.013

McCall, W. V., Riley, M. A., Hodges, C., McCloud, L., Phillips, M., & Rosenquist, P. B. (2014). Asenapine-induced restless legs syndrome: Differentiation from akathisia. *Journal of Clinical Sleep Medicine*, *10*(12). https://doi.org/10.5664/jcsm.4296

Meharaban, Z., Yahya, S., & Sadegniiat, K. (2015). Restless legs syndrome during pregnancy and preterm birth in women referred to health centers of ardabil. *Iranian Red Crescent Medical Journal*, *17*(12). https://doi.org/10.5812/ircmj.24438

Merlino, G., Fratticci, L., Valente, M., del Giudice, A., Noacco, C., Dolso, P., Cancelli, I., Scalise, A., & Gigli, G. L. (2007). Association of restless leqs syndrome in type 2 diabetes: A case-control study. *Sleep*, *30*(7). https://doi.org/10.1093/sleep/30.7.866

Merlino, G., Valente, M., Serafini, A., Fratticci, L., del Giudice, A., Piani, A., Noacco, C., & Gigli, G. L. (2010). Effects of restless legs syndrome on quality of life and psychological status in patients with type 2 diabetes. *Diabetes Educator*, *36*(1), 79–87. https://doi.org/10.1177/0145721709351252

Meyer, F. P., Rimasch, H., Blaha, B., & Banditt, P. (1997). Tramadol withdrawal in a neonate. *European Journal of Clinical Pharmacology*, *53*(2). https://doi.org/10.1007/s002280050356

Michopoulos, I., Ferentinos, P., Oulis, P., & Gournellis, R. (2014). Restless legs syndrome associated with the combined use of quetiapine and venlafaxine. In *Journal of Clinical Psychopharmacology* (Vol. 34, Issue 1). https://doi.org/10.1097/JCP.0b013e3182a95af2

Mindell, J. A., Cook, R. A., & Nikolovski, J. (2015). Sleep patterns and sleep disturbances across pregnancy. *Sleep Medicine*, *16*(4). https://doi.org/10.1016/j.sleep.2014.12.006

Mizuno, S., Mihara, T., Miyaoka, T., Inagaki, T., & Horiguchi, J. (2005). CSF iron, ferritin and transferrin levels in restless legs syndrome. *Journal of Sleep Research*, *14*(1). https://doi.org/10.1111/j.1365-2869.2004.00403.x

Modarresnia, L., Golgiri, F., Madani, N. H., Emami, Z., & Tanha, K. (2018). Restless Legs Syndrome in Iranian People With Type 2 Diabetes Mellitus: The Role in Quality of Life and Quality of Sleep. *Journal of Clinical Sleep Medicine*, *14*(2). https://doi.org/10.5664/jcsm.6938

Mohri, I., Kato-Nishimura, K., Tachibana, N., Ozono, K., & Taniike, M. (2008). Restless legs syndrome (RLS): An unrecognized cause for bedtime problems and insomnia in children. In *Sleep Medicine* (Vol. 9, Issue 6). https://doi.org/10.1016/j.sleep.2007.08.005

Möller, J. C., Stiasny, K., Cassel, W., Peter, J. H., Krüger, H. P., & Oertel, W. H. (2000). ["Sleep attacks" in Parkinson patients. A side effect of nonergoline dopamine agonists or a class effect of dopamine agonists?]. *Der Nervenarzt*, *71*(8).

Molnar, M. Z., Novak, M., Ambrus, C., Szeifert, L., Kovacs, A., Pap, J., Remport, A., & Mucsi, I. (2005). Restless legs syndrome in patients after renal transplantation. *American Journal of Kidney Diseases*, *45*(2). https://doi.org/10.1053/j.ajkd.2004.10.007

Molnar, M. Z., Novak, M., & Mucsi, I. (2006). Management of restless legs syndrome in patients on dialysis. In *Drugs* (Vol. 66, Issue 5). https://doi.org/10.2165/00003495-200666050-00003

Molnar, M. Z., Novak, M., Szeifert, L., Ambrus, C., Keszei, A., Koczy, A., Lindner, A., Barotfi, S., Szentkiralyi, A., Remport, A., & Mucsi, I. (2007a). Restless legs syndrome, insomnia, and quality of life after renal transplantation. *Journal of Psychosomatic Research*, *63*(6). https://doi.org/10.1016/j.jpsychores.2007.06.007

Molnar, M. Z., Novak, M., Szeifert, L., Ambrus, C., Keszei, A., Koczy, A., Lindner, A., Barotfi, S., Szentkiralyi, A., Remport, A., & Mucsi, I. (2007b). Restless legs syndrome, insomnia, and quality of life after renal transplantation. *Journal of Psychosomatic Research*, *63*(6). https://doi.org/10.1016/j.jpsychores.2007.06.007

Molnar, M. Z., Szentkiralyi, A., Lindner, A., Czira, M. E., Szeifert, L., Kovacs, A. Z., Fornadi, K., Szabo, A., Rosivall, L., Mucsi, I., & Novak, M. (2007). Restless Legs Syndrome and Mortality

in Kidney Transplant Recipients. *American Journal of Kidney Diseases, 50*(5). https://doi.org/10.1053/j.ajkd.2007.08.003

Montouris, G. (2003). Gabapentin exposure in human pregnancy: Results from the gabapentin pregnancy registry. *Epilepsy and Behavior, 4*(3). https://doi.org/10.1016/S1525-5050(03)00110-0

Montplaisir, J., Boucher, S., Poirier, G., Lavigne, G., Lapierre, O., & Lespérance, P. (1997). Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. *Movement Disorders*, *12*(1). https://doi.org/10.1002/mds.870120111

Moon, H. J., Chang, Y., Lee, Y. S., Song, H. J., Chang, H. W., Ku, J., & Cho, Y. W. (2014). T2 relaxometry using 3.0-tesla magnetic resonance imaging of the brain in early- and late-onset restless legs syndrome. *Journal of Clinical Neurology (Korea), 10*(3). https://doi.org/10.3988/jcn.2014.10.3.197

Morrow, J., Russell, A., Guthrie, E., Parsons, L., Robertson, I., Waddell, R., Irwin, B., McGivern, R. C., Morrison, P. J., & Craig, J. (2006). Malformation risks of antiepileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*(2). https://doi.org/10.1136/jnnp.2005.074203

Mucsi, I., Molnar, M. Z., Ambrus, C., Szeifert, L., Kovacz, A. Z., Zoller, R., Barótfi, S., Remport, A., & Novak, M. (2005). Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrology Dialysis Transplantation*, *20*(3). https://doi.org/10.1093/ndt/gfh654

Nader, P., Coralie, L., Baleydier, B., Andrei, C., Susanne, M., & Damsa, C. (2007). Restless legs syndrome induced by citalopram: a psychiatric emergency? *General Hospital Psychiatry*, *29*(1). https://doi.org/10.1016/j.genhosppsych.2006.10.006

Nikolaou, K. N., Michopoulos, I., Douzenis, A., Papazahos, C., Papageorgiou, C., & Gournellis, R. (2015). Restless legs syndrome associated with the combined use of duloxetine plus paroxetine. In *Journal of Clinical Psychopharmacology* (Vol. 35, Issue 3). https://doi.org/10.1097/JCP.0000000000000306

Novak, M., Winkelman, J. W., & Unruh, M. (2015). Restless Legs Syndrome in Patients With Chronic Kidney Disease. In *Seminars in Nephrology* (Vol. 35, Issue 4, pp. 347–358). W.B. Saunders. https://doi.org/10.1016/j.semnephrol.2015.06.006

Oertel, W., Trenkwalder, C., Beneš, H., Ferini-Strambi, L., Högl, B., Poewe, W., Stiasny-Kolster, K., Fichtner, A., Schollmayer, E., Kohnen, R., & García-Borreguero, D. (2011). Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: A 5-year open-label extension study. *The Lancet Neurology*, *10*(8). https://doi.org/10.1016/S1474-4422(11)70127-2

Ohayon, M. M., O'Hara, R., & Vitiello, M. v. (2012). Epidemiology of restless legs syndrome: A synthesis of the literature. In *Sleep Medicine Reviews* (Vol. 16, Issue 4). https://doi.org/10.1016/j.smrv.2011.05.002

O'Mara, K., Gal, P., & DaVanzo, C. (2010). Treatment of neonatal withdrawal with clonidine after long-term, high-dose maternal use of tramadol. *Annals of Pharmacotherapy*, *44*(7–8), 1342–1344. https://doi.org/10.1345/aph.1M758

Ondo, W. G. (2010). Intravenous iron dextran for severe refractory restless legs syndrome. *Sleep Medicine*, *11*(5). https://doi.org/10.1016/j.sleep.2009.12.002

Ortiz, E., Pasquini, J. M., Thompson, K., Felt, B., Butkus, G., Beard, J., & Connor, J. R. (2004). Effect of manipulation of iron storage, transport, or availability on myelin composition and brain iron content in three different animal models. *Journal of Neuroscience Research*, *77*(5). https://doi.org/10.1002/jnr.20207

Oskarsson, E., Ulfberg, J., & Wåhlin-Larsson, B. (2014). Reduced daytime intramuscular blood flow in patients with restless legs syndrome/Willis-Ekbom disease. *Psychiatry and Clinical Neurosciences*, *68*(8). https://doi.org/10.1111/pcn.12170

Öztürk, Ö., Eraslan, D., & Kumral, E. (2006). Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. In *General Hospital Psychiatry* (Vol. 28, Issue 3). https://doi.org/10.1016/j.genhosppsych.2006.02.009

Pae, C. U., Kim, T. S., Kim, J. J., Chae, J. H., Lee, C. U., Lee, S. J., Paik, I. H., & Lee, C. (2004). Re-administration of mirtazapine could overcome previous mirtazapine-associated restless legs syndrome? [1]. In *Psychiatry and Clinical Neurosciences* (Vol. 58, Issue 6). https://doi.org/10.1111/j.1440-1819.2004.01319.x

Page, R. L., Ruscin, J. M., Bainbridge, J. L., & Brieke, A. A. (2008). Restless legs syndrome induced by escitalopram: Case report and review of the literature. *Pharmacotherapy*, *28*(2). https://doi.org/10.1592/phco.28.2.271

Park, Y. M., Lee, H. J., Kang, S. G., Cho, J. H., & Kim, L. (2009). Resolution of pregabalin and mirtazapine associated restless legs syndrome by bupropion in a patient with major depressive disorder. *Psychiatry Investigation*, *6*(4). https://doi.org/10.4306/pi.2009.6.4.313

Perez-Lloret, S., Rey, M. V., Bondon-Guitton, E., Rascol, O., & Montastruc, A. J. L. (2012). Drugs associated with restless legs syndrome: A case/noncase study in the French pharmacovigilance database. In *Journal of Clinical Psychopharmacology* (Vol. 32, Issue 6). https://doi.org/10.1097/JCP.0b013e318272cdd8

Phillips, B., Hening, W., Britz, P., & Mannino, D. (2006). Prevalence and correlates of restless legs syndrome: Results from the 2005 National Sleep Foundation Poll. *Chest*, *129*(1). https://doi.org/10.1378/chest.129.1.76

Picchietti, D. L., & Stevens, H. E. (2008). Early manifestations of restless legs syndrome in childhood and adolescence. *Sleep Medicine*, *9*(7). https://doi.org/10.1016/j.sleep.2007.08.012

Picchietti, D. L., Wang, V. C., & Picchietti, M. A. (2012). Intravenous iron given prior to pregnancy for restless legs syndrome is associated with remission of symptoms. *Journal of Clinical Sleep Medicine*, *8*(5). https://doi.org/10.5664/jcsm.2168

Pinheiro, T., Thomas, T., Devaraj, U., Ramachandran, P., & Krishnaswamy, U. M. (2020). Prevalence of restless legs syndrome and quality of sleep in type 2 diabetics. *Journal of Diabetes and Its Complications*, *34*(12). https://doi.org/10.1016/j.jdiacomp.2020.107727

Pinninti, N. R., Mago, R., Townsend, J., & Doghramji, K. (2005). Periodic restless legs syndrome associated with quetiapine use: A case report [6]. In *Journal of Clinical Psychopharmacology* (Vol. 25, Issue 6). https://doi.org/10.1097/01.jcp.0000186870.75042.25

Plancoulaine, S., Flori, S., Bat-Pitault, F., Patural, H., Lin, J. S., & Franco, P. (2017). Sleep Trajectories Among Pregnant Women and the Impact on Outcomes: A Population-Based Cohort Study. *Maternal and Child Health Journal*, *21*(5). https://doi.org/10.1007/s10995-016-2212-9

Polydefkis, M., Allen, R. P., Hauer, P., Earley, C. J., Griffin, J. W., & McArthur, J. C. (2000). Subclinical sensory neuropathy in late-onset restless legs syndrome. *Neurology*, *55*(8). https://doi.org/10.1212/WNL.55.8.1115

Prosperetti, C., & Manconi, M. (2015). Restless Legs Syndrome/Willis-Ekbom Disease and Pregnancy. In *Sleep Medicine Clinics* (Vol. 10, Issue 3, pp. 323–329). W.B. Saunders. https://doi.org/10.1016/j.jsmc.2015.05.016

Prospero-Garcia, K. A., Torres-Ruiz, A., Ramirez-Bermudez, J., Yelazquez-Moctezuma, J., Arana-Lechuga, Y., & Teran-Perez, G. (2006). Fluoxetine-mirtazapine interaction may induce restless legs syndrome: Report of 3 cases from a clinical trial [4]. In *Journal of Clinical Psychiatry* (Vol. 67, Issue 11). https://doi.org/10.4088/JCP.v67n1122d

Rafie, S., Jafari, M., Azizi, M., Bahadoram, M., & Jafari, S. (2016). Brief Communication Restless Legs Syndrome in Hemodialysis Patients. In *Saudi J Kidney Dis Transpl* (Vol. 27, Issue 2). http://www.sjkdt.org

Rangarajan, S., & D'Souza, G. A. (2007). Restless legs syndrome in Indian patients having iron deficiency anemia in a tertiary care hospital. *Sleep Medicine*, *8*(3). https://doi.org/10.1016/j.sleep.2006.10.004

Raux, M., Karroum, E. G., & Arnulf, I. (2010). Case scenario: Anesthetic implications of restless legs syndrome. *Anesthesiology*, *112*(6). https://doi.org/10.1097/ALN.0b013e3181de2d66

Raveendranathan, D., Shiva, L., Venkatasubramanian, G., Rao, M. G., Varambally, S., & Gangadhar, B. N. (2013). Clozapine-induced restless legs syndrome treated with aripiprazole. In *Journal of Neuropsychiatry and Clinical Neurosciences* (Vol. 25, Issue 2). https://doi.org/10.1176/appi.neuropsych.12050128

Razeghi, E., Sahraian, M. A., Heidari, R., & Bagherzadeh, M. (2012). Association of inflammatory biomarkers with sleep disorders in hemodialysis patients. *Acta Neurologica Belgica*, *112*(1). https://doi.org/10.1007/s13760-012-0003-7

Riemann, D., & Voderholzer, U. (2003). Primary insomnia: A risk factor to develop depression? *Journal of Affective Disorders*, *76*(1–3). https://doi.org/10.1016/S0165-0327(02)00072-1

Rijsman, R. M., de Weerd, A. W., Stam, C. J., Kerkhof, G. A., & Rosman, J. B. (2004). Periodic limb movement disorder and restless legs syndrome in dialysis patients. *Nephrology*, *9*(6). https://doi.org/10.1111/j.1440-1797.2004.00330.x

Rinaldi, F., Galbiati, A., Marelli, S., Ferini Strambi, L., & Zucconi, M. (2016). Treatment Options in Intractable Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED). In *Current Treatment Options in Neurology* (Vol. 18, Issue 2). https://doi.org/10.1007/s11940-015-0390-1

Rittmannsberger, H., & Werl, R. (2013). Restless legs syndrome induced by quetiapine: Report of seven cases and review of the literature. In *International Journal of Neuropsychopharmacology* (Vol. 16, Issue 6). https://doi.org/10.1017/S1461145712001599

Rizzo, G., Manners, D., Testa, C., Tonon, C., Vetrugno, R., Marconi, S., Plazzi, G., Pizza, F., Provini, F., Malucelli, E., Gramegna, L. L., & Lodi, R. (2013). Low brain iron content in idiopathic restless legs syndrome patients detected by phase imaging. *Movement Disorders*, *28*(13). https://doi.org/10.1002/mds.25576

Rodrigues, R. N. D., Rodrigues, A. A. A. D. A. E. S., Faber, J., Corso, J. T., & Peixoto, T. F. (2009). Evolution of non-treated restless legs syndrome. *Arquivos de Neuro-Psiquiatria*, *67*(1). https://doi.org/10.1590/S0004-282X2009000100005

Romero-Peralta, S., Cano-Pumarega, I., & García-Borreguero, D. (2020). Emerging Concepts of the Pathophysiology and Adverse Outcomes of Restless Legs Syndrome. In *Chest* (Vol. 158, Issue 3, pp. 1218–1229). Elsevier Inc. https://doi.org/10.1016/j.chest.2020.03.035

Romigi, A., Izzi, F., Placidi, F., Sperli, F., Cervellino, A., & Marciani, M. G. (2007). Topiramate-induced restless legs syndrome: A report of two cases [3]. In *Journal of Neurology* (Vol. 254, Issue 8). https://doi.org/10.1007/s00415-007-0243-z

Rottach, K. G., Schaner, B. M., Kirch, M. H., Zivotofsky, A. Z., Teufel, L. M., Gallwitz, T., & Messer, T. (2008). Restless legs syndrome as side effect of second generation antidepressants. *Journal of Psychiatric Research*, *43*(1). https://doi.org/10.1016/j.jpsychires.2008.02.006

Roy Byrne, P. P., Uhde, T. W., & Post, R. M. (1986). Effects of One Night's Sleep Deprivation on Mood and Behavior in Panic Disorder: Patients With Panic Disorder Compared With Depressed Patients and Normal Controls. *Archives of General Psychiatry*, *43*(9). https://doi.org/10.1001/archpsyc.1986.01800090085011

Rulong, G., Dye, T., & Simakajornboon, N. (2018). Pharmacological Management of Restless Legs Syndrome and Periodic Limb Movement Disorder in Children. *Pediatric Drugs*, *20*(1). https://doi.org/10.1007/s40272-017-0262-0

Saletu, M., Anderer, P., Saletu-Zyhlarz, G., Prause, W., Semler, B., Zoghlami, A., Gruber, G., Hauer, C., & Saletu, B. (2001). Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): Acute placebo-controlled sleep laboratory studies with clonazepam. *European Neuropsychopharmacology*, *11*(2). https://doi.org/10.1016/S0924-977X(01)00080-3

Salminen, A. v., Rimpilä, V., & Polo, O. (2014). Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). *Neurology*, *82*(21). https://doi.org/10.1212/WNL.0000000000000454

Sanz-Fuentenebro, F. J., Huidobro, A., & Tejadas-Rivas, A. (1996). Restless legs syndrome and paroxetine. *Acta Psychiatrica Scandinavica*, *94*(6). https://doi.org/10.1111/j.1600-0447.1996.tb09896.x

Satija, P., & Ondo, W. G. (2008). Restless Legs Syndrome Pathophysiology, Diagnosis and Treatment. In *CNS Drugs* (Vol. 22, Issue 6).

Schmidauer, C., Sojer, M., Seppi, K., Stockner, H., Högl, B., Biedermann, B., Brandauer, E., Peralta, C. M., Wenning, G. K., & Poewe, W. (2005). Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. *Annals of Neurology*, *58*(4). https://doi.org/10.1002/ana.20572

Serikawa, T., Shimohata, T., Akashi, M., Yokoseki, A., Tsuchiya, M., Hasegawa, A., Haino, K., Koike, R., Takakuwa, K., Tanaka, K., Tanaka, K., & Nishizawa, M. (2011). Successful twin pregnancy in a patient with parkin-associated autosomal recessive juvenile parkinsonism. *BMC Neurology*, *11*. https://doi.org/10.1186/1471-2377-11-72

Sikandar, R., Khealani, B. A., & Wasay, M. (2009). Predictors of restless legs syndrome in pregnancy: A hospital based cross sectional survey from Pakistan. *Sleep Medicine*, *10*(6). https://doi.org/10.1016/j.sleep.2008.06.011

Silber, M. H., Becker, P. M., Buchfuhrer, M. J., Earley, C. J., Ondo, W. G., Walters, A. S., & Winkelman, J. W. (2018). The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome. *Mayo Clinic Proceedings*, *93*(1). https://doi.org/10.1016/j.mayocp.2017.11.007

Silber, M. H., Buchfuhrer, M. J., Earley, C. J., Koo, B. B., Manconi, M., Winkelman, J. W., Becker, P., Berkowski, J. A., Clemens, S., Connor, J. R., Ferré, S., Hensley, J. G., Jones, B. C., Karroum,

E. G., Koo, B., Ondo, W., Richards, K., Sharon, D., Trotti, L. M., … Walters, A. S. (2021). The Management of Restless Legs Syndrome: An Updated Algorithm. In *Mayo Clinic Proceedings* (Vol. 96, Issue 7, pp. 1921–1937). Elsevier Ltd. https://doi.org/10.1016/j.mayocp.2020.12.026

Silver, N., Allen, R. P., Senerth, J., & Earley, C. J. (2011). A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. *Sleep Medicine*, *12*(5). https://doi.org/10.1016/j.sleep.2010.11.002

Simpson, J. S. A. (1996). Familial akathisia and depression treated with nefazodone [2]. In *Canadian Journal of Psychiatry* (Vol. 41, Issue 8). https://doi.org/10.1177/070674379604100821

Skomro, R. P., Ludwig, S., Salamon, E., & Kryger, M. H. (2001). Sleep complaints and restless legs syndrome in adult type 2 diabetics. *Sleep Medicine*, *2*(5). https://doi.org/10.1016/S1389-9457(01)00110-1

Snyder, A. M., Wang, X., Patton, S. M., Arosio, P., Levi, S., Earley, C. J., Allen, R. P., & Connor, J. R. (2009). Mitochondrial ferritin in the substantia nigra in restless legs syndrome. *Journal of Neuropathology and Experimental Neurology*, *68*(11). https://doi.org/10.1097/NEN.0b013e3181bdc44f

Srivanitchapoom, P., Pandey, S., & Hallett, M. (2014). Restless legs syndrome and pregnancy: A review. In *Parkinsonism and Related Disorders* (Vol. 20, Issue 7). Elsevier Ltd. https://doi.org/10.1016/j.parkreldis.2014.03.027

Stefanidis, I., Vainas, A., Dardiotis, E., Giannaki, C. D., Gourli, P., Papadopoulou, D., Vakianis, P., Patsidis, E., Eleftheriadis, T., Liakopoulos, V., Pournaras, S., Sakkas, G. K., Zintzaras, E., & Hadjigeorgiou, G. M. (2013). Restless legs syndrome in hemodialysis patients: An

epidemiologic survey in greece. *Sleep Medicine*, *14*(12). https://doi.org/10.1016/j.sleep.2013.05.022

Sun, E. R., Chen, C. A., Ho, G., Earley, C. J., & Allen, R. P. (1998). *Iron and The Restless Legs Syndrome*. https://academic.oup.com/sleep/article/21/4/381/2731968

Sunwoo, J. S., Kim, W. J., Chu, M. K., & Yang, K. I. (2019). Association between restless legs syndrome symptoms and self-reported hypertension: A nationwide questionnaire study in Korea. *Journal of Korean Medical Science*, *34*(16). https://doi.org/10.3346/jkms.2019.34.e130

Suzuki, K., Ohida, T., Sone, T., Takemura, S., Yokoyama, E., Miyake, T., Harano, S., Motojima, S., Suga, M., & Ibuka, E. (2003). The prevalence of restless legs syndrome among pregnant women in Japan and the relationship between restless legs syndrome and sleep problems. In *Sleep* (Vol. 26, Issue 6). https://doi.org/10.1093/sleep/26.6.673

Symvoulakis, E. I., Anyfantakis, D. I., & Lionis III, C. (2010). Restless legs syndrome: literature review Síndrome de las pernas inquietas: revisión de la literatura. In *Sao Paulo Med J* (Vol. 128, Issue 3).

Szentkiralyi, A., Molnar, M. Z., Czira, M. E., Deak, G., Lindner, A. V., Szeifert, L., Torzsa, P., Vamos, E. P., Zoller, R., Mucsi, I., & Novak, M. (2009). Association between restless legs syndrome and depression in patients with chronic kidney disease. *Journal of Psychosomatic Research*, *67*(2). https://doi.org/10.1016/j.jpsychores.2009.05.004

Telarović, S., & Čondić, L. (2019). Frequency of iron deficiency anemia in pregnant and non-pregnant women suffering from restless legs syndrome. *Hematology (United Kingdom)*, *24*(1). https://doi.org/10.1080/16078454.2018.1560935

Telarović, S., Relja, M., & Trkulja, V. (2007). Restless legs syndrome in hemodialysis patients: Association with calcium antagonists - A preliminary report. *European Neurology*, *58*(3). https://doi.org/10.1159/000104718

Telstad, W., Sørensen, O., Larsen, S., Lillevold, P. E., Stensrud, P., & Nyberg-Hansen, R. (1984). Treatment of the restless legs syndrome with carbamazepine: A double blind study. *British Medical Journal*, *288*(6415). https://doi.org/10.1136/bmj.288.6415.444

Terao, T., Terao, M., Yoshimura, R., & Abe, K. (1991a). Restless legs syndrome induced by lithium. *Biological Psychiatry*, *30*(11). https://doi.org/10.1016/0006-3223(91)90185-O

Terao, T., Terao, M., Yoshimura, R., & Abe, K. (1991b). Restless legs syndrome induced by lithium. *Biological Psychiatry*, *30*(11). https://doi.org/10.1016/0006-3223(91)90185-O

Trenkwalder, C., Paulus, W., & Walters, A. S. (2005). *The restless legs syndrome*. http://neurology.thelancet.com

Tunç, T., Karadağ, Y. S., Doğulu, F., & Inan, L. E. (2007a). Predisposing factors of restless legs syndrome in pregnancy. *Movement Disorders*, *22*(5). https://doi.org/10.1002/mds.21291

Tunç, T., Karadağ, Y. S., Doğulu, F., & Inan, L. E. (2007b). Predisposing factors of restless legs syndrome in pregnancy. *Movement Disorders*, *22*(5). https://doi.org/10.1002/mds.21291

Tuo, H., Tian, Z., Ma, X., Cui, Y., Xue, Y., Che, J., Xu, C., Chen, K., Zhang, Y., Zhang, L., Bi, H., Le, W., & Ondo, W. (2019). Clinical and radiological characteristics of restless legs syndrome following acute lacunar infarction. *Sleep Medicine*, *53*, 81–87. https://doi.org/10.1016/j.sleep.2018.06.004

Uglane, M. T., Westad, S., & Backe, B. (2011). Restless legs syndrome in pregnancy is a frequent disorder with a good prognosis. *Acta Obstetricia et Gynecologica Scandinavica*, *90*(9). https://doi.org/10.1111/j.1600-0412.2011.01157.x

Unruh, M. L., Levey, A. S., D'Ambrosio, C., Fink, N. E., Powe, N. R., & Meyer, K. B. (2004). Restless Legs Symptoms among Incident Dialysis Patients: Association with Lower Quality of Life and Shorter Survival. *American Journal of Kidney Diseases*, *43*(5). https://doi.org/10.1053/j.ajkd.2004.01.013

Urbano, M. R., & Ware, J. C. (2008). Restless legs syndrome caused by quetiapine successfully treated with ropinirole in 2 patients with bipolar disorder. In *Journal of Clinical Psychopharmacology* (Vol. 28, Issue 6). https://doi.org/10.1097/JCP.0b013e31818b2764

Vadasz, D., Ries, V., & Oertel, W. H. (2013). Intravenous iron sucrose for restless legs syndrome in pregnant women with low serum ferritin. *Sleep Medicine*, *14*(11). https://doi.org/10.1016/j.sleep.2013.05.018

Velasco, P. E. B., Goiburu, J. A. Z., & Pinel, R. S. (2007). Restless legs syndrome induced by zonisamide [4]. In *Movement Disorders* (Vol. 22, Issue 10). https://doi.org/10.1002/mds.21449

Vohra, A. (2015). Quetiapine induced restless legs syndrome: A series of four cases. In *Asian Journal of Psychiatry* (Vol. 16). https://doi.org/10.1016/j.ajp.2015.05.045

Wåhlin Larsson, B., Kadi, F., Ulfberg, J., & Piehl Aulin, K. (2007). Skeletal muscle morphology in patients with restless legs syndrome. *European Neurology*, *58*(3). https://doi.org/10.1159/000104712

Wåhlin-Larsson, B., Ulfberg, J., Aulin, K. P., & Kadi, F. (2009). The expression of vascular endothelial growth factor in skeletal muscle of patients with sleep disorders. *Muscle and Nerve*, *40*(4). https://doi.org/10.1002/mus.21357

Webb, J. (2012). Co-occurring akathisia and restless legs syndrome Likely induced by quetiapine. In *Journal of Neuropsychiatry and Clinical Neurosciences* (Vol. 24, Issue 2).

Wesström, J., Skalkidou, A., Manconi, M., Fulda, S., & Sundström-Poromaa, I. (2014). Pre-pregnancy restless legs syndrome (Willis-Ekbom Disease) is associated with perinatal depression. *Journal of Clinical Sleep Medicine*, *10*(5). https://doi.org/10.5664/jcsm.3704

Wetter, T. C., Brunner, J., & Bronisch, T. (2022). *Restless Legs Syndrome Probably Induced By Risperidone Treatment*.

Wijemanne, S., & Ondo, W. (2017). Restless Legs Syndrome: Clinical features, diagnosis and a practical approach to management. In *Practical Neurology* (Vol. 17, Issue 6). https://doi.org/10.1136/practneurol-2017-001762

Willaschek, C., Wolter, E., & Buchhorn, R. (2009). Tramadol withdrawal in a neonate after long-term analgesic treatment of the mother. In *European Journal of Clinical Pharmacology* (Vol. 65, Issue 4). https://doi.org/10.1007/s00228-008-0598-z

Winkelman, J. W., Allen, R. P., Tenzer, P., & Hening, W. (2007). Restless legs syndrome: Nonpharmacologic and pharmacologic treatments. In *Geriatrics* (Vol. 62, Issue 10).

Winkelman, J. W., Chef-Tow, G. M., & Lazarus, J. M. (1996). *Restless Legs Syndrome in End-Stage Renal Disease*.

Winkelman, J. W., Redline, S., Baldwin, C. M., Resnick, H. E., Newman, A. B., & Gottlieb, D. J. (2009). Polysomnographic and health-related quality of life correlates of restless legs syndrome in the sleep heart health study. *Sleep*, *32*(6). https://doi.org/10.1093/sleep/32.6.772

Winkelmann, J., Prager, M., Lieb, R., Pfister, H., Spiegel, B., Wittchen, H. U., Holsboer, F., Trenkwalder, C., & Ströhle, A. (2005). "Anxietas Tibiarum": Depression and anxiety disorders in patients with restless legs syndrome. In *Journal of Neurology* (Vol. 252, Issue 1). https://doi.org/10.1007/s00415-005-0604-7

Winkelmann, J., Stautner, A., Samtleben, W., & Trenkwalder, C. (2002). Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. *Movement Disorders*, *17*(5). https://doi.org/10.1002/mds.10231

Winkelmann, J., Wetter, T. C., Collado-Seidel, V., Gasser, T., Dichgans, M., Yassouridis, A., & Trenkwalder, C. (2000). Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep*, *23*(5). https://doi.org/10.1093/sleep/23.5.1b

Yasuda, T., Nishimura, A., Katsuki, Y., & Tsuji, Y. (1986). Restless legs syndrome treated successfully by kidney transplantation--a case report. *Clinical Transplants*.

Yu, G. S. M., Steinkirchner, T. M., Rao, G. A., & Larkin, E. C. (1986). Effect of prenatal iron deficiency on myelination in rat pups. *American Journal of Pathology*, *125*(3).

Z. Soyata, A., Celebi, F., & I. Yargc, L. (2015). Restless Legs Syndrome After Single Low Dose Quetiapine Administration. *Current Drug Safety*, *11*(2). https://doi.org/10.2174/1574886311207040298

Zhao, M., Geng, T., Qiao, L., Zhang, M., Shi, J., Huang, F., Lin, X., Wang, J., & Zuo, H. (2014). Olanzapine-induced restless legs syndrome. *Journal of Clinical Neuroscience*, *21*(9). https://doi.org/10.1016/j.jocn.2014.01.007

Zintzaras, E., Kitsios, G. D., Papathanasiou, A. A., Konitsiotis, S., Miligkos, M., Rodopoulou, P., & Hadjigeorgiou, G. M. (2010). Randomized trials of dopamine agonists in restless legs syndrome: A systematic review, quality assessment, and meta-analysis. In *Clinical Therapeutics* (Vol. 32, Issue 2). https://doi.org/10.1016/j.clinthera.2010.01.028

Zucconi, M., Galbiati, A., Rinaldi, F., Casoni, F., & Ferini-Strambi, L. (2018). An update on the treatment of Restless Legs Syndrome/Willis-Ekbom Disease: prospects and challenges. In *Expert Review of Neurotherapeutics* (Vol. 18, Issue 9, pp. 705–713). Taylor and Francis Ltd. https://doi.org/10.1080/14737175.2018.1510773

Mustafiz Project

ORIGINALITY REPORT

7%	6%	7%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Richard P. Allen. "Restless Leg Syndrome/Willis-Ekbom Disease Pathophysiology", Sleep Medicine Clinics, 2015 Publication	2%
2	Yves Dauvilliers, Juliane Winkelmann. "Restless legs syndrome", Current Opinion in Pulmonary Medicine, 2013 Publication	1%
3	dspace.bracu.ac.bd Internet Source	1%
4	Leschziner, G., and P. Gringras. "Restless legs syndrome", BMJ, 2012. Publication	1%
5	dspace.bracu.ac.bd:8080 Internet Source	1%
6	www.researchgate.net Internet Source	1%
7	archive.org Internet Source	1%

8	docksci.com Internet Source	1 %

Exclude quotes	Off	Exclude matches	< 1%
Exclude bibliography	On		