Simple Response

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Restless leg syndrome associated with Multiple Sclerosis, schizophrenia and antipsychotic medication

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The Research Team are unable to ensure that the information listed below provides an accurate & up-to-date snapshot of these matters

Research question: Is restless legs syndrome associated with multiple sclerosis, schizophrenia or antipsychotic medication? What is the best practice management for restless legs syndrome associated with multiple sclerosis?

Date: 13/07/2022

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1. Contents

2. Summary

Restless legs syndrome (RLS) is a neurological sensorimotor disease which often disturbs sleep. Symptoms become worse during periods of inactivity or rest, particularly at night. Moving can alleviate symptoms in the short term. RLS is associated with multiple sclerosis (MS), schizophrenia and some antipsychotic medications. Treatment can include lifestyle changes or medication though it is not known how the commonly used drugs interact with MS symptoms or commonly prescribed MS drugs. There is some evidence that exercise alleviates symptoms of RLS in the general population and in people with MS, however further evidence is required to demonstrate efficacy in people with MS.

3. Restless legs syndrome and Multiple sclerosis

There is consensus in the research literature that incidence of RLS is higher in MS than in the general population. However, a 2021 systematic review compared 19 prevalence studies and found significant heterogeneity in prevalence rate, between 13.2% and 65.1%. The mean prevalence based on these studies is 27.5% (Ozdogar & Kalron, 2021). This is similar to recent studies which found a prevalence rate of 23.3% in a sample of 120 (Lebrato Hernandez et al, 2022), 23.9% in a sample of 117 (Monschein et al, 2021), 31.3% in a sample of 102 (Gunes et al, 2021).

The reason for the higher prevalence of RLS in MS in not known. Possible mechanisms can include genetic factors, demyelinated lesions localized in the basal ganglia, dopaminergic system dysfunction, or iron metabolism disorders in the CNS. RLS may also be caused by side-effects of disease modifying treatments (Ozdogar & Kalron, 2021). Of note, both Monschein et al (2021) and Lebrato Hernandez et al (2022) found no statistically significant correlation between RLS and disease modifying treatment.

Some correlations are observed in various studies between RLS and age, sex, severity of MS symptoms or progression of MS symptoms. However, Ozdogar & Kalron (2021) observe that most studies find no statistically significant correlations between disability, disease duration, type of MS, age or sex.

4. Restless legs syndrome, schizophrenia and anti-psychotic medication

People with schizophrenia often have associated sleep disorders including insomnia, sleep apnoea or RLS (Kaskie et al, 2017). Antipsychotic medication used to treat schizophrenia is also linked with RLS. For example, Elrassas et al found that of 200 people treated with antipsychotics or antidepressants, 40% had RLS (Elrassas et al, 2022). Patanian and Claborn

(2018) find some evidence of RLS associated with the antipsychotics haloperidol, olanzapine, clozapine, quetiapine, risperidone, asenapine, and lurasidone.

5. Treatment for restless legs syndrome associated with MS

The International Restless Legs Syndrome Study Group lists essential diagnostic criteria:

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping). (International Restless Legs Syndrome Study Group, 2012)

Of note, criteria 3 states that symptoms are fully or partially relieved by movement at least as long as the activity continues. The National Institute of Neurological Disorders and Stroke RLS Factsheet reiterates that moving the affected limbs may provide temporary relief from symptoms (National Institute, 2017; Browne, 2021).

First-line treatment for RLS may involve dietary or lifestyle changes, dopaminergic drugs or anti-seizure medication in the general population. Opioids and benzodiazepines may also be used (National Institute, 2017). However, it's unclear how drugs used to treat RLS interact with MS symptoms or commonly prescribed MS drugs. There is some evidence that non-pharmacological treatments such as repetitive transcranial magnetic stimulation, exercise, compression devices, counterstrain manipulation, and infrared therapy are effective as treatments for RLS. However, the quality of evidence is not high and further evidence is required to recommend treatment (Ozdogar & Kalron, 2021; Harrison et al, 2019).

In particular, further evidence is required to draw conclusions about optimal treatment for people with MS experiencing RLS (Ozdogar & Kalron, 2021). Cederberg and Motl (2021) showed increasing lifestyle physical activity (mainly step count in daily activities) could result in a 30% reduction in RLS symptoms in a treatment group of 8 people with MS. While this study shows feasibility, further research is required.

6. References

Assimakopoulos, K., Karaivazoglou, K., Skokou, M., Kalogeropoulou, M., Kolios, P., Gourzis, P., Patrinos, G., & Tsermpini, E. (2018). Genetic variations associated with sleep disorders in patients with schizophrenia: A systematic review. *Medicines (Basel, Switzerland)*, *5*(2), 27. https://doi.org/10.3390/medicines5020027

Browne, Adam. (2021). *Developing your coping strategy for restless legs*. MS Australia. https://www.msaustralia.org.au/news/developing-your-coping-strategy-for-restless-legs/

Cederberg, K. L. J., & Motl, R. W. (2021). Feasibility and efficacy of a physical activity intervention for managing restless legs syndrome in multiple sclerosis: Results of a pilot randomized controlled trial. *Multiple Sclerosis and Related Disorders*, *50*(102836), 102836. https://doi.org/10.1016/j.msard.2021.102836

Elrassas, H. H., Elsayed, Y. A. R., Abdeen, M. S., Shady, M. M., Shalash, A., & Morsy, M. (2022). Restless Legs Syndrome among patients receiving antipsychotic and antidepressant drugs. *Human Psychopharmacology*, *37*(2), e2817. https://doi.org/10.1002/hup.2817

Güneş, T., Emre, U., Erdal, Y., & Yalin, O. Ö. (2021). Restless Legs Syndrome in multiple sclerosis. *Noro Psikiyatri Arsivi*, *58*(2), 94–98. https://doi.org/10.29399/npa.23429

Harrison, E. G., Keating, J. L., & Morgan, P. E. (2019). Non-pharmacological interventions for restless legs syndrome: a systematic review of randomised controlled trials. *Disability and Rehabilitation*, *41*(17), 2006–2014. https://doi.org/10.1080/09638288.2018.1453875

International restless legs syndrome study group. (2012). *Diagnostic Criteria*. Irlssg.org. Retrieved July 13, 2022, from http://irlssg.org/Diagnostic-criteria

Kaskie, R., Graziano, B., & Ferrarelli, F. (2017). Schizophrenia and sleep disorders: links, risks, and management challenges. *Nature and Science of Sleep*, *9*, 227–239. https://doi.org/10.2147/nss.s121076

Lebrato Hernández, L., Prieto León, M., Cerdá Fuentes, N. A., Uclés Sánchez, A. J., Casado Chocán, J. L., & Díaz Sánchez, M. (2022). Restless legs syndrome in patients with multiple sclerosis: evaluation of risk factors and clinical impact. *Neurología (English Edition)*, *37*(2), 83–90. https://doi.org/10.1016/j.nrleng.2018.12.018

Monschein, T., Schestak, C., Schillerwein-Kral, C., Leutmezer, F., Berger, T., Bsteh, G., & Seidel, S. (2021). Restless Legs Syndrome in Multiple Sclerosis: Risk factors and effect on sleep quality - a case-control study. *Multiple Sclerosis and Related Disorders*, *51*(102916), 102916. https://doi.org/10.1016/j.msard.2021.102916

National Institute of Neurological Disorder and Stroke. (2017). Restless Legs Syndrome Fact Sheet. *National Institutes of Health*. NIH Publication No. 17-4847. Available from: https://www.ninds.nih.gov/health-information/patient-caregiver-education/fact-sheets/restless-legs-syndrome-fact-sheet

Patatanian, E., & Claborn, M. K. (2018). Drug-induced restless legs syndrome. *The Annals of Pharmacotherapy*, *52*(7), 662–672. https://doi.org/10.1177/1060028018760296

Ozdogar, A. T., & Kalron, A. (2021). Restless legs syndrome in people with multiple sclerosis: An updated systematic review and meta-analyses. *Multiple Sclerosis and Related Disorders*, *56*(103275), 103275. https://doi.org/10.1016/j.msard.2021.103275

7. Version control

Version	Amended by	Brief Description of Change	Status	Date
1.0	Aaron H[s47F - personal priva]	Research on association between RLS and MS, schizophrenia and antipsychotic medication and consideration of best practice treatments of RLS	Cleared	13/07/2022