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Case Report

Augmentation of Restless Legs Syndrome Associated with Methadone: A Case Report

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Abstract

Augmentation of RLS symptoms has been observed in the vast majority of cases following treatment with dopaminergic drugs. Here we report clinical and polysomnographic data of a patient who developed augmentation after long-term treatment with methadone, a highly potent long-term opioid used with great success in the US as a "last resort" treatment for particularly severe and intense RLS symptoms and advanced cancer pain. Our case report raises the question of the extent to which augmentation is limited to treatment with dopamine-based drugs.

Keywords: Restless Legs Syndrome; Augmentation; Opioid; Methadone.

List of Abbreviations: AHI: Apnea Hypopnea Index; AI: Apnea Index; ASRS: Augmentation Severity Rating Scale; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; EU: European Union; HI: Hypopnea Index; IRLS: International Restless Legs Severity Scale; LM: Limb Movement; N1: Sleep Stage N1; N2: Sleep Stage N2; N3: Sleep Stage N3: PLM: Periodic Limb Movement; PLMS: Periodic Limb Movement of Sleep; REM: Rapid Eye Movement: RLS Restless Legs Syndrome.

Introduction

Restless legs syndrome (RLS) is characterized by abnormal sensations in the legs or more rarely in the arms as well as in the bladder, rectal or genital region. These sensations occur, at least initially, in a circadian rhythm when the patient is resting and are associated with an urge to move. In 85% of patients, RLS correlates with periodic limb movements during sleep (PLMS), and symptoms decrease with movement of the affected body parts. The German S2k guidelines for RLS recommend iron supplementation as a first-line treatment when necessary [1]. Secondly, drug treatment with dopamine agonists such as rotigotine, ropinirole and pramipexole is recommended at the lowest effective dose to avoid augmentation effects. Treatment with levodopa is no longer recommended in the guidelines, as it carries a particularly higher risk of augmentation than dopamine agonists [1-3]. In levodopa-induced augmentation of RLS, a reduction in the levodopa plasma level induces a hyperkinetic- hypersensitive state, which manifests itself in the typical augmentation symptoms, which are defined as the onset of RLS symptoms about two hours earlier than before dopaminergic treatment and the possible spread of symptoms to other parts of the body (e.g. arms), an increase in the intensity of symptoms since the start of treatment and a decrease in the effect of dopaminergic drugs at the same dose [1]. It has been postulated that augmentation results from compensatory mechanisms of the dopaminergic system that may reduce tolerance to dopaminergic effects, particularly in relation to the circadian system [4].

According to the S2k guidelines, opioids are generally reserved for patients in whom other pharmacologic agents have failed or who have already developed augmentation under dopaminergic medication [5,6]. Vetrugno et al. (2007) postulated that with carefully supervised use and appropriate counselling, chronic opioid therapy may be also appropriate for selected patients with otherwise untreatable restless legs syndrome7. Oxycodone-naloxone (Targin®) is the only approved opioid medication for the treatment of RLS in Germany [5]. Therapy with tilidine or oxycodone has also been frequently described in the literature, even though the use of this medication for RLS is off label in the EU. Methadone, a high-potent, long-term opioid, is used less frequently in Europe for the treatment of RLS, probably because

of the stigma attached to methadone, as it is often used as part of heroin detoxification. In the US, methadone is used successfully as a "last resort" in the treatment of particularly severe and intense RLS symptoms, often in the context of augmentation caused by high-dose dopaminergic drugs [7,8]. The usual strategy is an initial dose of 5 mg daily, which is titrated in steps of 2.5 mg to 5 mg to a total daily dose of 20 to 30 mg depending on need and tolerability [6,9].

In this case report, we present clinical and polysomnographic data of a patient with an increase in RLS symptoms after long-term use of methadone as part of cancer pain therapy and the resolution of symptoms after discontinuation of the drug.

Case Presentation

The 58-year-old woman, 170 cm, 83 kg, BMI = 28,7 kg/m², presented to our practice for the first time in December 2019, when she lived in Illinois/USA but often came to Germany to visit her grandchildren. She had been first time diagnosed with restless legs syndrome 10 years ago - even if she had already noticed the first symptoms in her childhood - and had been treated with ropinirole 1mg (0-1-0-2) and tilidine 50 mg as on-demand medication. The family history revealed that her son has RLS and that a granddaughter is showing the first possible symptoms. The patient herself has three children and her RLS has worsened with each pregnancy. In retrospect, she described the symptoms as so severe that she had reached her mental limits and sometimes even suffered from suicidal thoughts.

The neurological-psychiatric examination and nerve conduction velocity revealed no pathological findings. Type 2 Diabetes was diagnosed in Illinois in 2022. Our laboratory analysis showed that HbA1c was 5.6% in December 2019 and 6.56% in June 2024.RLS relevant laboratory parameters were normal; in particular, ferritin (137 ng/ml), transferrin (2,16 g/l) and transferrin saturation (26%) were all within the normal range.

At her first visit to our doctor's office in 2019 the patient complained of a loss of efficacy of ropinirole with an increase in the intensity of the symptoms and an earlier onset of symptoms in the evening. Due to the loss of efficacy of ropinirole, we switched the medication to 2-3mg/24h rotigotine dermal patches. Unfortunately, the patient developed an allergy to the dermal patch, so that in February 2022 the medication was switched to pramipexole sustained release 0.52 mg (0-0-1-0), pramipexole 0.18 mg (0-0-0-1) and 50/4 mg tilidine/naloxone as on-demand medication, which resulted in a significant relief.

After the patient had spent the next 5 years during the COVID pandemic in the USA, she returned to our doctor's office again in June 2024. In the meantime, she was diagnosed with breast cancer, followed by a total of four surgeries since 2021. Treatment with methadone was also started in 2021 because of cancer pain in addition to RLS. Since it is also common in the USA to treat RLS symptoms with methadone, the original medication with pramipexole and tilidine/naloxone was discontinued there. This methadone monotherapy initially also showed a very good effect at 5 mg half a tablet BID for both, the cancer pain and the RLS. For a complete list of medications at that time see Table 1.

During the patient history interview at her follow-up visit in June 2024, the patient reported that during the previous months she had noticed a mounting increase in RLS symptoms during methadone monotherapy treatment. She had the impression that despite a methadone dose increase to 6 mg half a tablet BID her RLS symptoms had worsened, occurring earlier in the day and additionally affecting her arms. Her International RLS Severity Scale (IRLS) [10] indicated 35 out of 40 possible points in line with a very severe RLS.The Augmentation Severity Rating Scale (ASRS) [11] also showed an early onset of symptoms at around 3 pm in the afternoon.The patient scored 19 points in this questionnaire, which indicated augmentation under the current medication. Her Epworth Sleepiness Scale (ESS) [12] result was 16 points, which pointed to severe daytime sleepiness. Based on the reported complaints at the follow-up visit in June 2024, we performed a PSG, which revealed a PLMS index of 102.8/h and a reduced sleep efficacy of 73,7%. All PSG parameters at a glance are shown in table 2 and figure 1. Unfortunately, there were no PSG baseline data available, as the patient had already presented to our practice with ten years ago pre-diagnosed and medically treated RLS.

The PSG results and clinical symptoms pointing to an RLS augmentation under methadone medication were discussed with the patient and it was decided to discontinue methadone 6 mg half a tablet BID and replace it with the equivalent dose of tilidine/naloxone 50/4 mg (2-0-3-0) and pramipexole 0,18mg (0-0-1-1). In a telephone consultation in August 2024, the patient reported an excellent therapeutic benefit of the new medication. Any withdrawal symptoms after the switch of methadone to the equivalent dose of tilidine had completely disappeared and the RLS symptoms were significantly improved. In, addition she reported longer and more restful sleep than before. The new IRLS score resulted in a score of 13 points (vs. 35 points with methadone), indicating moderate RLS symptoms.

Due to the excellent feedback and the improved RLS symptoms, we made an appointment for a long-term follow-up examination in the sleep laboratory in January 2025. During the medical history interview, she reported that the RLS symptoms were still very well controlled with pramipexole 0.18mg (0-0-1-1), tilidine/naloxone 100/8mg (1-0-0-1) and tilidine/naloxone 50/4mg (0-0-0-1) (see table 3 for a complete list of medications). The PSG also showed normal sleep-related movement and respiratory parameters almost

12 months after the medication change from methadone (see Table 4 and Figure 2). The improvement in RLS symptoms is also reflected in an IRLS score of 20 points (moderate RLS) vs. 35 points (very severe RLS symptoms) before the change of the medication. Daytime sleepiness had decreased significantly (ESS = 4 points) and in the Augmentation Severity Rating Scale the patient reported 7 pm as the time of day for the earliest symptom onset (previously 3 pm) and a score of 8 points (previously 19 points), which also indicated a significant improvement under the current medication. In addition, the patient was under a stable dose of 2,5 mg letrozole during and after remission of augmentation, making an association of letrozole and augmentation unlikely.

MEDICATION	DOSAGE	TIMING OF MEDICATION
METHADONE	6 mg	1/2-0-1/2-0
ATORVASTATINE	20mg	0-0-1-0
PANTOPRAZOLE	20mg	1-0-0-0
METFORMIN	1000mg	0-0-1-0
OXYBUTYNIN	5mg	1-0-1-0
LETROZOLE	2,5mg	0-0-1-0

Table 1: Patient's medication plan in June 2024.

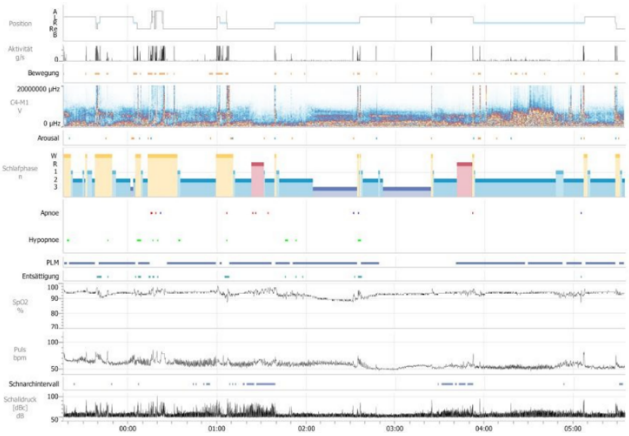

Figure 1: PSG 06/16/2024. PLM events.

Sleep parameter	
Total sleep time	313,3 minutes
Sleep efficacy	82,8%
REM	6,1%
N1	9,1%
N2	64,4%
N3	20,4%
Latency falling asleep	5,3 minutes
REM-latency	121,5 minutes
N2-latency	1,5 minutes
PLM-Index in TST	102,8/h
PLM-Index in wake	65,3/h
Arousal-Index in TST	2,3/h
PLMS-Arousal-Index	1,1/h
AHI	2,3/h
AI	1,1/h
HI	1,1/h
Desaturation index	1,3/h
Average oxygen saturation	93,7%

Table 2: PSG parameters from PSG at 06/2024.

MEDICATION	DOSAGE	TIMING OF MEDICATION
PRAMIPEXOLE	0,18 mg	0-0-1-1
TILIDINE	100/8 mg	1-0-1-0
TILIDINE	50/4 mg	0-0-0-1
LETROZOLE	2,5mg	0-0-1-0
METFORMIN	1000mg	0-0-1-0

Table 3: Patient's medication plan in January 2025.

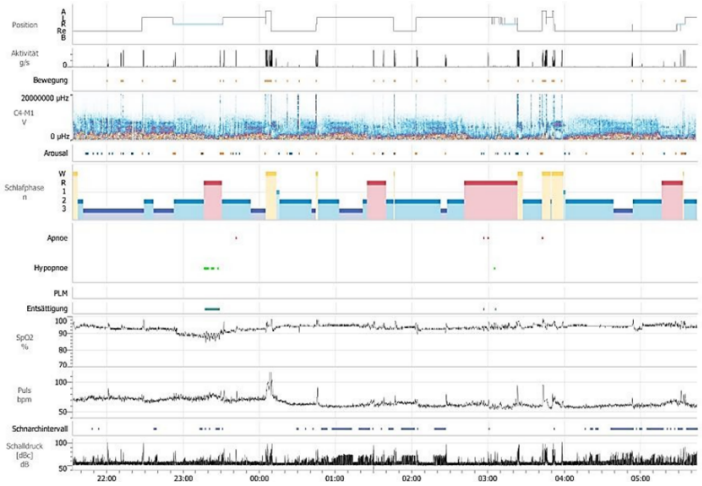

Figure 2: PSG illustration 01/21/2025.

Sleep parameter	
Total sleep time	455 minutes
Sleep efficacy	92,6%
REM	19,3%
N1	0,9%
N2	53,7%
N3	26,0%
Latency falling asleep	4,4 minutes

REM-latency	99,5 minutes
N2-latency	0,0 minutes
PLM-Index in TST	0,5/h
PLM-Index in wake	0,0/h
Arousal-Index in TST	8,0/h
PLMS-Arousal-Index	0,0/h
AHI	1,6/h
AI	0,3/h
HI	1,3/h
Desaturation index	1,6/h
Average oxygen saturation	94,0%

Table 4: PSG parameters from PSG at 01/2025.

Discussion

In the present case report a patient developed an augmentation under long-term treatment with methadone. Under this monotherapy, the initial benefit of methadone with regard to RLS weakened, the dose of methadone was increased and simultaneously the patient developed RLS augmentation symptoms with an earlier diurnal onset, increased intensity of symptoms and a spread of RLS symptoms to previously unaffected parts of the body such as the arms. After switching the medication to tilidine/naloxone 100/8 mg, tilidine/naloxone 50/4 mg and pramipexole 0,18 mg BID, the patient quickly experienced an amelioration of RLS symptoms. To our knowledge, this is the first case report of augmentation development after long-term administration of methadone. However, data reporting RLS augmentation associated with opioids are rare in the current literature. Walters et al. (2001) reported in a long-term follow-up with 16 patients - who for various reasons had been receiving RLS opioid monotherapy for more than seven months at the time of the study - that only one patient had to discontinue therapy due to development of addiction and tolerance [6]. Trenkwalder et al. (2013) showed in a 12-week RCT study with 40 weeks open-label extension phase that no augmentation occurred when taking oxycodone/naloxone [5]. So far, only two studies on augmentation development after treatment with tramadol have been described in the scientific literature: one small case report collection of four patients [13] and one case report [14]. As a possible explanation for the exacerbation of RLS symptoms under the administration of tramadol, the authors of these studies suggested that the opioid system could be directly involved through the effect of tramadol on the μ-receptors, or that its effect could be mediated by the action of dopamine. Just like tramadol, the pain-relieving effects of methadone are mediated via the μ-receptors as the primary mechanism of action. The fact that the pain-relieving effect of opioids at the spinal and supraspinal level is partially mediated via dopaminergic mechanisms of action has already been described earlier in the literature [15-18]. Furthermore, the agonistic effect especially of methadone on the D2/D3 receptors has also been revealed [19]. In keeping with this, Faron-Gorecka et al. (2004) describe that repeated administration of tramadol induces locomotor hyperactivity primarily through increased dopamine transmission with upregulation of D2 and D3 receptors [20]. To our knowledge, so far, augmentation under long-term opioid monotherapy has only been described for tramadol and methadone. Whether this represents a particular "susceptibility" of these opioids to augmentation and other opioids that have a different receptor affinity generally have a lower risk of augmentation should be the subject of future studies. In this context it remains unclear why augmentation effects have not yet been described with opioids such as oxycodone/naloxone or tilidine/naloxone, which are more commonly used in the treatment of RLS in Europe.

Conclusion

The phenomenon of augmentation in RLS is the most frequent complication of RLS treatment and has mainly been observed in association with dopaminergic medication in clinical practice up to now. Augmentation with opioid therapy has been described much less in the literature to date. Closer observation of this correlation could possibly provide new insights into the mechanisms underlying augmentation and into the pathogenesis of RLS itself.

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Ethical Guidelines: Written informed consent for publication of the clinical details was obtained from the patient.

Conflict of Interest

CG Bachmann has been a member of advisory boards of UCB Pharma and Mundipharma and has received honoraria from GSK, UCB, Bayer, Vifor Pharma and grants from Oxycare and RLS eV, Deutsche Restless Legs Vereinigung e.V.

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