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Sleep disorders in neurology

French consensus: Pharmacoresistant restless legs syndrome



Download Clinical Guidelines

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ABSTRACT

Dopaminergic agonists, $\alpha 2\delta$ ligands and opioids are, as single-drug therapy, the first line treatment for restless legs syndrome (RLS/Willis-Ekbom disease). However, despite treatment efficacy, exacerbations of RLS may occur with overall worsening in symptoms severity, development of pain and symptoms spreading to other parts of the body, without meeting augmentation syndrome criteria. This development of “drug-resistant” RLS can cause pain, severe insomnia and psychiatric disorders that affect considerably patients’ quality of life. The lack of French recommendations for this form of RLS leave physicians with few options to help patients with physical and emotional distress. Our group of neurological experts and sleep specialists proposes a diagnostic and therapeutic strategy to provide better care and appropriate treatment through searching for the organic, psychiatric and/or iatrogenic causes of drug resistance. Once a drug-resistant RLS diagnosis has been confirmed, we recommend an obligatory work-up including: a video-polysomnogram, a biological evaluation including iron status, standard numeration and C-reactive protein level. Treatment will be comorbidity-dependent: dopaminergic agonist would be recommended in case of depression or associated periodic leg movements, $\alpha 2\delta$ ligand in case of insomnia, complaint of pain, or general anxiety, in association with low-dose opioids if necessary. Strong opioids should be preferred for multiresistant RLS.

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1. Abbreviations

DA	dopaminergic agonists
AD	antidepressants
EMG	electromyography
SSRI	selective serotonin reuptake inhibitors
SNRIs	serotonin-norepinephrine reuptake inhibitors
IRLS	International Restless Legs Syndrome Study Group rating scale
IRLSSG	International Restless Legs Syndrome Study Group
PLM	periodic limb movements
RLS	restless legs syndrome

2. Introduction

In patients with restless legs syndrome (RLS/Willis-Ekbom disease) the aim of treatment is to reduce symptom severity knowing that only few patients require medical treatment [1]. Pharmacological treatments should indeed be restricted only for patients suffering from severe to very severe forms of the disease. However, and despite an initially satisfactory therapeutic response, a large number of patients present a recurrence of symptoms over the long-term related to decrease in treatment efficacy and/or disease's natural progression. For other patients, despite correct compliance, medical treatment may be ineffective.

The absence of French recommendations for drug-resistant forms of RLS, taking into account the characteristics of this population and treatments available in France, leaves physicians in difficulties faced with patients with severe suffering. We propose a consensus for a simple and practical diagnostic and therapeutic strategy to help physicians improve treatment strategies for patients with drug-resistant RLS. The recommendations formulated in this article are based on methodology approved by the European Federation of Neurological Societies (EFNS) [2].

3. Definition of drug-resistant RLS

There is no consensual definition of drug-resistant RLS, also called "refractory" or "intractable" RLS. Silber et al. propose a practical clinical definition, but this is limited to patients treated with dopaminergic agonists (DAs) [3]. The International Restless Legs Syndrome Study Group (IRLSSG) does not provide a definition of drug resistance in RLS.

It is important to differentiate drug-resistant RLS from augmentation syndrome, from the loss of effect at the end of dose, from the natural evolution of the disease and from mild RLS associated with insomnia, depression or pain as the main complaint. Transient exacerbations and complaints associated with well-treated RLS are covered below. It is also essential to distinguish drug-resistant RLS from the short-term exacerbations of RLS related to contraindicated medication (for example antidepressant, or neuroleptic derived medication), from forced bed rest (e.g. post-surgery) or a drop in iron levels (for example following occult colic bleeding or surgery).

Our definition of drug-resistant RLS is severe to very severe RLS—severity score of $> 20/40$ on the RLS severity scale (International Restless Legs Syndrome Study Group rating scale, IRLS)—persistent or recurrent over a period of more than 1 month, despite 2 treatments from different classes whose effectiveness is recognised consensually in RLS treatment, taken alone or in combination, with good compliance, sufficient dosage, suitable schedule and for a sufficiently long duration. Drug-resistant RLS must not meet augmentation syndrome criteria.

4. Drug-resistant RLS epidemiology

The frequency of drug-resistant RLS is unknown, but in current clinical practice the reappearance or worsening of pre-existing but tolerable RLS symptoms is frequent in the long-term, particularly with the use of DAs. This can occur despite a treatment taken correctly at optimal dosages. Aggravation lead to an increase in the intensity of unpleasant sensations or their transformation; for example paraesthesia that becomes painful, symptoms spreading to upper limbs or their occurrence during the daytime, without meeting augmentation syndrome criteria. In a cohort of 160 patients monitored over a duration of 8.1 ± 2.9 years, more than 10% of patients reported aggravated symptoms and 59.4% had benefited from one or several therapeutic modifications [4]. In another series of 2751 RLS patients monitored over a 3 year period, 12.5% of RLS patients had experienced an increase in symptoms severity (increase of 5 points on the International Restless Legs Syndrome Study Group rating scale [IRLS]) [5].

5. Clinical diagnosis of drug-resistant RLS

The clinical diagnosis of RLS is not as easy as it would appear based on the consensual criteria. It is a purely clinical diagnosis and many other pathologies can mirror RLS symptoms (Table 1), misleading physicians and resulting in inappropriate treatment. Therefore it is important to first confirm or disprove diagnosis and subsequently eliminate augmentation syndrome. Fig. 1 summarises the main steps in the diagnosis and treatment of drug-resistant RLS.

5.1. Is it RLS?

RLS diagnosis is based on the presence of the 5 essential criteria [6], clinical examination data which must be started over again in the case of drug resistance. In the event of doubt, support criteria can help the physician to establish the diagnosis. We have indicated in italics the specific elements that, during the diagnosis phase, or when the question of diagnosis arises anew when a treated patient is referred for drug resistance, may point to a diagnosis other than RLS.

5.2. Essential criteria

5.2.1. Sensory disorder

Investigation into the patient's sensory complaint must be clearly identified as described in the "diagnostic" article. Sensations of cold (and painful cold) as well as numbness

Table 1 – RLS differential diagnosis and clinical presentation.

Differential diagnosis	Dysesthesia at rest: type and topography	Improved by movement	Worsened by immobility	Worse in the evening	Clinical examination	Further examination	Therapeutic treatment
Polyneuropathy/ Mononeuropathy	Pains, paraesthesia, (LL for polyneuropathy)	No	No	No	Sensory deficiency > motor	EMG	AE, SNRI, opioids
Small fiber neuropathy	Pains Lower limbs	No	No	No	Reduced pain and temperature sensitivity, dysautonomic symptom	Biopsy	AE, SNRI, opioids
Positional discomfort	Paraesthesia LL, UL	Yes	No	No	Normal	–	–
Fibromyalgia	Pains, Spine, joints, muscles	No	No	No	Muscle pain under pressure	–	AE, SNRI, opioids
Osteoarthritis	Joint pain	No	No	No	Pain caused; oedema	–	NSAID
Chronic venous insufficiency of the LL	Heaviness LL whilst standing	Yes	Yes	No	Varicose veins, LL oedema	Echo-Doppler of the LL	Support hosiery/ Veinotonic
Peripheral artery disease	Lameness, pain from decubitus	No	No	Yes (advanced stage)	Weak/ asymmetric pulse. Reduced distal BP	Echo-Doppler of the LL	Vascular surgery
Anti-psychotic induced akathisia	Desire to move, impossibility of remaining seated	Yes	Yes	No	Extrapyramidal syndrome	–	Reduction of neuroleptics
Akathisia secondary to hypotension	Desire to move the LL in a seated position	Yes	Yes	No	Dysautonomia	–	Support hosiery Gutron
Nocturnal cramps	Calves, thighs, UL	Yes	No	Yes	Normal	Electrolyte levels	Hexaquine
Myelopathy and radiculopathy	Systematised neuropathic pains	No	No	No	–	Imagery	Analgesic/ surgical infiltration
Painful legs and moving toes	Pains LL (UL rare)	No	No	No	Possible peripheral damage	EMG	AE

EMG: electromyogram; AE: antiepileptic; AD: antidepressants; DA: dopaminergic agonists; LL: lower limbs; UL: upper limbs.

(detectable on the DN4 neuropathic pain evaluation questionnaire) must be absent; which differentiates them from neuropathic pain. The painful form of RLS remains on the same sensory register, but is more intense, for example heat feels like burning [7]. The most frequent emotional descriptions are “annoying” (18%), irritating (11%) and unbearable (11%).

The topography of sensations: abnormal sensations start in the lower limbs. An unusual topography involving the sole of the foot, the buttocks, the perineum, the abdomen, the back, the dorsal or palmar side of the hand, the torso, the neck and head, a strictly unilateral topography, and a topography within a radicular or truncal territory should trigger suspicion of another pathology: radicular compression, painful neuropathy, rheumatic or traumatic pains, diffused pain syndrome, growing pains in case of children (Table 1).

Our work group advises physicians to draw a map of the affected areas including the nature of the sensations and their spatial-temporal scope during the first examination. This enables the syndrome's evolution to be monitored over time.

5.2.2. Dysaesthesia aggravated by immobility

The dysaesthesiae and the urge to move the legs are worsened by immobility when the subject is at rest, prone or seated. They are triggered or worsened by forced immobility, for example when the subject is wearing a safety belt during a flight, has to sit still at the theatre or during a long dinner, or immobilised in a hospital bed with a fracture, following surgery, a stroke or any another reason. All of these experiences must be looked into during the examination. For example, if long-haul flights are well tolerated a diagnosis of RLS should reconsidered.

5.2.3. Dysesthesia improved by movement

The dysesthesia and the urge to move the legs are improved by movement, by rubbing, and by cold water. It is important to distinguish these movements, which intentionally aim to relieve the unpleasant sensation, from stereotypic motor movements which are very common in the general population, such as agitating the foot or leg when seated. They are also distinct from hypnagogic foot tremors, which consist of

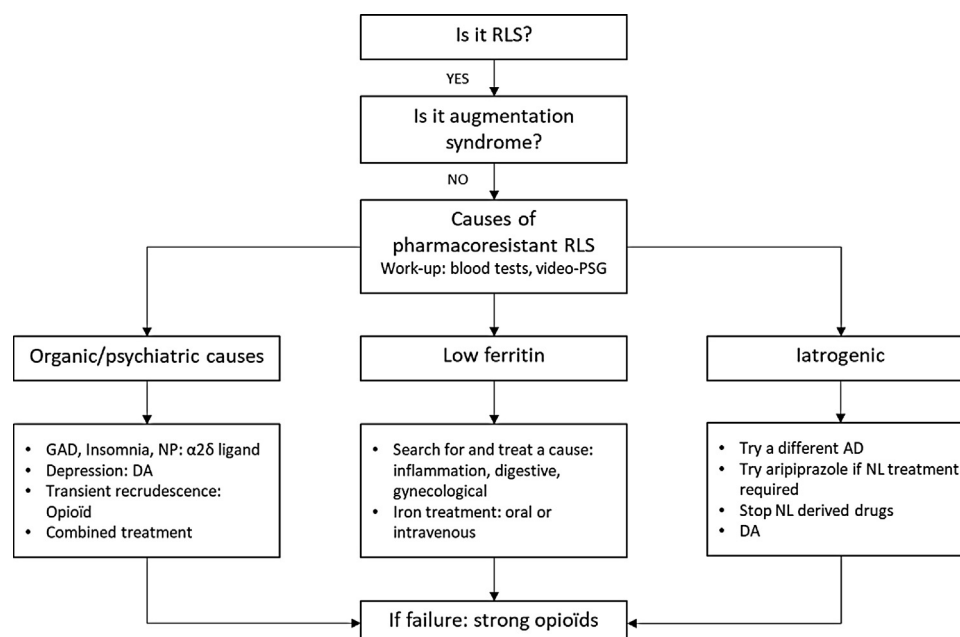


Fig. 1 – Treatment algorithm for Pharmacoresistant RLS. DA: dopaminergic agonists; AD: Antidepressants; GAD: generalised anxiety disorders; NL:neuroleptics; PN: peripheral polyneuropathy; v-PSG: video polysomnogram.

high frequency physiological contractions (2 Hz) visible during micro-arousals or when falling asleep. Some patients pinch themselves or strike the painful limbs for short-lived pain relief, therein illustrating a basic physiological principle that one pain can mask another.

5.2.4. Dysesthesia increase during the evening or night

The dysesthesia and the urge to move the legs are more severe during the evening and night compared to daytime (evening resurgence). Consequently, the period from 4 a.m. to midday remains free from symptoms for longtime. The diagnosis of RLS is questionable when symptoms continue over a 24 hour period, when they are worse in the morning, or when no evening exacerbation is reported.

5.3. Support criteria

Support criteria that should always be looked for:

- family history of RLS;
- the presence of periodic leg movements (PLM) during wake or sleep;
- positive response to DA treatment.

5.4. Additional criteria

5.4.1. Additional supporting criteria

Associated sleep disorder: the most frequent is the complaint of insomnia [8]. It is however fundamental to distinguish distressing insomnia, secondary to sensations that prevent the patient from falling asleep again, from comorbid insomnia without abnormal sensation. In fact RLS and chronic insomnia (primary or secondary to a psychiatric pathology) are both

syndromes highly prevalent in the adult population [9,10], particularly in women. Great care must be taken to establish a causal link between RLS and insomnia: a patient can complain that everything is going wrong while the RLS is well treated, but the insomnia persists. The complaint of unrefreshing sleep, of fatigue and excessive daytime sleepiness can affect up to a third of patients.

Once RLS diagnosis is definite, augmentation syndrome must be eliminated.

5.4.2. Is it augmentation syndrome?

Patients with long-term DA treated RLS have a high risk of developing augmentation syndrome. Augmentation syndrome is suspected if the patient presents with 3 of the 5 following clinical elements:

- symptoms start earlier in the day;
- symptoms appear faster when the subject is at rest;
- the intensity of symptoms increases;
- a shorter duration of action of treatment;
- symptoms spread to other parts of the body.

If augmentation syndrome is suspected, a reduction or withdrawal of DAs can sometimes improve the patient's complaint and confirm augmentation syndrome. Augmentation syndrome and its treatment are covered in another article.

6. Possible causes of pharmacoresistant RLS

Once augmentation syndrome is excluded it is imperative to search for causes of the aggravated RLS symptoms. The first

causes to be suspected are psychiatric and organic, an iron deficiency even if moderate, lifestyle changes and iatrogenic causes.

6.1. Psychiatric causes

6.1.1. Depression

Depression is one of the most common factors of drug resistance to an organic disease, even more so if pain is involved, as with RLS. Depression also causes insomnia, which can, in turn, exacerbate the RLS. It can lead to catastrophism, meaning the impression that everything is wrong, that treatments no longer work, that one feels worse and worse, with patients focusing on their symptoms. Patients with RLS often present mood disorders [11–13], which we believe to be related mainly to the chronic difficulty of living with RLS. Mood generally improves once RLS is treated. But in the case of persistence or recurrence, or when depression, which is also highly prevalent in the general population, is associated with RLS without particular reason, the severity of the depressive episode must be evaluated and treated (hospitalisation and/or therapy, and/or medication) jointly by the psychiatrist and the neurologist or sleep specialist treating the RLS. If a pharmacological treatment is proposed, the antidepressant least likely to trigger RLS should be used (Table 2). In certain cases, improvement of the depression can also translate into an improvement in the RLS possibly through a change in the perception of pain due to the symptom. Conversely, in patients treated by antidepressants who develop iatrogenic RLS, an alternative DA treatment, bupropion (this antidepressant does not induce RLS but is not reimbursed in France), or taking an antidepressant in the morning could improve symptoms.

6.1.2. Anxiety disorders

More frequent in RLS patients than control subjects [13,14], anxiety disorders can cause sleep onset insomnia when the RLS symptoms are at their most intense. A pregabalin or gabapentin treatment can improve RLS symptoms, insomnia and anxiety disorders. If ineffective and/or contraindicated, cognitive-behavioural therapy or antidepressants least likely to trigger RLS, taken in the morning could be used to treat the anxiety itself.

6.2. Organic causes

6.2.1. Iron deficiency

Iron plays an important role in the physiopathology of RLS [15]. Iron deficiency may be a frequent cause of drug

resistance in RLS, as it may contribute to DA loss of efficacy even if ferritin level is slightly below 75 µg/l and/or the transferrin saturation below 20% in a RLS patient. The common causes of iron deficiency are menorrhagia related loss (use of a coil for example), chronic occult bleeding from intestinal polyps, haemorrhoids, gastroduodenal ulcers and bleeding during surgery. There can also be poor intestinal absorption of oral iron. Dietary deficiencies should be actively sought (strict vegetarian diet, aversion to red meat in the elderly).

6.2.2. Sleep apnea syndrome

Apnea syndrome, like RLS, is highly prevalent and affects middle-aged people: the two pathologies can therefore be found in the same patient, especially if they have gained weight. In addition to the fatigue and drowsiness, apnea can cause nocturnal arousal with difficulty getting back to sleep due to the restless legs. The underlying issue is that sleep must be stabilised and continuous to limit the risk of sensing the RLS during the night. Hence it is useful to identify sleep apnea syndrome in this population if suspected (loud snoring, detected apnea, nocturia). The sleep deprivation caused by the apnea syndrome can worsen the RLS but care must be taken in interpreting causality between pharmacoresistant RLS and the presence of mild or moderate apnea, since 8 to 38% of the general population presents an apnea-hypopnea index higher than 5/h [16]. In addition, pharmacoresistant RLS can compromise good compliance with continuous positive airway pressure treatment.

6.2.3. Chronic pain syndrome or fibromyalgia

Chronic pain syndrome, or fibromyalgia, can sometimes coexist with real RLS. Diagnosis of fibromyalgia is clinical since there are no biomarkers for the pathology. In this condition pain do not have a circadian component: in general these are muscular and tendon pains, affecting the back and joints, and are not sensitive to DAs.

6.2.4. Polyneuropathy

RLS has been reported in 40% of the subjects presenting peripheral nerve damage. This prevalence is however overestimated and falls to 12.2% when nocturnal cramps and diurnal dysaesthesia are excluded [17]. Polyneuropathy is more of a differential diagnosis than a cause of RLS.

6.2.5. Forced bed rest

Any pathology that forces the patient to be bedridden can exacerbate the restless legs: this is typical following a stroke or post operatively.

6.2.6. Change of lifestyle

A change in lifestyle, especially reduced physical activity can worsen RLS symptoms. Note that intense activity during the day and especially during the evening can also exacerbate the restless legs.

Sleep deprivation can aggravate RLS, which, in turn then aggravates the sleep debt. Changing sleep time can cause a patient to go to bed too late, after midnight when RLS symptoms are, for circadian reasons, more intense.

Table 2 – Frequency of appearance or aggravation of RLS//antidepressants [21].

Antidepressant	Appearance or resurgence of pre-existing RLS
Mirtazapine	28%
Paroxetine	10%
Sertraline, Escitalopram, Venlafaxine, Duloxetine	5–10%
Fluoxetine, Citalopram	2–5%
Reboxetine	0%

6.3. Iatrogenic causes

A survey of the French pharmacovigilance database gathered between 1984 and 2009 reveals that RLS symptoms are a relatively uncommon side effect reported with the use of medication including certain antidepressants, neuroleptics and tramadol hydrochloride [18]. The report confirms the results of a previous survey demonstrating that the prevalence of neuroleptic-induced RLS does not exceed 1% of patients treated with neuroleptics (prevalence identical to the control group) [19]. Hence some medication can induce RLS symptoms in people already vulnerable to the pathology. This is especially surprising for tramadol, which is considered as a part of the RLS treatment arsenal. All of this data encourages us to recommend that the greatest caution be taken with interpreting the potentially aggravating role of certain psychotropic treatments (neuroleptics or antidepressants) use in RLS patients. Each individual requires a specific, unique and potentially multidisciplinary treatment (psychiatric, neurological, somnology). Our work group nevertheless recommends monitoring a pharmacoresistant RLS with a psychiatric comorbidity requiring a psychotropic treatment. Deciding whether a potentially deleterious medication is linked to an aggravation of RLS is time-based: RLS is worsened by the introduction of a psychotropic medication, and improved on its withdrawal.

6.3.1. Antidepressants

All antidepressants with serotonergic activity can induce or aggravate pre-existing RLS to various degrees [20,21] (Table 2). Tetracyclic antidepressants (mianserin, mirtazapine) appear to be the most powerful triggers of RLS: approximately 28% of subjects on mirtazapine develop or notice an exacerbation of their RLS, but overall RLS affects about 9% of subjects on antidepressants [21]. Tricyclics, selective serotonin reuptake inhibitors (SSRIs), as well as selective serotonin and noradrenaline reuptake inhibitors (SSNRIs) can also trigger RLS. There is no reliable data on monoamine oxidase inhibitors. Bupropion [22] (a dopaminergic agonist, not reimbursed, prescribed in France to help with tobacco withdrawal), and trazodone [11] (5-HTA2 antagonist, unavailable in France) are not known to induce RLS, even if bupropion has been suspected of provoking periodic limb movements in sleep (PMS) [20].

6.3.2. Neuroleptics

All neuroleptics with the exception of aripiprazole (partial dopaminergic agonist) can worsen or induce RLS. They can also cause akathisia which can mimic RLS symptoms but without the evening worsening or improvement through movement characteristic of RLS. The majority of antiemetics (metoclopramide, metopimazine, droperidol), with the exception of domperidone, and certain tranquilizers (phenothiazines), are derived from neuroleptics.

The use of droperidol is frequent in perioperative anaesthesia and when starting a morphine pump, to limit nausea and constipation: it is important to warn the anaesthetist of its contraindication in a patient with RLS [23,24].

6.3.3. Sodium oxybate

Oxybate sodium treatment indicated for narcolepsy can sometimes induce RLS and periodic movements in sleep [25].

6.3.4. Lithium

Lithium treatment has been associated with the emergence of RLS cases, probably in predisposed subjects [26].

6.3.5. Tramadol hydrochloride

Often used to treat RLS and occasional exacerbation of RLS, tramadol hydrochloride has been shown to increase RLS symptoms [18,20]. Nevertheless several physicians in our group use it regularly and with success to treat chronic RLS. Its use must not be ruled out for treating pharmacoresistant RLS, especially in patients with contraindications for other morphinics and their derivatives.

6.3.6. Antihistamines

Since hypnotic antihistamines are phenothiazines, derived from neuroleptics, they can worsen RLS.

7. Additional examination recommended for pharmacoresistant RLS patients

7.1. Biological work-up

The initial biological work-up must be repeated and include at least haemoglobin and ferritin. This can be completed with a full blood count, transferrin and transferrin saturation coefficient, ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) as inflammatory processes can interfere with iron metabolism. A decrease in ferritin levels can be associated with aggravated symptoms despite otherwise effective treatment. If iron levels are low (ferritin below 75 µg/l), it is important to search for the cause, especially if oral iron treatment has failed. Inflammation, malabsorption, excessive loss and iron deficiency must be looked for.

7.2. Polysomnography

A sleep recording with video is indicated for pharmacoresistant RLS, even more so if atypical clinical features exist. The aim is to quantify the degree of RLS related discomfort during waking periods (in order to confirm that it is indeed RLS and not another type of pain syndrome or evening behaviour), to check for periodic limb movements in sleep, exclude other sleep pathologies and assess the RLS's impact on the quality and quantity of sleep.

The video enables observation of the patient's motor and pain-related behaviour during restless periods, and evaluate the severity, topography and times at which they occur. The recording should start as early as possible in the evening with the patient reading in bed or watching a screen, to maximise the chances of observing motor agitation before falling asleep. It is also possible to observe motor agitation during wake after sleep onset. The presence of lower limb agitation in bed, leg movements during wake, or the fact that the patient doesn't stay in bed but gets up all the time in order to walk around the bed or sit in a chair, are relatively specific to severely exacerbated RLS.

Sleep recording allows an objective evaluation of the sleep debt. Indeed, exacerbations of RLS are often accompanied by very limited sleep, generally composed of short episodes of

sleep interspersed with long periods of agitated wakefulness, leading to a total sleep period of 2 to 4 hours and sleep deprivation plays a role in the vicious circle of exacerbated RLS. The PLM index (which is generally very high during exacerbation) and the timing of PLM during the night should be evaluated. Comorbid sleep apnea should be sought along with EEG patterns characteristic of pain during sleep: K complexes systematically followed by micro-arousal and the presence of alpha wave intrusion in slow wave sleep (also called alpha-delta sleep).

Sleep recording must be made, when possible, after medication withdrawal, particularly if augmentation syndrome is suspected in a DA treated patient. However, if the patient claims drug resistance, by definition the presence or absence of treatment will not modify their nocturnal behaviour.

7.3. Potentially useful tests

7.3.1. Suggested immobilisation test

This test objectifies discomfort during extended immobilisation. The patient is placed in a semi-seated position, with the instruction to not move the legs, to not read or distract themselves. The test starts at 8 p.m. and is continued until 9 p.m. Every 10 minutes the patient notes the degree of discomfort felt on an analogic visual scale from 0 to 10. The test is considered positive if there is a linear increase in discomfort ≥ 5 [27]. It can be negative in patients whose dysaesthesiae present later in the evening. However, this standardised test is not performed in France in routine practice and is currently reserved for research purposes.

7.3.2. Electromyography

The electromyography (EMG) is useful, after a clinical neurological examination, to diagnose a peripheral neuropathy whose clinical presentation can at times be confused with RLS.

No expert consensus has been reached about the use of the EMG in relation to pharmacoresistant RLS in the absence of an abnormal neurological examination, however it is possible that neuropathy related paraesthesiae and dysaesthesiae could exacerbate those related to RLS and consequently alter the treatment strategy. SNRI antidepressants are highly recommended in the treatment of neuropathic pains but can exacerbate the RLS.

8. Treatment of pseudo-resistant RLS

8.1. Temporary RLS resurgence

8.1.1. Hemochromatosis

Hemochromatosis with or without genetic mutation is associated with RLS [28]. An exacerbation of RLS symptoms has been described after therapeutic phlebotomy. An on-demand mild opioid treatment can be proposed after therapeutic bleeding.

8.1.2. Chronic renal insufficiency

RLS frequency is high in chronic renal insufficiency patients [29], especially those needing dialysis [30]. Restless legs are

particularly present during dialysis sessions, and occasional treatment by a mild opioid can be considered. Dialysis centres may propose pedalling in a reclining position on exercise machines during sessions to relieve RLS. It is sometimes useful to organise dialysis to avoid the time at which RLS occurs. Dopaminergic agonists can also be necessary. A recent study demonstrated good effectiveness and tolerance of a 1 to 3 mg/d patch of rotigotine [31].

8.1.3. Temporary RLS resurgence without identified cause

RLS progresses slowly but some patients can experience a short-term worsening of symptoms over several days or even several weeks, without any cause being found. An orally or patch opioid treatment can be used during this time with follow-up.

8.1.4. Case of correctly treated RLS but with the complaint of poor sleep

It is important to clearly differentiate between patients treated effectively for RLS, but with persistent insomnia and pain that cannot be attributed to RLS. In this case the comorbidity should be treated. Cognitive and behavioural therapy with or without an $\alpha 2\delta$ ligand can help improve the insomnia. Short half-life benzodiazepines as well as small doses of clonazepam can relieve both the insomnia and the RLS. The duration of this type of treatment must be evaluated on a case-by-case basis based on the evolution of symptoms and tolerance of treatment.

9. Therapy strategy for pharmacoresistant RLS and basic recommendation: proposal

9.1. Treatment of psychiatric and organic comorbidities

9.1.1. Depression

Dopamine agonists can improve mood in RLS patients, but in the case of a confirmed depressive disorder, a treatment with antidepressants with a low risk of triggering RLS should be proposed following a psychiatric opinion (Table 2).

Likewise, patients treated with antidepressants that have developed or aggravated pre-existing RLS can benefit from an alternative therapy with another antidepressant less likely to trigger RLS, or combined with an AD provided there is no contraindication. Psychiatric follow-up is recommended at the same time to consolidate the effect of treatment. Restless leg syndrome with co-morbid depression requires close collaboration between the psychiatrist treating the depression and the neurologist/sleep specialist treating the RLS.

9.1.2. Anxiety disorder

Pregabalin is indicated to treat generalised anxiety disorders. $\alpha 2\delta$ ligands improve RLS symptoms, anxiety disorders and insomnia. Recommendations for psychiatric follow-up of mood disorders also apply to the treatment of anxiety disorders.

9.1.3. Polyneuropathy

In the case of polyneuropathy, an aetiology should be sought. Treatment with $\alpha 2\delta$ ligands alone or combined with opioids is

Table 3 – Conversion tables for the main strong opioids. The conversion coefficient for methadone is dose dependent.

DCI	Conversion coefficient	Oral morphine dose equivalence
Codeine	1/6	60 mg of codeine = 10 mg of morphine
Tramadol	1/5	50 mg of tramadol = 10 mg of morphine
Dihydrocodeine	1/3	60 mg of dihydrocodeine = 20 mg of morphine
Oral morphine	1	Reference opioid
Subcutaneous morphine	2	5 mg of morphine SC = 10 mg of oral morphine
Oral oxycodone	2	5 mg of oxycodone = 10 mg of oral morphine
Transdermal fentanyl	2.4	A 25 µg/h patch = 60 mg of oral morphine
Hydromorphone	7.5	8 mg of hydromorphone = 60 mg of oral morphine

suggested. Other proven treatments for the symptomatic treatment of polyneuropathies, such as SNRIs, should be avoided in RLS associated with polyneuropathy.

9.1.4. Sleep apnea syndrome

Use of continued positive-pressure mechanical ventilation, or a mandibular advancement device, can improve RLS by improving sleep continuity. However it should be noted that RLS can cause poor compliance with continuous positive pressure.

9.1.5. Fibromyalgia

In the presence of fibromyalgia or any other chronic pain syndrome, $\alpha 2\delta$ ligands are preferable to DAs. If they do not work an SNRIs treatment could be used, preferably taken in the morning, to avoid exacerbating the RLS. Opioids should be considered as a third-line option.

9.2. Treatment of iron deficiency

The effectiveness of iron treatment in RLS has been long recognised. It is effective when ferritin is $< 75 \mu\text{g/l}$. The cause of the iron deficiency must be established and treated. If an orally iron supplementation is ineffective, the intravenous route can be considered as an alternative.

9.2.1. Stopping medication that can trigger RLS

When possible, antidepressants, neuroleptics and antihistamines must be stopped.

or at an inappropriate time) followed by checking for external and internal causes.

Once all the causes of drug resistance have been eliminated or treated prescribing the untested medical class is logical. For the opioids, the starting point is generally with mild opioids (tramadol hydrochloride; paracetamol-codeine; dihydrocodeine) progressing, if necessary, based on the effectiveness and tolerance, to major opioids (oxycodone; morphine; fentanyl). The alternative of a stronger opioid must take into account the analgesic equivalences of the molecules in order to avoid excessive or inadequate doses (see Table 3 for analgesic equivalences). The experts of our working group are all accustomed to working with these molecules. We determine the smallest, effective and best tolerated dose. Experts note that pharmacoresistance can sometimes be transient, over a few months, and that once the patient is more stable, the treatment should be reduced, especially since hyperalgesia related to the chronic use of morphine derivatives has been reported [32].

In case of partial efficacy of one or two therapeutic classes, the combination therapy with a third class, in a two- or three-drug regimen, can provide adequate efficacy and reduce the risk of side effects related to high doses, like augmentation syndrome with DA. The combination of $\alpha 2\delta$ ligands and a small dose of DA can be effective.

With drug resistance to all 3 therapeutic classes, a treatment of 5 mg/d of methadone could be considered. One expert has (very positive) experience with this molecule, with the agreement of the French “Drug users’ diseases co-ordination and intervention team” (Equipes de Coordination et d’Intervention sur les Malades Usagers de Drogue), for extremely severe and resistant RLS. Methadone is more commonly used for resistant RLS in the United States. Experts have no experience with subcutaneous or intrathecal morphine pumps in resistant hyperalgesic RLS.

10. Recommendations for the treatment of pharmacoresistant RLS

All pharmacoresistant RLS recommendations made by our expert group are based on clinical experience, and are to be considered as expert opinions, with the exception of oxycodone classified as level C in the treatment of RLS after treatment failure with AD and $\alpha 2\delta$ ligands.

It is important to distinguish between a primary and secondary pharmacoresistant RLS. In the first case at least two drug classes have not been beneficial to the patient or, have not been well tolerated, either alone or in combination at recommended doses and well conducted. At this point the third class is recommended. In the second case although effective for several months or years, the treatment progressively or suddenly loses its efficacy. If loss of efficacy is sudden, a change in compliance and adherence of the treatment must be sought (i.e. treatment taken irregularly

11. Conclusion and outlook

Exacerbated, pharmacoresistant RLS, causes patients great physical and psychological suffering, sleepless and distressing nights, daytime exhaustion, which can lead to driving accidents, confusion and falls. Hospitalising these patients can be helpful to reassure and relieve them as quickly as possible, total withdrawal of medication should only be considered in a hospital setting.

In the absence of randomised trial data our therapeutic approaches to these cases are currently experience-based.

More epidemiological, pathophysiological and therapeutic research into these forms of RLS are needed.

Disclosure of interest

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