

TARGIN IN  
**RLS**



**BEYOND**  
DOPAMINERGICS



# What is RLS?

## Also known as Willis Ekblom Disease

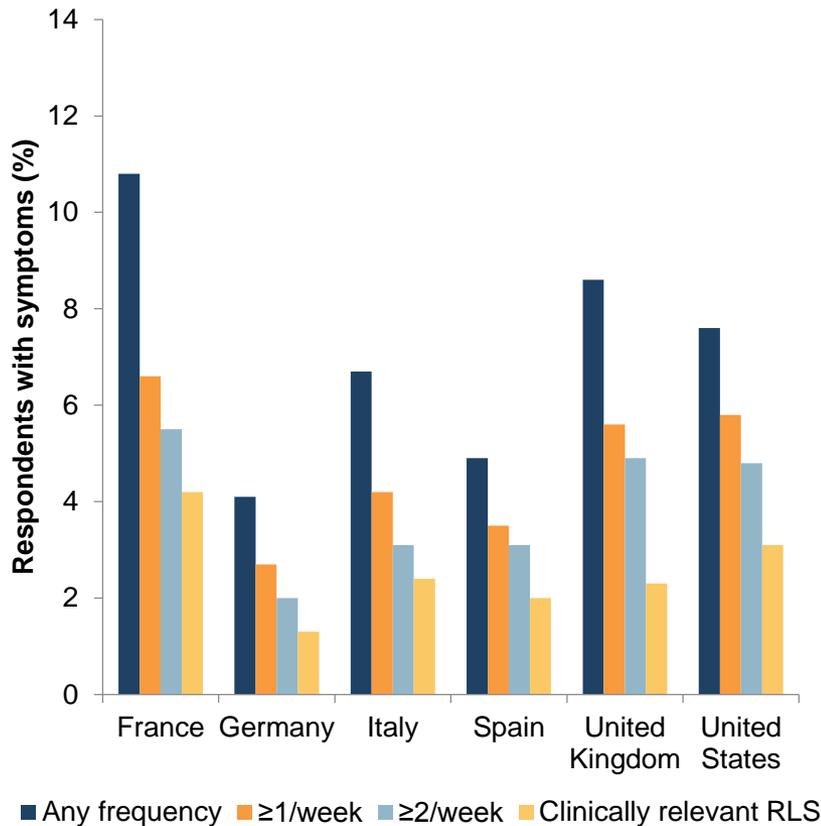
- Irresistible urge to move in order to stop uncomfortable or odd sensations<sup>1</sup>
  - A common mostly night-time movement disorder<sup>2,3,5</sup>
  - A common cause of sleep disturbances<sup>4</sup>
  - A common neurological disorder<sup>2-5</sup>

# Characteristics of RLS

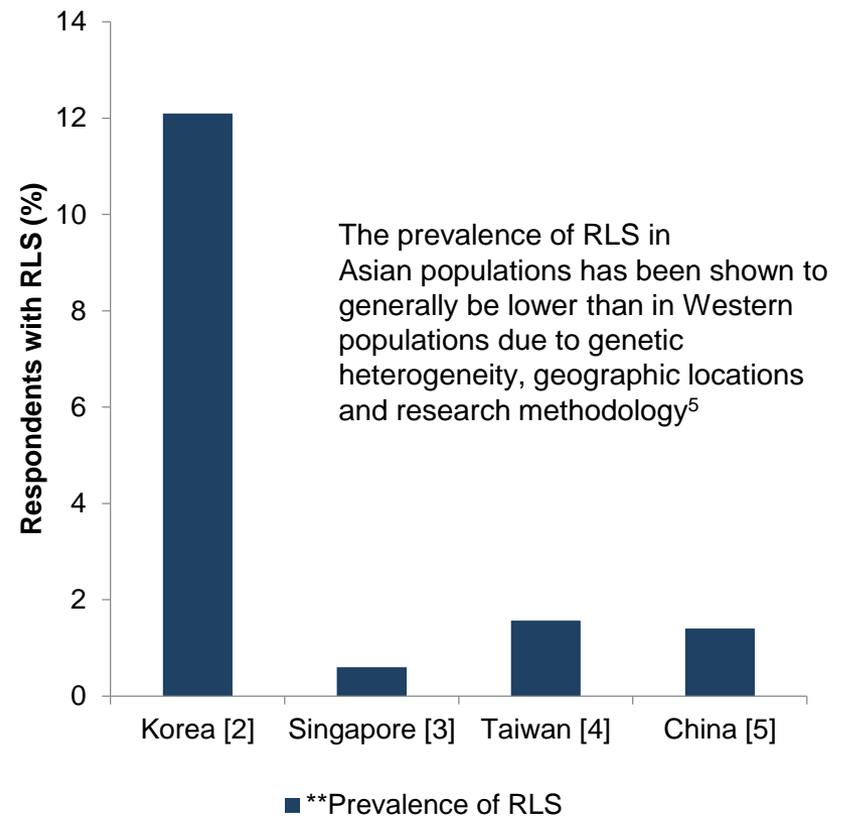
- Considerable urge to move the legs, and sometimes the arms and other parts of the body<sup>1,2</sup>
- Only occurs at rest although severe cases may affect all times<sup>1,2</sup>
- Urge to move improved through movement<sup>1</sup>
- Particularly noticeable in the evening and at night-time<sup>1</sup>



# RLS prevalence worldwide



Prevalence of RLS symptoms [1]\*



\*RLS symptoms: sensory, sleep, disturbance of daytime functioning, abnormal movement, mood; \*\* patients meeting IRLSG diagnostic criteria  
 1. Allen RP et al. Arch Intern Med 2005;165:1286–92; 2. Kim J et al. Psych Clin Neurosci 2005;59:350-53; 3. Tan EK et al. Mov Disord 2001;16:577-8; 4. Chen NH et al. Psych Clin Neurosci 2010;64:170-8; 5. Shi Y et al. PLOS One 2015; DOI:10.1371/journal.pone.0121215

# Typical course of RLS

- Onset of disorder is variable<sup>1</sup>
- Course of the disorder<sup>1</sup>
  - Generally chronic progression
  - Also intermittent, with spontaneous remissions lasting years (particularly at the onset of the disorder)

Early onset	Later onset
<50 years	>50 years
Course slow	Course more rapid and more severe
Family history important	History of the underlying disorder important

# Types of RLS

- Primary / idiopathic RLS<sup>1-3</sup>
  - Most common type
  - Sporadic or hereditary<sup>2,4</sup>
  - Disorder of the CNS<sup>5</sup>
  - No further obvious underlying condition diagnosable<sup>2</sup>
- Secondary / symptomatic RLS<sup>1-3</sup>
  - Related to an underlying health condition<sup>1-3</sup>
  - Medication can aggravate existing symptoms<sup>2</sup>

CNS = central nervous system

# Clinical presentation – paraesthesia

- Unpleasant / agonising sensations of numbness in the legs<sup>1</sup>
  - Associated in RLS with a considerable urge to move<sup>1</sup>
- Localised from ankle through to thigh<sup>2</sup>
  - Can be one-sided (41% of patients<sup>2</sup>), or on both sides (59%<sup>2</sup>)
  - In 50% of patients, arms and hands are also affected (particularly in severe cases)<sup>1,2</sup>
  - Can be paroxysmal or occur in clusters<sup>3</sup>
- Occurs particularly<sup>1</sup>
  - In the evening or at night
  - When relaxing, at rest and when falling asleep
  - During activities such as visits to the theatre, long car and train journeys or flights<sup>4</sup>

# Aetiology and pathophysiology

- The aetiology and pathophysiology of RLS are not fully understood
- There is evidence of a connection between RLS and the dopamine/iron and opioid systems in the CNS<sup>1</sup>
- These systems interact with each other
  - Dopamine synthesis is dependent on iron levels<sup>2,3</sup>
  - Direct interaction between opioid and dopamine systems in the CNS<sup>4,5</sup>
- Investigations indicate a close connection between genetic factors and the risk of suffering from RLS<sup>6-9</sup>
- As the pathophysiology of RLS is not fully understood the causes of RLS are currently unknown

1. Jones R et al. Behav Neurobiol 2013;26:283-92; 2. Ramsey AJ et al. J Biol Chem 1996;271:24395-400; 3. Daubner SC et al. Arch Biochem Biophys 2011;508:1-12; 4. Walters AS. Sleep Med 2002;3:301-4; 5. Walters AS et al. J Neurol Sci 2009;279:62-5; 6. Winkelmann J et al. Nat Genet 2007;39:1000-6; 7. Schormair B et al. Nat Genet 2008;40:946-8; 8. Winkelmann J et al. PLoS Genet 2011;7:e1002171; 9. Stefansson H et al. N Engl J Med 2007;357:639-47

# Essential diagnostic criteria

## Diagnostic criteria that every RLS patient should meet

### 1. Urge to move the legs

- Mostly associated with sensory disorders of differing quality or pain
- Rarely, arms or other areas of the body also affected

### 2. Starts or worsens while at rest

- At rest or when inactive, e.g. when sitting or lying down

### 3. Improves with movement

- Urge to move and associated unpleasant feelings are partially or fully improved while movement continues (e.g. walking or stretching)

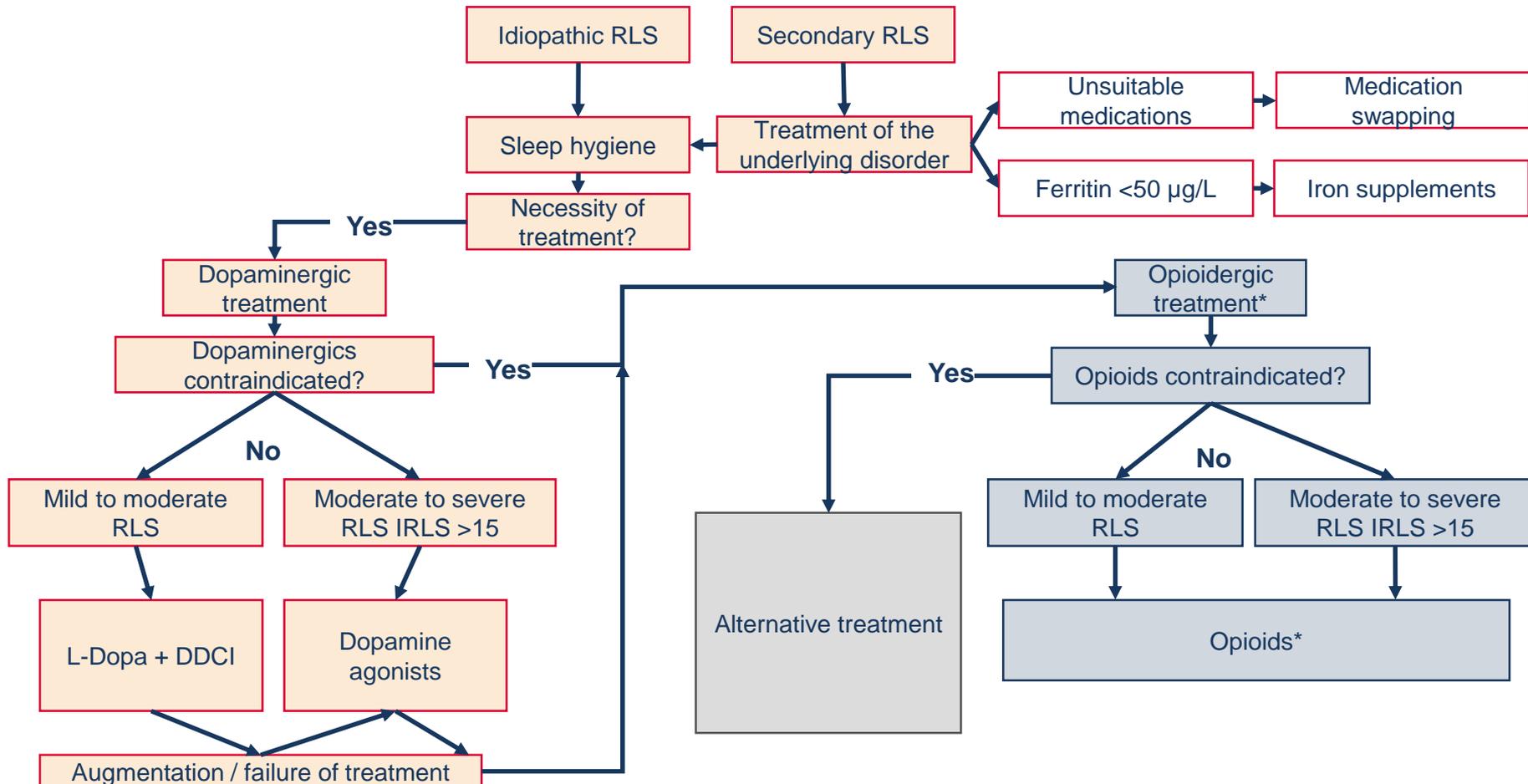
### 4. Symptoms experienced mainly in the evenings or at night

- Urge to move and associated unpleasant feelings are stronger in the evening and at night than in the daytime
- When the symptoms are very marked this difference is possibly no longer detectable, but must have existed initially

### 5. Differential diagnosis

- The occurrence of the above features cannot be accounted for as symptoms of another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

# Treatment planning



\*off-label use – except for oxycodone PR/naloxone PR; DDCI = dopamine-decarboxylase inhibitor; IRLS = International RLS Severity Scale

Adapted from Oertel WH et al. *Mov Disord* 2007;22 Suppl 18:S466-75; TARGIN® Summary of Product Characteristics 2015 <https://www.medicines.org.uk/emc/medicine/22908> Accessed April 2015

# Treatment following augmentation

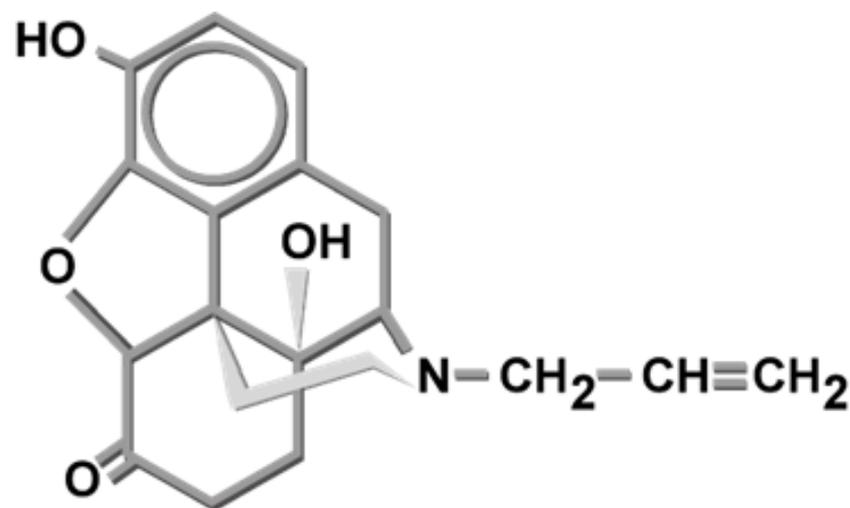
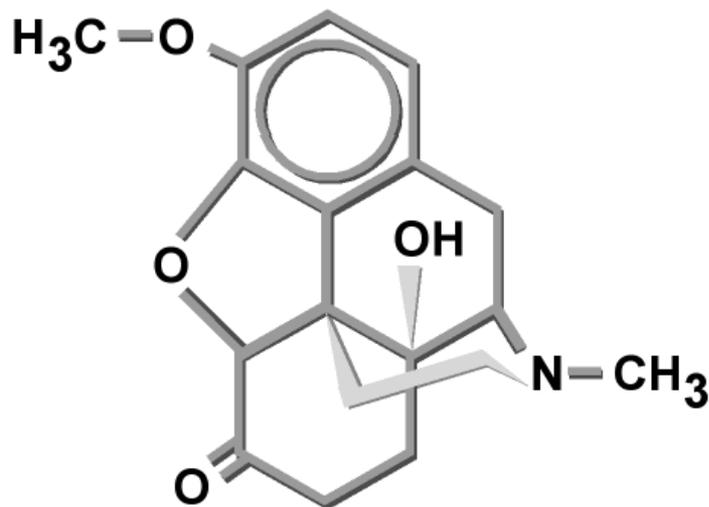
- Augmentation is the paradoxical worsening or RLS symptoms while on dopaminergic therapy
- Augmentation is managed in the first instance by a dose reduction or switch to an agonist with a longer half-life e.g. rotigotine
- If dose reduction or switch therapy is ineffective a low dose of opioid can be considered

# TARGIN<sup>®</sup> (oxycodone / naloxone)

Fixed combination

2 x oxycodone PR

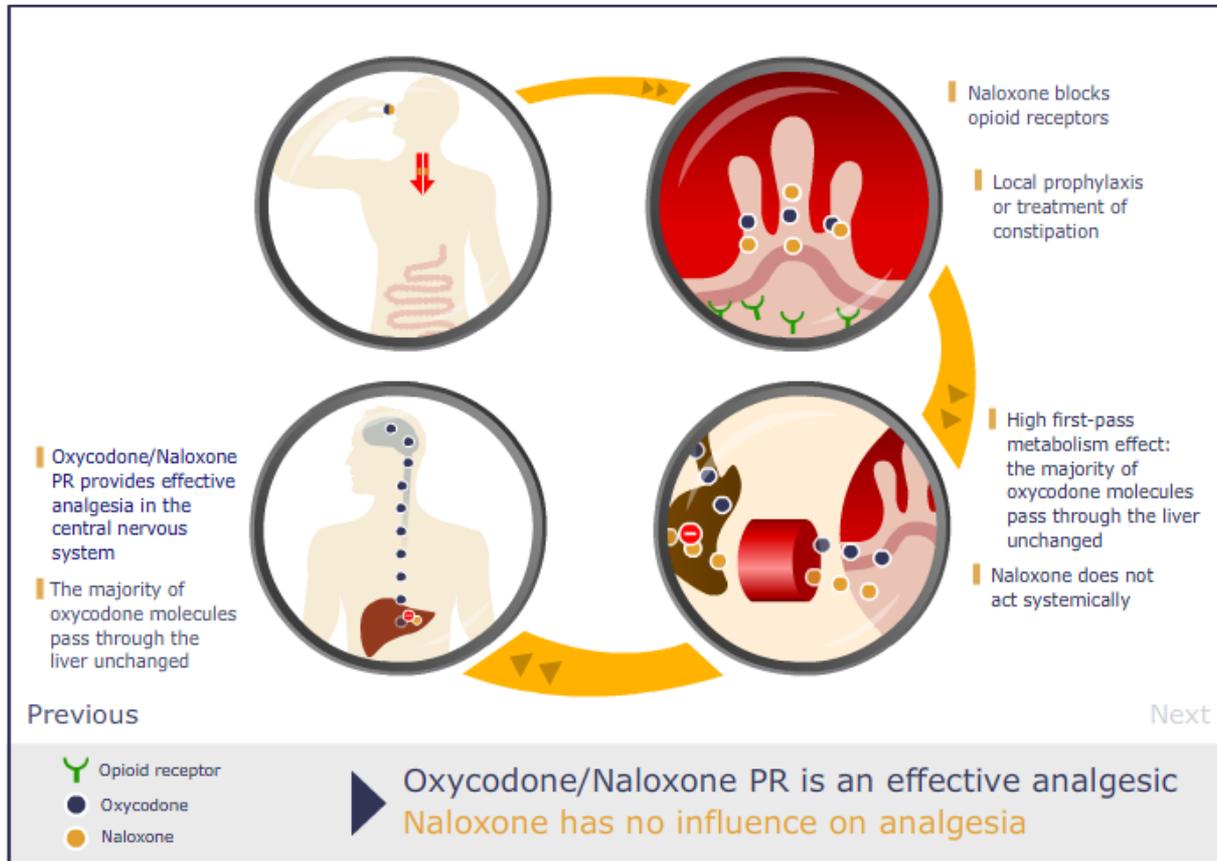
1 x naloxone PR



PR = prolonged release

<http://pubchem.ncbi.nlm.nih.gov/compound/oxycodone>; <http://pubchem.ncbi.nlm.nih.gov/compound/5284596> Accessed April 2015; TARGIN<sup>®</sup> Summary of Product Characteristics 2015 <https://www.medicines.org.uk/emc/medicine/22908> Accessed April 2015

# TARGIN<sup>®</sup> – mechanism of action in pain



Naloxone undergoes extensive first-pass metabolism and ~2% reaches the systemic circulation<sup>1</sup>

1. Lowenstein O et al. Exp Opin Pharmacother 2009;10:531–43. Adapted from Smith K et al. Int J Clin Pharmacol Ther 2012;50:360–7. See next slide for additional information

# Summary

- The clinical picture of RLS is characterized by a variable onset and usually by chronic progression
- Patient symptoms include paraesthesia, periodic limb movement (PLM), as well as severe sleep disturbance, leading to reduced quality of life
- RLS is diagnosed on the basis of five essential diagnosis criteria
- Dopamine agonists remain the cornerstone of first line therapy for RLS
- Second line therapy with opioids is recommended when dopamine agonists fail or augmentation occurs