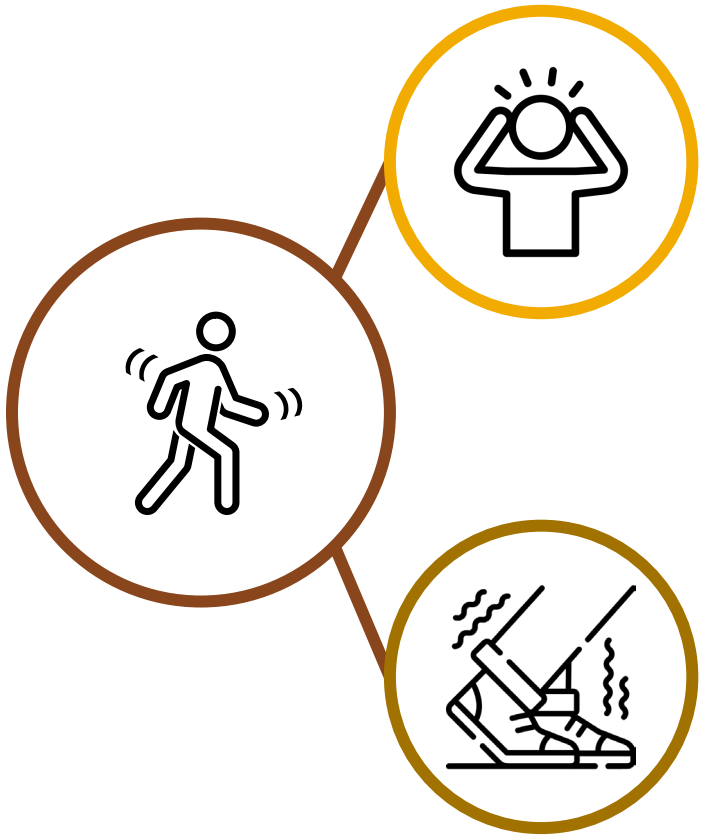
REAGILA®
CARIPRAZINE

AKATHISIA GUIDE

What is akathisia?

Akathisia is an **abnormal state of excessive restlessness** that has two fundamental components: a sensory component and a motor component.[1,2]

DEFINITION



Sensory component:
The unpleasant sensation of inner restlessness

Motor component:
Movements mostly of the lower extremities

It is mostly **iatrogenic**, often associated with the use of certain types of medications, especially antipsychotics.[1,2]

Incidence:
20%–75%

Prevalence:
20%–35%

How is akathisia different than…?

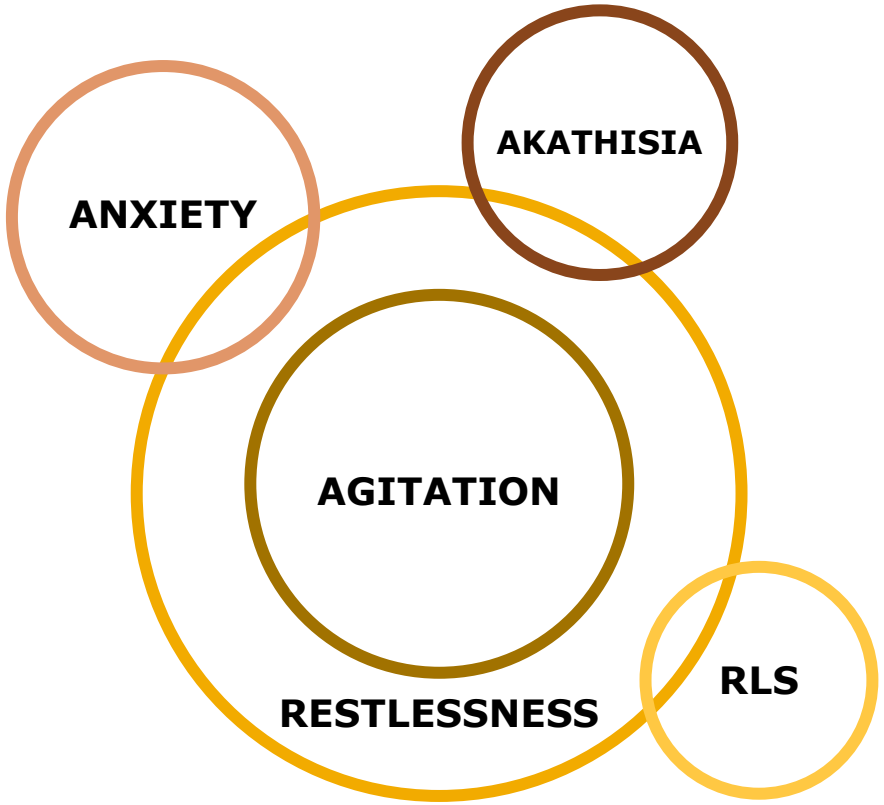
Akathisia **may be hard to distinguish from other neurological and psychiatric disorders**, especially restlessness, anxiety and agitation.[2]

Restlessness, the quality of being unwilling or unable to stay still or to be quiet and calm, is a more general term, and can be a symptom of many different conditions, including:

- **Akathisia**
- Anxiety
- Agitation
- **Restless legs syndrome (RLS)**
- ADHD
- Side effects of stimulating medications
- or physiological responses to too much caffeine.[3]

Agitation is a feeling of irritability or severe **restlessness**, which may accompany many psychiatric disorders.[4,5]

Anxiety is a mental health disorder characterized by feelings of worry or fear. **Restlessness** can be a symptom of anxiety, but anxiety also involves other symptoms like rapid heartbeat, sweating, and feelings of impending doom.[4]

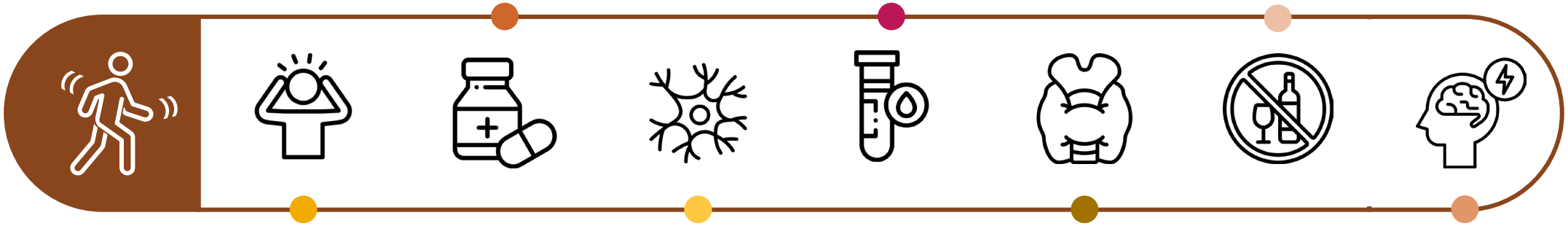


How is akathisia different than…?

Akathisia is often **underdiagnosed** because its symptoms can mimic and/or overlap with other disorders and conditions.[6,7]

The differential diagnosis of **akathisia** includes differentiation from:

- **Anxiety**, agitation & restlessness
- **Levodopa-induced dyskinesia** in patients who take levodopa
- Peripheral **neuropathy** (restlessness associated with pain or tingling)
- Low **iron** levels
- High **triiodothyronine** (T3) or **thyroxine** (T4) levels
- **Drug** withdrawal
- or **intoxication**.[6,7]



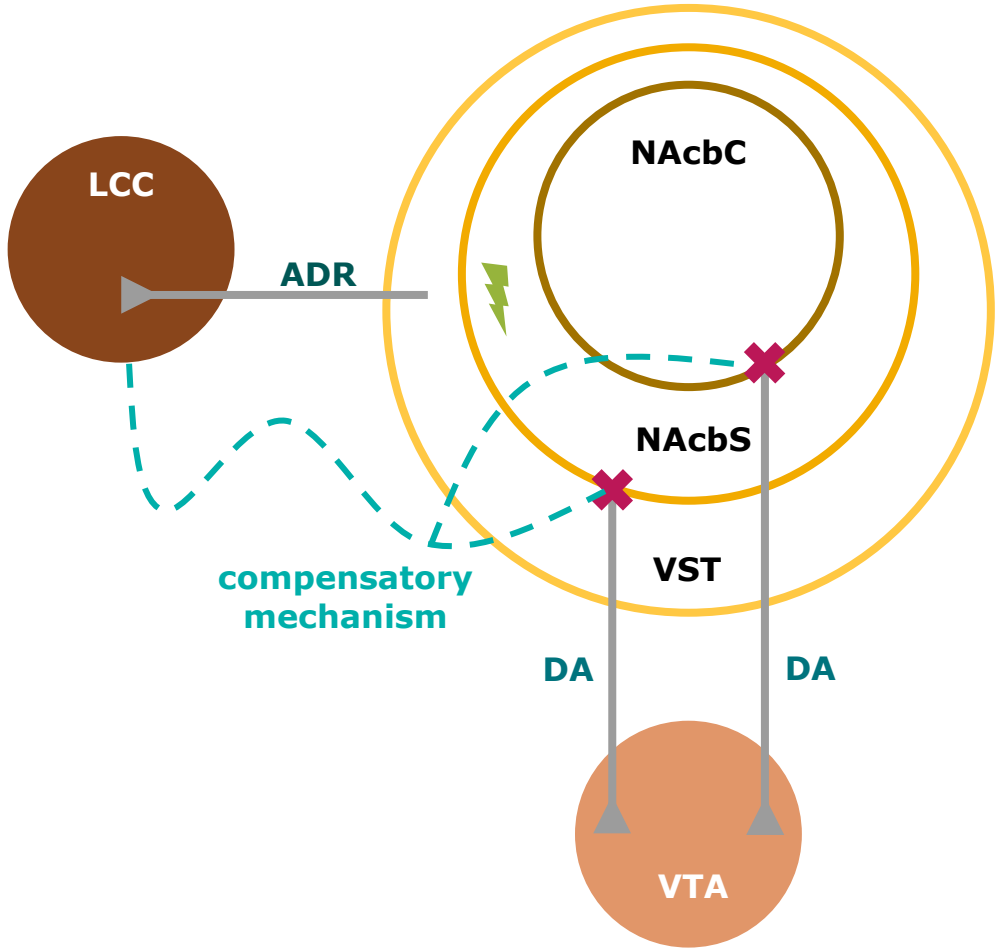
Why does akathisia develop?

The pathophysiology of akathisia is still poorly understood.[6] Mechanisms likely impact of dopamine[8], serotonin, and noradrenergic systems on the somatosensory system in the brain.

Much evidence exists to support the idea that **akathisia** is related to a decrease in **dopaminergic (DA)** neurotransmission. This likely results in decreased activity of the entire **ventral striatum (VST).**

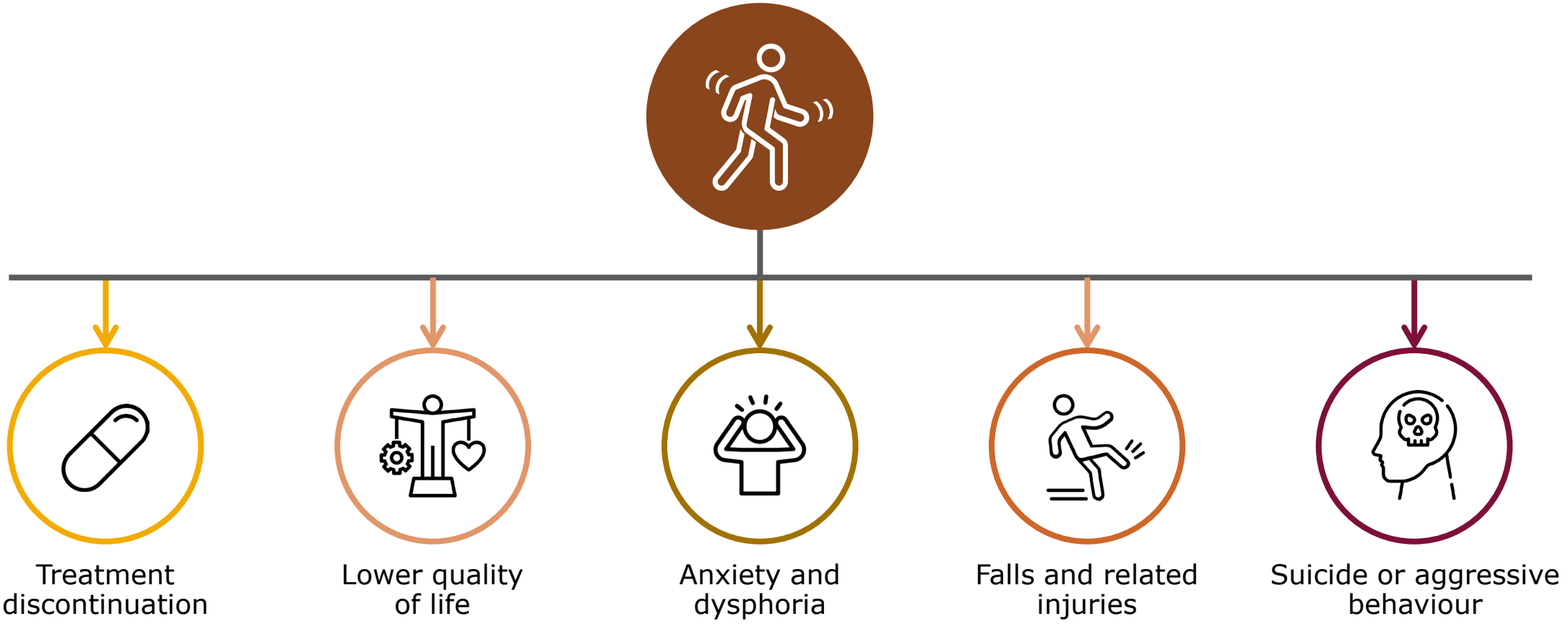
The dopaminergic underactivity in the nucleus accumbens results in compensatory enhancement of the activity of **adrenergic (ADR)** projections from the **locus coeruleus complex (LCC)**.

Because these projections selectively stimulate the shell portion of the **nucleus accumbens (NAcbS),** a mismatch between the activities of the **NAcbS** and the core portion of the **nucleus accumbens (NAcbC)** results. Relative overstimulation of the **NAcbS** results in the typical urge to display senseless restless behaviour and is accompanied by dysphoric feelings.



Impact of akathisia

Akathisia is associated with a **lower quality of life** and **non-adherence**. In extreme cases akathisia is associated with an increased risk of **suicide** and **aggressive behavior**.[9]



Timeline of akathisia

Akathisia occurs acutely or sub-acutely with dopamine receptor-blocker therapies and improves with removal of the drug. It can also develop as a chronic or tardive disorder (occurring after chronic therapy) and worsens with removal of the drug.[6]

TIMELINE

1. **Acute akathisia**
   6 months or less
2. **Chronic akathisia**
   More than 6 months
3. **Tardive akathisia**
   Delayed onset
4. **Withdrawal akathisia**
   Within 2 weeks of antipsychotic discontinuation or dose reduction
   Generally self-limited, resolves within 6 weeks

Typically, the onset of akathisia occurs within **2-3 weeks of initiation of treatment** (90% develop withing 73 days) or shortly after an increase in dosage.[4]

Drugs that cause akathisia

Medications that are most often associated with akathisia are antipsychotics. However, other medications can also initiate it as side effect.[7]

- First- and second-generation antipsychotics
- Antidepressants at high doses
- Dopamine-blocking antiemetics
- Antihypertensives
- Lithium
- Calcium channel blockers
- Tetrabenazine, VMAT2 inhibitors

Recommendations for management

Antipsychotic-induced akathisia may be managed by a slow up-titration, reducing the dose of the causing agent or anti-akathisia medication.[6]

Prophylactic treatment is generally **not recommended**.

When newly introducing a drug, the **up-titration should be slow**.[10]

Anti-akathisia medication can be added to treat symptoms of akathisia.

If akathisia develops during treatment, the dose of **the causal agent should be reduced**.[11]

Pharmacological treatment

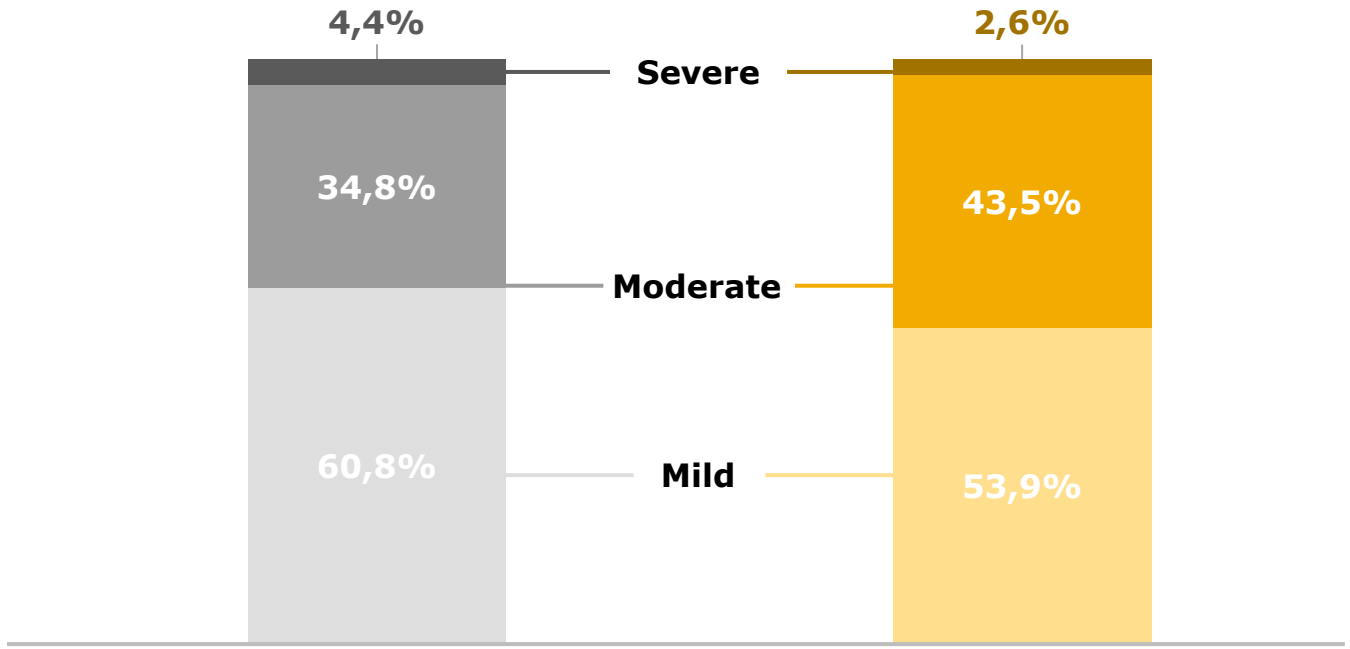
State of the art treatment for akathisia is propranolol (40-80 mg po BID); but some other agents might also be used.[11,2]

Beta blockers	Gold standard: propranolol is especially effective
Benzodazepines	Less evidence, but longer acting agents are better e.g., clonazepam or lorazepam
Anticholinergics	Increase the risk of dementia
Clonidine	Some benefit
Amantadine	Some benefit
Mirtazapine	Less evidence
Cyproheptadine & mianserine	Less evidence

Akathisia with cariprazine: What to expect?

Akathisia is the most common side effect of cariprazine treatment. In the clinical studies it occurred in 14.6% of patients, mostly in mild to moderate severity (>95%).[12]

	Placebo n = 683	Cariprazine n = 2048
Patients with Akathisia, n (%)	23 (3.4)	299 (14.6)
Akathisia events, n*	23	334



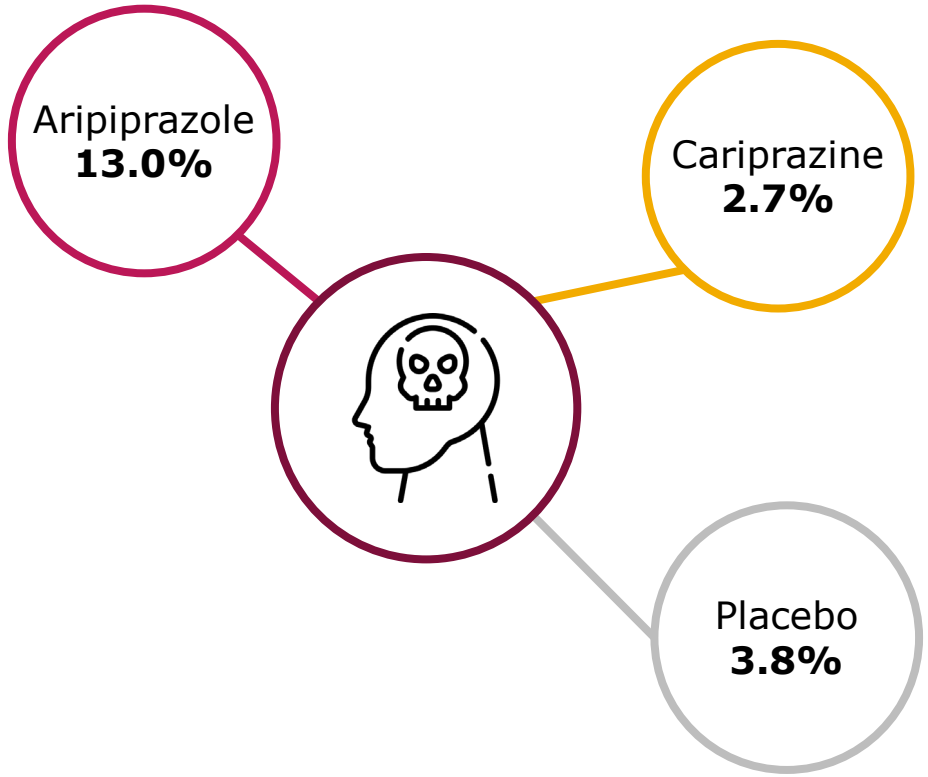
*One patient might have experienced more than one akathisia event. Events were counted separately if there were 3 or more days between them.

Akathisia with cariprazine: What to expect?

A relationship between akathisia and suicidal tendency was not observed in the cariprazine schizophrenia program. Rate of any suicidality was comparable to placebo.[12]

In the short-term studies, more patients experienced concurrent akathisia and suicidal ideation on **placebo** and **aripiprazole** treatments than on **cariprazine** treatment.

In the overall, pooled schizophrenia studies, rates of any suicidal ideation were **comparable** between **placebo** (3.6%) and **cariprazine** (5.2%). None of the patients showed suicidal behaviour.[12]



Akathisia with cariprazine: What to do?

Despite being the most reported side effect, the rate of akathisia-related discontinuation was relatively low: 6.3%.[12]

To address akathisia, doctors either prescribed **anti-EPS treatment** or **reduced the dose** of cariprazine.

As **akathisia with cariprazine is dose dependent**, lower doses (1.5 or 3.0 mg) and a slow up-titration may also be benefitial.[12]

1.5 mg
3.0 mg

Acute akathisia resolves **without any intervention** in **less than six months**, especially when it is mild in intensity.[6]

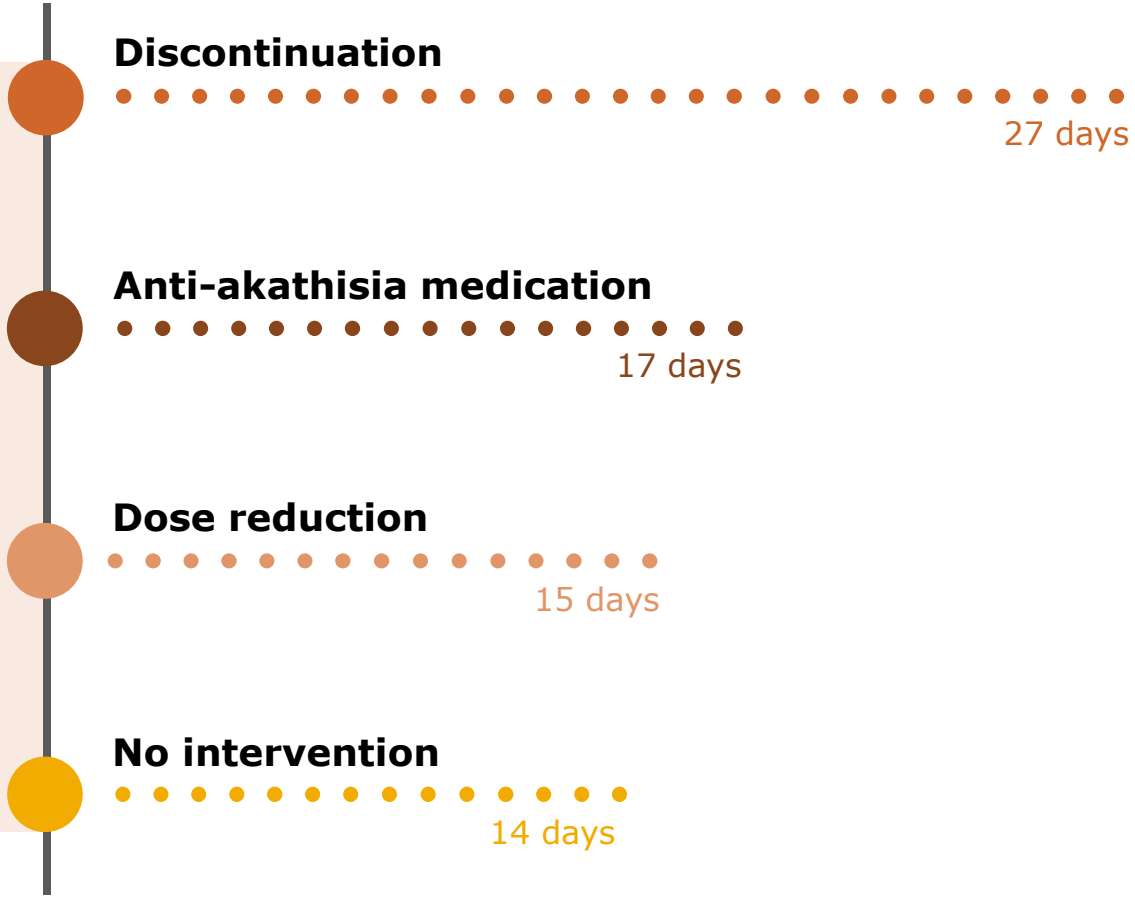
6 months

CARIPRAZINE

Akathisia with cariprazine: What to do?

Most akathisia events resolve with time[6], generally in 7 days after discontinuation[4].

In the clinical studies with cariprazine**, time to resolution of akathisia** was 14 days with no intervention, 15 with dose reduction and 17 with anti-EPS medication. Time to resolution of akathisia was 27 days with discontinuation.[12]



Summary

KEY POINTS

- Akathisia is a **class side effect of antipsychotic treatment**. It occurs in 1/3 of patients treated for chronic mental illness.
- It is **difficult to distinguish** akathisia from restlessness, agitation and anxiety. Look for **time correspondence** with onset of antipsychotic treatment.
- **Acute akathisia resolves within 6 month**. Slow up-titration, low doses, dose reduction and anti-akathisia medication (propranolol) may help in preventing or resolving akathisia.
- Akathisia can be treated with various agents; however best results are seen with **propranolol treatment** (40-80 mg po BID).
- **Cariprazine-induced akathisia** was mostly **mild** and **well-manageable** with dose reduction and anti-akathisia medication. **Severe side effects** such as suicidality related to akathisia **did not occur**.

Abbreviated Summary of Product Characteristics

Reagila® (cariprazine) 1.5 mg; 3 mg; 4.5 mg; 6 mg hard capsule.[1]

SMPC

Name of the medicinal product
Reagila (cariprazine) 1.5 mg; 3 mg; 4.5 mg; 6 mg hard capsule, ATC code: N05AX15.

Therapeutic indications
Reagila is indicated for the treatment of schizophrenia in adult patients.

Posology
The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks.

Contraindications
Hypersensitivity to the active substance or to any of the excipients, concomitant administration of strong or moderate CY- P3A4 inhibitors or inducers.

Special warnings
Precautions for use: in case of suicidal thoughts or behaviour; in those who are prone to or already exhibit symptoms of akathisia; in patients with Parkinson disease; in patients with risk factors for stroke; in patients with medical history of seizure, cardiovascular disease (blood pressure changes, QT prolongation, risk for venous thromboembolism), diabetes mellitus. If signs and symptoms of tardive dyskinesia appear discontinuation should be considered. Drug discontinuation is recommended if signs and symptoms of neuroleptic malignant syndrome develops. Patients who would develop symptoms potentially related to cataract should be advised to ophthalmologic examination. Weight should be monitored regularly. Not recommended to treat elderly patients with dementia. Capsules of 3 mg, 4.5 mg and 6 mg contain Allura red AC which can cause allergic reactions.

Most common adverse reactions
Akathisia, extrapyramidal symptoms, body weight increase, increased or decreased appetite, dyslipidaemia, sleep disorders, anxiety, sedation, dizziness, blurred vision, tachyarrhythmia, hypertension, nausea, constipation, vomiting, increased liver enzymes and creatinine phosphokinase in blood, fatigue. Not recommended during pregnancy or for fertile women not using reliable contraception. The medicinal product has minor or moderate influence on the ability to drive and use machines.

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