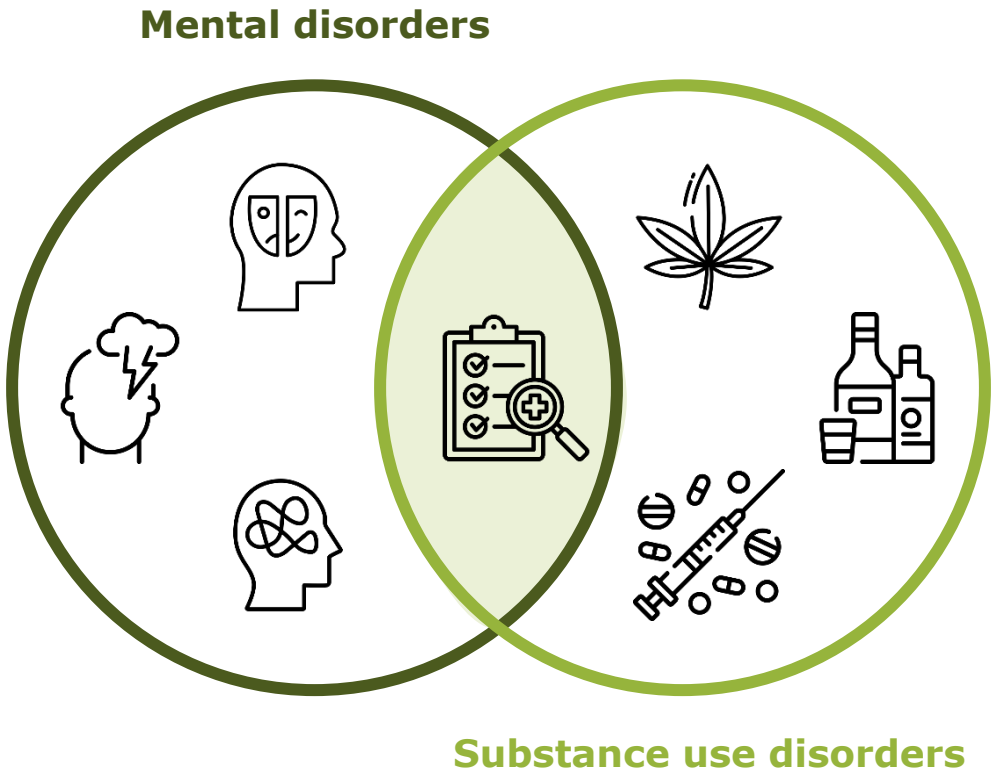
REAGILA®
CARIPRAZINE

DUAL DISORDER GUIDE

What are dual disorders?

DEFINITION

Dual disorder (co-occurring disorder or dual diagnosis) is a term used when someone experiences **a mental illness and a substance use disorder (SUD) at the same time**.[1]



Given the broadness of the term, both parts - the mental disorder part the substance use disorder part - may vary.

Mental disorders can be:
- schizophrenia,
- bipolar disorder,
- major depressive disorder etc.

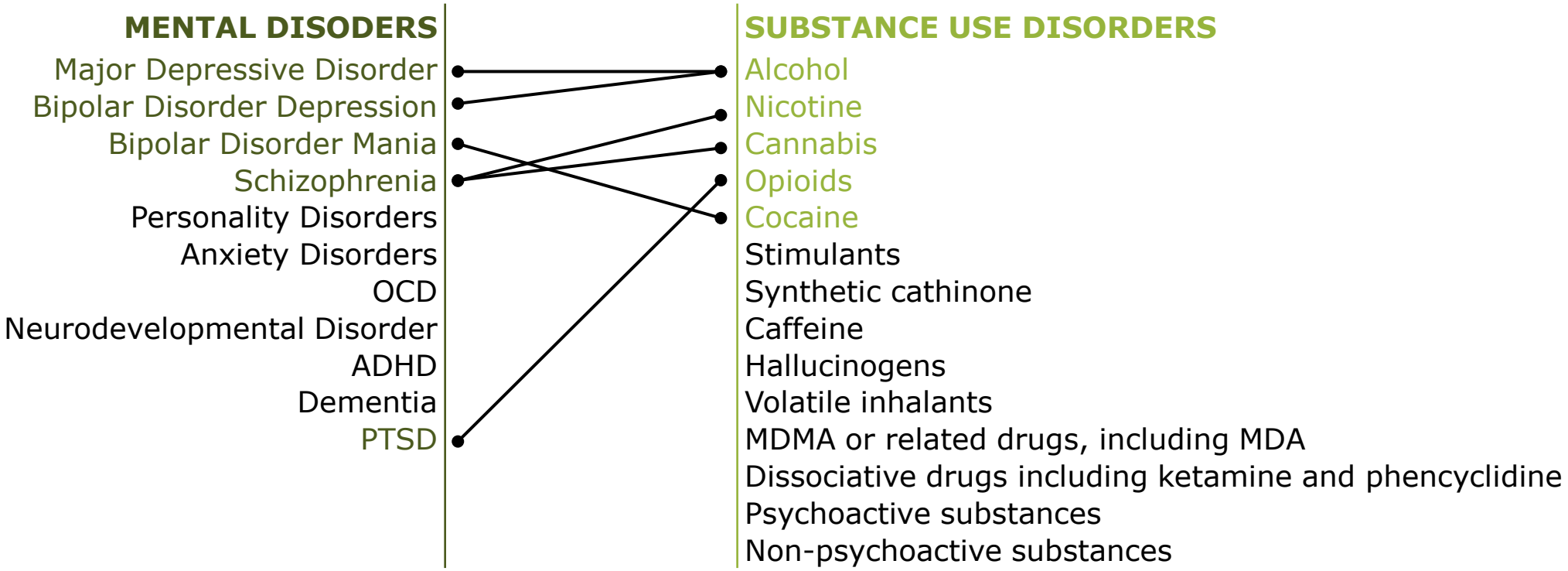
Substances can be:
- nicotine,
- alcohol,
- cannabis
- opioids etc.

Therefore, a lot of different combinations are possible, and all can be called dual disorder.

Most common dual disorders

There are sixteen substance classes listed in the eleventh revision of the International Classification of Diseases (ICD-11).[2] **Some combinations are more common than others**.

Some of the most common combinations are listed below[3]:



The impact of dual disorders

Dual disorders can result in greater incidence of **adverse health outcomes**, suicide, unplanned hospital admissions, and early mortality. Consequences include violence, homelessness, involvement with criminal justice system, and relationship breakdowns have also been suggested.[4]

75% of patients with severe mental health disorder also have substance use disorder.[4]

60% of adults with substance use disorder have at least one type of severe mental health disorder diagnosis as well.[4]

In the dual disorder concept, it is not important to clarify whether the mental health disorder or the substance use was first. The most important is to **provide an integrated treatment**.[4]

Lack of appropriate treatment

Patients with dual disorders may be **misdiagnosed** and **mistreated**, often "falling through the cracks" of the health care system. They may be rejected by both drug programs and mental health programs due to their cooccurring disorder.[1]

Patients **do not get the treatment they need**.[1]

Patients have **lower quality of life**, and **higher mortality** and **suicide rates**. [1]

Only **9%** of mental health programs had sufficient capacity to provide simultaneous services for patients with coexisting disorder.[4]

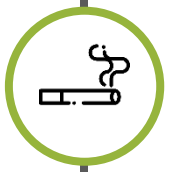
Only **18%** of addiction treatment programs had sufficient capacity to provide simultaneous services for patients with coexisting disorder.[4]

Dual schizophrenia in numbers

Patients with schizophrenia and substance use disorder are at high risk of **mortality**, **suicide**, and **other medical illnesses**.[5] This underscores the importance of treating dual schizophrenia, however, only a few patients receive adequate treatment.[5]

42% of patients with schizophrenia have substance use disorder.[7]

47% of patients with cannabis use transition to schizophrenia.[8]



60% of people with schizophrenia smoke, three times the general prevalence.[9]

Only **7%** receive treatment for both disorders.[5]

Dual schizophrenia is underreported

Rates of under-reported drug use are considerable among individuals with schizophrenia when compared to laboratory assays. Patients who under-report their drug use are more likely to **manifest neurocognitive deficits**, which could be improved by a more optimized treatment.[10]

In the **CATIE study**, over a thousand people with schizophrenia completed self-assessment questionnaires on the use of: cannabis, cocaine, and amphetamine, followed by laboratory tests.[10]

38% of participants tested positive for drug use on laboratory measures.[10]

58% did not report using these drugs.[10]

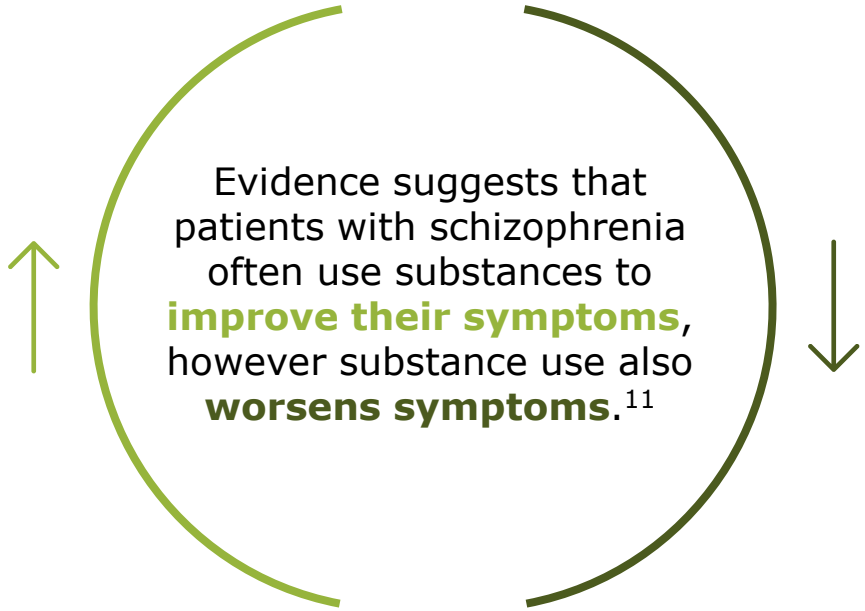
Patients who under-reported their drug use were **older** & **more likely to manifest neurocognitive deficits**.[10]

Patients who accurately reported drug use tended to have **greater involvement** with the criminal justice system.[10]

Self-medication in dual schizophrenia

What are the reasons for the use of substances by individuals with psychotic disorder?

Results suggest the high prevalence of **nicotine** use in schizophrenia may be an attempt to **improve cognition**.[9]



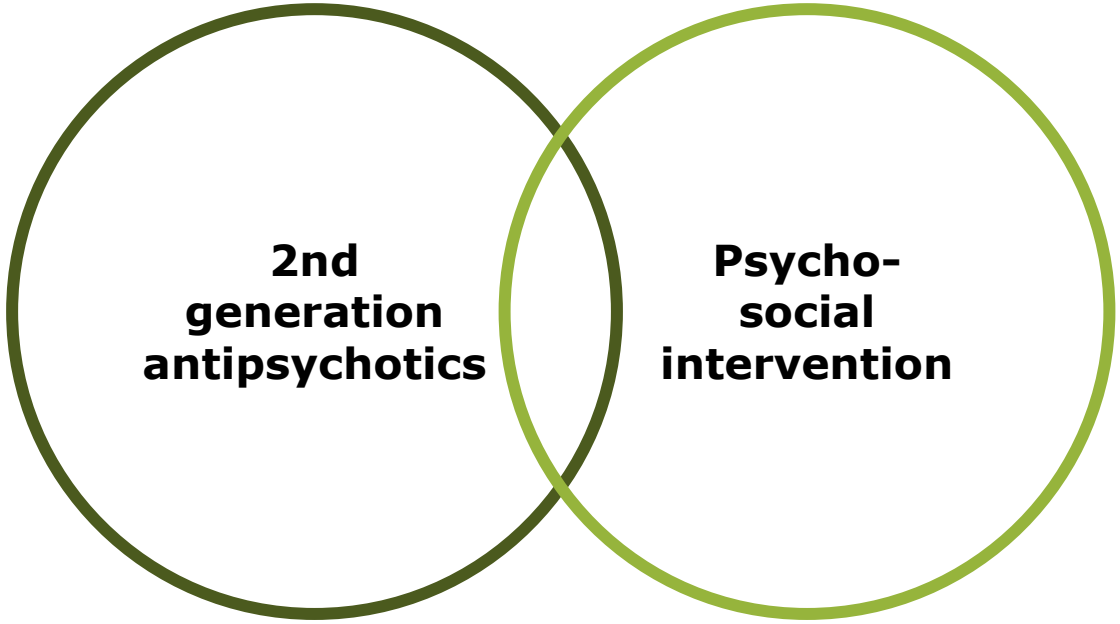
Consistent with the notion of self-medication, **alcohol** use was most likely to follow increases in **anxious mood or psychotic symptoms**. [11]

Cannabis and other illicit substances are used to **control negative emotions** but were also associated with the **onset of subsequent psychotic symptoms**. [11]

Dual schizophrenia treatment

Treating patients with dual schizophrenia can be **challenging**. Current guidelines recognize a need to treat dual disorders but the give **very little guidance**. [12]

The need for integrated treatments have been recognized as an unmet medical need. Research suggests that individuals with DD access mental health and substance use treatment at unequal rates compared to individuals without such co-morbidities.[5]



First-generation antipsychotics

First generation antipsychotics (FGAs) are **not recommended** in the treatment of dual disorders, because they have several characteristics that are **not beneficial** for the treatment of these disoders.[14]

1st

- FGA have been linked to an **increase in craving** and **self-administration** of **cocaine** and other substances in experimental animal models.[14]
- FGA have been linked to **elevated incidence of SUD**.[14]
- Dual disorder patients show **worse tolerability** to FGA.[14]
- First generation of antipsychotics drugs (Dopaminergic D2 receptor antagonists) **could further reduce the basal dopaminergic tone** described in drug users.[14]
- This greater blockage could sometimes lead to a **greater consumption of psychoactive substances** to alleviate anhedonia[15] and cognitive deficits[16].

Second-generation antipsychotics

Current guidelines and scientific articles suggest second generation antipsychotics (SGAs) for the treatment of dual disoders.[13]

A study examining the effects of SGAs on schizophrenia plus cannabis or alcohol consumption found that the most used drug was aripiprazole.[17] Nonetheless, it is important to note that the efficacy of aripiprazole in this population might be a potential **class effect of dopamine partial agonists.**

Indeed, antipsychotics with a dopamine partial agonism provide potential clinical advantages in the treatment of psychosis and SUD[17]. Therefore, Martinotti et al. recommend these drugs **first line treatment** in maintenance settings for dual disorders; as second line in acute settings.[17]

Aripiprazole, Cariprazine, Brexpiprazole

Both are partial agonists at dopamine 2 receptors reducing dopamine output when dopamine concentrations are high, thus improving positive symptoms and mediating antipsychotic actions; conversely, they increase dopamine output when dopamine concentrations are low, thus improving cognitive, negative, and mood symptoms (including anhedonia).

For aripiprazole, the blockade of serotonin type 2C and 7 receptors as well as partial agonist actions at 5HT1A receptors may contribute to antidepressant actions.

For cariprazine, the binding to dopamine 3 over dopamine 2 receptors at low doses might theoretically contribute to cariprazine's efficacy for negative symptoms and be useful for treating cognition, mood, emotions, and reward/ substance use.[17]

The Role of D3 Receptors in Dual Disorders

Recent studies postulate that drugs targeting dopamine D3 receptors might be pharmacological alternatives,[17] as the **D3 receptors are involved in drug-related reward, drug-intake** as well as **behavioural sensitization**, including reinstatement and drug-seeking behavior.[18]

Drugs of abuse may **up-regulate D3 receptors**: selective upregulation of D3 receptor expression has been shown following repeated drug exposures.[18]

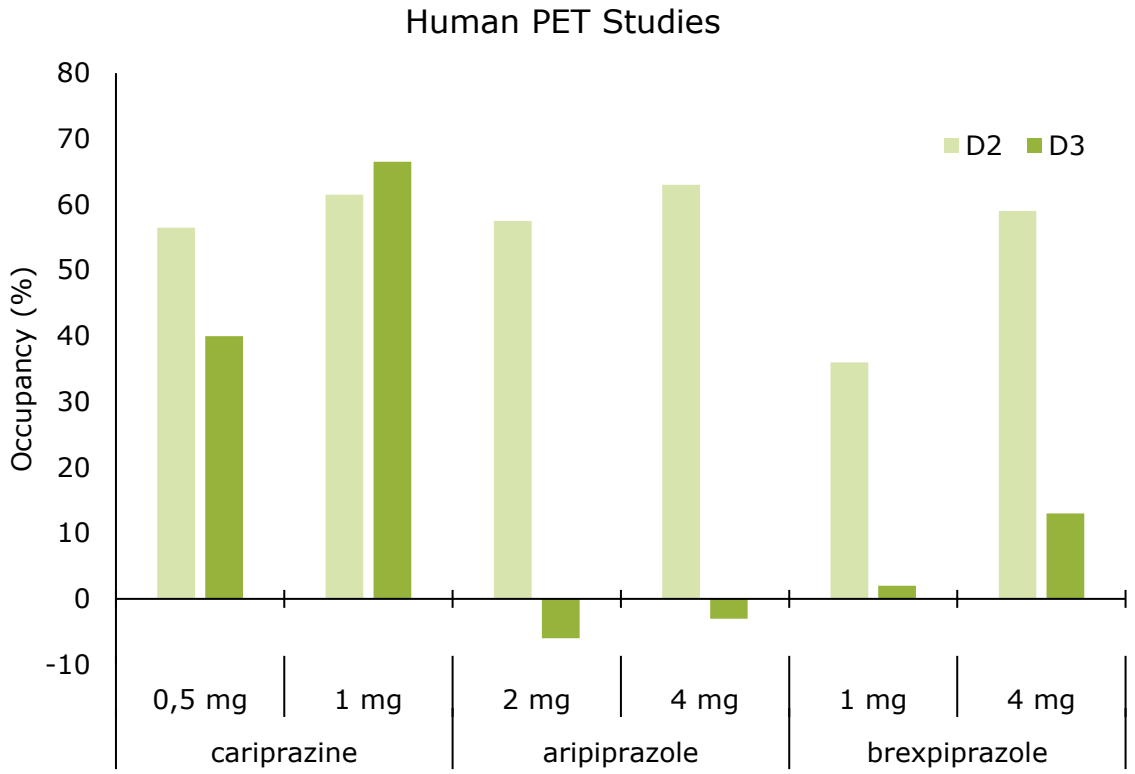
D3-KO mice, in contrast to wild type mice, display a higher rate of heroin (and cocaine) self-administration, greater motivation for drug, and a higher level of drug-seeking.[18]

D3

D3 receptor antagonists or partial agonists can reduce motivation to psychostimulant seeking in multiple animal models of relapse.[18]

Cariprazine as a potential drug candidate

One compound that has both partial agonist and D3 receptor activity is cariprazine.
In fact, **cariprazine has the highest affinity to the D3 receptors**; its affinity is higher than that of dopamine and all other used antipsychotics.[19]



Dopamine also has a preferential binding to the D3 receptors. Therefore, in the living brain (in the presence of dopamine), **D3 receptors are not blocked by any other antipsychotic than cariprazine**.[19]

A comparison between the three partial agonists in a PET study shows that **only cariprazine is able to occupy the D3 receptors in the human brain**.[20]

Cariprazine as a potential drug candidate

The efficacy of cariprazine had been shown in **animal studies** and **human case studies**: in rats, cariprazine attenuated relapse to cocaine seeking and decreased the reward value of cocaine.[21] The abuse preventing potency of cariprazine was ~20-fold higher than that of aripiprazole.[21]

SUBSTANCE	DIAGNOSIS	OTHER SUBSTANCES	OUTCOME
CANNABIS	Schizophrenia[22]	Amphetamine	▪ Improvement of positive, negative and cognitive symptoms ▪ Cut down and eventually ceased smoking entirely
	Psychotic episode[24]	-	▪ Stability with good mood and cooperativeness
	Psychotic disorder[25]	-	▪ Improvement in positive and negative symptoms ▪ Stopped cannabis
	Paranoid schizophrenia[29]	Alcohol	▪ Absence of positive, negative and cognitive symptoms ▪ Moderate capacity for insight and planning
METHAMPHETAMINE	PTSD & Stimulant-induced psychotic disorder[23]	Opioid	▪ Improvement of psychosis & 11 pounds of weight loss ▪ No cravings for methamphetamine
	PTSD & Stimulant-induced psychotic disorder[23]	Opioid	▪ No cravings with negative UDS ▪ Weight stabilized: stopped binging and purging
	Psychotic episode[24]	Mephedrone, Cocaine Alcohol	▪ Improvement in anxiety & mood ▪ Repercussion of the psychotic symptoms
	Stimulant-induced psychotic disorder[27]	-	▪ Full baseline level of social and occupational functioning ▪ Reduction of positive and negative symptoms ▪ Significant decreases in self-reported methamphetamine use and craving
	Stimulant-induced psychotic disorder[30]	Cannabis	▪ Significant decrease in visual, auditory, and tactile hallucinations ▪ Complete cessation
COCAINE	Schizophrenia[26]	-	▪ Continues to abstain from consuming the substance
	Bipolar disorder[31]	-	▪ A state of euthymia was observed with good tolerability ▪ No cocaine consumption
ALCOHOL	Schizophrenia[26]	Cocaine, THC, MDMA	▪ Denies having cravings for or consuming any psychoactive substances
	Schizoaffective disorder[28]	Tobacco	▪ Weight loss without dieting ▪ Sustained remission in psychotic symptoms

Summary

KEY POINTS

- Dual disorder represents a **challenge** in psychiatric pharmacotherapy.
- There are **no comprehensive guidelines** for the management of these patients.
- Partial agonists are the drugs of choice, but D3 preferring agents might have more benefits. **D3 receptors** may play an important role in the mechanism of **craving**.
- Cariprazine is a **D3 preferring D3/D2 partial agonist**.
- Although clinical trials are lacking, **preclinical** and **real-life evidence** suggest a potential role of cariprazine in this patient population.

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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