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CARIPRAZINE

POLYPHARMACY GUIDE

Antipsychotic Polypharmacy

Although guidelines recommend schizophrenia treatment with a single antipsychotic agent, polypharmacy - the use of more than one compound - is common in everyday practice.[1]

The prevalence of antipsychotic polypharmacy in real-world practice is around 20-30%. Despite this high prevalence rate, randomized controlled trials still focus on monotherapies. Therefore, evidence on polypharmacy primarily comes from real-world data, such as observational studies or published case reports. Drawing conclusions regarding different antipsychotic combinations from these types of evidence is rather difficult, given the lack of rigorous design and control groups, as well as the high level of subjectivity. Hence, the observed effects are often mixed.

It is also important to note that the combination of different antipsychotics does not only include the promise of better efficacy, but also the risk of adverse drug reactions resulting from the interaction of the medications.

In order to combine antipsychotics mindfully, the consideration of the antipsychotics' pharmacokinetic and pharmacodynamic properties is essential.

Reasons & Concerns

There are several reasons for initiating antipsychotic polypharmacy as well as many concerns related to the outcome.[1]

REASONS

- The combination of antipsychotics can enhance the efficacy of treatment.
- Since lower doses of individual antipsychotics are administered during polypharmacy, the emergence of side effects might be less likely.
- If certain symptoms such as negative or cognitive symptoms persist despite antipsychotic treatment, adding another compound that targets different receptors might decrease such symptoms.

CONCERNS

- The combination of antipsychotics might increase the risk of adverse events due to drug-drug interactions.
- Although lower doses of individual antipsychotics are thought to be administered during polypharmacy, the actual doses used in real life are high therefore increasing the risk of adverse events.
- Increased number of medications might have a negative impact on adherence as well.

General considerations

There are many factors that can mimic non-response to antipsychotic treatment. These factors should be excluded before applying antipsychotic polypharmacy.[1]

Incorrect diagnosis.

Psychiatric comorbidities such as substance abuse.

Non-compliance in terms of medication intake.

Insufficient dose of the antipsychotic drug or duration of treatment.

Adverse effects masking the response.

Pharmacological considerations

To mindfully combine antipsychotics, it's key to understand the most commonly targeted receptors by antipsychotics and their impact on different symptoms and adverse events.[1-3]

	RECEPTOR	IMPACT	ADVERSE EVENTS
DOPAMINE	**D2**	Decreased positive symptoms	Extra-pyramidal symptoms, prolactin increase, sexual and cognitive dysfunction
	D3	Decreased negative symptoms, cognitive symptoms and mood	-
SEROTONIN	**5-HT1A**	Decreased anxiety, depressive symptoms, and extra-pyramidal symptoms	Headache, nausea and weight gain
	5-HT2A	Decreased extra-pyramidal symptoms and mild sedative effect	Increased non-REM sleep
	5-HT2C	Decreased depressive symptoms	Increased appetite, weight gain and metabolic effects
OTHER	**H1**	Increased sedation	Cognitive impairment, increased appetite and weight gain
	Alpha1	Decreased depressive symptoms and obsessive-compulsive symptoms	Hypotension and sexual dysfunction
	Muscarinic	Decreased extra-pyramidal symptoms	Dry mouth, constipation, blurry vision and cognitive impairment

Pharmacokinetic considerations

Understanding the pharmacokinetic characteristics of antipsychotics such as half-lives is also key when combining antipsychotics mindfully.[1,4]

Half-life of antipsychotics

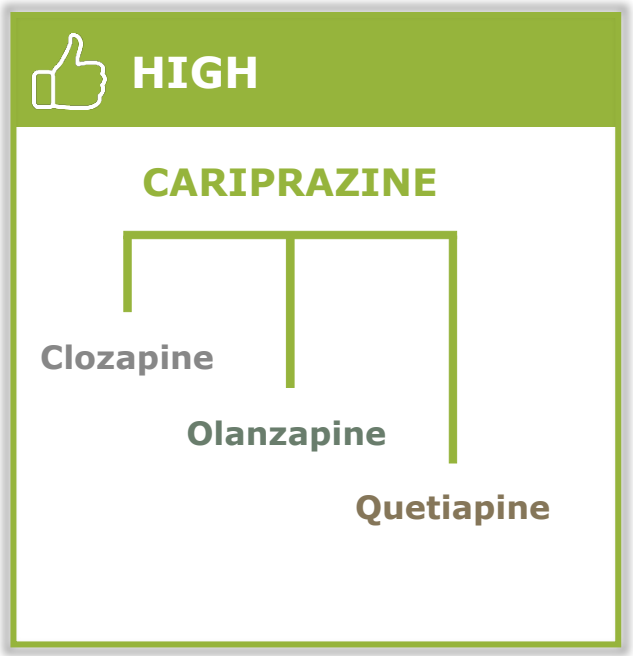
Metabolism of antipsychotics*

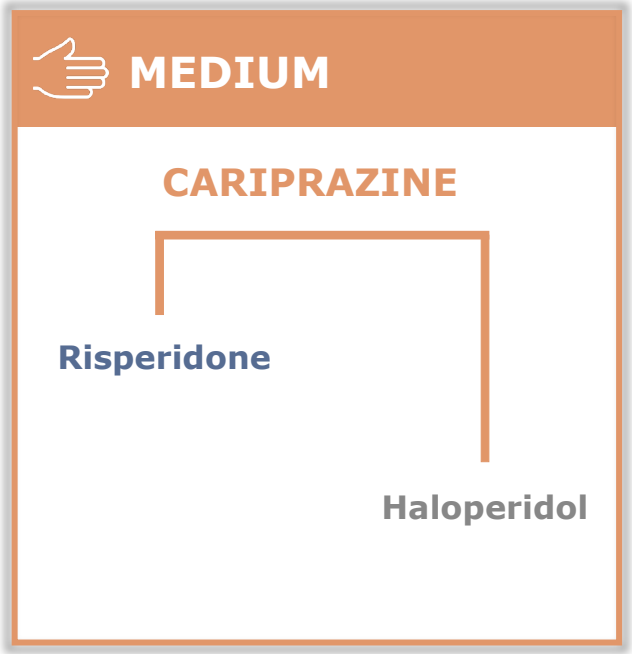
1A2			Clozapine		Olanzapine		
3A4	Aripiprazole	Cariprazine	Clozapine	Haloperidol		Quetiapine	Risperidone
2C19			Clozapine				
2D6	Aripiprazole	Cariprazine	Clozapine	Haloperidol	Olanzapine	Quetiapine	Risperidone

*CYP type

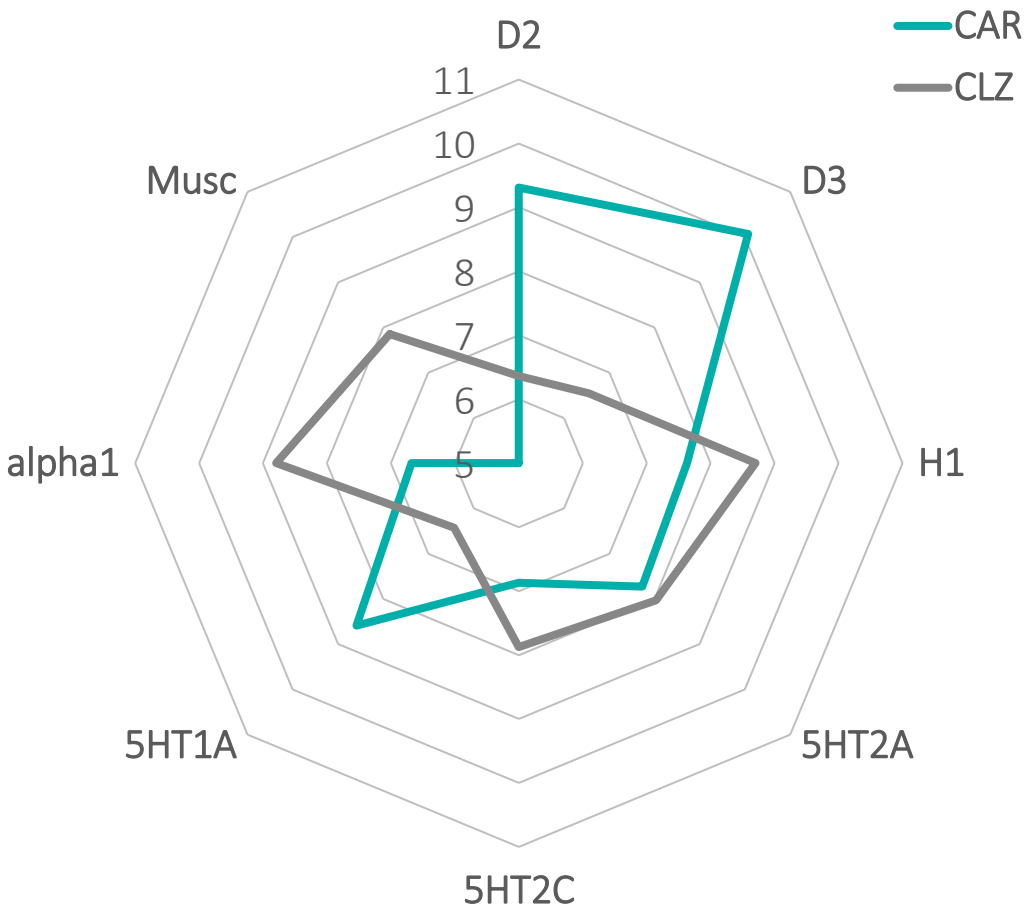
Overview of combinations

Polypharmacy combinations can be ranked based on the compatibility of the antipsychotics: high compatibility, medium compatibility, low compatibility.[1]





Cariprazine & Clozapine



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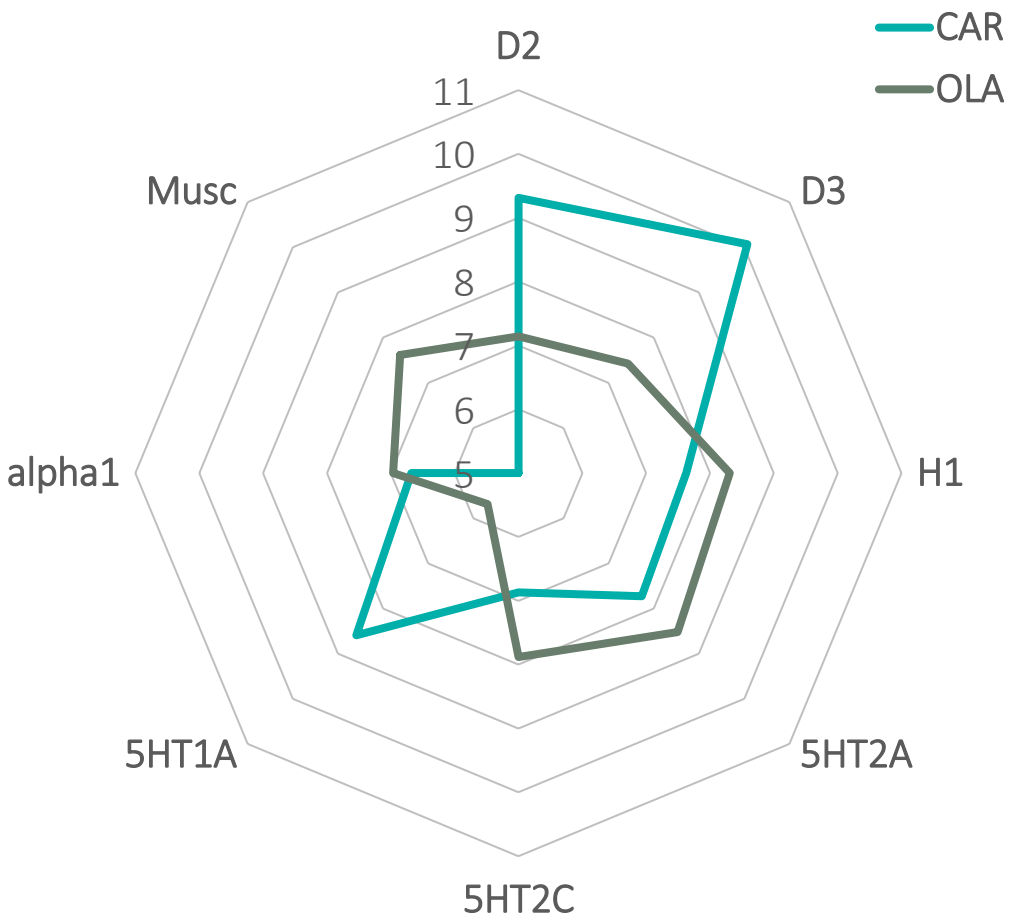
PROS

- Receptor profile of cariprazine is complementary to that of clozapine.
- This combination may improve overall efficacy and counterbalance sedative and metabolic issues of clozapine with keeping the low propensity of extrapyramidal symptoms.
- Also, the 5-HT2A antagonism present with clozapine may play a role in attenuating antipsychotic-induced akathisia.
- Effects on receptors D3 and D2 may improve negative, cognitive and positive symptoms.
- The pharmacokinetic profiles of cariprazine and clozapine are complementary too.

CONS

- This combination may potentially elicit akathisia.

Cariprazine & Olanzapine



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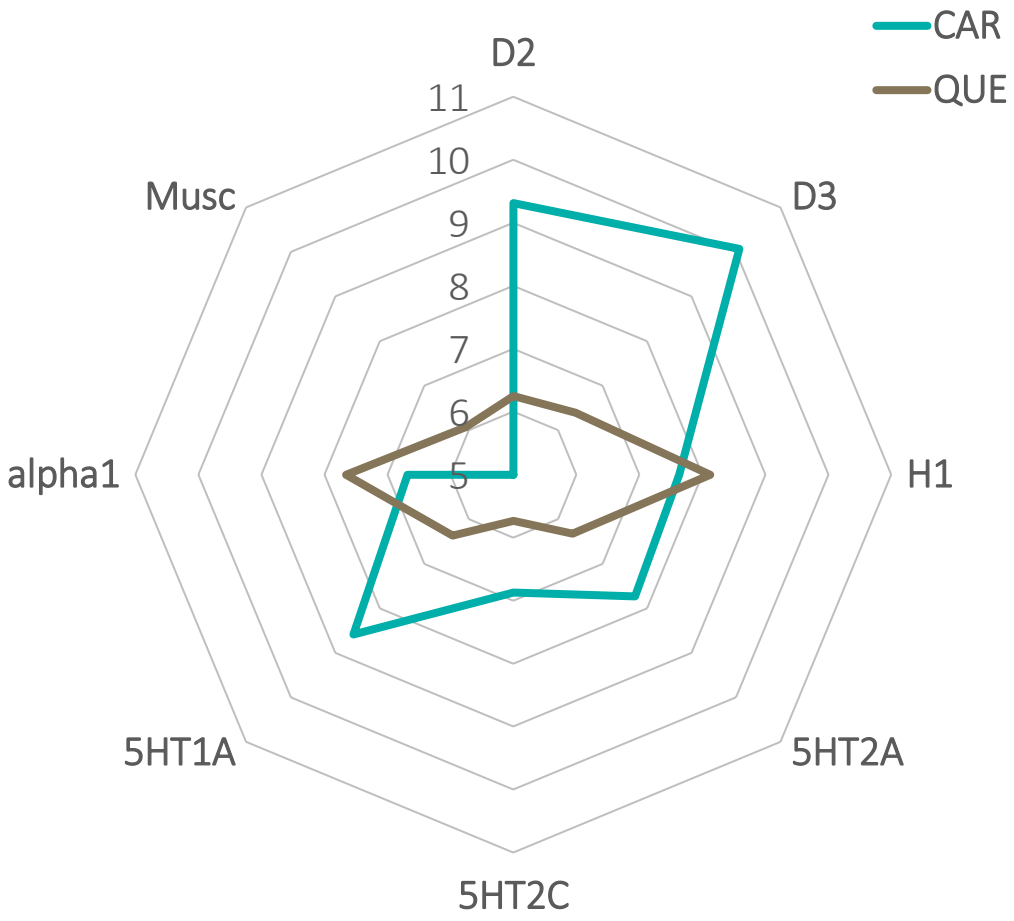
PROS

- Receptor profile of cariprazine is complementary to that of olanzapine.
- This combination may improve overall efficacy and counterbalance sedative and metabolic issues of olanzapine with keeping the low propensity of extrapyramidal symptoms.
- Also, the 5-HT2A antagonism present with olanzapine may play a role in attenuating antipsychotic-induced akathisia.
- Effects on receptors D3 and D2 may improve negative, cognitive and positive symptoms.
- The pharmacokinetic profiles of cariprazine and olanzapine are complementary too.

CONS

- This combination may potentially elicit akathisia.

Cariprazine & Quetiapine



pKi[1,5]

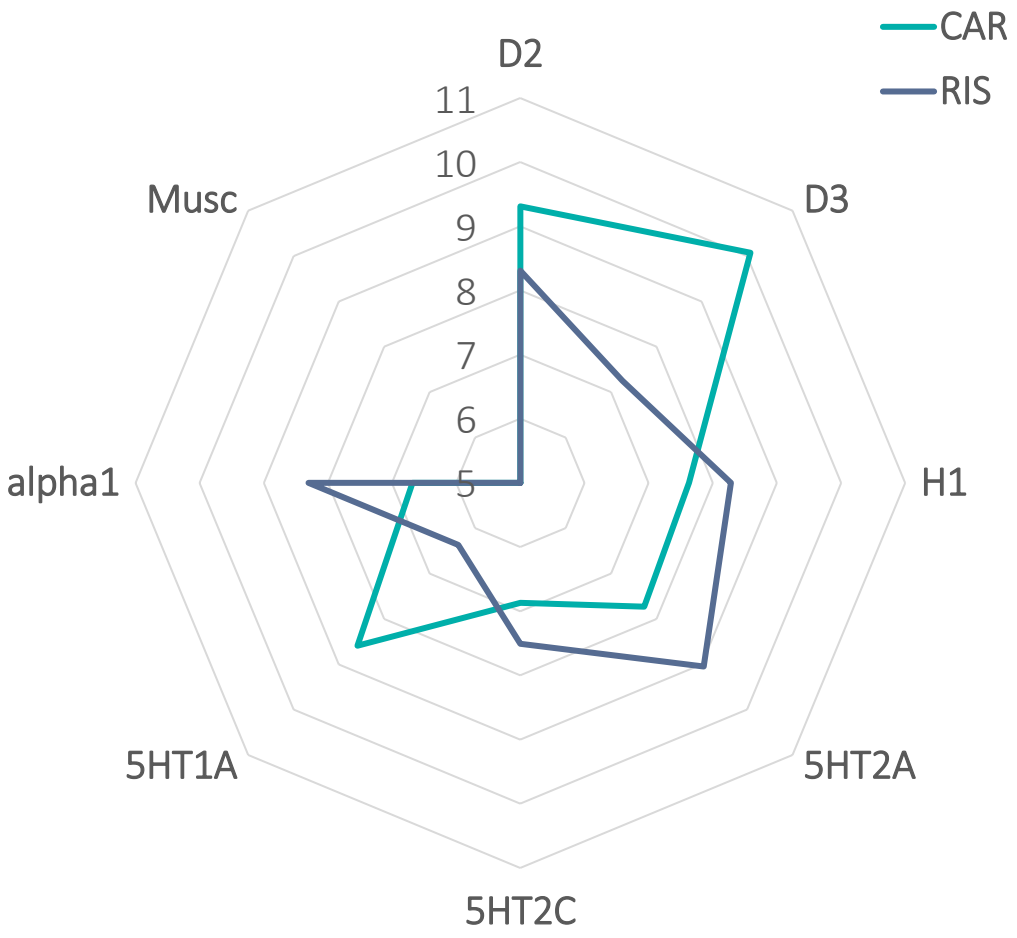
PROS

- Receptor profile of cariprazine is complementary to that of quetiapine.
- This combination may improve overall efficacy and counterbalance sedative and metabolic issues of quetiapine with keeping the low propensity of extrapyramidal symptoms.
- Also, the 5-HT2A antagonism present with quetiapine may play a role in attenuating antipsychotic-induced akathisia.
- Effects on receptors D3 and D2 may improve negative, cognitive and positive symptoms.
- The pharmacokinetic profiles of cariprazine and quetiapine are complementary too.

CONS

- This combination may potentially elicit akathisia.

Cariprazine & Risperidone



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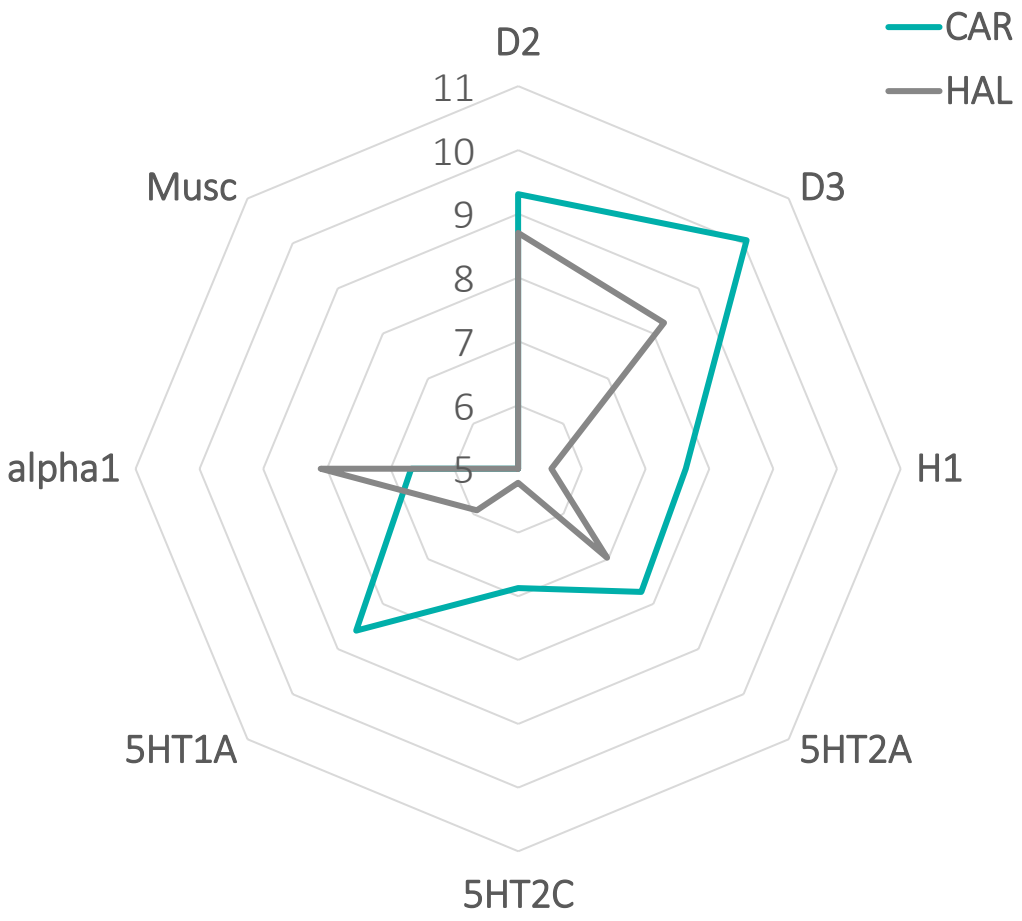
PROS

- The D3 receptor partial agonism of cariprazine adds a complementary target effect, thus may improve negative and cognitive symptoms.
- The high affinity and partiality of cariprazine at the D2 and 5-HT1A receptors may contribute to a lower risk for risperidone-induced extrapyramidal symptoms and hyperprolactinemia.

CONS

- By blocking the D2 receptors, risperidone might reduce the therapeutic benefits of cariprazine.
- Due to partial compatibility, it is difficult to forecast the overall clinical outcome with this combination.
- Since finding the optimal dosing strategy might be challenging, a switch from risperidone to cariprazine might be a better option.

Cariprazine & Haloperidol



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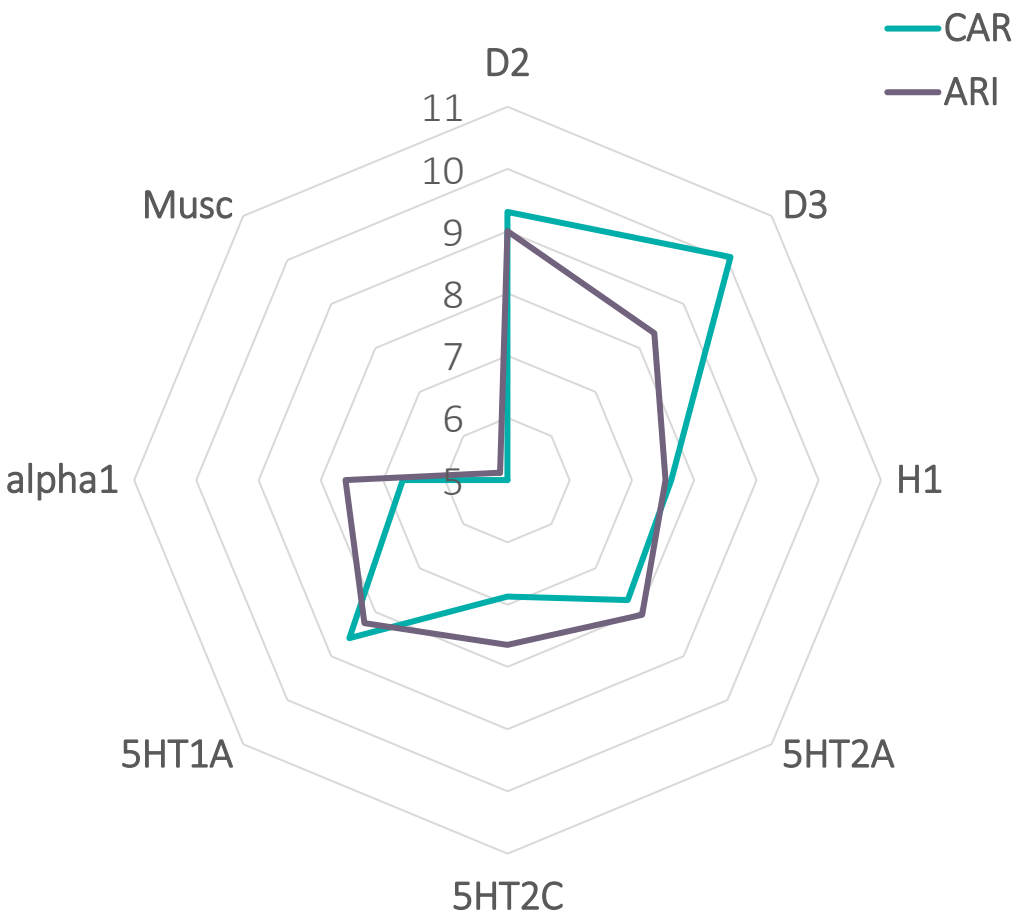
PROS

- The D3 receptor partiality of cariprazine adds a complementary target effect, thus may improve negative and cognitive symptoms.
- The high affinity and partiality of cariprazine at the D2 and 5-HT1A receptors may contribute to a lower risk for haloperidol-induced extrapyramidal symptoms and hyperprolactinemia.

CONS

- By blocking the D2 receptors, haloperidol might reduce the therapeutic benefits of cariprazine.
- Due to partial compatibility, it is difficult to forecast the overall clinical outcome with this combination.
- Since finding the optimal dosing strategy might be challenging, a switch from haloperidol to cariprazine might be a better option.

Cariprazine & Aripiprazole



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PROS

- No evidence of pros.

CONS

- The receptor profiles of cariprazine and aripiprazole are overlapping, therefore this combination is unlikely to enhance efficacy.
- Given the overlapping receptor profile, increased adverse events might appear.
- Currently, there is a lack of evidence in terms of successful case reports using this combination.
- In case of insufficient efficacy with aripiprazole, a switch from aripiprazole to cariprazine might be a more feasible option because of the dominant D3 receptor partial agonism.

Key considerations

Antipsychotic polypharmacy might be useful in selected patients when switching is not an option, however it is not recommended to be used routinely.[1]

- **Antipsychotic polypharmacy should be considered only if there have been two failed monotherapy trials with adequate dose and duration.**
- **The selected agents for combination should have a complementary receptor profile to ensure enhanced efficacy, not safety issues.**
- **The selected agents for combination should be evaluated based on pharmacokinetic characteristics as well to increase safety and tolerability.**
- **Patients on polypharmacy should be carefully monitored and further decisions regarding treatment should only be made after sufficient time has passed.**

References

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