

Partial agonists of dopamine receptors: mechanisms and clinical effects of aripiprazole, brexpiprazole and cariprazine[†]

John Cookson  & Jonathan Pimm

ARTICLE

SUMMARY

Aripiprazole, brexpiprazole and cariprazine are partial dopamine (and serotonin) agonists developed as novel antipsychotics. This article discusses their pharmacology, evidence on their licensed and off-licence uses (including psychosis, mania, bipolar depression, Tourette syndrome and autism spectrum disorder) and side-effects. In schizophrenia, they have a low risk of Parkinsonism or hyperprolactinaemia, cause modest increases in body weight and are of moderate efficacy.

LEARNING OBJECTIVES

After reading this article you will be able to:

- compare the pharmacological actions of the three partial agonists currently approved for treatment
- understand the uses of aripiprazole, brexpiprazole and cariprazine in the treatment of different psychiatric disorders
- be aware of the different side-effect profiles of the individual agents.

KEYWORDS

Partial dopamine agonists; aripiprazole; brexpiprazole; cariprazine; antipsychotics.

derivatives, each with subtly different pharmacological actions, clinical benefits and side-effects. They are intended to have fewer extrapyramidal side-effects than older antipsychotics that are full neutral antagonists of dopamine.

Pharmacology

In cloned human receptors, all three have high affinities for D₂-like dopamine receptors and for 5-HT_{1A} serotonin receptors (being partial agonists at both), low affinities as full antagonists for histamine H₁ and muscarinic acetylcholine M₁ receptors, and intermediate affinities as full antagonists for many other receptors, including 5-HT_{2A} and 5-HT₇ (Tables 1 and 2). Clinical studies of receptor binding in positron emission tomography (PET) scans confirm some but not all these relative values.

They have ‘intrinsic activity’ as agonists, a property explained in our previous article (Cookson 2021).

They have long elimination half-lives (days) and are metabolised by the cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4 to metabolites, which in the case of aripiprazole and cariprazine are active with a similar receptor binding profile to the parent compound.

John Cookson is a consultant in general adult psychiatry at the Royal London Hospital and at Tower Hamlets Centre for Mental Health, Mile End Hospital, East London NHS Foundation Trust, UK. He trained in physiology and pharmacology at the University of Oxford and he has a career-long interest in psychopharmacology. **Jonathan Pimm** is a consultant in general adult psychiatry working for the East London NHS Foundation Trust. He completed an MD thesis under the supervision of Prof Hugh Gurling looking at transport mechanisms at the synapse.

Correspondence John Cookson. Email: john.cookson1@nhs.net

First received 29 Mar 2021
Final revision 7 Jun 2021
Accepted 8 Jun 2021

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[†]See also Cookson & Pimm ‘Partial agonists of dopamine receptors: receptor theory and the dopamine hypothesis of psychosis’, this issue.

This is the second of our articles on partial agonists of dopamine receptors. In it we use the receptor theory introduced in the first article (Cookson 2021) to discuss the specific pharmacology and clinical uses of aripiprazole, brexpiprazole and cariprazine. Detailed laboratory investigations have led to the selection of these three partial agonists, which have been proven by clinical trials and licensed for use in psychiatry. Their development as novel antipsychotics has built on understanding of neurotransmission, using laboratory and computational techniques that visualise receptor structures and detect biochemical changes. Aripiprazole, brexpiprazole and cariprazine are phenylpiperazine

Aripiprazole

Aripiprazole is a partial agonist with very high affinities for dopamine D₂ and D₃ and serotonin 5-HT_{1A} receptors (Roth 2017). Its active metabolite dehydroaripiprazole has similar activity and reaches similar blood levels.

The contribution of CYP3A4 to its metabolism is usually minor but in the presence of carbamazepine the enzyme is induced and doses may need to be doubled (to 20–30 mg/day). However, the CYP2D6 status is a major determinant and it is advised that doses are reduced in those on strong inhibitors (duloxetine, fluoxetine, paroxetine, risperidone, metoprolol or propranolol) and in poor

TABLE 1 Pharmacokinetic and pharmacodynamics characteristics of aripiprazole, brexpiprazole and cariprazine

Drug	Intrinsic activity	Receptor binding affinity (partial agonism)	Half-life	Metabolites
Aripiprazole	25% (D ₂ receptors)	D ₂ > D ₃ > 5-HT _{1A}	Aripiprazole: 75 h Dehydroaripiprazole: 94 h Steady state: 2–3 weeks	Dehydroaripiprazole (similar affinities for D ₂ receptors) 40% of parent drug exposure in plasma
Brexpiprazole	Less than aripiprazole	5-HT _{1A} > D ₂ > D ₃	Brexpiprazole: 91 h DM-3411: 86 h Steady state: 10–12 days	DM-3411 (probably inactive)
Cariprazine	60% (D ₃ receptors) 40% (D ₂ receptors)	D ₃ > D ₂ > 5-HT _{1A}	Cariprazine: 48–96 h Metabolites: 3 weeks Steady state: 3–15 weeks	DCAR and DDCAR (similar affinities) DDCAR blood level three times cariprazine at steady state

DM-3411, brexpiprazole S-oxide; DCAR, desmethyl cariprazine; DDCAR, didesmethyl cariprazine.

metabolisers (Kiss 2020). Beta blockers may be co-administered to treat akathisia.

Just 1 mg aripiprazole daily produces 50% occupancy of D₂ receptors at steady state (which is reached after 2–3 weeks of regular doses); 10 mg daily produces 95% occupancy and near maximum efficacy in schizophrenia. Intrinsic activity has been estimated as 25%, so that its maximum effective antagonism of dopamine could reach 75% (Sparshatt 2010). This would be expected to limit its ability to improve the most severe mania or agitation (Cookson 2021).

The most common adverse events are akathisia, restlessness, tremor and insomnia (all of which can contribute to agitation) and nausea.

Brexpiprazole

In cloned receptors, brexpiprazole is a high-affinity partial agonist at 5-HT_{1A}, D₂ and D₃ receptors (Roth 2017). However, its main receptor binding actions in clinical studies are at D₂ and 5-HT_{2A} receptors, with negligible occupancy at D₃ or 5-HT_{1A}; a dose of 4 mg/day reached 80% occupancy of D₂ receptors after 10 days, and little D₃ occupancy (Girgis 2020).

Brexpiprazole has less intrinsic activity than aripiprazole at D₂ receptors and was therefore expected to cause less akathisia and insomnia than aripiprazole, trends that are seen in treating schizophrenia (Huhn 2019). It failed to show efficacy in mania, consistent with the view that mania commences in more ventral dopamine pathways, richer in D₃ than D₂ (Cookson 2013). There are no published controlled trials in bipolar depression.

Brexpiprazole is licensed in both the USA and UK but there are no plans yet to launch in the UK. Additional information about its use in schizophrenia is provided by Ward & Citrome (2019), suggesting a possible advantage over aripiprazole in terms of reduced akathisia and weight gain.

Cariprazine

Cariprazine is a partial agonist at D₂-like dopamine receptors and a full agonist at 5-HT_{1A} receptors. Its affinity is greatest for D₃ receptors (where it is a partial agonist with about 60% intrinsic activity) and less for D₂ (with about 40% intrinsic activity) (Roth 2017; Citrome 2018).

After 2 weeks of 3 mg/day, the mean D₃ and D₂ receptor occupancies were 92 and 79% (Girgis 2016).

Cariprazine has active metabolites with similar receptor binding activities, but very long half-lives (1–3 weeks). Its main metabolite didesmethyl cariprazine (DDCAR) reaches three times higher plasma levels at steady state and has higher selectivity for D₃ receptors than cariprazine, and is a full agonist at 5-HT_{1A} receptors (Tadori 2005; Kiss 2019).

Cariprazine is primarily metabolised through CYP3A4. Co-administration with a strong inhibitor of CYP3A4 (fluoxetine, ketoconazole) or grapefruit juice may necessitate a halving of the usual dose but clinical interactions have not been reported (Citrome 2018).

The licensed dose is 1.5–6 mg/day for acute schizophrenia and maintenance treatment, and in the USA it is also licensed for mania and for bipolar depression.

Clinical use of aripiprazole, brexpiprazole and cariprazine

Licensed uses

The licensed indications of the three drugs vary and are shown in Table 3. Aripiprazole is also licensed for irritability associated with autism spectrum disorder. Only aripiprazole (intramuscular injection) is licensed for agitation in schizophrenia or mania. Aripiprazole is also available for long-acting

TABLE 2 Receptor affinity of aripiprazole, brexpiprazole and cariprazine^a

Drug and affinity	K _i , nmol
Aripiprazole	
High affinity	
Dopamine D ₂	0.34 Partial agonist
Dopamine D ₃	0.8–9.7 Partial agonist
Serotonin 5-HT _{1A}	1.7–5.6 Partial agonist
Medium affinity	
Serotonin 5-HT _{2A}	3.4–35 Full antagonist
Serotonin 5-HT ₇	9.6–39 Full antagonist
Dopamine D ₄	44–514 Partial agonist
Low affinity	
Noradrenaline α ₂	26–102 Full antagonist
Histamine H ₁	27.9–61 Full antagonist
Noradrenaline α _{1A}	25.9 Full antagonist
Serotonin 5-HT _{2C}	15–180 Partial agonist
Muscarinic acetylcholine M	>1500 Full antagonist
Cariprazine	
High affinity	
Dopamine D ₂	0.49–0.69 Partial agonist
Dopamine D ₃	0.085 Partial agonist
Serotonin 5-HT _{1A}	2.6 Full agonist
Medium affinity	
Serotonin 5-HT _{2A}	18.8 Full antagonist
Low affinity	
Histamine H ₁	23.2 Full antagonist
Serotonin 5-HT ₇	111 Full antagonist
Noradrenaline α _{1A}	155 Full antagonist
Serotonin 5-HT _{2C}	134 Inverse agonist
Muscarinic acetylcholine M	>1000 Full antagonist
Brexpiprazole	
High affinity	
Dopamine D ₂	0.3 Partial agonist
Dopamine D ₃	1.1 Partial agonist
Serotonin 5-HT _{1A}	0.12 Partial agonist
Medium affinity	
Serotonin 5-HT _{2A}	0.47 Full antagonist
Serotonin 5-HT ₇	3.7 Full antagonist
Dopamine D ₄	6.3 Full antagonist
Low affinity	
Noradrenaline α ₂	0.59–17 Full antagonist
Noradrenaline α _{1A}	3.8 Full antagonist
Histamine H ₁	19 Full antagonist
Serotonin 5-HT _{2C}	12–34 Partial agonist
Muscarinic acetylcholine M	>1000 Full antagonist

a. The most potent effects are highlighted in bold; smaller K_i indicates higher affinity.

K_i, binding affinity; K_d, dissociation constant.

Source: adapted from Roth & Driscoll (2017) and Citrome (2018).

injection (with steady state reached after 5 months and a notional half-life of 1 month).

Side-effects

In general, partial agonists of dopamine receptors cause fewer receptor blockade-related side-effects than full antagonists (few Parkinsonian or dystonic

side-effects and fewer side-effects related to increased prolactin). However, the most common are akathisia, restlessness, dyspepsia, nausea, vomiting, dizziness, diarrhoea, constipation, insomnia and sedation (Zhao 2016; Huhn 2019; Ward 2019).

A common adverse event in long-term treatment is worsening of symptoms in both schizophrenia and mania. In a long-term study using continuation on medication as a measure of effectiveness, aripiprazole was not as effective as most other antipsychotics for continuation or preventing readmission to hospital (Zhao 2016).

Over 1 year, the most common adverse events were akathisia, headache, insomnia, and increase in body weight.

Weight changes

Short-term (8 weeks) weight gain with these drugs is slight, comparable with haloperidol and much less than with olanzapine or clozapine (Pillinger 2020).

In maintenance treatment, gradual weight gain and metabolic effects occur. In early-episode psychosis, no advantage was seen for cohorts on aripiprazole compared with paliperidone in weight change over 1 year, although aripiprazole was associated with lower triglycerides and prolactin levels (Shymko 2021). A 1-year randomised controlled trial (RCT) of aripiprazole, quetiapine and ziprasidone in drug-naïve first-episode non-affective psychosis found overall increases in weight, low-density lipoprotein (LDL) cholesterol and triglycerides, but no significant differences between drugs (Vázquez-Bourgon 2018).

Impulsivity and compulsive sexual urges

All three drugs can cause new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges (Etminan 2017).

Tourette syndrome

The verbal and motor tics of Tourette syndrome are improved by aripiprazole (Sallee 2017).

Stimulant misuse

In people dependent on methamphetamine, use of the stimulant drug was increased on aripiprazole at a dose of 15 mg/day (Tiihonen 2007). This cautions against its use in methamphetamine psychosis; a network meta-analysis found it inferior to olanzapine, quetiapine, haloperidol and paliperidone, with no difference in drop-out rates (Srisurapanont 2020).

TABLE 3 Licensed indications for aripiprazole, brexpiprazole and cariprazine in the UK and/or USA in 2020

Drug	Acute schizophrenia	Schizophrenia maintenance	Agitation in mania and schizophrenia	Mania	Bipolar depression	Mania prevention	Adjunct in unipolar depression
Aripiprazole	Yes	Yes	Yes	Yes	No	Yes	Yes
Brexpiprazole	Yes in USA	Yes in USA	No	No	No	No	Yes in USA
Cariprazine	Yes	Yes	No	Yes in USA	Yes in USA	No	No

Schizophrenia

In a network meta-analysis of the efficacy of 32 anti-psychotics in RCTs in acute schizophrenia, the rank order of efficacy of partial agonists on overall symptoms was aripiprazole > cariprazine > brexpiprazole, with little difference between them (Huhn 2019). All were less efficacious than risperidone; brexpiprazole was less efficacious than haloperidol.

Cariprazine required more anti-Parkinsonian medication than placebo. Akathisia was seen more often with aripiprazole and cariprazine than with placebo.

Prolactin was lowered by aripiprazole and unchanged with brexpiprazole or cariprazine.

The corrected QT interval (QTc) was unchanged. Sedation was rare and seen more often with aripiprazole. No anticholinergic side-effects were seen.

The network analysis showed no obvious advantage on negative symptoms, but aripiprazole and cariprazine were among the best for the improvement of depressive symptoms.

However, in an RCT involving stable patients with predominantly negative symptoms of schizophrenia, a change of medication to cariprazine (mean 4.2 mg/day) led to greater improvement in negative symptoms than a change to risperidone (3.8 mg/day) over 26 weeks (effect size 0.3) (Németh 2017), and this was not attributable to a change in depressive symptoms.

Autism spectrum disorder

A network meta-analysis concluded that risperidone and aripiprazole were the two best atypical antipsychotics, with comparable efficacy and safety, for young people with autism spectrum disorder, beneficial in improving irritability (Fallah 2019).

Mania

Aripiprazole and cariprazine are superior to placebo in mania. Aripiprazole is significantly less efficacious than haloperidol or risperidone; the efficacy of cariprazine (up to 12 mg/day) is intermediate between aripiprazole and risperidone (Cipriani 2011; Yildiz 2015), but the trials permitted additional benzodiazepines for agitation.

There are guidelines for the use of aripiprazole in mania that advise combination with a benzodiazepine initially; it is rarely a first-line choice,

perhaps because of lack of sedation and lower efficacy than full antagonists of D₂-like receptors (Aitchison 2009; Goodwin 2011). By contrast, cariprazine has a greater effect than aripiprazole on ventral striatal D₃ receptors, which may be important for treating mania (Cookson 2013).

Agitation in mania or schizophrenia

Aripiprazole has been used in rapid tranquillisation (Cookson 2018).

Intramuscular aripiprazole as monotherapy improves moderately severe agitation in people with mania (mean Young Mania Rating Scale (YMRS) score 24 out of maximum 60) (Zimbroff 2007) and in people with schizophrenia (mean Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score 19 out of maximum 35) (Tran-Johnson 2007).

Bipolar depression

Aripiprazole has been investigated for depression in bipolar I disorder and has no proven efficacy.

Two large RCTs of cariprazine in bipolar I depression showed efficacy. The number needed to treat (NNT) for response 50% improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) score with a dose of 1.5 mg/day was 4 (95% CI 4–16) and with 3 mg/day 8 (95% CI 5–58) (Durgam 2016a). Earley (2019) found an NNT of 9 with 3 mg/day but at 1.5 mg/day the result was not significant. At the higher dose, the drop-out rate was greater; the side-effects were mainly akathisia, insomnia, nausea and irritability.

This striking difference between aripiprazole and cariprazine may relate to the greater stimulant action of cariprazine on D₃ receptors.

Maintenance in bipolar disorder

Aripiprazole has mood-stabilising properties, reducing manic relapses without evident benefit for depressive relapses (Miura 2014).

Unipolar depression

Aripiprazole and brexpiprazole are efficacious as adjuncts to antidepressants in unipolar depression. From five pooled studies, aripiprazole had the largest effect size (ES) of any antipsychotic as an

adjunct to antidepressants (including selective serotonin reuptake inhibitors and mirtazapine) (ES = 0.50, 95% CI 0.31–0.67); for brexpiprazole the effect size was small (ES = 0.18, 95% CI 0.10–0.26) (Carter 2020) and the NNT for response was 14 (Thase 2019). Cariprazine was also efficacious as an adjunct in an RCT, with ES = 0.5 and NNT = 9 for response on 2–4.5 mg/day. The most common side-effects were akathisia (22%), insomnia (14%) and nausea (13%) (Durgam 2016b); it is not currently licensed for this indication. The adjunctive efficacy in unipolar depression may relate to actions stimulating 5-HT_{1A} and blocking 5-HT_{2A} (brexpiprazole) and 5-HT₇ receptors (aripiprazole and brexpiprazole).

Conclusions

Partial agonists at dopamine D₂-like (and 5-HT_{1A}) receptors have been developed as novel antipsychotics primarily for schizophrenia, with low risks of Parkinsonism or hyperprolactinaemia, modest increases in body weight and moderate efficacy. They are also useful in some stages of bipolar disorder and as adjuncts for unipolar depression. Each has a distinct profile of efficacy rather than a unified class effect. Their side-effect profiles make them attractive potential alternatives to other antipsychotics in some people; these might include those with lesser degrees of excessive dopamine release, requiring lower antagonistic occupancy, for example in early phases of schizophrenia (Kane 2020) and in very late-onset schizophrenia-like psychosis (Rado 2012).

However, switching to, or adding, partial agonists to full antagonists has theoretical implications that call for careful judgements in prescribing to avoid triggering relapse by displacing antagonist occupancy.

The efficacy of cariprazine in bipolar disorder and for negative symptoms in schizophrenia highlights the importance of D₃ dopamine receptors which are predominant in ventral areas of dopamine pathways involved in reward and motivation (Sokoloff 2017).

Author contributions

J.C. and J.P. contributed equally to this manuscript.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

J.C. is a member of the *BJPsych Advances* editorial board and did not take part in the review or decision-making process for this article.

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MCQ answers

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MCOs

Select the single best option for each question stem

1 Regarding the pharmacology of aripiprazole, brexpiprazole and cariprazine:

- a all three act as full antagonists at the D₂-like receptor and the 5-HT_{1A} receptor
- b all three have high affinities for the D₂-like receptor and low affinities for the 5-HT_{1A} receptor
- c all three have low affinities for the D₂-like receptor and the 5-HT_{1A} receptor
- d all three have high affinities for the D₂-like receptor and the 5-HT_{1A} receptor
- e all three act as partial agonists at the H₁ and acetylcholine M₁ receptors.

2 Elimination and metabolism of all three partial agonists aripiprazole, brexpiprazole and cariprazine from the body:

- a is rapid compared with other antipsychotics
- b takes place over several days because they have long half-lives
- c takes place over hours because they have short half-lives
- d involves the production of active metabolites with similar receptor profiles to the parent compound
- e may need to be increased in patients who are also taking fluoxetine or drinking grapefruit juice.

3 Regarding aripiprazole's occupancy of the D₂ receptors:

- a 1 mg daily will reach 50% occupancy after 14–21 days
- b 10 mg daily will reach 10% occupancy after 14–21 days
- c 4 mg daily will reach occupancy of 20% after 10 days
- d 3 mg daily will reach 50% occupancy after 10 days
- e 1 mg daily will reach 10% occupancy after 14–21 days.

4 Which of the following pairings of common adverse effects and partial agonist is correct?

- a aripiprazole and worsening of verbal and motor tics in Tourette syndrome
- b brexpiprazole and akathisia
- c cariprazine and weight loss
- d aripiprazole and decrease in the use of methamphetamine in dependent patients
- e cariprazine and tardive dyskinesia.

5 Little evidence for the efficacy of treating psychiatric disorders using partial agonists has been shown with:

- a aripiprazole in schizophrenia and rapid tranquillisation
- b cariprazine in bipolar I depression and in mania
- c aripiprazole in bipolar I depression and on the negative symptoms of schizophrenia
- d brexpiprazole as an adjunctive treatment to antidepressants in unipolar depression
- e aripiprazole in autism spectrum disorder and in mania.