ARTICLE

# Partial agonists of dopamine receptors: clinical effects and dopamine receptor interactions in combining aripiprazole with a full antagonist in treating psychosis

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## SUMMARY

Partial agonists of dopamine receptors are used in combination with full antagonists in treating psychosis, either to mitigate side-effects or in the hope of increasing effectiveness. We examine how combinations may affect the occupancy of $D_2/D_3$ dopamine receptors and explore how these can explain the outcomes in the light of the dopamine hypothesis of psychosis. The combinations considered here are from published studies combining aripiprazole with amisulpride, with risperidone in people with hyperprolactinaemia and with olanzapine to mitigate weight gain. We discuss possible worsening of symptoms by the addition of a partial agonist or switching. We also examine the potentially adverse interaction with a full antagonist such as haloperidol given during a subsequent relapse to control severe agitation.

## LEARNING OBJECTIVES

After reading this article you will be able to:

- critically appraise the use of combinations of a partial agonist and a full antagonist antipsychotic in the treatment of schizophrenia
- appreciate the relevance of dopamine receptor occupancy by a full antagonist and displacement by a partial agonist
- understand how changes in receptor occupancy by the addition of a partial agonist can be calculated.

## KEYWORDS

Antipsychotics; drug interactions and side-effects; neuroendocrinology; polypharmacy; schizophrenia.

We have previously reviewed the nature of partial agonism of dopamine receptors (Cookson 2023a) and the qualities of three partial agonists, aripiprazole, brexpiprazole and cariprazine (Cookson 2023b). We have also described the practice of combining different antipsychotics, possible rationales and a theoretical model to analyse dopamine receptor occupancy with single or combined antipsychotics (Cookson 2023c).

Several scenarios for combining the partial agonist aripiprazole with another antipsychotic have been reported: a recent Finnish nationwide cohort study of people treated for schizophrenia found that more than half had been exposed to antipsychotic polypharmacy over a 20-year period (Tiihonen 2019). The use of a combination with aripiprazole was found commonly in people receiving clozapine or olanzapine, but many people on other antipsychotics were also given aripiprazole.

Here we analyse situations where aripiprazole is combined with another antipsychotic and use published studies as the source for doses and outcomes. We base this analysis on the levels of dopamine $D_2/D_3$ receptor occupancy required at different stages of schizophrenia – namely, 66% occupancy for treating a first episode or in long-term maintenance to prevent relapse and 70–80% occupancy to treat an acute relapse. The figures associated with 50% occupancy of $D_2/D_3$ receptors in the striatum by individual antipsychotics, as reported previously, are assumed (Cookson 2023c).

## Intuitive understanding of combinations

We have seen in a previous article (Cookson 2023c) that increasing doses of a partial agonist with 25% intrinsic activity, given alone, can achieve antagonistic occupancy up to a maximum of 75%.

Conversely, if one considers a patient on a full antagonist in a large dose, sufficient to occupy nearly all receptors, the addition of a partial agonist with 25% intrinsic activity will displace the full antagonist and thus lower the degree of antagonistic occupancy while adding a degree of agonism. At

a very high dose the partial agonist could cause 75% antagonistic occupancy, by displacing the full antagonist entirely.

Thus, the addition of that partial agonist to any dose of a full antagonist will shift the extent of antagonism either upwards or downwards towards 75%.

At the same time the extent of agonism is shifted towards 25%. For this reason partial agonists are sometimes described as transmitter system stabilisers.

## Quantitative examples

### *Combining amisulpride with aripiprazole*

Amisulpride and aripiprazole are both relatively selective for dopamine $D_2/D_3$ receptors and are not sedative. Amisulpride is licensed for schizophrenia, including patients with predominantly negative symptoms at lower doses (Krause 2018). Aripiprazole does not share this advantage, which has been attributed to presynaptic $D_3$ receptor antagonism (Frank 2018), although other receptor mechanisms have also been implicated. Amisulpride has greater efficacy than aripiprazole in reducing positive symptoms of schizophrenia but also greater occurrence of QT prolongation and diminished libido (Huhn 2019; Johnsen 2020). Because of their different side-effects, it may be desirable to taper between one drug and the other, thus balancing the benefits of receptor occupancy (in terms of efficacy) against the side-effects.

### *Flexible occupancy by combining a full antagonist (amisulpride) and a partial agonist (aripiprazole)*

The maximum degree of antagonist occupancy that can be achieved by aripiprazole is 75%, assuming intrinsic activity of 25% (see Cookson 2023c). This means that by combining the two drugs in varying proportions at high doses, the level of antagonistic occupancy can be manipulated to anywhere between 73% (aripiprazole 30 mg/day alone) and 91% (amisulpride 1200 mg/day); at lower doses it is between 68% (aripiprazole 10 mg/day alone) and 80% (amisulpride 600 mg/day).

### *Potential worsening of psychosis after addition or switch*

Eight reports reviewed by Takeuchi and Remington (Takeuchi 2013) described patients whose psychosis worsened or agitation increased after the addition of aripiprazole to another antipsychotic or switching to aripiprazole. Fourteen reports described worsening after a switch to aripiprazole. In most patients the doses of antipsychotics had exceeded recommended guidelines. A meta-analysis of randomised trials of such changes reported an excess of early discontinuation owing to lack of efficacy after switching but no increase in relapses after addition of aripiprazole (Takeuchi 2018).

Worsening is sometimes (Takeuchi 2013) but not often seen as a problem in combination with clozapine (Fleischhacker 2010). $D_2/D_3$ receptor occupancy in acute treatment with clozapine is less than 70% (Farde 1992). Hence, any displacement by aripiprazole will increase blockade of dopamine, although adding some agonistic activity.

### *Psychosis worsened when adding aripiprazole to haloperidol*

A 24-year-old female graduate with a 5-year history of schizophrenia was on haloperidol 20 mg daily and showed only slight improvement (Grover 2006). Addition of aripiprazole led to worsened symptoms in the following weeks. Her condition improved when aripiprazole was discontinued.

The striking change in occupancy when aripiprazole was combined is that antagonistic occupancy was reduced from 94% to 83% while agonistic occupancy increased from at the most 6% to 14% (Table 1). This outcome was clear to recognise because the original dose of antipsychotic was such as to occupy a high proportion of receptors, leaving few to be occupied by dopamine.

### *Adding aripiprazole to risperidone to reduce hyperprolactinaemia*

Antipsychotics raise plasma prolactin and lower testosterone variably; the largest rises in prolactin are caused by amisulpride, risperidone and paliperidone;

**TABLE 1** Adding 20 mg aripiprazole to 20 mg haloperidol daily

| | | | | Alone | | Combined | | | |
|---|---|---|---|---|---|---|---|---|---|
| Drug 1 Haloperidol | | Drug 2 Aripiprazole | | Haloperidol occupancy, % | Aripiprazole occupancy, % | Haloperidol occupancy, % | Aripiprazole occupancy, % | Total antagonist occupancy, % | Agonistic occupancy, % |
| DssOcc50: 1.3 mg | Dose: 20 mg | DssOcc50: 1 mg | Dose: 20 mg | 94 | 95 (75% = 71) | 42 | 55 (75% = 41) | 42 + 41 = 83 | 14 |

DssOcc50, the dose that produces 50% occupancy at steady state blood levels. Aripiprazole occupancy consists of 75% antagonism, as shown in parenthesis, and 25% agonism.

**BOX 1** Antipsychotics, prolactin and the blood–brain barrier

Several mechanisms underly antipsychotic-induced hyperprolactinaemia (see Gudelsky 1981). A major factor is drug antagonism at the $D_2$ receptors on the pituitary lactotrophs. These receptors respond to dopamine as the prolactin inhibitory factor secreted from the hypothalamus into the portal blood supply and are outside the blood–brain barrier, so $D_2$ antagonist drugs reverse the inhibition of prolactin secretion by dopamine.

The distribution of drug between the brain and blood is influenced by several factors; one is the activity of the *P*-glycoprotein (Pgp) pump in the blood–brain barrier, which actively transports many drugs out of the brain. Risperidone and paliperidone are thus transported and have relatively low brain:blood ratios (Loryan 2016) and hence are likely to have greater antagonism at pituitary than at striatal $D_2/D_3$ receptors.

olanzapine causes only small increases (Huhn 2019). However, aripiprazole lowers plasma prolactin levels in a dose-dependent manner (Tasaki 2021). Thus, the intrinsic agonist activity of aripiprazole alone is more than sufficient to compensate for its blockade of endogenous dopamine in the pituitary (Box 1, Box 2).

A randomised controlled trial of 30 people with schizophrenia found that addition of aripiprazole to risperidone normalised prolactin levels in 46% and improved erectile dysfunction in 5 out of 6 affected men (Raghuthaman 2015). A typical 45-year-old male was on 6 mg daily of risperidone and had been stable for more than 12 weeks. The patient developed erectile dysfunction; his plasma prolactin concentration was 2000 μIU/mL (normal <324). Aripiprazole 10 mg daily was added to his medication. Within 8 weeks, the prolactin concentration was within the normal range, his erectile function had improved; his mental state remained stable and he reported no other side-effects.

Risperidone 6 mg/day would normally occupy and antagonise 83% of $D_2/D_3$ receptors in the brain: more than enough to treat a relapse (Table 2).

Aripiprazole 10 mg would normally occupy 91% of $D_2/D_3$ receptors. As a partial agonist with 25% intrinsic activity, this would correspond to an antagonist occupancy of 68%.

In the combination, risperidone occupied 31% of $D_2/D_3$ receptors and aripiprazole occupied 63%. As a partial agonist with 25% intrinsic activity, this would correspond to an antagonist occupancy of 47% by aripiprazole in the combination.

The resulting total antagonist occupancy was 78% (31 + 47): still enough to prevent relapse despite the intrinsic activity of aripiprazole.

We have now to consider the interaction at the lactotroph cells of the anterior pituitary, where expression levels for $D_2$ are 100-fold higher than for $D_3$. Plasma prolactin rises above the normal range when $D_2$ antagonist occupancy in the pituitary overcomes the inhibitory effect of dopamine on prolactin secretion. We can use plasma concentrations of the drug to calculate pituitary $D_2$ receptor occupancy. As the great majority of the risperidone active moiety in plasma is its 9-hydroxy metabolite paliperidone, this dominates in raising prolactin levels (Knegtering 2005). For paliperidone alone, calculating free drug by accounting for protein binding (77%) gives 21.2 nM which, with a dissociation equilibrium constant $K_d$ of 2.8 nM (Richelson 2000), indicates 88.3% occupancy.

The corresponding values for the parent compound risperidone are levels of 4.87 nM/L and a $K_d$ of 3.77 nM. Table 3 shows the calculated

**BOX 2** Equations to determine the likely occupancy of $D_2/D_3$ dopamine receptors before and during addition of aripiprazole

DssOcc50(drug 1) is the dose of drug 1 producing 50% occupancy at steady state blood levels.

The values for DssOcc50 for each drug were derived from positron emission tomography studies

$$\%\ \text{occupancy by drug 1} = \frac{100\ [\text{Dose of drug 1}]}{[\text{Dose of drug 1}] + \text{DssOcc50(drug1)}\left(1 + \frac{[\text{Dose of drug 2}]}{\text{DssOcc50(drug2)}}\right)}$$

$$\%\ \text{occupancy by drug 2} = \frac{100\ [\text{Dose of drug 2}]}{[\text{Dose of drug 2}] + \text{DssOcc50(drug2)}\left(1 + \frac{[\text{Dose of drug 1}]}{\text{DssOcc50(drug1)}}\right)}$$



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**TABLE 2** Predicted striatal dopamine $D_2/D_3$ receptor occupancy and antagonistic activity by risperidone (drug 1) and aripiprazole (drug 2) alone and in combination in the doses stated

| Drug 1 Risperidone | | Drug 2 Aripiprazole | | Alone | | Combined | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Risperidone occupancy, % | Aripiprazole occupancy, % | Risperidone occupancy, % | Aripiprazole occupancy, % | Total Antagonist occupancy, % | Agonistic occupancy, % |
| DssOcc50: 1.2 mg | Daily dose: 6 mg | DssOcc50: 1 mg | Daily dose: 10 mg | 83 | 91 (75% = 68) | 31 | 63 (75% = 47) | 31 + 47 = 78 | 16 |

DssOcc50, the dose that produces 50% occupancy at steady state blood levels. Aripiprazole occupancy consists of 75% antagonism, as shown in parenthesis, and 25% agonism.

**TABLE 3** Predicted pituitary dopamine $D_2$ receptor occupancy on risperidone 6 mg/day by the risperidone moieties (drug 1 risperidone and drug 2 paliperidone, alone and in combination)

| Drug 1 Risperidone | | Drug 2 Paliperidone | | Separately | | As moieties | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Risperidone occupancy, % | Paliperidone occupancy, % | Risperidone occupancy, % | Paliperidone occupancy, % | Total occupancy, % |
| $K_d$, nM: 3.77 | Level, nM/L: 4.87 | $K_d$, nM: 2.8 | Level, nM/L: 21.2 | 56.4 | 88.3 | 13.1 | 76.8 | 89.9 |

$K_d$, dissociation equilibrium constant.

occupancies. The paliperidone moiety alone would cause 88.3% occupancy, and the combined occupancy is 89.9%, substantiating the findings of Knegtering et al (2005). Note that the pituitary $D_2$ receptor occupancy on risperidone 6 mg/day (89.9%) exceeds the calculated occupancy in the brain (83%).

For aripiprazole, the equivalent calculation – 180 ng/ml and 0.64% unbound (Hirata 2021) – yields 2.57 nM free drug from which, with a $K_d$ of 0.34 nM (Burris 2002), an occupancy of 88.3% is again calculated.

Applying the equation in Box 2 but substituting the $K_d$ for the DssOcc50 (the dose producing 50% occupancy at steady state blood levels) and the drug concentration for the dose gives a combined occupancy with a paliperidone component of 46.5% and aripiprazole component of 46.9% (Table 4). Note that pituitary $D_2$ antagonistic occupancy has fallen from 89.9% to 81.7%. This contribution of $D_2$ partial agonism is presumably enough to overcome the antagonist block of the inhibitory effect of endogenous dopamine on prolactin secretion. (This calculation was simplified by ignoring the lesser contributions of risperidone parent compound and aripiprazole metabolites.)

It seems likely that the intrinsic activity of aripiprazole may be higher at lactotroph $D_2$ receptors than within the brain; studies of the functional effects of aripiprazole on lactotrophs *in vitro* indicate maximum activity of up to 70% that of dopamine (Kucka 2015), well above the 25% reported for central $D_2$-like receptors.

There are many uncertainties in these calculations associated with extrapolation from experimental data and model systems. Calculated $K_d$ values vary and, for example, the affinity of aripiprazole at the lactotroph $D_2$ sites may be higher than is generally quoted for brain tissue, which would result in a larger aripiprazole occupancy. Protein binding of drugs varies with physical health.

In summary, the beneficial effect of aripiprazole on prolactin in people on risperidone arises from a lowering in risperidone's antagonistic occupancy combined with the partial agonistic effect of aripiprazole.

Although the effectiveness of this intervention has been confirmed in a narrative review (Besag 2021), an alternative strategy might have been a switch to a different antipsychotic with a lower propensity to raise prolactin.

Regarding dose, a meta-analysis found doses of only 5 mg aripiprazole daily could be effective in reducing prolactin levels raised by risperidone or haloperidol (Li 2013). Further, Chen et al (2010) found aripiprazole less effective in lowering prolactin in people on amisulpride than in those on risperidone.

Jen et al (2020) observed prolactin levels during a switch from other antipsychotics to aripiprazole in people with schizophrenia. Those whose prolactin levels became abnormally low during the switch were more likely to experience a worsening of psychosis. They interpret this as meaning that lowering of prolactin represented supersensitivity of dopamine receptors in the pituitary through upregulation during prolonged exposure. An alternative

**TABLE 4** Predicted pituitary dopamine $D_2$ receptor occupancy and antagonistic activity by paliperidone moiety (drug 1) and aripiprazole (drug 2) alone and in combination in the doses stated

| Drug 1 Paliperidone moiety in risperidone 6 mg/day | | Drug 2 Aripiprazole 10 mg/day | | Alone | | Combined | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Paliperidone occupancy, % | Aripiprazole occupancy, % | Paliperidone occupancy, % | Aripiprazole occupancy, % | Total antagonistic occupancy, % | Agonistic occupancy, % |
| $K_d$, nM: 2.8 | Level nM/L: 21.2 | $K_d$, nM: 0.34 | Level nM/L: 2.57 | 88.33 | 88.32 | 46.5 | 46.9 (75% = 35.2) | 46.5 + 35.2 = 81.7 | 11.7 |

$K_d$, dissociation equilibrium constant. Aripiprazole occupancy consists of 75% antagonism, as shown in parenthesis, and 25% agonism.

explanation is that lower prolactin indicates greater displacement of the previous antipsychotic by aripiprazole and therefore less antagonist occupancy to prevent relapse.

### *Adding aripiprazole to olanzapine for metabolic side-effects*

For a review of the management of weight gain developing with antipsychotics, see Cooper et al (2016).

The mechanism of weight gain with olanzapine is likely to involve blockade primarily of 5-$HT_{2C}$ receptors, although antagonism at other receptors, including histamine H1 and $D_2/D_3$, may also be involved in antipsychotic-induced weight gain (Reynolds 2017). Addition of aripiprazole would have minimal effect on $H_1$ receptors, but its partial agonism at 5-$HT_{1A}$ sites may be protective in reducing the orexigenic effects of olanzapine (Snigdha 2008). The addition of aripiprazole to clozapine, which also blocks histamine $H_1$ and 5-$HT_{2C}$ (similarly to olanzapine) led to a mean weight loss of 2 kg over 16 weeks compared with adding placebo, according to meta-analysis by Choi (2015).

A 50-year-old man with schizophrenia was maintained on olanzapine 20 mg daily for over a year and had a body mass index (BMI) of 32. Aripiprazole was added (15 mg daily). After 4 weeks he had lost 2 kg in weight and no change in mental state was noted (Henderson 2009).

Olanzapine 20 mg daily would be expected to occupy and antagonise approximately 83% of $D_2/D_3$ receptors: more than enough to treat a relapse (Table 5).

Aripiprazole 15 mg would typically occupy 94% of $D_2/D_3$ receptors. As a partial agonist with 25% intrinsic activity this would correspond to antagonist occupancy of 70%.

In the combination, olanzapine occupied 23% of $D_2/D_3$ receptors and aripiprazole occupied 72%. As a partial agonist with 25% intrinsic activity, this would correspond to antagonist occupancy of 54% by aripiprazole in the combination. The agonistic occupancy is 18%.

The resulting total antagonist occupancy was 77% (23 + 54), sufficient to counteract the roughly 18% agonistic occupancy by aripiprazole for the purpose of controlling psychotic symptoms. A longer follow-up than 4 weeks would be important to confirm that weight loss and stability of symptoms were maintained.

### *Controlling a relapse with severe agitation during treatment with aripiprazole*

In a psychiatric intensive care setting, it is common to see a patient admitted with a psychotic episode in whom aripiprazole has been used in the community but who is now severely agitated.

A young man had been taking aripiprazole 30 mg daily but developed a psychotic episode with severe agitation and manic symptoms and required tranquillisation. Aripiprazole was discontinued and haloperidol 20 mg daily was commenced, an electrocardiogram (ECG) having been normal. Promethazine and lorazepam were also given, in keeping with guidelines (Cookson 2018).

Haloperidol 20 mg daily would normally occupy and antagonise 94% of $D_2/D_3$ receptors, well

**TABLE 5** Predicted striatal dopamine $D_2/D_3$ receptor occupancy and antagonistic activity by olanzapine (drug 1) and aripiprazole (drug 2) alone and in combination in the doses stated

| Drug 1 Olanzapine | | Drug 2 Aripiprazole | | Alone | | Combination | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Olanzapine occupancy, % | Aripiprazole occupancy, % | Olanzapine occupancy, % | Aripiprazole occupancy, % | Total antagonistic occupancy, % | Agonistic occupancy, % |
| DssOcc50: 4.1 mg | Dose: 20 mg | DssOcc50: 1 mg | Dose: 15 mg | 83 | 94 (75% = 70) | 23 | 72 (75% = 54) | 23 + 54 = 77 | 18% |

DssOcc50, the dose that produces 50% occupancy at steady state blood levels. Aripiprazole occupancy consists of 75% antagonism, as shown in parenthesis, and 25% agonism.

**TABLE 6** Predicted striatal dopamine $D_2/D_3$ receptor occupancy and antagonistic activity by haloperidol (drug 1) and aripiprazole (drug 2) alone and in combination in the doses stated

| Drug 1 Haloperidol | | Drug 2 Aripiprazole | | Alone | | Combination | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Haloperidol occupancy, % | Aripiprazole occupancy, % | Haloperidol occupancy, % | Aripiprazole occupancy, % | Total antagonistic occupancy, % | Agonistic occupancy, % |
| DssOcc50: 1.3 mg | Dose: 20 mg | DssOcc50: 1 mg | Dose: 30 mg | 94 | 97 (75% = 73) | 33 | 65 (75% = 48) | 33 + 48 = 81% | 17% |

DssOcc50, the dose that produces 50% occupancy at steady state blood levels. Aripiprazole occupancy consists of 75% antagonism, as shown in parenthesis, and 25% agonism.

above the level needed to treat most relapses. However, occupancy data from positron emission tomography (PET) scans are not available for people with severe agitation (Table 6).

Aripiprazole 30 mg would normally occupy 97% of $D_2/D_3$ receptors. As a partial agonist with 25% intrinsic activity, this would correspond to antagonist occupancy of 73%. This is not always sufficient to prevent a relapse.

In the combination, haloperidol occupied 33% of $D_2/D_3$ receptors and aripiprazole occupied 65%. As a partial agonist with 25% intrinsic activity, this would correspond to antagonist occupancy of 48% by aripiprazole in the combination.

The resulting total antagonist occupancy was 81% (33 + 48); although usually enough to treat acute relapses of schizophrenia, this, we are assuming, was not sufficient to treat the psychosis in the presence of 17% agonistic occupancy by aripiprazole.

The man remained extremely agitated and refused oral medication.

Having discontinued aripiprazole 30 mg/day, even after 6 days, with an elimination half-life of 3 days, aripiprazole levels would still be equivalent to those resulting from a steady dose of 7.5 mg a day, sufficient alone (with a DssOcc50 of 1 mg/day) to cause $D_2/D_3$ receptor occupancy of 88%.

In summary, the psychotic manic agitation would be improving more slowly than expected with haloperidol.

To achieve greater antagonistic occupancy would require exceeding the upper limit of dose for haloperidol recommended in the British National Formulary, with concerns about potential ECG changes. An alternative approach would be the use of intramuscular zuclopenthixol acetate (Patel 2018). Using the DssOcc50 of less than 12.5 mg, the recommended initial dose of 150 mg would produce occupancy of 92% alone; a cumulative dose of 450 mg would produce 97% occupancy alone.

## Conclusions

Aripiprazole can counteract hyperprolactinaemia caused by risperidone without worsening psychosis. This is shown to be the result of displacing risperidone's high level of antagonistic occupancy at the pituitary $D_2$ receptor (through its metabolite paliperidone) with the partial agonism of aripiprazole.

Adjunctive aripiprazole can mitigate the metabolic effects of certain other antipsychotics without necessarily compromising antipsychotic efficacy. In view of the risk of relapse, when adding aripiprazole to another antipsychotic it would be prudent not to reduce the dose of the other drug unless the psychotic symptoms remained under control and the dose of aripiprazole had been stabilised.

The addition of aripiprazole to amisulpride is a flexible way to avoid high $D_2/D_3$ receptor antagonistic occupancy and avoid sedation, but risks worsening psychosis.

The enduring presence of a partial agonist can markedly undermine the effectiveness of other antipsychotics in treating severe agitation during a psychotic relapse.

The use of other partial agonists in combination with a full antagonist is likely to expand with the development of drugs with different intrinsic activity and selectivity for $D_3$ over $D_2$ subtypes of dopamine receptors, such as cariprazine (Oloyede 2022).

### *Limitations*

The figures used in the analyses for DssOcc50 are the means of published results and there are twofold individual variations for most drugs. Similarly, there is much variability in data associated with therapeutic drug concentrations, protein binding and receptor affinities, as there is also in measures of intrinsic activity.

There is very little direct evidence about levels of receptor occupancy by dopamine itself at synapses, so it is unclear how the presence of endogenous neurotransmitter might affect these calculations.

The degree of dopamine receptor occupancy by antipsychotics required to control acute agitation is largely unknown.

Presynaptic autoreceptor blockade by antipsychotics may contribute to the clinical effects of some drugs (e.g. amisulpride at low doses) and would complicate the calculation by increasing dopamine release. Other receptor mechanisms, including $5\text{-HT}_{2A}$ antagonism, affect the

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consequences of dopamine receptor occupancy by, for example, effects on dopamine release.

Antipsychotics vary in their selectivity for the $D_2$ and $D_3$ subtypes of receptors. Most have greater affinity for the $D_2$ subtype. The contributions of these subtypes in the brain cannot be separated for the present analyses.

We have treated $D_2$ antagonist antipsychotics as 'silent' antagonists, yet they mostly possess an inverse agonism. This may not be important in our calculations relating to post-synaptic receptor occupancy in the brain, although it may play a role in the mechanism of prolactin release.

We have not discussed here the potential effects of receptor upregulation – also known as supersensitivity (Silvestri 2000) – which may develop with prolonged exposure to antagonists, nor have we considered other regulatory feedback mechanisms, such as that of prolactin on tuberoinfundibular dopamine release (Gudelsky 1981).

Finally, it is important to be aware that we are using a model of receptor effects to understand drug action. The concept of separate agonist and antagonist components in a partial agonist is a construct that we believe to clarify the effects of aripiprazole, particularly in relation to its combination with other $D_2$ antagonist antipsychotics. In reality of course, these components are not separable: the drug acts on dopamine receptors through a single and specific mechanism to a greater or lesser extent depending on its ability to displace other competing ligands (antagonist drugs, neurotransmitter) from the receptor.

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## Author contributions

J.C. and J.P. developed the form of the manuscript. G.R. provided scientific advice refining the concepts. All three authors contributed to writing and editing the paper.

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## MCQs

Select the single best option for each question stem

1 After combining aripiprazole with a full dopamine receptor antagonist in treating schizophrenia:
- a aripiprazole is less potent than risperidone in occupying dopamine receptors
- b histamine receptor blockade will be increased
- c metabolic side-effects will be increased
- d testosterone levels may be increased
- e the degree of antagonist occupancy may be reduced.

2 Hyperprolactinaemia occurring in people receiving risperidone
- a arises from blockade of dopamine receptors in the hypothalamus
- b can lead to increased libido
- c is increased by addition of aripiprazole
- d is mainly due to a metabolite of risperidone
- e reduces thyroid function.

3 When combined with haloperidol, the intrinsic activity of aripiprazole:
- a is the same at all the receptors to which it binds
- b is the same in all areas of the brain
- c determines the degree of occupancy at receptors
- d determines the level of antagonistic occupancy at a high dose
- e worsens extrapyramidal side-effects.

4 Six days after discontinuing regular aripiprazole 30 mg/day, the residual drug will be sufficient to occupancy what proportion of $D_2/D_3$ receptors in the brain?
- a 50%
- b 60%
- c 70%
- d 80%
- e more than 90%.

5 Combining aripiprazole with a full antagonist of dopamine receptors in people with schizophrenia:
- a is rarely done in people taking clozapine
- b has been shown to improve negative symptoms of schizophrenia
- c may increase or decrease the degree of blockade of dopamine in the brain
- d reduces the QT interval in the ECG
- e improves akathisia.