Partial agonists of dopamine receptors: theoretical principles of combining antipsychotics including partial agonists to treat schizophrenia

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SUMMARY

Partial agonists such as aripiprazole are often used in addition to a full antagonist such as amisulpride, risperidone or olanzapine in an attempt to mitigate side-effects such as sedation, hyperprolactinaemia and weight gain. However, there can be unintended consequences, including worsening of psychosis. Moreover, previous exposure to a partial agonist may impair the subsequent response to a potent antipsychotic such as haloperidol used to control symptoms of relapse. To understand the mechanisms involved, a method is needed to compare potency in the pharmacological effects of different drugs used in combinations. This article is intended to explore and explain the theoretical principles based on the dopamine hypothesis of schizophrenia. We apply the method to analyse a recently described trial in which two full antagonists (olanzapine and amisulpride) are compared individually and in combination.

LEARNING OBJECTIVES

After reading this article you will be able to:
- critically appraise using combinations of antipsychotics in the treatment of schizophrenia – specifically the use of partial agonists and dopamine blockade
- understand how receptor occupancy of antipsychotics during treatment can be calculated
- review an example of an antipsychotic combination from a recently published study using the theoretical underpinnings.

KEYWORDS

Antipsychotic combinations; partial agonist; dopamine receptor; schizophrenia; receptor occupancy.

In three other articles in this issue we review the nature of partial agonism of dopamine receptors (Cookson 2023a) and the qualities of three partial agonists, aripiprazole, brexpiprazole and cariprazine (Cookson 2023b), and discuss the combination of a partial agonist with a full antagonist (Cookson 2023c).

Combining antipsychotics to treat schizophrenia is discouraged for several reasons (Barnes 2020):

- side-effects may be exacerbated – especially those that are dose-dependent, such as hypotension, QT prolongation, weight gain and extrapyramidal symptoms
- lack of evidence of effectiveness, particularly when one drug is already used at the maximum recommended dose
- absence of proven theoretical underpinnings
- adverse interactions – although pharmacokinetic interactions between antipsychotics are few, phenothiazines may inhibit drug-metabolising enzymes (Loga et al., 1975), notably CYP2D6.

However, combinations are frequently used for:

- mitigation of side-effects (combining a non-sedative antipsychotic with a sedative one)
- treatment failure with one antipsychotic at optimal dose
- obtaining another therapeutic effect, for example combining an antipsychotic without antidepressant effects with one with antidepressant effects
- part of cross-tapering.

In practice, the combinations used by clinicians give little consideration to their therapeutic receptor profiles. Often, they are simply combined because of an attempt to personalise treatments based on clinical intuition.

Combining a full antagonist with a partial agonist has been shown in certain circumstances to be of benefit. For example, addition of aripiprazole to risperidone has been shown able to reduce symptoms of hyperprolactinaemia without worsening

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psychosis. The antipsychotics most commonly combined with aripiprazole are clozapine and olanzapine, but only the combination with clozapine has shown greater effectiveness in preventing hospital admission than the antagonist (clozapine) alone in naturalistic studies (Tiihonen 2019); this may reflect better adherence to medication when side-effects such as weight gain are addressed. Such uses have – in contrast to the combination of full antagonists – a possible theoretical basis (Reynolds 2021).

Dopamine hypothesis, receptor occupancy and dose

Schizophrenia arises from an interaction of genetic and environmental factors in development, resulting in specific and subtle neuronal dysfunction. According to the dopamine hypothesis, a consequence of this is a dysregulation of dopaminergic neurons, resulting in increased release of presynaptic dopamine that underlies positive psychotic symptoms; this can be relieved by antipsychotic drugs that antagonise the excess, primarily by competitive blockade of dopamine D_2/D_3 receptors (McCutcheon 2020).

Occupancy and quantification of receptor blockade

The main measure used to estimate the strength of an antagonist is the dissociation equilibrium constant K_d, also called the dissociation constant. This is the ratio between the rate constant of association and that of dissociation. It corresponds to the concentration that will occupy 50% of receptors at equilibrium.

D_2 occupancy in treating schizophrenia

Key in understanding treatment of schizophrenia are the concentrations (or doses) needed to reach sufficient levels of blockade of the D_2/D_3 receptors so that psychotic symptoms are controlled. The different stages of schizophrenia – first episode, chronic-relapsing and stable with maintenance treatment – require different levels of occupancy that result from different drug concentrations, which can be expressed as multiples of the dissociation constant K_d (Table 1). This might be the consequence of dopamine release increasing and decreasing in the course of the illness; other factors, such as changes in receptor numbers, would complicate the calculation.

Receptor occupancy and dose

The relationship between dose and receptor occupancy is determined by the affinity of the drug for the receptor and can be predicted over a wide range of doses by the 'law of mass action', according

TABLE 1 Clinical stage, required occupancy of D_2/D_3 dopamine receptors by antagonist antipsychotic, and concentration (or dose) expressed as multiples of the dissociation constant

Clinical stage	P	$[B]/K_d$
No antagonist	0	0
Reference level of antagonist[a]	50	1
Stable maintenance treatment (Ozawa 2019)	66.6	2
First episode acute (Kapur 2000)	66.6	2
Acute exacerbation (Farde 1992)	70–80	2.3–4
Parkinsonian side-effects	80	4

P, the proportion of receptors occupied (receptor occupancy); [B], concentration of the drug; K_d, dissociation constant.
a. The reference level of 1 gives an occupancy or P of 50%. Doubling the reference level blocks about 66% of the receptors, and trebling blocks about 75%.

to an equation describing a rectangular hyperbola:

$$P = 100[B]/(K_d + [B])$$

where P is the proportion of receptors occupied; [B] is concentration of the drug; and K_d is the dissociation constant of the drug at that receptor (Lazareno 1993). This signifies that when the concentration is the same as the K_d, the occupancy is 50%.

For efficacy in an acute relapse of schizophrenia in adults, occupancy of up to 80% of receptors is required (Farde 1992). This would correspond to a concentration up to four times the K_d (Table 1). Importantly, with older antipsychotics the onset of Parkinsonian side-effects in young adults has been shown to occur with occupancies above 80% (Table 1). Only 65% occupancy is observed in some patients in the long-term maintenance phase of schizophrenia (Ozawa 2019) and in people with a first episode (Kapur 2000).

Replacing concentrations with doses

In practice, the dose of an antipsychotic is known but the concentration is usually unknown. It is therefore helpful to know the dose of drug that will produce a concentration leading to 50% occupancy at steady state blood levels. We call that dose the DssOcc50 (the dose producing 50% occupancy at steady state blood levels), and it can be derived from positron emission tomography (PET) scans. Nyberg & Farde (2000) called this measure K_i, but to be unambiguous we use DssOcc50 here.

The formula above can use doses in place of concentrations, provided that the K_d value is substituted by DssOcc50. But there are complications in the relationship between dose and blood level (Box 1). These complications mean that the relationship between concentration and occupancy is more

robust than that between dose and occupancy. The
latter shows more variation between individuals
due, for example, to genetic differences in drug
metabolism or transport.

The formula tells us that the concentration or dose
required to produce extrapyramidal side-effects is
twice the dose needed to treat a first episode but
not always higher than the dose needed for an
acute relapse.

An additional complication is that a blood–brain
barrier exists whereby drugs are extruded from the
brain and the efficiency of this extrusion varies
between drugs and with age, with corresponding dif-
ferences in brain/plasma concentration ratios.

Example converting blood level from mg/ml to nM/L

The following data are from Mamo et al (2007).

The mean blood level on aripiprazole 10 mg/day
was 126 ng/ml. Aripiprazole has a molar mass of
448.385 g/mol:

$$126/448.385 = 0.281 \text{ nM/ml or } 281 \text{ nm/L}$$

The protein binding of aripiprazole is 99.36%,
giving a free aripiprazole level of 0.64% or 1.8 nM/L

Understanding occupancy with combinations of drugs

The consequence (in terms of receptor occupancy,
Occ) of combining two antipsychotics depends on
the concentration (or dose) and the dissociation con-
stants (K_d values) of the two drugs. The formulae are:

$$\% \text{ Occ drug 1} = \frac{100[B_1]}{[B_1] + K_{d1}\left(1 + \dfrac{[B_2]}{K_{d2}}\right)}$$

$$\% \text{ Occ drug 2} = \frac{100[B_2]}{[B_2] + K_{d2}\left(1 + \dfrac{[B_1]}{K_{d1}}\right)}$$

where B_1 is the concentration of drug 1; B_2 the con-
centration of drug 2; K_{d1} the dissociation constant
of drug 1; and K_{d2} the dissociation constant of drug
2 (Salahudeen 2017).

Using dopamine receptor affinity and occupancy to compare doses

The main laboratory measure used to estimate the
strength of a receptor antagonist is the dissociation
constant K_d introduced above and this is the concen-
tration that will occupy 50% of those receptors at
equilibrium.

Since clinicians seldom have access to blood levels
of antipsychotics (and their interpretation would be
complicated by protein binding) it would be more
clinically useful to know the proportion of receptors
occupied when the drug has reached a steady state
level on regular dosing.

Substituting dose for concentration and assuming
they are linearly related:

$$P = 100 \times \text{dose}/(\text{DssOcc50} + \text{dose})$$

where DssOcc50 is the dose producing 50% occu-
pancy at steady state.

Published data from PET scans using ligands
that bind to D_2/D_3 receptors (particularly [^{11}C]
raclopride) provide values for DssOcc50 for several
antipsychotics: amisulpride (Sparshatt 2009), halo-
peridol and risperidone (Nyberg 2000), aripiprazole
(Sparshatt 2010) and olanzapine (Bishara 2013).
The doses shown are averaged and there is a
two-fold range in the dose between individuals in
the cases of risperidone, haloperidol and amisul-
pride (Table 2). A very high occupancy is reported
for zuclopenthixol acetate (used to control severe
agitation in psychosis), where the DssOcc50 is less
than 12.5 mg and the maximum recommended
dose is 400 mg over 3 days (Nyberg 1995).

For efficacy in an acute relapse of schizophrenia,
occupancy by D_2/D_3 antagonists of up to 80% of
receptors is required (Farde 1992). This would cor-
respond to a concentration four times the K_d or a
dose four times the DssOcc50.

Leucht et al (2020) presented graphs of dose–
response relationships for a range of antipsychotics
in acute schizophrenia, to compare their relative
potency. Their preferred measure of potency is the
ED95, 95% of the effective dose or 'maximal effect-
ive dose', defined as the lowest dose that produces
the maximum effect.

Furthermore, examination of the ED95 values cal-
culated by Leucht et al (2020) shows that they are
similar to four times the DssOcc50. Notably, aripi-
prazole is an exception (Table 2). We can therefore substitute DssOcc50 for K_d in
formulae (c) and (d) above, as shown in Box 2.

TABLE 2 Doses of antipsychotics producing 50% occupancy of D_2/D_3 receptors in positron emission tomography scans at steady state (DssOcc50) compared with lowest doses for maximum efficacy

Antipsychotics	DssOcc50, mg/day	Four times DssOcc50, mg/day	ED95, mg/day
Amisulpride	100–200	400–800	537
Aripiprazole	1	4	11.5
Haloperidol	1.3	5.2	6.3
Olanzapine	4.1	16.4	≥15.1
Risperidone	1.2	4.8	6.3

ED95, 95% of the effective dose, defined as the lowest dose that produces the maximum effect.
Source: Leucht et al (2020).

Other pharmacological mechanisms in antipsychotics

Many newer antipsychotics (e.g. olanzapine and risperidone) block serotonin at $5\text{-}HT_{2A}$ receptors and are thought to increase presynaptic dopamine release in motor areas of the basal ganglia (Dewey 1995). This is thought to contribute to the avoidance of extrapyramidal side-effects (EPSE). Such an increased release would require an increase in the concentration of drug to reach the level of D_2/D_3 receptor occupancy that would cause EPSE.

Antipsychotic effects can arise from mechanisms other than D_2/D_3 blockade – clozapine being a clear example involving other mechanisms.

Example: olanzapine combined with amisulpride

The COMBINE trial, a randomised controlled trial comparing olanzapine with amisulpride or a combination of the two in acutely ill people with schizophrenia, found that the combination of olanzapine and amisulpride brought greater improvement over 8 weeks than olanzapine alone, but not significantly greater than amisulpride alone (Schmidt-Kraepelin 2022). However, the authors noted higher dose equivalents in the combined treatment. The mean daily doses were olanzapine 14.1 mg, amisulpride 659 mg and the combination 14.4 mg olanzapine plus 567 mg amisulpride (Table 3). The equations imply occupancy levels of 80% for olanzapine alone, 81% for amisulpride alone and 88% for the combination. One possible explanation is that for some patients occupancy levels over 80% brought about greater improvement.

Exploring the exceptional partial agonism of aripiprazole

Aripiprazole monotherapy

When a partial agonist occupies receptors it competes with the transmitter – to produce some blockade – but it has an important stimulating effect, which is also known as intrinsic activity.

Aripiprazole's intrinsic activity has been calculated to be about 25% (Cosi 2006; Mace 2009). Therefore, to achieve 75% blockade, near complete (99%) receptor occupancy is necessary with aripiprazole. It should be emphasised that although intrinsic activity is a robust measure of individual receptor responses, differences can arise in whole tissues according to the number of receptors available and which second messenger is involved.

Interestingly, the maximum recommended clinical dose of 30 mg produces about 73% antagonistic occupancy or blockade (Table 4); this would avoid Parkinsonian side-effects and could be sufficient to treat a first episode of psychosis (Robinson 2015; Pagsberg 2017).

However, it would not necessarily be sufficient to achieve remission in an acute relapse; there, the full

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BOX 2 Formulae to determine receptor occupancy for two drugs in combination

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

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

where DssOcc50(drug1) is the dose of drug 1 producing 50% occupancy of D_2/D_3 receptors (seen in positron emission tomography scans) at steady state blood levels.

TABLE 3 Striatal dopamine D_2/D_3 occupancy in the COMBINE study (Schmidt-Kraepelin 2022) of olanzapine, amisulpride and their combination

Olanzapine alone		Amisulpride alone		Combination		Alone		Combined olanzapine 14.4 mg/day and amisulpride 567 mg/day		
DssOcc50, mg/day	Dose, mg/day	DssOcc50, mg/day	Dose, mg/day	Olanzapine dose, mg/day	Amisulpride dose, mg/day	Olanzapine Occupancy, %	Amisulpride Occupancy, %	Olanzapine Occupancy, %	Amisulpride Occupancy, %	Total antagonist Occupancy, %
4.1	16.8	150	659	14.4	567	80	81	42	46	88

DssOcc50, the dose that will produce a concentration leading to 50% occupancy at steady state blood levels.

antagonists amisulpride, risperidone and olanzapine have greater overall efficacy than aripiprazole (Huhn 2019). Aripiprazole has efficacy is preventing relapse in maintenance therapy of schizophrenia compared with placebo (Kane 2012), but in a long-term study of effectiveness, aripiprazole was not as effective as most other antipsychotics for continuation or preventing re-admission to hospital (Zhao 2016).

Conclusions

We suggest that estimates of D_2/D_3 receptor occupancy by individual antipsychotics used in combination can be derived from formulae (c) and (d) above by substituting the dose found to produce 50% occupancy at steady state in PET scans (DssOcc50) for the dissociation constant (K_d), and using the dose of drug in place of the drug concentration (Box 2).

The formulae in Box 2 can been used to explore various combinations of antipsychotics, including combining a partial agonist with a full antagonist, in the hope of clarifying clinical findings.

Limitations

Individual antipsychotics vary in their ratios of D_2 and D_3 receptor binding in striatal and extra-striatal areas (Schwartz 2000). Furthermore, the two receptor types are differentially antagonised by antipsychotic agents, with effects reflecting their different functional activity and anatomical distribution. Nor does the model presented here account for drug effects at presynaptic D_2/D_3 receptors.

Some antipsychotics do not show a clear hyperbolic dose–response relationship. For example, quetiapine has proved difficult to quantify in this way, with low apparent occupancy levels perhaps related to its shorter half-life and fast dissociation kinetics. Furthermore, clozapine cannot be included in this model of drug interactions because its additional efficacy in otherwise non-responsive patients likely depends on mechanisms other than D_2/D_3 receptor antagonism, and occupancy in acute treatment is less than 70% (Farde 1992). Hence, any displacement by aripiprazole will not reduce blockade of dopamine (see Cookson et al, 2023c).

The extent of occupancy by dopamine itself is largely unknown.

The intrinsic activities of the D_2 partial agonists, including aripiprazole and cariprazine, are determined from *in vitro* studies and may not be accurate measures of their activity in human brain. Intrinsic activity is dependent on cellular environment and second messenger systems associated with the receptor, which may vary between different tissues.

Nevertheless, we believe that the theoretical model described here provides a reasoned basis for

TABLE 4 Doses of aripiprazole, total D_2/D_3 receptor occupancy and antagonistic occupancy based on P = 100[dose]/(DssOcc50 + [dose]), assuming DssOcc50 is 1 mg (Sparshatt 2010)

Aripiprazole dose, mg/day	Dose/DssOcc50	Occupancy	Antagonist occupancy (estimated as 75% of total)
1	1	50%	37.5%
2.5	2.5	71%	53%
5	5	83%	62%
10	10	91%	68%
20	20	95%	71%
30	30	97%	73%

P, the proportion of receptors occupied (receptor occupancy); DssOcc50, the dose that will produce a concentration leading to 50% occupancy at steady state blood levels.

qualitative understanding of complex clinical situations involving combinations of antipsychotics.

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Author contributions

J.C. and A.B. discussed and developed the project and the concept of DssOcc50. J.P. developed the form of the manuscript. We all contributed to writing and editing the paper.

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; he declares no other conflicts for the past 3 years. A.B. is commercial associate at Otsuka Pharmaceuticals.

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MCQs

Select the single best option for each question stem:

1 Regarding the use of antipsychotic combinations in schizophrenia:
a doses of both drugs should be reduced by 50% in all cases
b side-effects produced by the single drugs are always made worse
c clinicians may be unaware of the resulting levels of occupancy at the D₂ receptors
d pharmacokinetic interactions between antipsychotics are irrelevant
e extensive evidence from randomised controlled trials has been published.

2 A partial agonist with 25% intrinsic activity must occupy what proportion of receptors to achieve antagonistic occupancy of 53% of dopamine receptors?
a 99%
b 91%
c 83%
d 73%
e 71%.

3 An antipsychotic that occupies 50% of brain dopamine receptors at a dose of 5 mg daily, at steady state is likely to achieve maximum therapeutic efficacy at which daily dose?
a 5 mg
b 10 mg
c 15 mg
d 20 mg
e 25 mg.

4 In the COMBINE trial, using olanzapine together with amisulpride resulted in:
a greater improvement over 8 weeks compared with olanzapine alone
b greater improvement over 8 weeks compared with amisulpride alone
c no difference between the combination compared with olanzapine alone or amisulpride alone
d lower levels of receptor occupancy compared with the individual drugs
e greater improvement only in the extrapyramidal side-effects.

5 The following total dopamine receptor occupancy is required in patients with schizophrenia who have relapsed after responding to a combination of antipsychotics:
a 90%
b 80%
c 70%
d 60%
e 50%.