High dose antipsychotic polypharmacy and dopamine partial agonists - time to rethink guidelines?

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Critique/Commentary

High dose antipsychotic polypharmacy and dopamine partial agonists - time to rethink guidelines?

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Abstract

Guidelines for the treatment of schizophrenia limit the use of antipsychotic agents to clinically-established maximum doses. This acknowledges both the absence of additional efficacy of dopamine D2 receptor antagonists above a receptor occupancy threshold, and the increases in side effects that can occur at higher doses. These limits restrict the dosing of combinations of antipsychotics as they do single agents; drugs sharing the major antipsychotic mechanism of D2 receptor antagonism will act additively in blocking these receptors.

Several newer antipsychotic drugs, including aripiprazole and cariprazine, act as partial agonists at the D2 receptor site and avoid action at several other receptors, effects at which are responsible for some non-dopaminergic adverse effects. This pharmacology imparts different characteristics to the drugs resulting often in a more favourable side effect profile. Their partial agonism, along with high affinities for the D2 receptor, also means that these drugs given adjunctively may in part replace, rather than enhance, the D2 antagonism of other antipsychotic agents. This can result in an improvement in certain side effects without loss of antipsychotic efficacy.

This article makes the case for distinguishing the D2 partial agonists from antagonists in defining maximum doses of combined treatments, which would increase the options available to the prescriber, emphasising that pharmacological mechanisms need to be understood in identifying optimal treatments for psychotic illness.

Keywords

Antipsychotic agents, adjunctive treatment, dopamine D2 receptor, antagonists, partial agonists

The dopamine D2 antagonists used as antipsychotic treatments are invaluable for many people with schizophrenia but can be limited by a range of adverse effects. These depend on the pharmacological profile of the antipsychotic drug used, as well as on genetic and other individual features of the patient, and include *inter alia* extrapyramidal symptoms (EPS), elevated prolactin, sedation, postural hypotension, weight gain and QT interval prolongation. The underlying receptor mechanisms relate to antagonism at, respectively but not exclusively, striatal and pituitary D2 receptors, histamine H1, alpha1 adrenergic, H1 and 5-HT2C receptors and hERG ion channels. In general, these side effects are dose-dependent, consideration of which has prompted the introduction of guidelines aimed at avoiding excessively high doses of antipsychotic drug. Furthermore, it has been established that for most dopamine D2 antagonists a D2 receptor blockade of approximately 60%–70% is adequate for an antipsychotic action and that drug doses above those required to achieve this threshold are likely to increase side effects without a concomitant increase in efficacy (Farde et al., 1992; Kapur et al., 2000).

This argument is also true for combinations of D2 antagonist drugs; the UK consensus guidelines indicate that the 'high dose' threshold is reached when the sum of the percentage of the maximum recommended dose for each antipsychotic drug exceeds 100% (Royal College of Psychiatrists, 2014). The rationale is clear: Combining two D2 antagonists at half maximum dose should approximate to the effects of one drug at maximum dose, although it is limited by inconsistencies in determining maximum doses, with newer drugs generally having more constrained dose ranges.

The availability of aripiprazole and cariprazine, as well as brexpiprazole in many countries outside the UK, has provided psychiatry with useful alternatives to the various dopamine D2 receptor antagonists that have been the mainstay in the treatment of psychosis for over 60 years. These three drugs are dopamine D2 receptor partial agonists which also have some further pharmacological properties; for aripiprazole this includes 5-HT1A partial agonism and 5-HT2A antagonism, whilst cariprazine has a partial agonist affinity for D3 higher than that for D2 and antagonist action at 5-HT2B (Frankel and Schwartz, 2017). Both drugs have minimal or, at most, weak effects at histamine H1, muscarinic or adrenergic receptors.

These pharmacological profiles have resulted in the availability of antipsychotic pharmacotherapy that is relatively free of some limiting side effects including hyperprolactinaemia and QT prolongation, as well as reductions in sedation (particularly for cariprazine) and in the requirement for antiparkinsonian medication (particularly for aripiprazole) (Huhn et al., 2019).

There is little evidence to support switching between antipsychotic drugs to improve efficacy (Barnes et al., 2020), although

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recent studies have indicated some differences in which amisulpride, olanzapine and risperidone, as well as clozapine, show small advantages in overall efficacy (Smith et al., 2019). Stronger justification for switching is found in response to side effects which may differ substantially between drugs. Here the D2 partial agonists may demonstrate particular benefits. With these drugs, however, switching from a D2 antagonist may not be immediately necessary; the benefits of aripiprazole (and likely cariprazine too) in reducing drug-induced hyperprolactinaemia, for example, can be seen when the drug is added to current treatment (Zheng et al., 2019). Similarly, adjunctive aripiprazole can ameliorate weight gain and other metabolic problems associated with olanzapine or clozapine treatment (Cooper et al., 2016; Mizuno et al., 2014). Usually there is no deterioration of psychotic symptoms associated with adding a dopamine partial agonist; further symptomatic improvement may even be seen (e.g. Zheng et al., 2019). Such adjunctive prescribing would be off-label but has a strong evidence base. It could, however, also serve as an initial step towards D2 partial agonist monotherapy, prior to a gradual withdrawal of the D2 antagonist drug.

Combination of two antipsychotic agents in this way may exceed the high dose threshold. Such cumulative doses are perceived as high risk and understandably may require explicit justification for their prescription. British Association for Psychopharmacology guidelines indicate that antipsychotic augmentation to address inadequate symptom response should only be considered after other treatment options have been exhausted, including 'several, adequate, sequential trials of antipsychotic monotherapy' (Barnes et al., 2020). This both reflects and guides current UK practice where switching is generally preferred to augmentation with another antipsychotic drug, despite the acknowledged paucity of supportive evidence. This often means that drug combinations are avoided with alternative, but perhaps sub-optimal, strategies being employed.

As mentioned above, the pharmacological basis for this high dose risk is clear; additional blockade of D2 receptors above what is necessary for an antipsychotic response will increase the liability for dopaminergic side effects such as EPS and prolactin secretion without increasing efficacy. Furthermore, and depending on the particular drugs being combined, other receptor-mediated side effects are likely to increase, some of which, such as metabolic effects and QT prolongation, may contribute to increased mortality. However, this pharmacological argument does not consistently hold up for the combination of partial agonists with antagonists. In terms of the main antipsychotic mechanism, drug action at the dopamine D2 receptor, the dopamine D2 partial agonists should be differentiated from D2 antagonists. As can be seen in their effects in avoiding, and reversing, D2 antagonist-induced hyperprolactinaemia, adjunctive partial agonists can ameliorate, rather than enhance, unwanted dopaminergic effects of D2 antagonists. Aripiprazole and cariprazine have high (sub-nanomolar) affinities at the D2 receptor greater than most D2 antagonists (Frankel and Schwartz, 2017). Thus they will preferentially bind to the receptor site, resulting in replacing antagonism with partial agonism, thereby providing a level of receptor stimulation which depends on the drug's intrinsic activity; for aripiprazole this is around 25% of that of dopamine (Cosi et al., 2006).

This provides a strong argument for differentiating the D2 partial agonists from the D2 antagonist drugs and considering them a separate class when it comes to combining drugs for the optimal treatment of people with psychotic illness. Of course, polypharmacy is to be avoided where possible and drugs need to be given at the lowest dose consistent with optimising efficacy and minimising side effects. However, it is clearly wrong to restrict adjunctive use of D2 partial agonists, where they may have clinical value, on the basis of the inappropriate application of a 'maximum cumulative dose' concept.

As a postscript, I suggest that the issue highlighted here is related to the common view of 'antipsychotic agents' as a single drug class or, at best, one divided into first- and second-generation antipsychotics. The application of neuroscience-based nomenclature, in which drugs are differentiated on the basis of their pharmacological mechanisms (Nutt and Blier, 2016), takes one step towards avoiding this oversimplification and its consequences for psychiatric pharmacotherapy.

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Commentary on 'High dose antipsychotic polypharmacy and dopamine partial agonists – time to rethink guidelines?' by Prof Gavin Reynolds

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Clinical guidelines for the treatment of schizophrenia consistently recommend the use of a single antipsychotic in a standard dose (Barnes et al., 2020; National Institute for Health and Care Excellence, 2014; Galletly et al., 2016); this strategy is underpinned by both a large body of evidence supporting the efficacy of individual antipsychotic medications and by tolerability data that have been systematically, although not always comprehensively, garnered (Pope et al., 2010). These guidelines further recommend switching to an alternative antipsychotic medication if the first antipsychotic is not tolerated or the illness fails to respond, although the paucity of supportive evidence for such switching is acknowledged. Should there be a persistent lack of adequate therapeutic response, timely progression to clozapine treatment should be the next step, in advance of the use of high-dosage antipsychotic medication or combined antipsychotic medication strategies (which commonly result in a high-dose regimen), for which the evidence regarding treatment outcomes and safety is considerably slimmer.

Reynolds argues that, when added to another antipsychotic medication, D_2 partial agonists reduce metabolic and prolactin-related side effects and potentially improve symptom control: therefore the use of such combinations should be considered earlier when seeking to optimise treatment for schizophrenia. But any additional beneficial effect on symptoms and side-effects with a D_2 partial agonist/D_2 antagonist combination is likely to be very modest and the combination may be associated with new side effects, so a favourable balance of risks and benefits cannot be assumed. Most of the clinical literature relating to D_2 partial agonists focuses on aripiprazole as this antipsychotic medication was first in class. Therefore, aripiprazole is used to expand on these points below.

Efficacy and tolerability of aripiprazole as monotherapy

While aripiprazole has evident antipsychotic efficacy, it may be slightly less effective overall for treating the symptoms of schizophrenia than the more commonly used D_2 antagonists (Leucht et al., 2013; Tiihonen et al., 2019), suggesting that D_2 partial agonism may provide less than optimal control of symptoms in some cases. There are a further group of patients whose illness has shown an insufficient response to non-clozapine antipsychotic medication that is not related to factors such as poor adherence or comorbid substance use. Such treatment-resistant schizophrenia may have a distinct pathophysiology involving a range of neurobiological pathways (Potkin et al., 2020). Therefore, pharmacological strategies that are limited to modulating D_2 receptor activity, either as monotherapy or in combination, may have minimal if any effect on symptoms and pursuing such strategies could result in an avoidable delay in initiating clozapine treatment, potentially worsening outcomes (Shah et al., 2018; Yoshimura et al., 2017).

When used alone, aripiprazole is undoubtedly relatively well tolerated with respect to metabolic and prolactin-related side effects (Leucht et al., 2013) but it is not free of side effects, with treatment-emergent akathisia, insomnia, headache and nausea reported for more than 1 patient in 10 in clinicial trials (Aripiprazole SmPC). With respect to QTc prolongation, epidemiological studies have linked aripiprazole to weak/moderate tosardogenicity (Polcwiartek et al., 2015). Further, recent evidence points to an association between D_2 partial agonists and the development of impulse control disorders (Corbeil et al., 2021; Grall-Bronnec et al., 2016). Therefore, as is the case for all antipsychotic medications, the decision to prescribe aripiprazole should take into consideration the potential harms associated with this medication and ongoing clinical review is essential.

Efficacy and tolerability of aripiprazole in combination with another antipsychotic medication

While to our knowledge there are no randomised controlled trials of aripiprazole augmentation of non-clozapine antipsychotic medication, the real life effectiveness of such combinations has been reported by Tiihonen et al. (2019). In a Swedish, population-based cohort of 62,500 patients with an established diagnosis of schizophrenia, those patients who were prescribed clozapine, olanzapine or a long-acting injectable antipsychotic preparation as monotherapy were less likely to be readmitted to hospital than those prescribed aripiprazole combined with a non-clozapine antipsychotic. Further, olanzapine monotherapy fared slightly better than olanzapine combined with aripiprazole. Thus, these findings failed to suggest any systematic efficacy advantage for the addition of aripiprazole to a non-clozapine antipsychotic medication.

With respect to aripiprazole augmentation of clozapine, a meta-analysis of mostly very small randomised controlled trials found no advantage with respect to psychotic symptoms in clozapine responders who received aripiprazole as a strategy to manage weight gain but a potential modest advantage with respect to improvement in negative symptoms where the illness had not responded to clozapine (Srisurapanont et al., 2015). In the naturalistic study by Tiihonen et al. (2019) described above, the combination of clozapine and aripiprazole was most effective

in preventing readmission but, compared with clozapine monotherapy, the effect size was small. When considered together, these studies do not exclude a modest advantage for an individual treatment trial of the combination over clozapine monotherapy for some particular patients, but the evidence so far falls short of supporting routine use.

Aripiprazole binds strongly to D_2 receptors but the degree of dopamine blockade it produces is limited as it is a partial agonist rather than an antagonist. Through this mechanism, adjunctive aripiprazole has been shown to reverse the hyperprolactinaemia that is associated with some potent D_2 antagonists, such as risperidone (Yasui-Furukori et al., 2010). However hyperprolactinaemia that is asymptomatic does not always require treatment and where it is symptomatic or the patient is otherwise at greater risk of sequelae, the most logical strategy would be to switch to an antipsychotic medication with a low propensity for elevating plasma prolactin.

With respect to the amelioration of weight gain associated with antipsychotic treatment, published meta-analyses (Choi, 2015; Srisurapanont et al., 2015) have concluded that the addition of aripiprazole to clozapine or olanzapine results in a mean weight change of around -2 kg compared with clozapine or olanzapine monotherapy. This mean change is modest and while it does not exclude a larger effect in some patients, it suggests that for the majority the effect on body weight is unlikely to be clinically relevant. The use of adjunctive aripiprazole to reduce weight gain in patients receiving antipsychotic medications other than clozapine or olanzapine has not been systematically tested. While the BAP guidelines for the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic treatment (Cooper et al, 2016) identified augmentation of clozapine or olanzapine with aripiprazole as a possible intervention for weight gain, it added the caveat that the possible disadvantages of such polypharmacy should be considered versus the degree of benefit obtained. For example, the meta-analysis by Choi (2015) also noted that there were clear signals for treatment-emergent akathisia and nausea, along with one report of sinus tachycardia and two of significant worsening of psychotic symptoms in the aripiprazole augmentation arms.

The meta-analysis by Srisurapanont (2015) reported modest improvement in LDL cholesterol with aripiprazole augmentation but did not find any beneficial effects of the combination with respect to fasting plasma glucose, although it should be noted that the durations of the included studies were short, ranging from 8 to 24 weeks.

Definition of high-dose antipsychotic medication and recommendations in evidence-based clinical guidelines

A number of approaches have been used to determine whether a combination of antipsychotic medication is considered to be high dose or not (Barnes et al., 2014); the most common are (1) the use of 'chlorpromazine equivalents' where the doses of each antipsychotic medication are converted to an equivalent dose of chlorpromazine, based partially on known affinity for D_2 receptors, and a total equivalent dose of chlorpromazine above 1000 mg is defined as a high dose, and; (2) the more commonly used 'percentage method' where the percentages of the maximum licensed dose for each antipsychotic medication co-prescribed are added and a cumulative dose of more than 100% is defined as a high dose. While both methods are essentially arbitrary and have their limitations, they provide a dosage threshold above which the evidence suggests that the risk-benefit balance becomes more uncertain and potentially unfavourable (Leucht et al., 2020) and which should be a prompt that such regimens should be prescribed as individual therapeutic trials, with close monitoring of target symptoms and potential side effects. Guideline recommendations relating to the use of high-dose or combined antipsychotic medication strategies are not based simply on whether a dosage threshold has been exceeded, but consider the available evidence relating to efficacy and safety, to inform the rational prescription of such regimens. Nevertheless, as the evidence base is constantly developing and changing, there is a need to keep all guideline recommendations under review.

Conclusion

Where evidence-based medication strategies (including clozapine) for schizophrenia have failed or are not tolerated, an individual therapeutic trial of combined antipsychotic medications is a potential treatment option. In this context, a trial of aripiprazole augmentation of another antipsychotic medication may offer worthwhile benefits for some patients in some clinical circumstances. However, given the relatively poor evidence base underpinning the use of combined antipsychotic medications, the advice that other pharmacological interventions with more consistent evidence for a favourable risk-benefit balance should be given priority and that if such a regimen is prescribed there is a responsibility to document the rationale for the chosen combination and carefully monitor the benefits and harms, should support judicious prescribing.

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Response to Paton and Barnes

Arguably the biggest concern in schizophrenia research is that of people with schizophrenia whose symptoms do not respond to standard antipsychotic agents (James Lind Alliance, 2011). Until more effective drugs are introduced which address this problem, it is important to provide a therapeutic environment that offers clinicians and their patients the most flexibility in treatment choice without restrictions that are not firmly grounded in evidence. To my mind, this includes the opportunity to provide a relatively safe treatment with a D2 partial agonist additional to a D2 antagonist, while recognising of course that, as with all pharmacotherapy, there is a balance to be struck between risk and benefit.

Paton and Barnes have prepared an extensive response to my commentary, starting by summarising the guidelines for the treatment of schizophrenia. These recommend monotherapy and switching to an alternative antipsychotic agent if this is not tolerated or if the illness fails to respond. Only the first of these reasons to switch has a strong evidence base. They also discuss at length the evidence for the efficacy and tolerability, or otherwise, of aripiprazole treatment for schizophrenia. They repeatedly describe benefits of adjunctive aripiprazole as modest; however, less than modest supporting evidence is no barrier to inclusion in guidelines, as we see with the recommendation to switch drugs for lack of response. We can recognise this as a pragmatic recommendation – 'what else can be done?' - in the hope that some individual factor may result in improvement, but evidence suggests it remains unlikely to be effective.

There is much opportunity for further debate around the effects of aripiprazole that Paton and Barnes discuss so comprehensively. One point they make is, however, misleading. They reiterate a comment in the abstract of Polcwiartek et al. (2015) that epidemiological studies have linked aripiprazole to weak/moderate torsadogenicity. Yet the authors also state that a 'lack of adequate data . . . confounds the interpretation of any epidemiological findings'. More importantly, the main finding of this review and meta-analysis of aripiprazole's cardiac safety in patients at high risk for torsade is that QTc prolongation risk is lower compared with both placebo and active controls. In a more recent population-based Danish study (Polcwiartek et al., 2020), the same research group report that, while antipsychotic prescribing in people with schizophrenia was associated with a greater frequency of abnormal ECGs compared to non-psychiatric control subjects, this was not true for aripiprazole which was additionally associated with a decreased risk of QTc prolongation. It would be reasonable to conclude that aripiprazole is relatively safe in terms of this measure of cardiac toxicity.

One final point: while I have not specifically considered the adjunctive use of partial D2 agonists with clozapine, Paton and Barnes have helpfully drawn attention to the study of Tiihonen et al. (2019). The key finding from this nationwide Finnish study is that aripiprazole and clozapine polypharmacy is significantly more effective in reducing rehospitalization than clozapine or any antipsychotic monotherapy alone. While the effect size may be small, we are reminded by the authors that this may be an underestimate as adjunctive treatment is generally in response to a worsening of symptoms with monotherapy. Tiihonen et al. (2019) conclude that a rational polypharmacy with two particular drugs of differing receptor profiles appears feasible, and that treatment guidelines which discourage all antipsychotic polypharmacy should be modified accordingly. While this has not been the main point of my commentary, such evidence-based polypharmacy would be facilitated by the removal of a 'high dose' restriction on adjunctive D2 partial agonists that has no pharmacological rationale.

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