

Graylands Hospital Drug Bulletin

Antipsychotic Polypharmacy - *time to review practice*

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Introduction

Antipsychotic polypharmacy (APP) is the concurrent use of two or more different antipsychotic drugs by one patient.¹ Although this is a common clinical scenario, there is no convincing evidence that APP is more effective than a single antipsychotic for the treatment of schizophrenia.²

APP is also a major cause of high-dose prescribing, increased side-effect burden, and possibly increased mortality (it has even been labeled psychiatry's 'dirty little secret').² As a result, most treatment guidelines for schizophrenia recommend a single antipsychotic in standard dosage.³

Despite this, a recent audit of APP at Graylands hospital found that patients are routinely exposed to APP and high-dose regimens. Given these findings, and the continued interest in this subject, we thought that it would be timely to review this contentious practice.

This Bulletin broadly covers some of the key issues concerning APP and high-dose prescribing. Hopefully this information will lead to a greater awareness and understanding of this complex issue, and go some way to reduce the ever-widening gap that seems to exist between evidence and current practice.

Prevalence of APP

Recent studies reveal that up to a quarter of psychiatric inpatients are prescribed APP, with the highest prevalence figures being found in psychiatric intensive care units, rehabilitation and forensic wards.⁴ In one large study, the overall prevalence rate of APP across decades and global regions was 19.6%.⁵

Several surveys conducted in the UK over the past decade, involving a total of 4200 inpatients, found that about one quarter of patients were prescribed APP.⁴ For the great majority of these, high-dose was prescribed by virtue of APP.

The largest UK audit of APP was conducted by the Prescribing Observatory for Mental Health (POMH-UK).⁶ A baseline audit of 3492 patients on 218 wards found that 43% were prescribed APP, and over one-third prescribed a high-dose of antipsychotic medication. A recent audit of APP at Graylands

hospital, using a similar methodology to POMH-UK, found that 89.8% of patients were prescribed more than one antipsychotic and 79% of patients were prescribed a high dose. 39.2% of high-dose prescribing was attributable to 'as required' (PRN) medication.

The results from this audit demonstrate a worrying increase in the prevalence of APP/high-dose prescribing. Previous audits at Graylands hospital show that the prevalence of APP has increased from 37% in 2002 to 55% in 2007, and 89.8% in the current audit. However, data from the earlier audits were restricted to regular prescriptions; the rates would have been higher if PRN medication had been included as well.

Routes to APP

The pharmacological rationale sometimes given for APP includes seeking to achieve greater therapeutic potential by optimisation of dopamine D2 receptor occupancy, and/or seeking to achieve activity across a wider range of receptors.

This is on the basis that certain non-dopaminergic receptors, such as serotonergic, glutamatergic and adrenergic receptors, may be relevant to the pathogenesis of positive and negative symptoms. However, there are few clinical trial data or other sources of evidence to support these notions.⁷ Clinical reasons often cited for APP include:

- Switching patients from one antipsychotic to another. Sometimes, during the switch, patients' symptoms can improve, and this may lead to reluctance to complete the switch.
- Stable patients with psychosis may develop an acute exacerbation of psychotic symptoms, or worsening of agitation or insomnia and be prescribed an additional antipsychotic on an 'as required' basis. 'As required' prescriptions may develop into long-term adjuvant treatments, particularly if considered successful in the short term.
- Adding aripiprazole to clozapine, as it helps patients to lose weight and may also improve other metabolic parameters. Co-therapy with aripiprazole has also been shown to normalise prolactin levels in those treated with prolactin-elevating antipsychotics.

The influence of 'as required' (PRN) medication

One of the most common reasons for APP is the use of PRN prescribing. PRN prescribing allows medication to be administered at the nurses' discretion for psychiatric symptoms (usually for the management of disturbed behaviour). Among psychiatric inpatients, PRN prescriptions are written for approximately 75% and administered to around 50% depending on the setting.⁷

Despite this widespread practice there is no published evidence comparing risks and benefits of PRN versus regular psychotropic drug regimens. Injudicious PRN prescribing can lead to polypharmacy, high-dose prescribing and potentially harmful drug interactions.⁸ The clinical audits organised by POMH-UK, identified PRN prescriptions as the principal cause of APP/high-dose prescribing.⁶ In the Graylands audit mentioned above, 39.2% of high-dose prescribing was attributable to PRN medication.

The use of PRN antipsychotic medication is clearly an embedded clinical practice, with some lack of clarity regarding individual responsibility with regard to initiating, reviewing, administering and monitoring the response to, and adverse effects of, such medication.

Such prescribing may be strongly influenced by requests from ward-based nursing staff. Once a PRN prescription has been written, nurses identify more indications for use than doctors; e.g. when administering a PRN antipsychotic for the management of hallucinations, delusions or thought disorder, their preferred drugs are haloperidol and chlorpromazine. When both an antipsychotic and a benzodiazepine have been prescribed, nurses will tend to administer the former.⁷

Evidence for efficacy of APP

The efficacy and safety of APP in schizophrenia has not been studied adequately in well-controlled, systematic trials. This is reflected in the many treatment guidelines that do not advocate the routine use of APP or high-dose regimens.

One large meta-analysis including a number of studies from the Chinese literature, found a slight therapeutic advantage for APP, but noted clear publication bias in favour of positive studies. This review included 19 RCTs and involved over 1200 patients.⁸

However, results were highly heterogeneous and the observed superiority seemed to be driven by combinations that included clozapine. The authors concluded that APP could not be endorsed based on

available data, partly because the majority of antipsychotic combinations in the western world did not include clozapine and were given in patients who were non-responsive to antipsychotic monotherapy.

Another RCT, this time examining aripiprazole augmentation of risperidone or quetiapine (n=323), was convincingly negative with respect to improvement in symptoms. In addition, changes in metabolic parameters were either non-existent or so small as to be clinically insignificant.⁹

The remaining evidence for APP comes from mostly small open-label studies and case series. For example, Chan & Sweeting¹⁰ identified four open-label studies, five case series and twelve case reports. The combinations most commonly referred to were olanzapine with amisulpride or risperidone, and quetiapine with risperidone.

Overall, the authors did report 'some' symptom improvement with these combinations. However, they concluded that the studies included had significant limitations and caution is recommended. Also, on the basis of early case reports, they noted that combining aripiprazole with a non-clozapine second-generation antipsychotic might possibly worsen psychosis.

Another open-label trial of note was conducted in seventeen treatment-refractory patients that had failed to respond to sequential trials of monotherapy with olanzapine, quetiapine and risperidone.¹¹ The combination chosen was olanzapine plus risperidone. By the end of the trial, seven patients demonstrated a therapeutic response.

Six of the responders were subsequently maintained at lower dosages and two were successfully switched to antipsychotic monotherapy. However, the investigators concluded that the value of antipsychotic polypharmacy in such patients, compared with other drug augmentation strategies or persistent longer-term antipsychotic monotherapy, remain to be determined.

Clozapine augmentation

There is better, if limited, evidence for the use of one particular antipsychotic combination strategy: the augmentation of clozapine with a second antipsychotic in people with treatment-resistant schizophrenia whose illnesses shows a poor response to an adequate trial of clozapine monotherapy.¹²

RCTs have tested risperidone, sulpiride, amisulpride and aripiprazole as the antipsychotic augmenting clozapine treatment, and there are several relevant open-label trials and case reports regarding augmentation with ziprasidone.¹³

In practice, the result of clozapine augmentation is

Key Messages

- APP is highly prevalent in clinical practice and often leads to high-dose prescribing.
- Current evidence does not justify the routine use of APP or high-dose regimens.
- Substantial evidence supports the potential for harm; therefore the use of APP/high-dose prescribing should generally be avoided.
- 'As required' (PRN) prescribing has been identified as a major cause of APP and high-dose prescribing.
- Reducing APP to monotherapy without clinical deterioration has been successfully demonstrated.
- Local systems should be developed to alert the responsible prescriber to patients currently administered, or at risk of receiving high-dose antipsychotic regimens.
- Before resorting to APP or high-dose antipsychotic, evidence-based strategies for treatment resistance should be exhausted, including the use of clozapine.
- As a minimum requirement, all patients who are prescribed APP/high dose regimens should have their side-effects assessed (including ECG monitoring) and any beneficial effect on symptoms documented. APP should be time limited and ceased if no benefit observed.

often disappointing and substantial changes in symptom severity are rarely observed. This clinical impression is supported by the equivocal results of many studies, which suggest a small effect size at best. Meta-analyses of antipsychotic augmentation of clozapine suggest no effect, a small effect in long-term studies or, in the largest meta-analyses, a very small effect overall.¹⁴

Evidence for harm

Problems related to APP include the risk of adherence problems associated with a more complicated regimen, an increased adverse effect burden mediated through drug-drug interactions and exposure of patients to high-dosage antipsychotic medication.²

There are a number of published case reports of clinically significant side-effects such as an increased prevalence of Extrapyramidal Side Effects (EPS), severe EPS, increased metabolic side-effects, paralytic ileus, grand mal seizures and prolonged QTc associated with combined antipsychotics.²

With respect to systematic studies, one that followed a cohort of patients with schizophrenia prospectively over 10 years found that receiving more than one antipsychotic concurrently was associated with substantially increased mortality.¹⁵ Another that followed 99 patients with schizophrenia over a 25-year period found that those who were prescribed three antipsychotics simultaneously were twice as likely to die as those who were prescribed only one.¹⁶

High-dose antipsychotic medication

The vast majority of high-dose regimens are through the cumulative effect of combinations (POMH-UK found that 80% of patients prescribed APP, were receiving a high-dose). A variety of methods have been used to identify high-dose prescribing in patients prescribed APP.

One method involves converting the dose of each drug into chlorpromazine equivalents (CPZeq) and adding these together.¹⁷ Anyone receiving over 1000mg of CPZeq is considered to be on a high dose. In the UK, the percentage method is most commonly used. This involves converting the dose of each drug into a percentage of the British National Formulary (BNF) maximum dose and adding these together. Anyone receiving over 100% aggregated BNF percentage is considered to be on a high dose.¹⁷

For example, for a person prescribed olanzapine 20mg/day and oral haloperidol 5mg TDS, the respective percentages would be 100% and 50%, giving a total antipsychotic prescribed dosage of 150% of the BNF maximum.

Both of these methods have their limitations, particularly as they aggregate doses of drugs with different mechanisms of action. The time honored CPZeq method provides a stable comparison point for the first generation antipsychotics. However, for the second-generation antipsychotics, dose-equivalences remain more elusive.¹⁷

Efficacy of high-dose antipsychotic prescribing

There appears to be some confusion about the dose-

response relationship of antipsychotics, as practice seems to suggest that many prescribers believe that 'more is better'. However, reviews of the dose-response effects of a variety of antipsychotics have revealed no evidence for increasing doses above accepted licensed ranges.

The most efficacious dose of risperidone is 4mg a day¹⁸, for aripiprazole 10mg a day¹⁹, for haloperidol 5mg a day²⁰, for quetiapine 300mg a day²¹ and for haloperidol decanoate 100mg a month.²² The largest fixed-dose study to-date (n=600) showed olanzapine 10mg to be just as effective as 20mg and 40mg a day.²³

These observations of a low ceiling effect tie-in nicely with receptor occupancy studies suggesting saturation of receptors at low doses. Thus, more is not better once a certain dose is reached, at least with antipsychotics used as single agents. To then assume that adding a second antipsychotic (very probably with an identical mode of action) will bring about improvement is probably beyond reason and logic.

Australian licensed maximum doses of antipsychotics:

Oral	mg/day	Depot	mg/week
Amisulpride	1200	Flupenthixol	50
Aripiprazole	30	Fluphenazine	50
Asenapine	20	Haloperidol	300 4/52
Chlorpromazine	800	Olanzapine	300 2/52
Clozapine	900	Paliperidone	150 4/52
Haloperidol	30	Pipothiazine	50
Olanzapine	20	Risperidone	25
Paliperidone	12	Zuclopenthixol	300
Quetiapine	800		
Risperidone	10		
Trifluoperazine	30		
Ziprasidone	160		

Adverse effects of high-dose antipsychotic prescribing

The majority of side-effects associated with antipsychotic treatment are dose related.² These include EPS, sedation, postural hypotension, anticholinergic effects, QTc prolongation and sudden cardiac death.² In addition, high-dose prescribing has been associated with poorer cognitive functioning.²⁴

Switching from APP to monotherapy

There is a lack of guidance on what to do when faced with patients on APP, in terms of dose reduction or switching. However, studies have shown that it may be possible to switch patients from APP to monotherapy without clinical deterioration. One such study (that included patients taking an average of three antipsychotics n=44) found that over half the

patients remained stable when switched from APP to monotherapy, while 23% of patients demonstrated an improvement in their clinical symptoms.²⁵

Monitoring patients on APP/high-dose regimens

Although treatment algorithms from Australia advise against the routine use of APP,²⁶ there is a lack of guidance on how to identify patients prescribed high-dose regimens. In addition, there is no specific guidance regarding the ongoing requirements for biochemical and ECG monitoring. Such guidance does exist in other countries, and it would be prudent to follow recommendations from the UK.²⁷ For example, the Royal College of Psychiatrists consensus statement²⁷ on the use of high-dose antipsychotic medication recommends that all patients on high-doses should have regular ECGs (baseline, when steady-state serum levels have been reached after each dosage increment, and then every 6-12 months).

Conclusion

The combined use of antipsychotics and high-dose prescribing is common in the treatment of schizophrenia. This appears to be an embedded clinical practice and the prevalence is increasing over time. Although there is some limited support for APP, there are valid concerns about this practice; not least, as APP is a major cause of high-dose prescribing, increased side-effect burden, and possibly increased mortality.

Before resorting to APP, evidence-based strategies for treatment resistance should be exhausted, including the use of clozapine. In addition, appropriate physical health monitoring should be carried out, and a patient's response to the medication regimen regularly reviewed. Combinations should only be continued if the benefits are clinically relevant and clearly outweigh any adverse consequences.

Given the gap that seems to exist between evidence and current practice, we need to identify effective strategies to raise knowledge and awareness of guideline recommendations and to ensure that these recommendations translate into routine clinical practice. High-dose monitoring protocols should be developed that alert prescribers to patients currently being administered, or are at risk of receiving, high-dose antipsychotic regimens. Such protocols should also include information concerning the risk-benefit profile for high-dose regimens and offer clear instruction on how to monitor such patients in the longer term.

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