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DRUG BULLETIN

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Antipsychotic Combinations

Graylands Hospital Drug Bulletin 2008 Vol. 15 No. 3 February ISSN 1323-1251

Antipsychotic combinations

Despite the development of efficacious medications for the treatment of schizophrenia, many people do not respond adequately. To address this problem, the use of two or more antipsychotics simultaneously is a commonly employed treatment strategy. Although the use of combination antipsychotics is common in clinical practice, the risks and benefits have not been systematically evaluated to date. As a result, current Australian treatment algorithms including the Royal Australian and New Zealand College of Psychiatry Schizophrenia Guidelines and the Western Australian Therapeutic Advisory Group Antipsychotic Guidelines advise against the use of combined antipsychotics, except for short periods of changeover[1,2]. Most data on antipsychotic combinations are derived from open studies and case series. The few randomised controlled trials that exist are described in this Drug Bulletin.

Incidence of antipsychotic combinations

Data from a Graylands Hospital drug utilisation review in November 2007 showed that 55% of all inpatients were prescribed two or more antipsychotics (excluding pro re nata (prn)). There has been an increasing trend to antipsychotic polypharmacy from 2002, where 37% of patients were receiving two or more regular antipsychotics. This is consistent with data from overseas, where prevalence rates of patients prescribed two or more antipsychotics simultaneously range from 10% to 64%[3].

Reasons for antipsychotic combinations

There are a number of theoretical benefits and reasons cited for antipsychotic combination prescribing, these include:

- Complementary mechanisms of action[4] (e.g. adding an antipsychotic with strong dopamine D2 blockade to a weak D2 blocker)
- Partial replacement of antipsychotic action for drugs with intolerable adverse effects at higher doses[5] (e.g. adding quetiapine to clozapine to minimise metabolic adverse effects)
- Alternative where clozapine cannot be used[6] (tolerability issues, patient refusal)
- Depot antipsychotic 'cover' where compliance with oral medication cannot be assured[7]
- To build on a partial response to monotherapy[4]
- To control symptoms of acute psychosis[4] (prn antipsychotics)
- To prevent exacerbation of psychiatric illness when switching antipsychotics[4]

Reasons against antipsychotic combinations

- Absence of evidence from clinical trials to support the practice[7]
- Additive adverse effects[4] (sedation, anticholinergic, QTc prolongation)

- Decreased compliance with complex treatment regimen[7]
- Increased costs[7]
- Increased risk of pharmacokinetic and pharmacodynamic drug interactions[4]

Contraindicated antipsychotic combinations

Combinations of antipsychotics that significantly prolong the QTc interval are contraindicated because when used together produce an additive effect that may increase the risk for ventricular arrhythmias or cardiac arrest[8,9]. Antipsychotics considered to increase QTc interval significantly include: amisulpride, ziprasidone, chlorpromazine, haloperidol, thioridazine*, pimozide* and droperidol*[9,10]. Combinations of these antipsychotics should be avoided.

Risks of antipsychotic combinations

In addition to the cardiac risks that may exist with contraindicated antipsychotic combinations, there are also a number of potential drug interactions involving certain antipsychotic combinations.

Pharmacodynamic interactions are interactions between drugs at the site of action and cause a change in the pharmacological action. Additive adverse effects are the most common type of pharmacodynamic interaction between antipsychotics. Published reports of severe extrapyramidal side effects, grand mal seizures and prolonged QTc interval have been reported with antipsychotic combinations[5]. Another concern is the unknown risk of developing tardive dyskinesia when antipsychotics are combined[11]. Other additive adverse effects that should be considered include excessive sedation, increased prolactin levels, postural hypotension, anticholinergic and metabolic adverse effects[4].

Pharmacokinetic drug interactions can also occur for certain antipsychotic combinations. Pharmacokinetic drug interactions involve changes in the absorption, distribution, metabolism or excretion of a drug or its metabolites. Most data on antipsychotic drug interactions come from case reports and limited uncontrolled studies, making assessment of the clinical significance of the interactions difficult. However, none of the antipsychotics are potent inhibitors or inducers of the CYP450 isoenzyme system, so significant pharmacokinetic interactions between antipsychotics are unlikely[4].

*No longer marketed in Australia

Evidence on the use of antipsychotic combinations

There are only five randomised controlled trials of currently marketed antipsychotic combinations described in the literature to date. The results from the trials are mixed and are outlined below.

Clozapine-risperidone study one

Josiassen et al[12] conducted a randomised, double-blind, placebo-controlled 12-week trial that compared a dose of up to 6mg of risperidone (n=20) to placebo (n=20) in 40 patients unresponsive or partially responsive to clozapine.

Background characteristics of the two groups were similar, although the average dose of clozapine was higher in the clozapine-risperidone group (529mg vs 402mg) and the initial Scale for Assessment of Negative Symptoms score lower, however these were not statistically significant.

Response to treatment was defined as a 20% reduction on the Brief Psychiatric Rating Scale (BPRS). At the end of 12 weeks, BPRS were reduced significantly in both groups, but the reductions were significantly greater in the clozapine-risperidone group (35% vs 10%).

The adverse effect profile for risperidone-clozapine therapy was similar to placebo-clozapine therapy. Two patients who received 6mg of risperidone experienced akathisia and required a dose reduction. Clozapine levels were not affected by risperidone in this study.

Clozapine-risperidone study two

Yagcioglu et al[13] also conducted a risperidone-clozapine study. In this study, 30 patients who had a partial response to clozapine were randomly assigned to risperidone up to 6mg (n=16) or placebo (n=14).

Baseline characteristics were similar in both groups, except that the mean number of hospitalisations and mean clozapine dose (516mg vs 414mg) were higher in the risperidone group.

The primary outcome measure was a 10% reduction in the Positive and Negative Syndrome Scale (PANSS). Patients in both groups showed significant improvement over a variety of measures at the end of the 6-week period, however patients in the placebo group showed a significantly greater improvement in the primary outcome measure, the positive symptom subscale on the PANSS.

There were no significant differences between the groups in terms of extrapyramidal symptoms, weight gain, QTc prolongation, vital signs or clozapine levels. Patients in the risperidone group experienced greater sedation and had significant increases in prolactin levels.

Clozapine-risperidone study three

Honer et al[14] conducted the largest randomised, double-blind antipsychotic combination study to date, where 68 patients with a poor response to clozapine were randomised to receive either 3mg of risperidone (n=34) or placebo (n=34) over an 8 week period.

Baseline characteristics were similar in both groups.

The primary outcome was reduction in total PANSS score, which significantly improved in both groups but did not differ between the risperidone and placebo groups at baseline or at eight weeks. There were no significant differences between the groups in Clinical Global Improvement Scale severity or improvement, which was the secondary outcome measure.

There were no significant differences in adverse effects reported between groups. Although, there was a mildly greater increase in fasting blood glucose levels in the risperidone group compared to the placebo group.

Clozapine- sulpiride study

A double blind randomised controlled trial conducted by *Shiloh et al*[15]compared the efficacy of a clozapine and sulpiride combination (N=16) with clozapine and placebo (n=12) in 28 patients over 10 weeks. Sulpiride is not marketed in Australia, but is a typical antipsychotic with a similar pharmacological profile to amisulpride.

The mean dose of clozapine was between 400-450mg for both groups and the dose of sulpiride used was 600mg. Although the groups were randomised, the control group had a longer total duration of hospitalization than the experimental group, which may obscure the results. There were no other significant differences between groups in terms of baseline clinical status.

There was a significantly greater reduction in positive and negative symptoms in the combination group, as measured by the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), and the total BPRS. Responses were more pronounced in younger experimental patients with lower baseline SAPS.

One patient in the experimental group experienced a worsening of pre-existing tardive dyskinesia. There was also a significant increase in serum prolactin levels in the experimental group, but not the control group.

Clozapine-chlorpromazine study

A randomised, double-blind flexible-dose 8 week trial compared clozapine (n=17), chlorpromazine (n=20) and a combination of the two (n=20) in 57 patients was described by *Potter et al*[16].

For the clozapine and placebo and chlorpromazine and placebo groups, the maximum dose of clozapine or chlorpromazine allowed was 600mg. For the clozapine-chlorpromazine group, the maximum dose allowed of either was 400mg. The mean doses used were not mentioned in the study. Study design including baseline characteristics of the patients, inclusion and exclusion criteria were not described.
Efficacy was measured on the BPRS. Response to treatment in terms of overall BPRS scores was similar in all three treatment groups. There were, however, significant improvements on the withdrawal, conceptual disorganisation, unusual thought and hostility items in both the clozapine and clozapine-chlorpromazine group when compared to the chlorpromazine group.

Adverse effects of therapy were not reported in this trial.

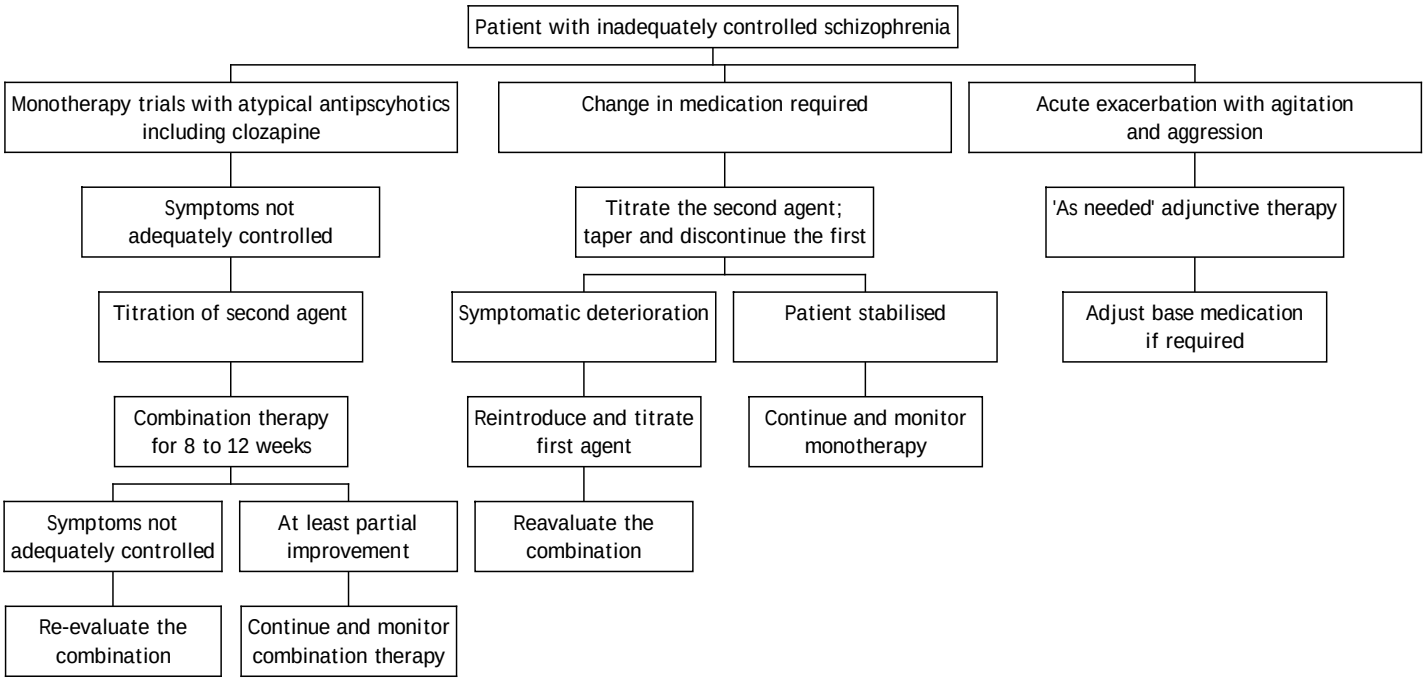
Other evidence

Several open-label studies and case reports show both positive and negative effects for antipsychotic combinations. Due to limitations of this bulletin, these are not discussed in detail, as they are a lower order of evidence than the randomised controlled trials. However, a recent review article found that 90% (9/10) of open trials and 37% (37/75) of case reports documented an overall positive outcome for antipsychotic combinations[3]. The most frequently reported combinations in these studies involved clozapine and risperidone[3].

Limitations of studies

There were two positive studies and three neutral or negative studies examining the efficacy of antipsychotic combinations. Due to small sample sizes and short durations, firm conclusions on the efficacy of antipsychotic combinations cannot be reached.

Figure 1: General recommendations for antipsychotic polypharmacotherapy in patients with schizophrenia



Antipsychotic combination guidelines

It is evident that an increasing number of patients are being prescribed combination antipsychotics, which is contrary to current evidence based guidelines. While there are inadequate data to formulate specific guidelines for the use of combinations, general patient care guidelines have been described in the literature and are outlined in *figure 1*[4,17]. In all cases, monotherapy, including a trial of clozapine should be optimised before utilising combination antipsychotics[4]. Combinations should not be continued unless clear clinical benefits are demonstrated[4]. It must be noted that use of combination antipsychotics represents an 'off-label' use and hence alters professional responsibility and liability to the patient[18].

Conclusions

There is insufficient evidence to support the use of antipsychotic combinations. Patients should be properly classified as treatment resistant by excluding the many confounding factors that may impede clinical response. Clinicians need to ascertain that treatment optimisation is achieved before antipsychotic combinations are implemented.

This bulletin was written by Karolinka Golebiewski and Daphine Ayonrinde and was reviewed by members of the Graylands Pharmacy Department and Dr Dodd

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