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COMBINING ANTIPSYCHOTICS; IS THIS STRATEGY USEFUL?

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SUMMARY

Antipsychotic drugs are commonly combined in psychiatric practice in an attempt to treat schizophrenia. Such practice is widespread, despite the lack of explicit endorsement by many of the main regulatory bodies. There are varying rationales behind combining these potent drugs-either to augment the effect of a drug whose action alone is inadequate for patients with treatment resistant schizophrenia (TRS), or to improve the side effects seen due to treatment. Augmentations are most frequently observed with clozapine, a drug reserved for use when other antipsychotic medications have failed. Several drugs have been chosen as adjuvants, including aripiprazole, sulpiride, amisulpiride and risperidone. A small number of RCTs (randomized controlled trials) have been performed but, despite this data and numerous case reports showing positive changes in symptomatology, Cochrane reviews of available studies have been unable to definitively confirm the efficacy of these combinations, frequently citing the need for larger, longer term, prospective studies.Evidence for benefits of combination therapy on side effects is also inadequate. Some RCTs and case series have shown they can positively alter side effects due to drugs such as clozapine, e.g. metabolic side effects. However, despite many of the combinations being relatively well tolerated, there is some evidence they can cause adverse effects of their own. More evidence is essential as, on the current data alone, it is not possible to make a firm recommendation on the efficacy and safety of antipsychotic combinations. In addition it is vital that the importance of a fair trial of monotherapy at adequate dosages is reinforced to clinicians, so that patients are not put onto these relatively unknown treatment strategies unnecessarily.

Key words: *antipsychotic – combination – augmentation – clozapine – aripiprazole – amisulpride – sulpiride – risperidone – schizophrenia - treatment-resistant*

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BACKGROUND

Combinations of antipsychotic drugs are commonly seen in clinical practice for treatment of schizophrenia, with 15% of out-patients and 50% of hospitalised patients receiving polytherapy(Freudenreich and Goff, 2002). However this practice is not explicitly endorsed by the guidelines of NICE on schizophrenia (NICE, 2014), by the World Federation of Societies of Biological Psychiatry (Falkai et al. 2005), nor the British Association for Psychopharmacology (Barnes and Psychopharmacology 2011). NICE states that regular combined antipsychotic medication should not be initiated, except for short periods of time, such as when changing medications (NICE 2014). Several reasons are proposed for the combination of antipsychotics. Firstly, another antipsychotic may be prescribed if the patient is treatment resistant or is having a limited or unsatisfactory response to monotherapy, in order to augment the drug's action. Alternatively, other antipsychotics may be added to counteract various side effects of effective antipsychotics, which may be impacting patient compliance or may be indicating cessation of therapy. The mechanistic rationale behind how these processes occur is not transparent and as such one would anticipate a strong evidence base to justify the utilisation of polytherapy. However, in order to fully assess the combination of antipsychotics, one would need to assess the effect of each drug separately and then determine the degree to which each drug counterbalances or modifies the other. Furthermore, one would need to measure any adverse or unexpected effects that arise from combining multiple drugs, each with varying modes of action. This is not feasible to perform in full in clinical trials and as such the main investigation that can be undertaken is to compare the effect of a combination of treatments to each treatment separately. This is far from ideal but currently, along with case studies, constitutes the extent of evidence available to determine whether combining antipsychotics is an effective and safe strategy.

AUGMENTATION STRATEGIES

One justification for combining antipsychotics is for augmentation purposes when monotherapy efficacy has been limited, or when the disease remains treatment resistant. The rationale behind the choice of drug combinations may not be clear (Barnes and Psychopharmacology 2011) but NICE only suggests choosing a drug that does not exacerbate existing side effects of the current antipsychotic (NICE 2014). There have been various suggestions as to why an augmentation strategy might be successful. One proposal was that a better

outcome might arise through an increased serum level of the original drug (Tyson et al. 1995). This theory however could not be validated in a study undertaken by (Henderson & Goff 1996). Other guidance suggests the selection of an augmenting antipsychotic which has a complementary receptor profile, e.g. a D2 dopamine receptor blocker, which pharmacologically rationalises their use (Genc et al. 2007, Kontaxakis et al. 2005).

Augmentation of Clozapine

In cases where the response to antipsychotic treatment is unsatisfactory, so called 'treatment resistant schizophrenia' (TRS), clozapine is often chosen. However even on this drug reserved for TRS, 40-70% of patients will not improve to the desired level (Mossaheb & Kaufmann 2012). Augmentation of clozapine is one of the most studied combinations of psychotropic medication. Various antipsychotics have been added to clozapine to examine their effect, to varying degrees of success, with several randomised double-blind, placebo-controlled trials carried out. Commonly antipsychotics such as risperidone, amisulpride, sulpiride, haloperidol and aripiprazole are used as the adjuvant.

Aripiprazole and clozapine

In recent research, aripiprazole has commonly been investigated as an adjuvant to clozapine monotherapy, presumably due to its favourable metabolic side effect profile. Data for the efficacy of such a strategy provides conflicting results. In a 2013 randomised superiority study, augmentation with aripiprazole was compared to haloperidol (Cipriani et al. 2013). They concluded that the only significant difference between haloperidol and aripiprazole augmentation came in tolerability- aripiprazole decreased the tolerability score significantly more than haloperidol. Both augmentation strategies were of similar efficacy. This study is somewhat limited due to its small size and lack of a placebo control, such that it is impossible to conclude if such augmentation improves tolerability vs clozapine monotherapy. However, similar improvements can be seen in other trials, such as that published by (Barbui et al. 2011). They showed that the 3-month Liverpool University Neuroleptic Side Effect Rating Scale total score was significantly higher in those taking aripiprazole than haloperidol, leading to their conclusion that improved perception of adverse effects was seen with aripiprazole. Taken together, these studies suggest that combination therapy may be beneficial in terms of side effect profiles, rather than symptom control.

There is, however, emerging evidence that such combination therapies may also improve patients' symptomatology. A retrospective case series of aripiprazole augmentation in clozapine-treatment resistant schizophrenia patients found significant improvements in psychopathology, functional outcome and metabolic indices after 6 weeks (De Risio et al. 2011). Four cases were reported in whom positive and negative symptomatology improved, whilst major side effects were absent on aripiprazole-clozapine combination therapy (Mossaheb et al. 2010). Furthermore, a retrospective study examined notes of adolescents on an aripiprazole-clozapine combination regime and found that the mean clinical global impression scores improved significantly, suggesting such a therapy may be effective in both adolescents and adults (Bachmann et al. 2009).

A 2008 RCT found that aripiprazole-clozapine compared to placebo did not significantly affect total symptomatology in schizophrenia, but the negative symptom improvement was significantly greater than placebo in secondary analysis (Chang et al. 2008), whilst (Muscatello et al. 2011) described the results of a 24-week double-blind, randomized, placebo controlled trial which found beneficial effects of combination therapy on positive and general symptomatology in a sample of TRS patients. One group (Ziegenbein et al. 2006) found that in 11 TRS patients on an aripiprazole-clozapine combination, the mean BPRS score was significantly reduced in seven patients over 3 months of treatment, with the therapy being well tolerated and allowing for a significant reduction in daily clozapine dose. This may be of benefit in treating so called 'treatment-intolerant' patients, reducing the rates of clozapine side effects such as agranulocytosis, sedation, weight gain, sialorrhoea, and enuresis. Other papers have reported similar dose reductions, such as (Englisch & Zink 2008) who showed that a mean dosage of 20.5 mg/day aripiprazole achieved clinical improvement of psychotic symptoms whilst simultaneously facilitating a dose reduction of clozapine from 476.7 to 425.1 mg/day.

Taken together, these trials suggest that a combination therapy may have some additional efficacy in treating schizophrenic symptoms, although larger scale prospective studies are needed.

Effect of clozapine and aripiprazole combination on side effects

Schizophrenics have a significantly increased risk of cardiometabolic disease leading to morbidity and mortality. Clozapine is often used in TRS, due to its apparent superior efficacy when compared to other atypicals. However, it is reserved for these treatment resistant cases due to its unfavourable side effect profile, with substantial evidence that it worsens cardiovascular risk factors including weight gain, dyslipidaemia, hypertension, and diabetes. These metabolic risks are believed to be at least partly due to its strong blockade of 5HT2C and Histamine H1 receptors (Kroeze et al. 2003) and stimulation of hypothalamic AMPK (adenosine monophosphate activated protein kinase), an enzyme that reverses the effects of leptin. (Kim et al. 2007). Unlike clozapine, aripiprazole has no histaminergic activity, and is a 5HT2C agonist (Herrick-Davis et al. 2000). Moreover, it has some agonist activity at 5HT1A receptors, believed to lower blood glucose levels. Monotherapy with aripiprazole often has minimal impact on a patient's metabolic profile, yet

lacks the efficacy of clozapine. Therefore, there is a mechanistic reasoning behind augmenting clozapine with aripiprazole- the effects of aripiprazole on 5HT2C and 5HT1A receptors may in fact protect against the diabetes, weight gain, and dyslipideamia induced by clozapine. Within the literature, there is some evidence of such beneficial effects. A 2013 randomised, double blind, placebo controlled study (Fan et al. 2013) examined the metabolic effects of adjunctive aripiprazole therapy in clozapine-treated schizophrenics over an 8 week period. Subjects received either 15mg/day aripiprazole or placebo in addition to their standard clozapine, and the impact on metabolism was compared via glucose tolerance test, MR spectroscopy, and DXA scans before and after the trial. The results show a significant improvement in insulin sensitivity, reduced LDL and reduced lean and total body mass. Despite the limitations of the study, including the small number of participants (n=30) and short study period, it does appear to lend support to such an augmentation strategy, with similar benefits found in other papers (Chang et al. 2008). For example, a randomised, double-blind, placebo controlled trial of a stable dose of clozapine augmented with 5-15mg/day of aripiprazole, was performed with patients who were not adequately controlled on clozapine for 3 months or more and had experienced weight gain of 2.5kg or more whilst taking clozapine (Fleischhacker et al. 2010). The authors found that weight loss from baseline was significantly different in patients on aripirazole vs placebo, and factors such as BMI and waist circumference were also reduced. Reductions in total and low density lipoprotein levels were also greater in the aripiprazole group over placebo, however positive and negative symptoms were not significantly affected. These studies therefore lend support to the rationale of improving side effect profiles.

Another potential benefit of combination therapy has been highlighted by a recent case report (Lee and Kim, 2010). Clozapine monotherapy can produce urinary system side effects, particularly enuresis, in 6-43% of patients (Lin et al. 1999). This can lead to non-compliance, and impact on quality of life. However, Lee et al. report on 2 cases where combination treatment with aripiprazole and clozapine effectively treated clozapine-induced enuresis. Larger, more systematic studies are required to provide confirmation of this effect, which may be a key benefit of combination therapy in such patients.

Despite the reported benefits on major metabolic side effects and enuresis, such combination therapies are not without their problems. In the aforementioned paper (Fan et al. 2013), certain side effects were reported in more than 5% of the aripiprazole-clozapine combination group, and these occurred at least twice as commonly as in the placebo controls. These side effects include over-arousal, drowsiness, headache, back pain, itching, nasal congestion, hypersalivation, stomach discomfort, nausea, and vomiting. Although these differences between combination and placebo groups were not statistically significant, and no subjects withdrew from the trial as a result of them, they should be borne in mind whilst deciding on initiating a patient on such combination therapies. There have also been rare cases of psychosis exacerbation following aripiprazole initiation (Mossaheb & Kaufmann 2012) which, although rare, are a concern.

Taken as a whole, trial data shows positive effects of this combination on psychopathology and, to some extent, negative symptoms. Moreover, the combination provides the possibility of reducing a patient's daily clozapine dosage. However, the precise size of these benefits on symptomatology is unclear. Perhaps the more significant beneficial effects come from modification of treatment side effects, with better metabolic outcomes. However, other side effects, such as akathesia and hypersalivation, are repeatedly reported. From current trial data, it is not possible to draw any firm conclusions regarding tolerability and long-term safety of an aripiprazole-clozapine combination. However, the promise of the aripiprazole-clozipine treatment regime warrants further investigation.

Amisulpride and clozapine

Another frequently used adjuvant to clozapine is amisulpride. Since amisulpride has high-affinity binding to D3/D2 dopamine receptors, this dopamine blockade can rationally be added to the relatively non-selective clozapine. Various publications support this rationale, with some evidence of improved symptomatology, along with substantial improvements in side effects. (Cook & Hoogenboom 2004) describe 6 cases where patients on clozapine monotherapy have their treatment augmented with amisulpride. On monotherapy, all 6 patients were suffering from unwanted effects, including hypersalivation, weight gain, and sedation. However, the regime change allowed for a significant clozapine dose reduction, leading to fewer side effects, without a recurrence of positive symptoms. In another case series of 15 patients, 6 had a major improvement of their positive and negative symptoms which, until augmentation, had been treatment resistant, whilst a further 8 had marked improvement in symptomatology. Again, a reduction in clozapine dose was possible, leading to significantly fewer side effects (Zink et al. 2004). In an open, non-randomized study of amisulpride augmentation of clozapine, (Munro et al. 2004) found no worsening of drug effects over a 6 month period, other than a large increase in serum prolactin. They noted no clinical manifestations of the elevated prolactin, possibly as most of the patients were male. After 6 months, this prolactin level was falling again, in line with previous data showing that prolactin levels decrease after an initial spike (Schlosser et al. 2002), and there was a very low drop-out rate amongst participants. Later, a randomised, double-blind, placebo controlled trial was carried out to evaluate amisulpride augmentation of clozapine. The authors noted

improvements only in the scores of secondary outcome measures such as GAF, CGI and MADRS, with primary outcomes (BPRS) failing to show significant improvement. The study was limited due to its small sample size (n=15), hence it was concluded that whilst such therapy may lead to improvements in overall outcome for TRS patients, a larger study with more power would benefit the analysis (Assion et al. 2008).

A recent study suggests that amisulpride-clozapine combination therapy may have benefits beyond improving symptomatology and side effects. (Hotham et al. 2013) found that in a subgroup of 6 violent schizophrenics who responded poorly to clozapine, addition of amisulpiride led to significant reduction in aggression whilst leaving metabolic parameters and side effects largely unchanged. Such a strategy warrants further exploration.

Taken together, the above data implies a positive effect of combination on psychopathology, whilst allowing for a simultaneous reduction in clozapine dosage. However, unlike the aripiprazole-clozapine combination, there seems to be no convincing evidence for a reduction in the metabolic side effects associated with clozapine above and beyond those due purely to a dose-reduction.

Sulpiride and clozapine

Whilst much of the current literature focuses on aripiprazole or amisulpride augmentation of clozapine, there have been numerous studies into using other adjuvant drugs. While combining clozapine with chlorpromazine revealed no benefit (Potter et al. 1989), adding sulpiride to clozapine led to a more than 20% decrease in psychopathology (BPRS total score) and superior improvement compared to placebo (Shiloh et al. 1997). The use of sulpiride, a selective D2 and D3 antagonist, can be rationalized mechanistically as one would anticipate an enhancement of clozapine's D2 receptor blockade. A double blind, placebo controlled study of 28 people found that the group treated with clozapine augmented by sulpiride had significant improvements in positive and negative symptoms, greater than those seen in the placebo group, leading the authors to conclude that a subgroup of patients with chronic schizophrenia may benefit greatly from this augmentation strategy (Shiloh et al. 1997). In a Cochrane review, 3 short term trials and one long-term trial in patients either with TRS or with schizophrenia with distinct negative symptoms were reviewed. The conclusions determined that the combination of sulpiride plus clozapine was more effective than clozapine alone but that further data would be required to make firm conclusions (Wang et al. 2010).

The side effects associated with such a combination are also addressed in the Cochrane review, with reports of extra-pyramidal movement disorders and an increased prolactin, although there were no reports of any clinical features associated with this (e.g. galactorrhoea). Additionally, there is some indication from the trials that patients experience less weight gain and hypersalivation versus clozapine monotherapy, which would be of great benefit. However, the data for such side effects is so small in size that much larger studies are needed before any definitive conclusions can be drawn.

Risperidone and clozapine

In addition to earlier open studies and case reports, a 2005 double-blind RCT showed significantly superior improvement of positive, negative and total psychopathology when adding risperidone of up to 6 mg/day to clozapine (mean dose 400 mg/day) (Josiassen et al. 2005). In contrast to these results another RCT revealed a significantly inferior improvement of positive symptoms by adding risperidone compared to placebo (Anil Yagcioglu et al. 2005).

COMPARING STRATEGIES

Many other drugs are commonly added to clozapine to increase its efficacy and perhaps to reduce side-effects including risperidone, haloperidol, quetiapine and olanzapine. However, most of the work done to investigate has focused on the above drugs. Despite the variability in the findings of each trial and case series, and the frequent conclusion that further, larger studies need to be done to truly expose any efficacy and reveal any adverse effects, it is also of importance to determine whether one combination of drugs is preferable to another.

In 2009, a Cochrane review of 3 small RCTs which evaluated the combination of risperidone, sulpiride, ziprasidone or quetiapine with clozapine was performed (Cipriani et al. 2009). They were unable to reach a conclusion as to whether one augmentation strategy was more effective than another, in part due to the limitations of study design and enactment. Conversely, in a single-blind randomised study comparing clozpine-amisulpride and clozapine-quetiapine combinations, as early as third week of treatment, scoring revealed that improvement was significantly greater with amisulpride than with quetiapine. This led to the authors concluding that amisulpride is effective and well-tolerated (Genc et al. 2007). As previously mentioned, in a similar comparison of aripiprazole and haloperidol augmentation of clozapine, aripiprazole was considered to be better tolerated but there was no significant difference in efficacy (Cipriani et al. 2013). It appears that there is no outstanding preferred treatment that has been demonstrated to be efficacious over other combination therapies. This makes the decisions to choose an augmentation therapy if a practitioner chooses to do so, much harder, as the evidence supporting the combination of treatments is lacking power, and there is little clear guidance from previous studies as to which combination is better tolerated and most efficacious.

Augmentation of other antipsychotics

Clozapine is not the only monotherapy on which augmenting strategies have been attempted, although it is the one on which most trials and case series have been done, due to its frequent selection in TRS cases. Olanzapine is another atypical antipsychotic which has been augmented. In a case series, augmentation of olanzapine with sulpiride improved positive and negative symptoms (Raskin et al. 2000). However, a randomised controlled study of patients with TRS concluded that sulpiride augmentation of olanzapine did not benefit positive or negative symptoms but improved depressive symptoms. This trial contained a small sample size and the therapies were studied over 8 weeks (Kotler et al. 2004). In addition, clozapine can be used to augment other psychotropic medications. For example, (Hung & Chen 2009) reported the case of a patient for whom administration of aripiprazole and risperidone respectively induced severe extra-pyramidal symptoms, but a combination of clozapine and aripiprazole resulted in control of symptoms and reduced EPS. Obviously this is a single case study, making it impossible to draw any conclusions. However, it does point to another potential benefit of combination therapies. Each combination will require thorough investigation, as results for one combination are not transferable to others due to the vast array of receptor binding profiles.

RECOMMENDATIONS

Currently available evidence for antipsychotic polypharmacy is insufficient to make definitive conclusions regarding efficacy and safety. There are multiple case reports, open trials, and even RCTs, yet they all suffer from issues regarding study numbers, power, and duration of follow up. However, there are also some more fundamental issues to overcome. Before any clinician considers commencing polytherapy, the patient must first undergo a fair monotherapy trial, with a variety of antipsychotics trialed at an effective dose. Only after these fail do the devastating effects of the illness outweigh the added risks and costs of polypharmacy. Moreover, this highlights a potential flaw in many publications surrounding the issue of polypharmacy. If a patient's initial monotherapy is at a clinically ineffective dose, a positive outcome following augmentation should not be thought of as superiority of the combination, but rather as the attainment of a clinically effective dose. Additionally, should improvement follow the addition of drug B to drug A, there are a number of possible mechanisms. Any positive response may be a consequence of more time on drug A, related only to the effects of drug B, due to a pharmacokinetic interaction between the two, or pharmacodynamic synergy between both antipsychotics. Determining which of these mechanisms is responsible is not likely to be feasible in clinical trials, although only the last explanation would warrant long term continuation of combination therapy.

There are also issues surrounding long-term safety of such combination therapies. By giving two drugs, there is clearly a greater risk of drug-drug interactions, which may have long term effects on morbidity and mortality not yet obvious from the limited, relatively short term trial data available. The addition of a second drug may also impact on patient adherence due to increased treatment complexity.

CONCLUSION

Current evidence does not allow for any endorsement of antipsychotic polypharmacy in routine practice. However, it is also not possible to confidently state that such a strategy would never have a reasonable risk-benefit balance for a given patient. Thus, combined antipsychotics should be prescribed on an individual basis, as a closely monitored, time-limited trial, considered only after a lack of response to several adequate trials of antipsychotic monotherapy, including clozapine. Future studies will undoubtedly shed more light on the potential benefits of combination therapy, and hopefully open up new avenues of treatment for patients suffering from not only their illness, but the effects of essential treatment.

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