Combination of clozapine with an atypical antipsychotic: a meta-analysis

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Abstract

Purpose - *The aim of this meta-analysis is to review the efficacy of atypical antipsychotics in combination with clozapine. Previous meta-analysis have assessed the use of both typical and atypical antipsychotics in combination with clozapine, combination treatment being withheld only for those patients deemed treatment resistant.*

Design/methodology/approach - *We conducted the meta-analysis in accordance with the Preferred Reporting Items for Sytematic Reviews and Meta-Analyses (PRISMA) guidelines. The following inclusion criteria was applied; i.) Trials and reports that were written in English; ii.) An antipsychotic was added to clozapine; ii.) The non-clozapine antipsychotic was atypical; iii.) Trials were randomised, double-blind placebo controlled; iv.) Trials were conducted between the years of 2000 and 2015*

Findings - *The effect sizes gained from analysis showed a small benefit of combination therapy over clozapine monotherapy.*

Research limitations/implications - *The initial trial search unveiled 1,412 studies. After the inclusion and exclusion criteria was applied, 10 trials were used in this meta-analysis.*

Practical implications - the recommendation of this analysis that alternative medications be sought in order to treat patients who have a sub-optimal response to clozapine with a combination other than two second generation antipsychotics. This route should only be used once all other treatment options have been exhausted

Originality/value - *This work extends existing meta-analysis by incorporating data from more recent trials.*

Keywords Schizophrenia, Atypical, Antipsychotics, Combination, risperidone, aripiprazole

Paper type Research paper

Introduction

It is generally accepted that over the course of their lifetime, about 1% of the UK population will develop schizophrenia, although one study suggests the true figure may be closer to 0.72% (Saha et al., 2005). Furthermore, we should be clear as to the working definition of treatment resistant schizophrenia as defined by Howes *et al* in their systematic review of randomized antipsychotic clinical trials where definitions of treatment resistance were extracted (Howes et al., 2017).

Clozapine is an atypical antipsychotic reserved only for those patients who have been adequately trialled unsuccessfully on at least two previous antipsychotics(NICE178, 2014). The failure is usually due to hematological side effects (Pirmohamed and Park, 1997). One of several side-effects that can be attributed to non-clozapine atypical antipsychotics. A patient should be trialled on clozapine for a minimum of 8-10 weeks before being classed as treatment resistant.

The term *Treatment Resistant Schizophrenia* was first coined by Kane et al (Kane et al., 1988), where it was determined that those patients who have not responded to two previous antipsychotic therapies should be given clozapine in doses equivalent of up 1000mg of chlorpromazine. The benefits of clozapine include reduced risk of suicide (Meltzer et al., 2003) and overall mortality

(Sernyak et al., 2001) in schizophrenia. Antipsychotic polypharmacy in which more than one antipsychotic drug is used to treat a patient's schizophrenia is becoming more common in practice (Langan and Shajahan, 2010), however it is advised against due to the increased risk of side effects such as sedation, weight gain, extra-pyramidal side effects and blood disorders (Dold and Leucht, 2014). It has been recommended by the National Institute of Clinical Excellence (NICE) that combining antipsychotic medication should not be initiated unless it is to change one medication to another, even this should only be for a short period of time (NICE82, 2008). However, despite the risks of polyphramacy, the basis for using clozapine is because of the association with significant clinical improvement relative to usual treatment, along with reduced suicidal thoughts and reduced rehospitalization rates.

The aim of this meta-analysis is to review the efficacy of atypical antipsychotics in combination with clozapine.

Methods

This meta-analysis was devised in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Databases searched include; Science Direct, PubMed, PubMed Central, Cochrane Library and the clinical trials register. The search for material was updated in June 2017. Key terms used in the search were; clozapine, augmentation, combination, treatment-resistant schizophrenia, refractory schizophrenia as well as the generic names of all the atypical antipsychotics.

Inclusion criteria.

The following inclusion criteria was applied; i.) Trials and reports that were written in English; ii.) An antipsychotic was added to clozapine; ii.) The non-clozapine antipsychotic was atypical; iii.) Trials were randomised, double-blind placebo controlled; iv.) Trials were conducted between the years of 2000 and 2015.

Exclusion criteria.

Trials were excluded on the basis; i.) Drugs were not in combination with clozapine but were a comparison; ii.) Drugs were compared to each other and not a placebo; iii.) Trials were open and single-blind; iv.) Case Reviews.

Statistical analysis.

Particular rating scales were used when developing the forest plots in order to obtain an effect size, we used the random-effects model as we believed the different studies had different effect sizes. The fixed-effect model assumes some heterogeneity of effect and that every study has a common true effect size, this cannot be assumed and the random-effects model is more appropriate under these circumstances. The Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein and Opler, 1987) and The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) were used to assess the efficacy of the drugs on schizophrenia. Some papers used a mixture of scales and some used only PANNS or BPRS, we used the method devised by Leucht to convert between them (Leucht et al., 2013). The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen et al., 1990) were used for the effect sizes of both negative and positive schizophrenic symptoms respectively.

Cohen's D was used to assess the impact of the treatments (Ferguson, 2009), 0.2, 0.5 and 0.8

showing either a small, medium or large effect respectively. Confidence intervals and Standardised Mean Deviations (SMD) were presented in the forest plots. A funnel plot and quantile-quantile plot was also generated to assess publication bias of the trials included in the meta-analysis. Comparison of trials lasting < 10 weeks and >10 weeks were compared to assess the impact of trial length on treatment efficacy as well as comparison of the same atypical agents.

The R statistical analysis software was used in conjunction with the RStudio Editor, the Metafor package was used in the generation of the forest plots and the funnel plot using a random effects model. We used the Standardised Mean Difference, giving the meta-analysis the ability to compare the outcome of all the trials together regardless of the rating scale. Forest plots were generated in order to gain an overall effect size for the combination of the atypical antipsychotic with clozapine in regards to overall symptoms.

Results

The initial search revealed 1,412 studies, after the inclusion and exclusion criteria was applied, a total of 10 studies with 588 patients (age range 18-65, average 35.3, 378 males and 210 females) were included. Randomised controlled trials included four atypical antipsychotics combined with clozapine, sertindole (n=1), olanzapine (n=1), aripiprazole (n=3) and risperidone (n=5) against a placebo. Trial characteristics used are given in figure 1.

The effect size (95% Confidence Intervals) in figure 1 for the impact of treatment on overall symptoms was -0.30 [-0.57, -0.02], for the impact of treatment on negative symptoms was -0.18 [-0.46, 0.11] in figure 3 and the impact of treatment on positive symptoms was -0.25 [-0.81, 0.30] in figure 4. The funnel plot, figure 2 and the quantile-quantile plot in figure 3 showed no obvious publication bias.

The standardised mean differences for overall change in BPRS/PANSS, negative and positive symptoms found were of small improvement, -0.19, -0.18 and -0.25 respectively. This showed that the combination of clozapine with a second generation antipsychotic, seen in figure 1, 2 and 3 showed a small improvement in patient‘s symptoms. So far this is the only meta-analysis to look solely at the efficacy of second generation antipsychotics combined with clozapine. Previous analyses (Taylor et al., 2012) looked at the combination of both typical and atypical antipsychotics with clozapine treatment. Similar to this study, an effect size of 0.239, showed small effect of co-therapy over monotherapy. Comparison of effect sizes of both first and patient symptomatology showed there is no distinct difference between the efficacy of either class of drugs.

A systematic review (Correll et al., 2009) assessed antipsychotic combinations of first and second generation antipsychotics including clozapine as a part of the combination against monotherapy in schizophrenia. This study showed that antipsychotic combination therapy was favourable compared to the control. In all the studies patients had been diagnosed using DSM-IV, and had been trialled, unsuccessfully on two or more previous antipsychotics before the initiation of clozapine.

4.1 Overall change in BPRS/PANSS

The forest plot in figure 1 was generated using a random effects model. It can be seen from the effect size that only two trials (Muscatello et al., 2011) and (Fleischhacker et al., 2010) completely favored co-therapy compared to the other trials in our study.

Study (year)	Characteristics	Trial length (weeks)	No of patients starting trial (M/F)	Control / placebo	Mean age years (range)	Drug patients stopped prior to trial or medications which warranted exclusion	Drugs patients had access to while on trial	Applicable outcomes measured
Yagcioglu (2005) Turkey	Patients were diagnosed with schizophrenia using DSM-IV. Entry into the trial was based on total PANSS score of at least 72, a CGI-S score of at least 4 and at least 3 on any 1 of the PANSS POS (0-7) scale. Patients who had been on clozapine for at least 6 months were entered into the trial. Clozapine doses ranged between 300-900 mg/day. Risperidone up to 6 mg/day was used for patients in the control arm of the trial.	6	30 (20/10)	15 in control and 14 in placebo	35.3 (18-55)	mood stabilisers, lithium, antidepressants, and/or antipsychotics other than clozapine.	Benzodiazepines (clonazepam 0.5 - 2.0 mg/day) were used to treat anxiety, and biperiden (2-6 mg/day) was used to treat EPSE.	PANSS
Josiassen (2005) USA	Patients were diagnosed with schizophrenia or schizoaffective disorder using DSM-IV. Clozapine use for 12 weeks with poor response. BPRS of 45 or 4 or more criteria on 2-4 BPRS positive symptom items. Clozapine dose of 528mg/day for risperdone group and 402.5 mg/day for placebo.	12	40(35/5)	20 control and 20 in placebo	40.3 (20-65)	N/A	N/A	BPRS, CGI, SANS
Honer (2006) Canada, Germany, China, UK	Patients were diagnosed with schizophrenia using DSM-IV. Entry into the trial was based on a total PANSS score of 80 or more, at least 4 or more on CGI and a SOFAS score of 40 or less. Patients had been on a stable dose of clozapine 400 mg/day or more for at least 12 weeks. Risperidone was given to the control group at a mean dose of 2.95 mg/day.	18	68 (50/18)	34 in control and 34 in placebo	37 (18-65)	Treatment with clozapine for movement disorder or of intolerable side effects from other medications. Previous treatment with risperidone. Patients were required to discontinue any drugs other than clozapine (mood stabilisers or anti-depressants or anti-convulsants) two weeks before the trial.	Any drugs being used to treat stable medical issues were permitted.	PANSS
Freudenreich (2007) USA	Patients were diagnosed with schizophrenia using DSM-IV. Entry into the trial was based on the patients have a PANSS score of greater than 60. Patients in the trial had been treated with clozapine for at least 6 months and had been on a stable dose for at least 8 weeks. Clozapine doses ranged from 200-700 mg/day. A 4 mg/day fixed dose of risperidone was given to those patients assigned to the control group.	6	24 (21/3)	11 control, 13 placebo	42.3 (27-55)	N/A	N/A	PANSS and SANS
Chang (2008) Korea	Patients were diagnosed with schizophrenia using DSM-IV. Entry into the trial was based on patients have a BPRS score of at least 35 or more than two on the SANS rating. Patients in the trial had been treated with clozapine at least one year prior to the study with at least 8 weeks on a stable dose of 400 mg/day or more. Patients in the treatment arm of the trial were given an aripiprazole dose of at least 30 mg/day.	8	62 (49/13)	30 in control and 32 in placebo	33.2 (18-65)	Prior history of non-response or tolerance to aripiprazole, participation in a clinical trial of another investigational drug within 3 months of the study	Concomitant medications for stable medical conditions including antidepressants, anticholinergics and benzodiazepines.	BPRS and SANS
Fleischacker (2010) USA, France, Finland, UK, Austria	Patients were diagnosed with schizophrenia using DSM-IV-TR criteria such as weight gain of more than 2.5Kg and safety issues on clozapine. Clozapine dose of 362.6 mg/day and 383.8 mg/day for aripiprazole.	16	205(106/99)	106 control and 99 in placebo	40.5 (18-65)	patients at risk of suicide excluded. Exculded for use of psychoactive substance use disorder.	Benzodiazepines and anticholinergics were allowe any time and also sleeping aids. Antidepressants and mood stabilizers were also allowed if prescribed before entry into study.	PANNS, CGI and weight
Weiner (2010) USA	Patients were diagnosed with schizophrenia using DSM-IV. Entry into the trial was based on patients having a total BPRS score of 45 or more, a CGI score of 4 or more and a BPRS positive symptom score of 8 or more. Patients were required to have had an adequate clozapine trial for 6 or more months on a dose that produced a plasma level of 350 mg/mL of more. Risperidone was given at 4 mg/day.	16	69 (44/25)	33 in control and 36 in placebo	44.4 (18-65)	Patients treated previously with adjunctive risperidone at more than 8 mg/day for at least 6 weeks were excluded.	N/A	BPRS and SANS
Muscatello (2011) Italy	Patients were diagnosed with schizophrenia using DSM-IV. Entry into the trial was based on patients have a BPRS score or 25 or more. Patients had been on the highest tolerable dose of clozapine for at least one year and doses in the range of 200-450 mg/day had been stable for at least one month. Aripiprazole was given at an initial dose of 10 mg/day and increased to 15 mg/day.	24	40 (23/17)	20 in control and 20 in placebo	31.9 (25-38)	N/A	Patients were allowed to take lorazepam up to 5 mg/day for insomnia and agitation.	BPRS, SANS and SAPS
Nielsen (2012) Dennmark	Patients diagnosed with schizophrenia and treated with clozapine for 6 months and scored at least 65 on PANNS at baseline. Doses of clozapine were 394mg/day for sertindole and 435.o mg/day for placebo.	12	50(30/20)	25 in control and 25 in placebo	41.8 (18-65)	N/A	Benzodiazepines and anticholinergics were allowe any time and also sleeping aids. Antidepressants and mood stabilizers were also allowed if prescribed before entry into study.	PANNS, UKU and CGI
Constantine (2015) USA	Patients were diagnosed with schizophrenia using DSM-IV-TR criteria who had been receiving 2 medications concurrently for at least 90 days.	52	104(50/54)	25 in control and 41 in placebo	43.9 (18-64)	Patients who had recent hopspitalization or emergency room visits in 90 days.		PANNS and CGI

Table 1: Details of the ten trials used in the meta-analysis.

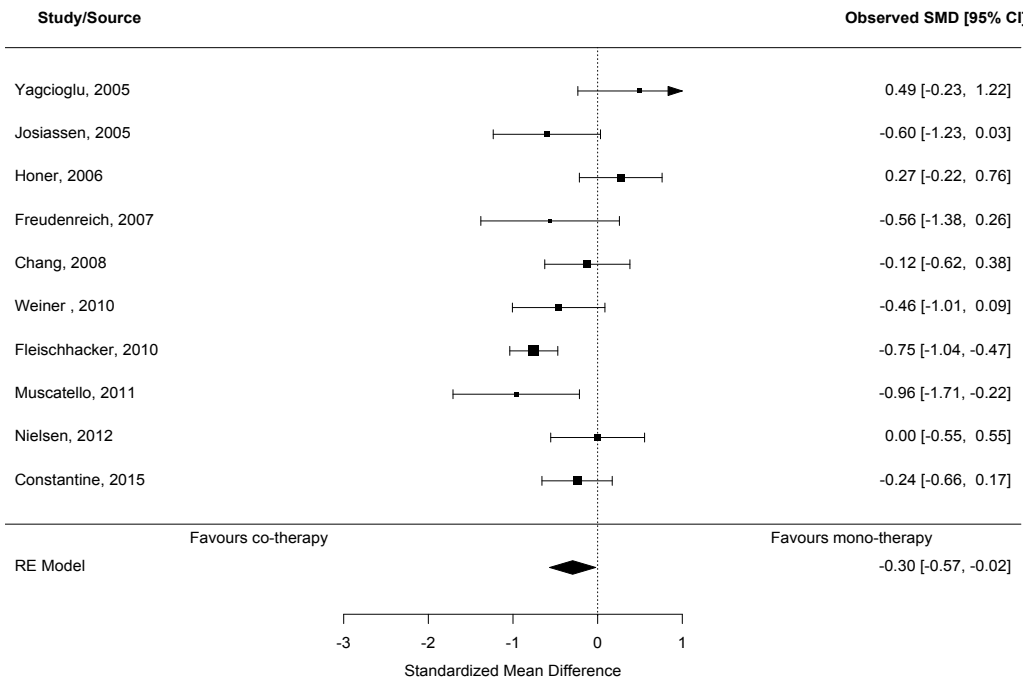

Figure 1: Forest plot indicating effect of each trial and overall outcome using a random effects model

The forest plot in figure 1, indicates the standardised mean differences (SMD) for the individual outcomes of each trial, the black diamond indicates the overall SMD for the meta-analysis (-0.30), this effect size indicates a small favour of cotherapy. Examining the results from previous meta-analyses in this area and systematic reviews, the value does not differ greatly (Taylor et al., 2012) and (Taylor and Smith, 2009), indicating that overall the combination of antipsychotics, which is often used in clinical practice, is only of small effect (Correll et al., 2009).

Figure 2 displays a funnel plot which is intended to highlight publication bias, larger studies with higher power are placed towards the top and lower powered studies are placed near the bottom. The funnel plot, is generally symmetrical with three trials outside the funnel triangle (Fleischacker, Honer and Yagcioglu) indicating heterogeneity but not necessarily publication bias.

Common flaws in treatment during trials which may affect bias shown in the funnel plot include; failure in randomization, poor blinding or large number of patients which are lost through follow up (Taylor and Smith, 2009). The heterogeneity of this meta-analysis was moderate-to-high (I^2= 61.82%) variability within the trials, using a random effects model. The full statistics output for the analysis is given below:

Random-Effects Model (k = 10; τ^2 estimator: Random Effects)
τ^2 (estimated amount of total heterogeneity): 0.1120 (SE = 0.0896)

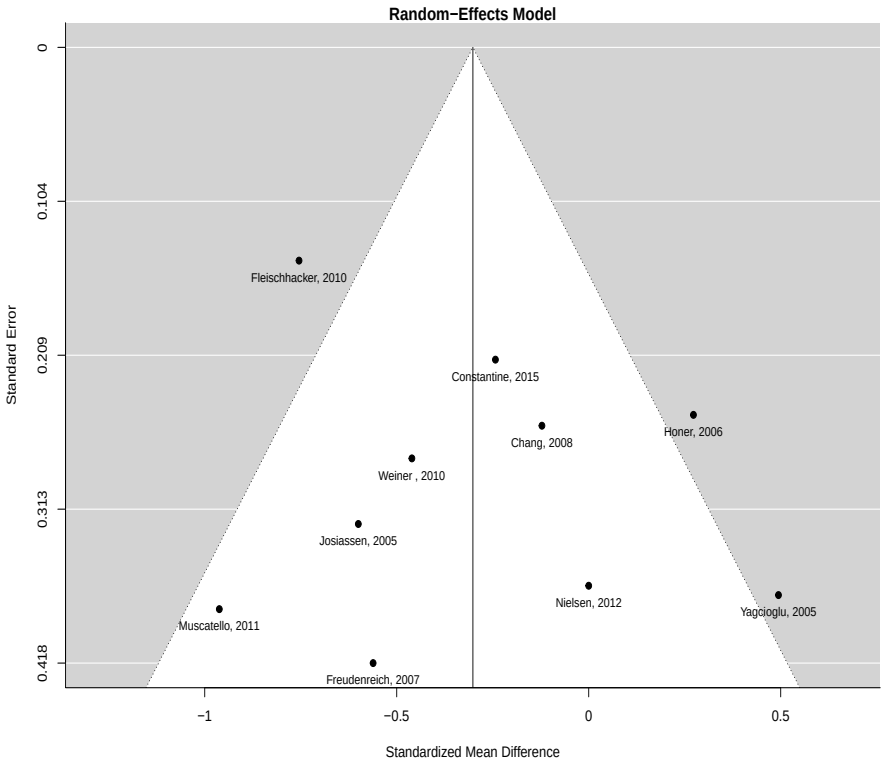

Figure 2: Funnel plot for the random effects model, indicating heterogeneity for some studies

τ (square root of estimated τ^2 value): 0.3346
I^2 (total heterogeneity / total variability): 62.11%
H^2 (total variability / sampling variability): 2.64

Test for Heterogeneity:
Q(df = 9) = 25.3604, p-val = 0.0026
Where: τ is the between studies standard deviation and τ^2 is the between studies variance of the true effect sizes, I^2 is the ratio of true heterogeneity to total observed variation, H^2 is the is the square root of the chi-square heterogeneity statistic divided by its degrees of freedom, Q is Cochran's statistic for estimating a measure of weighted squared deviations. Interpreting the values for I^2 are usually low at 25%, moderate at 50% and high at 75% based on work by Higgins (Higgins et al., 2003).

We investigated these potential problems further by plotting a quantile-quantile diagram, the studies should lie on the diagonal line with slope of 1, going through the (0,0) point. Deviations from this may indicate that (a) the (residual) heterogeneity in the true effects is non-normally distributed, (b) there are subgroups in the data that are not adequately modeled, and/or (c) that publication bias is present. We observe that the most of the studies are close the the diagonal and the three studies outside the original funnel plot are well within the confidence intervals.

4.2 Trials with aripiprazole
For the trials where aripiprazole combinations were used both groups showed favour of combi-

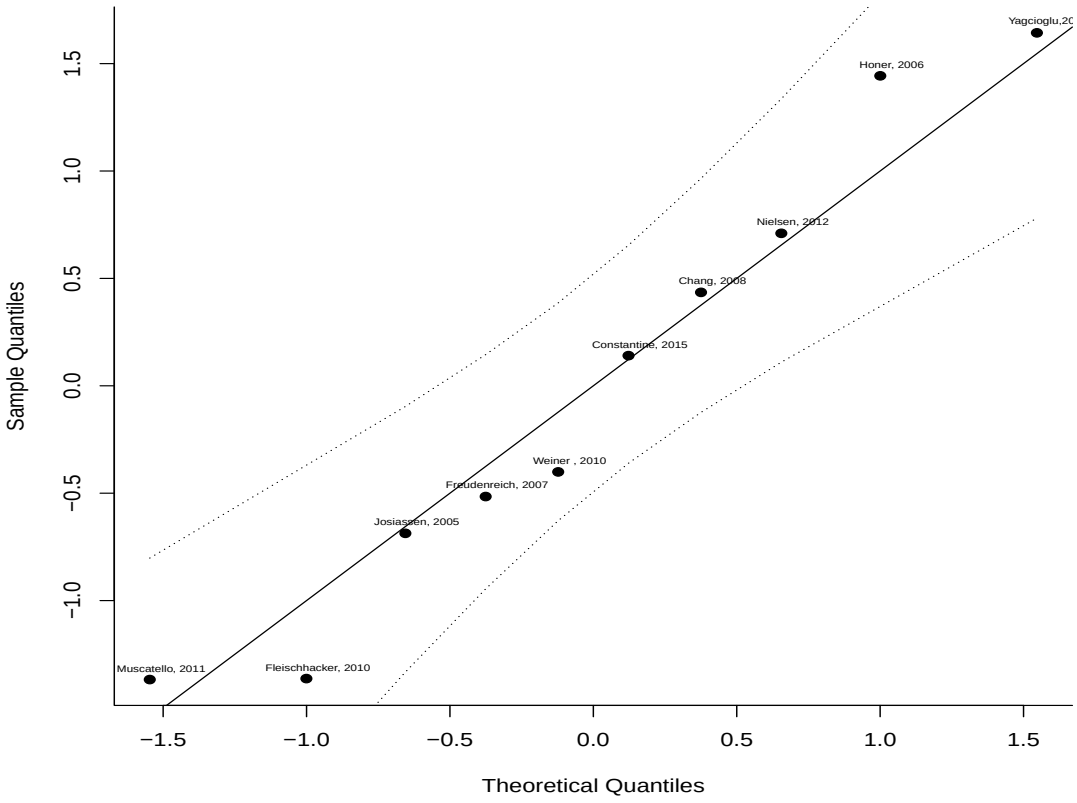

Figure 3: quantile-quantile plot of study heterogeneity

nation therapy. (Muscatello et al., 2011) Only one trial showed significant change in effects size compared to all trials within this meta-analysis. This could be due to several factors; a)patients may have been stabilised longer on clozapine although have partial response to the drug, b)longer trial length (24 weeks) c) Higher aripiprazole dose. Patients in this trial were allowed to take Lorazepam 5mg/day for insomnia or agitation. This may not have been acceptable in the other trials in this meta-analysis. However patients did not receive any antidepressants or anticonvulsants two months prior to this trial.

Aripiprazole augmentation in the second trial (Chang et al., 2008) had an effect size of -0.12, which implied a small change in the rating scale used, however in the conclusion of the study it was stated there was no improvement to overall BPRS rating however had a larger effect on patient‘s negative symptoms. In comparison to Muscatello, the study lasted only 8 weeks. This may have potentially affected the outcome of the trial even though it has been stated that 6 weeks is sufficient enough time for a patient to be treated with an antipsychotic. The study by Fleischhacker was included our analysis, (Fleischhacker et al., 2010) this work investigated the effect of combined aripiprazole and clozapine on the weight in patients. PANSS was measured in patients as a secondary outcome, this availed no effect in the forms of clinical efficacy. Primary outcomes of this trial included mean change in body weight from baseline to week 16. From the

primary outcome, aripiprazole-treated patients also showed a statistically significant difference in weight loss as well as a reduction in BMI, total and low-density lipoprotein. As weight gain and susceptibility of metabolic disorders increases when a patient is taking clozapine, the outcome of this trial is beneficial for patients.

Aripiprazole has a slightly different mechanism of action compared to other atypical antipsychotics. It is a partial D2 and 5-HT2 agonist which means it does not bind fully to the receptor. Clozapine binds to several receptors, D1-D5 and 5-HT2, as well as other receptors. Due to aripiprazole not fully binding to the receptor site, it is not competing with clozapine for that site and it is not causing the molecules to dissociate. The slight difference in the receptor profiles of these two drugs indicates why both trials had an effect size in preference of the combination treatment.

4.3 Trials with risperidone

In the trials where risperidone was combined with clozapine, it can be seen none of effect sizes of these trials is as significant as Muscatello's (Muscatello et al., 2011). Two trials (Weiner et al., 2010) and (Freudenreich et al., 2007) showed favour of the clozapine and risperidone combination. However, compared to the other two studies (Honer et al., 2006) and (Yagcioglu et al., 2005) where monotherapy was favoured there was no difference in the dose of the add-on drug which was 4mg/day. Therefore it is with difficulty to say where the changes in efficacy have arisen from. Randomised, controlled trials involving risperidone lasted a range of 6-16 weeks. Trials which lasted less than ten weeks did not show efficacy for the combinations used. risperidone, like clozapine, is an antagonist at both D2 and 5-HT2 receptor sites (Golan et al., 2007). Both drugs are competing for the same sites to bind to, this indicates why only some trials may have had an effect size in favour of co-therapy.

The problems with risperidone may have arisen where the patients had previously been trialled on this drug and were deemed unresponsive, or the patient was unable to tolerate the combinations. Another factor which may have affected trial outcome, was the sample size. Those with the diagnosis of schizophrenia may respond to a first or a second generation anti-psychotic without ever having to be treated with clozapine which is reserved for patients deemed to have refractory schizophrenia. Therefore, those patients who are treated with clozapine is a smaller sample than those who may have responded to prior treatment. This indicates that unless a multicentre trial, large sample sizes in randomised controlled trials where patients are treated with clozapine may be very difficult to find.

4.4 Trial with Olanzapine

The study undertaken by Constantine involved randomly switching the co-therapy patients to a clozapine + placebo, leaving the other patients to a clozapine+olanzapine therapy (Constantine et al., 2015). The initial motivation for this trial was to overcome certain polypharmacy issues involved with the treatment of schizophrenia. The followup investigation was longer than most trials and at the end of 360 days the patients PANNS score was more or less stable. The trial tended to suggest that those who stayed on co-therapy had better outcomes, while those who switched to clozapine alone appeared to have a n increase in positive symptoms

4.5 Trial with Sertindole

The study by Nielsen using a combination of clozapine and sertindole did not improve or worsen their cognitive functions, they discuss that sample size may be an issue but admit their studies results are comparative to the other studies (Nielsen et al., 2012) Their choice of sertindole was

motivated by it's low levels of sedation and seemed therefore an ideal cotherapy. However, after the 12 week trial was over, the results did not indicate any correlation between cognitive function and psychopathology as highlighted by the PANNS and GAF and CGI scores.

4.6 Trials lasting longer than 10 weeks and Trials shorter than 10 weeks.
Work by Taylor compared trials of less than 10 weeks in length to those longer than 10 weeks. A meta-regression plot was produced in order to see the relationship between the effect size and trial length (Taylor et al., 2012). Randomised controlled trials lasting longer than ten weeks showed a marginal increase in effect size (-0.223) when compared to those less than ten weeks in length (-0.103). This indicates that for a trial where clozapine is combined with a second drug, a longer trial, ideally $\geq$10 weeks, this coincides with guidance (NICE178, 2014) recommending a trial of combination treatment to last at least 8-10 weeks. This will allow patients to become accustomed to adhering to two different medications.

When comparing studies which lasted longer than 10 weeks (Muscatello et al., 2011) and (Weiner et al., 2010) it was possible to see a larger effect size when compared to those of a shorter duration. Both trials lasting long than ten weeks exhibited an effect size larger than -0.19, this indicates that the efficacy of the trials ranged from moderate to large. Effect size may have been affected if sample size was smaller than 30, or if the trial was biased in any way. Barbui et al (Barbui et al., 2009) found within the systematic review the effect size of none blinded trials was larger than the trials where double blinding was involved.

Studies that lasted less than 10 weeks varied in their favour of combination therapy over monotherapy. Two studies (Chang et al., 2008) and (Freudenreich et al., 2007) showed favor of combination treatment over monotherapy. Monotherapy was favoured in the other two studies (Honer et al., 2006) and (Yagcioglu et al., 2005). Again this may have been due to several factors; firstly, the patient may not have responded to the medication. Secondly, the patient may have been non-adherent or have a problem with compliance. Thirdly, the patient may have insufficient clozapine levels due to taking a second atypical antipsychotic.

4.9 Limitations
There are several limitations to this meta-analysis including the small number of patients recruited to several of the trials. The mean sample size of the trials was 69.2 (range 24-204, median 56), trials of less than 30 participants do not reflect well in effect size calculations due to the small range of results. This is likely to give the trial less power to change or show any significance, small trials are likely to be more biased via giving a larger effect than large multicentre studies.

Another limitation of the analysis is the small number of trials conducted using atypical antipsychotics in combination with clozapine for treatment resistant patients. Only studies including aripiprazole (3), sertindole (1), olanzapine (1) and risperidone (5) could be analysed.

This analysis looks at the efficacy of a second generation antipsychotic drug combined with clozapine for patients with refractory schizophrenia. Other therapies have been used to treat refractory schizophrenia with either some or little improvement in patient's symptoms. These include; ECT, CBT, combinations with different classes of drugs; mood stabilisers and antidepressants. It was not possible nor appropriate to include such studies into our analysis

Conclusions

The treatment of refractory schizophrenia is a common activity for mental health professionals. Schizophrenia places demands on and adversely effects the quality of life, social aspects and the patients ability to work. It is often a disorder that is associated with co-morbidities. Buckley found that co-morbidities such as substance abuse, anxiety, depression, panic disorder, post-traumatic stress disorder and obsessive compulsive disorder were highly prevalent among schizophrenic patients (Buckley et al., 2009). These have further effects upon the patient from medication to quality of life (Dold and Leucht, 2014).

Other factors to consider in regards to combination treatments, is the possible increased risk of adverse reactions when combining two drugs from the same class. All second generation antipsychotics come with an increased risk of weight gain and metabolic side effects. The only exception to this was (Fleischhacker et al., 2010) where the addition of aripiprazole to clozapine reduced weight, BMI and lipid profile in patients. Finally, it has been found through statistical techniques that combination of a second generation antipsychotic with clozapine, the gold-standard treatment for schizophrenia, is only marginally beneficial. The therapy may show some improvement within individual patients however, the overview of the therapy as a whole, is not beneficial for the group. Therefore, it is the recommendation of this analysis that alternative medications be sought in order to treat patients who have a sub-optimal response to clozapine with a combination other than two second generation antipsychotics. This route should only be used once all other treatment options have been exhausted.

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