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DOI link to article:

https://doi.org/10.3310/hta21490

Date deposited:

31/10/2017

AMISULPRIDE AUGMENTATION OF CLOZAPINE FOR TREATMENT-REFRACTORY SCHIZOPHRENIA: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Background

A second antipsychotic is commonly added to clozapine to treat refractory schizophrenia, notwithstanding limited evidence to support such practice.

Aims

To examine the efficacy and adverse effects of this pharmacological strategy.

Method

Double-blind, placebo-controlled, 12-week RCT of clozapine augmentation with amisulpride, involving 68 adults with treatment-resistant schizophrenia and persistent symptoms despite a trial of clozapine.

Results

By 12-week follow-up, amisulpride-treated participants were more likely to fulfil criteria for clinical response (OR 1.17 (95% CI 0.40, 3.42)) and had a greater reduction in negative symptoms, although neither finding was statistically significant, as well as a higher frequency of adverse effects, including cardiac side effects.

Conclusions

Any modest benefit with the clozapine-amisulpride combination may be delayed beyond the 4-6 week follow-up considered adequate for acute psychotic episodes. The associated side-effect burden has implications for the safety and tolerability monitoring of clozapine augmentation with a second antipsychotic in clinical and research settings.

Declaration of interest

Funding for this trial was provided by the Health Technology Assessment programme of the National Institute for Health Research. T.R.E.B. has acted as a member of scientific advisory boards for Sunovion and Otsuka/Lundbeck in relation to antipsychotic medication. C.P. has participated in a neurosciences advisory board in relation to neurodegenerative diseases for Eli Lilly.

P.K. received personal fees from Otsuka/Lundbeck for speaking at an educational meeting, received support in attending an international conference from Janssen, and acted as a member of a scientific advisory board for Otsuka/Lundbeck.

M.H. received a speaker’s honorarium from Otsuka pharmaceuticals.

H.B. received personal fees from Janssen Cilag, Lundbeck, and Eli Lilly.

P.H. received personal fees from Lundbeck for consultancy and lecturing, from Otsuka pharmaceuticals for consultancy, lecturing and conference support, from Sunovion for consultancy, lecturing and conference support, from Teva for consultancy, and from Quantum Pharmaceuetical for consultancy. PH also received speaker's honoraria from Roche and Tekeda.
All other authors have nothing to disclose.

INTRODUCTION

In around a third of people with schizophrenia, the illness shows an insufficient response to standard treatment with antipsychotic medication. Clozapine is the only antipsychotic medication with robust evidence for efficacy in strictly-defined treatment-resistant schizophrenia (Warnez & Alessi-Severini 2014). But even then, an adequate response is seen in only 30-60% of patients prescribed this drug. (Lieberman et al 1994, Chakos et al 2001). To improve efficacy, clinicians commonly augment clozapine with another antipsychotic, although the evidence base supporting such a strategy is weak (Barbui et al 2009, Muscatello et al 2014). The National Institute for Health and Care Excellence guideline for the treatment of schizophrenia (NICE 2009) supports clozapine augmentation with a second antipsychotic when there has been an inadequate response to clozapine alone, noting than an adequate trial of such an augmentation might need to be up to 8–10 weeks, reflecting the findings of our own meta-analysis of relevant RCTs (Paton et al 2007).

Clozapine is associated with potentially dangerous side effects such as agranulocytosis, myocarditis/cardiomyopathy and seizures as well as relatively common problems of potentially serious concern such as weight gain, metabolic side effects and constipation. Thus, the criteria for selecting an augmenting antipsychotic drug might reasonably include a low liability to compound these side effects. Given its perceived tolerability and safety advantages in relation to extrapyramidal side effects (EPS), weight gain and metabolic side effects, amisulpride may be considered particularly suitable for clozapine-augmentation therapy (Pani et al 2008). This may be one reason why, in the UK, amisulpride is a relatively common choice to augment clozapine in clinical practice (Prescribing Observatory for Mental Health 2006, 2007), despite the lack of robust clinical evidence on the potential risks and benefits of this drug combination. Another reason may be the perception that the selective dopamine D2/D3 blocking properties of amisulpride represent a complementary receptor profile to clozapine (Genç et al 2007).

Clozapine augmentation with a second antipsychotic has generally been found to have only modest efficacy although the combination is relatively well tolerated (Sommer et al 2012, Taylor et al 2012). The aims of this study were to further test the efficacy of an adequate trial of clozapine augmentation with amisulpride compared with placebo in treatment-resistant

schizophrenia that had shown an insufficient response to clozapine and to assess the risks and possible adverse effects of such a trial.

METHODS

Design and participants

The study was a randomised, double-blind, placebo-controlled trial lasting 12 weeks, approved by the London-Fulham Research Ethics Committee (Ref: 10/H0711/75), and the trial was registered (ISRCTN68824876). Patients were recruited from November 2011 to December 2014 from adult mental health services. The main inclusion criteria were treatment for at least 12 weeks at a stable dose of 400mg or more of clozapine a day, unless the size of the dose was limited by side effects, a total score of 80 or greater at baseline on the Positive and Negative Syndrome Scale (PANSS: Kay et al 1987, 1988), a Clinical Global Impression scale (CGI: Guy 1976) score of 4 or greater and a Social and Occupational Functioning Assessment Scale (SOFAS: Goldman et al 1992) score of 40 or less. In addition, at baseline, up to three critical symptoms and/or behaviours that were refractory to treatment were identified for each participant. These phenomena had to have been persistent problems and judged clinically to have had a major adverse impact on a participant's social function and community re-integration and/or been a major cause of psychological distress, and/or precluded discharge from hospital.

Participants were randomised to 400mg amisulpride or one placebo capsule for the first 4 weeks, with the option of titrating up to 800mg amisulpride or two placebo capsules for the remaining eight weeks. The amisulpride and placebo tablets had been encapsulated to look identical. A fully automated online (and telephone) randomisation service was provided by the Clinical Trials Research Unit, University of Sheffield. In addition, a 24-hour unblinding service was provided by ESMS Global, Medical Toxicology Information Service Ltd.

Changes to methods after trial commencement

Additional sites were added as the trial progressed, taking the total number of study sites from 4 to 23. Prior to randomisation of the first participant, electrocardiography was introduced to exclude cardiac contraindications and establish a baseline reference for any subsequent cardiac monitoring. In line with a number of active, contemporaneous studies that were remunerating participants for their time, a payment to participants of £20 for each assessment was introduced, in recognition of any expenses incurred (e.g. travel) and inconvenience.

Outcomes

The primary outcome measure was the proportion of patients with a criterion response threshold of a 20% reduction in total PANSS scale score. The inter-rater reliability of the PANSS ratings by researchers across the study sites was formally tested: the intra-class correlation for individual items was 0.63 (moderate agreement) and subscales at 0.86 (substantial agreement). The PANSS and the other ratings scale were administered at baseline, six weeks and twelve weeks.

Negative symptoms were assessed using the PANSS negative symptom subscale score. The impact on social and occupational function was measured using the SOFAS. The level of engagement with clinical services was assessed using the Service Engagement Scale (SES: Tait et al 2002). Depressive symptoms were assessed using the Calgary Depression Rating Scale for Schizophrenia (CDSS: Addington et al 1993). Insight was assessed using the Schedule for the Assessment of Insight (SAI: David 1990). The Antipsychotic Non-Neurological Side Effects Scale (ANNSERS: Ohlsen et al 2008), systematically and comprehensively assessed the full range of side effect, other than movement disorders, that are recognised as occurring with first and/or second generation antipsychotics. For this study, an enhanced version of the scale was generated (ANNSERS-E) by the addition of potential cardiac symptoms such as palpitations, dizziness and syncope. Metabolic side effects were assessed at baseline, and 12-week follow-up only, using an obesity measure and assessment of blood pressure, serum prolactin, plasma glucose (non-fasting sample) and lipid profile. In line with best practice safety monitoring (Royal College of Psychiatrists 2006), an ECG was carried out and reported on at baseline, before the study medication was initiated. This was in order to establish a baseline for any subsequent cardiac monitoring, and exclude cardiac contraindications to potentially high-dose antipsychotic medication, including long QT syndromes.

With regard to EPS, drug-induced Parkinsonism was assessed using the Simpson and Angus (1970) Extrapyramidal Side Effects Scale (EPSE: Janno et al 2005). The Barnes Akathisia Rating Scale (BARS: Barnes 1989) was used to assess akathisia and the Abnormal Involuntary Movement Scale (AIMS: Guy 1976, National Institute for Mental Health in England 2008) for rating tardive dyskinesia. The study researchers received thorough training on the use of these measures.

Statistical analysis

Our sample size calculation was based on results from previous studies (Josiassen et al 2005, Shiloh et al 1997), which were comparable with the current study in terms of length of follow-

up, the nature of the intervention and the primary outcome, a 20% or greater reduction in total PANSS score. To detect this criterion response in 30% of participants in the amisulpride arm and 10% in the placebo arm, with 90% power and an alpha of 0.05, would require 92 participants per group (two-sided).

All the main analyses were based on Intention-to-Treat. Baseline summary statistics by randomised group were calculated. Group differences in the primary outcome and other binary outcome measures were evaluated through the use of logistic regression after allowing for stratification by baseline symptom severity. Differences in continuous outcome measures were evaluated through corresponding analysis of covariance (ANCOVA) model, controlling for baseline symptom severity (the stratification variable), and baseline values of the outcome in question.

The six-week data were used to determine whether there was benefit from the intervention earlier than the twelve-week follow-up. The six-week outcome data were examined as a (tertiary) outcome, looking at the data longitudinally using mixed effects modelling using both six and twelve-week outcomes and controlling for baseline values of the given measure. Data were analysed using Stata version 13 for Windows (StataCorp. 2013).

RESULTS

Of the 96 patients recruited, 68 were randomised, with 52 completing their assigned treatment regimen and assessment at the 12-week follow-up. Figure 1 is the CONSORT diagram of progress through the phases of the trial. Table 1 shows the demographic characteristics and status of the participants in the two treatment groups at baseline while Table 2 provides information on the clinical characteristics. Of the critical symptoms and/or behaviours refractory to treatment identified at baseline by the responsible clinical team, positive symptoms were most the most common: hallucinations were reported for 51% of participants, delusions for 43%, and suspiciousness/persecutory or paranoid ideas for 33%. Reduced social interaction was identified as a problem for 37%. Anxiety was relatively common, being identified as a persistent issue for 35% of participants, while depression was a key symptom in only 9%. General negative symptoms were mentioned for 12% of participants but, more specifically, 20% of participants were reported as having lack of drive, motivation, volition and/or spontaneity.

At the 6-week study assessment, the mean PANSS total score was higher for the placebo group (85 [SD 23]) compared with the amisulpride group (80 [SD 15]), although the same proportion (25%) had a 20% drop in PANSS score from baseline in both groups. Median SES

was lower in the placebo group (7 [IQR 4, 14]) compared with the amisulpride group (10 [IQR 4, 13]). All other standardised scales showed similar scores between groups.

Table 1. Demographic characteristics and status of participants at baseline, by randomised groups

Variable	Amisulpride		Placebo	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Male	24/35	69	23/33	70
Age: years	39	(11)	40	(10)
Ethnicity: White	28/35	80	24/33	73
Living alone	12/32	38	11/28	39
Living with parents	5/32	16	8/28	29
Living with others	15/32	47	9/28	32
Owner occupied flat or house	0/34	0	0/29	0
Flat or house rented	19/34	56	21/29	72
Other accommodation	15/34	44	8/29	28
Not in paid employment because of treatment	24/25	96	23/25	92
Currently an inpatient	5/35	14	4/33	12
Psychiatric inpatient in the last 3 months	1/22	5	0/20	0

Figure 1. The CONSORT flow diagram. IMP, investigational medicinal product.

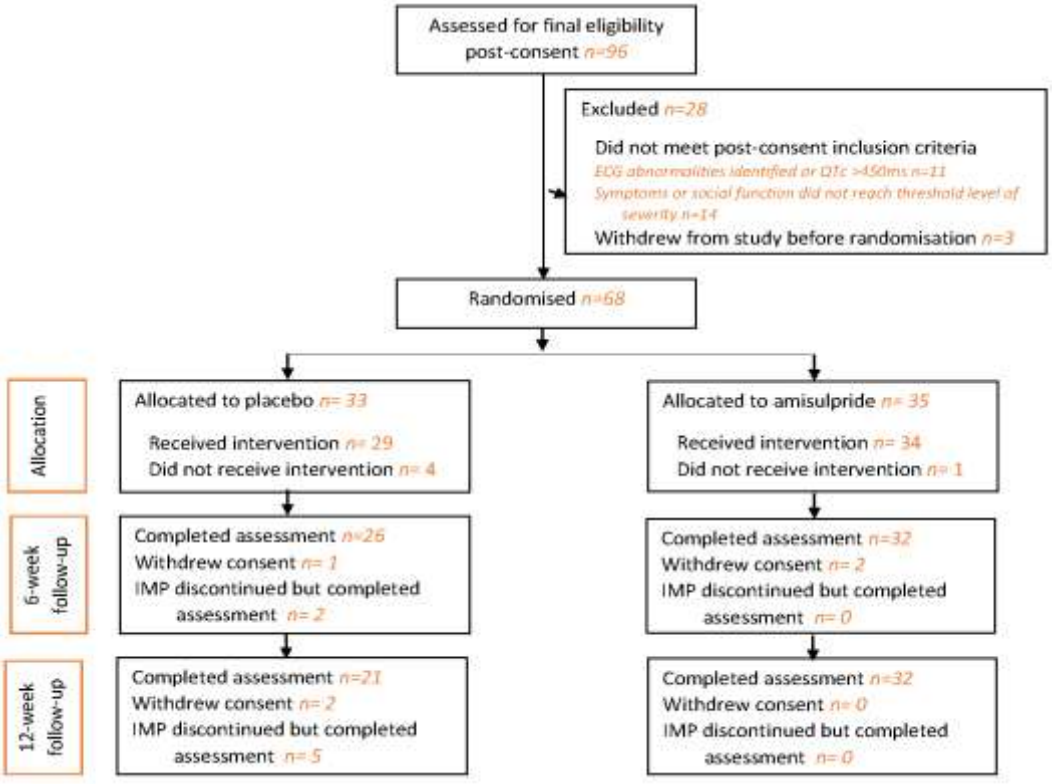

Table 2. Clinical characteristics of participants at baseline, by randomised groups

Variable	Amisulpride		Placebo	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Primary psychiatric diagnosis				
Schizophrenia	32/34	94	29/30	97
Schizophreniform disorder	1/34	3	0/30	0
Schizoaffective disorder	1/34	3	0/30	0
Psychosis NOS	0/34	0	1/30	3
Medication				
Any antidepressant	15/35	43	13/33	39
Any antipsychotic (excluding clozapine and amisulpride)	3/35	9	1/33	3
Any mood stabiliser	9/35	26	4/33	12
Cardiac symptoms, checked 7-10 days after starting study medication				
Irregular heartbeat	1/31	3	0/26	0
Shortness of breath	5/32	16	0/26	0
Dizziness	5/32	16	1/26	4
Fainting	0/31	0	0/26	0
Hypotension	0/30	0	0/26	0
Clinical assessment				
Mental state: PANSS	93	(13)	98	(24)
PANSS high score (stratification variable)	16/35	46	14/33	42
PANSS negative symptom subscale score	25	(6)	25	(7)
Depression: CDSS median (IQR)	5	(1, 10)	5	(2, 8)
Social function: SOFAS median (IQR)	35	(32, 39)	35	(30, 40)
Service engagement: SES median (IQR)	8	(4, 13)	10	(4, 18)
Insight: SAI median (IQR)	12	(8, 13)	12	(9, 14)
Side-effects				
ANNSERS-E median (IQR)	16	(11, 22)	13	(10, 24)
BARS: median (IQR)	0	(0, 2)	2	(0, 2)
Akathisia present (score 2+)	3/33	9	4/31	13
AIMS positive: tardive dyskinesia	4/35	11	4/33	12
EPSE: median (IQR)	0.1	(0, 0.3)	0.1	(0, 0.3)
Parkinsonism present	10/29	34	6/24	25

A 20% or greater reduction in PANSS total score by 12 weeks was found in 44% of those participants in the amisulpride group compared with 40% of those assigned to placebo. As can be seen from the data presented in Table 3, this reflects higher odds (OR 1.17 [95% CI 0.40, 3.42]) for the amisulpride group for achieving this criterion level of reduction in PANSS total score. Table 4 presents the results of mixed effects modelling to take time into account in terms of the amisulpride intervention. These reveal a time effect associated with >20% reduction in PANSS; the odds of a >20% reduction in PANSS at 12 weeks is 4.19 times that of 6 weeks (95% CI 1.20, 14.56), controlling for baseline PANSS score and including the randomised condition. Likewise, PANSS negative subscale scores show a slight decrease

in score at 12 weeks compared with 6 weeks (-1.32; 95% CI -2.20, -0.44) controlling for baseline negative PANSS score and including the randomised condition.

Table 3: Outcomes in terms of the amisulpride intervention

Variable	OR or coefficient	95% CI
Primary outcome		
>20% reduction in PANSS from baseline	1.17	(0.40, 3.42)
Secondary outcomes		
PANSS negative symptom subscale	-0.71	(-3.22, 1.81)
Service engagement: SES	1.17	(-1.63, 3.97)
Depression: CDSS	0.23	(-1.54, 2.00)
Insight: SAI	0.02	(-1.33, 1.37)
Side effects		
Non neurological		
ANNSERS-E	1.58	(-3.60, 6.76)
Metabolic/endocrine side effects		
Weight	0.79	(-1.40, 2.99)
Body mass index	-0.02	(-1.05, 1.01)
Waist circumference	1.05	(-2.33, 4.42)
Systolic blood pressure (mmHg)	3.49	(-3.66, 10.63)
Diastolic blood pressure (mmHg)	3.33	(-1.65, 8.31)
Serum prolactin (ng/ml)	50.47	(-8.86, 109.80)
Ln serum prolactin	1.43	(0.71, 2.14)
Plasma glucose (mmol/l): non-fasting blood sample	0.66	(-0.22, 1.54)
Total cholesterol (mmol/l)	0.48	(-0.11, 1.07)
HDL cholesterol (mmol/l)	0.09	(-0.23, 0.41)
LDL cholesterol (mmol/l)	0.11	(-0.62, 0.85)
Triglycerides (mmol/l)	0.78	(-0.10, 1.65)
Motor side effects		
Akathisia: BARS global item score ≥2 *	0.35	(0.06, 2.09)
Tardive dyskinesia: AIMS positive*	0.37	(0.03, 4.34)
Parkinsonism: EPSE	-0.04	(-0.22, 0.14)
Extrapyramidal side-effects present*	0.63	(0.18, 2.20)

*unadjusted result, too few events to do an adjusted analysis

Table 4: Mixed effects modelling to take time into account in terms of the amisulpride intervention

Variable	OR or coefficient	95% CI
Primary outcome		
20% reduction in PANSS from baseline	1.43	(0.24, 8.44)
Secondary outcomes		
PANSS negative symptom subscale	-0.60	(-2.58, 1.39)
Service engagement: SES	1.75	(-0.54, 4.04)
Depression: CDSS	0.19	(-1.10, 1.49)
Insight: SAI	-0.52	(-2.32, 1.28)
Side effects		
ANNSERS-E	3.11	(-0.91, 7.13)
Akathisia present: BARS global item score ≥2	0.29	(0.01, 7.82)
Tardive dyskinesia: AIMS positive	0.18	(0.00, 32.67)
Parkinsonism: EPSE	0.05	(-0.09, 0.19)

Side effects

The information in Table 2 shows a greater frequency of cardiac symptoms in the amisulpride group, when checked 7-10 days after starting study medication. The data in Table 4 regarding side-effect assessment using the ANNSERS-E, reveal that, over the course of the study, the mean ANNSERS-E total score in those participants assigned to amisulpride was 3 points higher than in the placebo group.

By 12 weeks, mean weight, BMI, waist circumference and blood pressure were greater in the amisulpride group than in the placebo group. Median plasma prolactin concentration was higher in the amisulpride group than in the placebo group [43 ng/ml (IQR 9–87 ng/ml) vs. 11 ng/ml (IQR 7–12 ng/ml), respectively], as was mean plasma glucose concentration [6.9 mmol/l (SD 2.8 mmol/l) vs. 5.4 mmol/l (SD 0.7 mmol/l), respectively].

During the course of the study, 65 adverse events were reported for 31 participants; more of these events were in the amisulpride intervention group than the placebo group (47 versus 18). Most of the adverse events reported were characterised as mild and eventually resolved. Almost a third of adverse events in the amisulpride group were judged by the reporting clinician to be either ‘probably’ or ‘definitely’ related to the study medication compared with a little over a tenth in the placebo group. In the amisulpride group, 60% had at least one adverse event compared with 30% in the control group. 40% of adverse events in the amisulpride group were cardiac symptoms (compared with 11% of the adverse events in the placebo group): dizziness and breathlessness were the most common, each reported by 6 participants, with postural dizziness, irregular heartbeat and tachycardia each reported by 2 participants. However,

serious adverse events were rare and none related to the study medication, with one participant experiencing such an event in the amisulpride group and two participants in the placebo group.

DISCUSSION

Efficacy

The only other double-blind, placebo-controlled study testing amisulpride augmentation of clozapine in patients with schizophrenia that has shown an insufficient response to clozapine treatment was by Assion et al (2008). These investigators concluded that this was a potentially helpful treatment option in such cases but acknowledged the limitations of their small sample size and relatively short, 6-week follow-up. Our trial had a much larger sample size and longer follow-up but we under-recruited against our target sample size and therefore the power of any statistical analysis to detect significant differences between the active and placebo groups was limited. Nevertheless, we found that the participants in the amisulpride group had higher odds of being clinical responders by the end of the 12-week study period, the response criterion being a 20% or greater reduction in the total PANSS score. This advantage was not evident at 6 weeks, reinforcing earlier indications that an adequate trial of clozapine augmentation with a second antipsychotic may be at least 10 to 12 weeks (Paton et al 2007, Correll et al 2009), that is, longer than the 4-6 weeks usually considered adequate for the treatment of an acute psychotic episode.

There was some evidence of a greater reduction in the PANSS negative symptom subscale score by 12 weeks in those participants assigned to amisulpride, compared with the placebo group. This finding is in accord with earlier reports of a greater improvement in negative symptoms than positive symptoms in randomised studies where clozapine augmentation with a second antipsychotic for treatment-refractory schizophrenia has proved to be beneficial (Chang et al 2008, Josiassen et al 2005) as well as some limited evidence for improvement in negative symptoms with amisulpride monotherapy (Boyer et al 1995, Loo et al 1997, Danion et al 1999, Storosum et al 2002, Arango et al 2013).

When considering these findings it should be borne in mind that a response criterion of a 20% or greater reduction in total PANSS score for people with treatment-refractory schizophrenia may be of limited clinical relevance. Its interpretation requires an understanding of the meaning of scores on a scale rarely used in clinical practice. Further, as Leucht et al (2006) demonstrated, even a 25% reduction in the PANSS total score may only reflect a reduction of

the Clinical Global Impression scale score by one severity step. Given the marked heterogeneity of the clinical presentation of treatment-refractory schizophrenia, a more clinically relevant outcome measure in future studies of this kind might be an individualised response criterion, based on the change in severity of each participant's critical target symptoms. This last point is reinforced by the diverse clinical profiles presenting in this study sample. While persistent positive symptoms were the most common features at baseline judged to be of clinical significance by the mental health professionals providing care, some participants presented other such target symptoms and behaviours, including anxiety, reduced social interaction, and negative symptoms in the avolition/amotivation domain.

Side effects

Amisulpride was chosen for this study because of the robust evidence for safety and tolerability benefits, particularly a low risk of compounding characteristic clozapine side effects. Amisulpride may be rather more likely than most other second-generation antipsychotics to cause hyperprolactinaemia (Fric & Laux 2003) but it causes little or no weight gain and has a relatively low liability for diabetes, lipid abnormalities and EPS (Tschoner et al 2007, Leucht et al 2013). With regard to cardiac side effects, QT interval prolongation and the potentially fatal arrhythmia, torsade de pointes, are not uncommon with overdose (Isbister et al 2010) but the risk at therapeutic dosages is rather uncertain (McKeage & Plosker 2004, Chung & Chua 2010).

Using the ANNSERS-E scale, we found a greater side-effect burden in those participants assigned to the clozapine-amisulpride combination. Their mean ANNSERS-E total over the course of the study was 3 points higher than the equivalent score in the placebo group. However, our separate scale assessments of EPS, such as akathisia and parkinsonism, revealed that these were not likely to be treatment-emergent problems with amisulpride augmentation of clozapine, despite the 'high rates' of tremor, bradykinesia and akathisia previously reported with the combination (Assion et al 2008, Porcelli et al 2012).

Considering the adverse events reported during the course of the study, 60% of participants in the amisulpride group had at least one reported, compared with 30% of participants in the placebo group. Cardiac symptoms proved to be a relatively common prompt for an adverse event report, occurring much more commonly in the amisulpride group. Further, an additional check for any emerging cardiac symptoms in the 7 to 10 days after starting study medication revealed that shortness of breath and dizziness were more common in the amisulpride group. Amisulpride augmentation was also associated with endocrine effects; the most common was raised plasma prolactin, an expected side effect that also provides some indirect but reassuring evidence of adherence to the study medication.

Mechanism of action

One proposed criterion for the choice of an augmenting antipsychotic in patients on clozapine is a complementary receptor profile, essentially potent D2 dopamine receptor blockade (Freudenreich & Goff 2002, Genç et al 2007, Kontaxakis et al 2006). This was partly the rationale for choosing amisulpride for this study: it preferentially binds to dopamine D2 and D3 receptors in limbic rather than striatal brain structures (Moller et al 2003, Perrault et al 1997) and has low affinity for other dopamine receptor subtypes, although it also has affinity for a range of other receptors, including serotonergic, histaminergic and adrenergic receptors.

However, the limited benefit seen with amisulpride in this study suggests that the notion that potent D2 blockade is a key determinant of response when adding a second antipsychotic to treat clozapine-unresponsive illness may be simplistic. Treatment-refractory schizophrenia may have a more complex pathophysiology than illness showing a good therapeutic response to standard antipsychotic therapy; the underlying pathophysiology may even be non-dopaminergic (Howes & Kapur 2014, Nakajima et al 2015, Mouchlianitis et al 2016). For example, dopamine synthesis capacity is lower in those patients with a treatment-resistant illness (indeed, no different from healthy controls) than in those with a responsive illness (Demjaha et al 2012). It has been speculated that treatment-resistant illness may benefit from a multi-site receptor effect rather than a stronger antidopaminergic effect (Vayisoğlu & Yağcioğlu 2014, Muscatello et al 2014).

Conclusions

We found that even amongst patients with a clozapine-refractory illness, there was a greater chance of improvement to a criterion level of overall symptom reduction within 12 weeks and some suggestion of modest improvement in negative symptoms. However, despite amisulpride being chosen for its favourable tolerability and safety profile, when combined with clozapine treatment in this study it was associated with a greater side-effect burden, including cardiac side effects. The identification of such problems may partly reflect the thorough assessment of side effects in this study, which was more systematic and comprehensive than is generally conducted in clinical trials of antipsychotics (Pope et al 2010). These findings have implications for the nature and frequency of safety and tolerability monitoring of clozapine augmentation with a second antipsychotic in both clinical and research settings.

The limited benefit with amisulpride seen in this trial challenges the rationale of potent dopamine D2 receptor blockade as a key criterion for selecting an augmenting antipsychotic to treat clozapine-unresponsive illness. Nevertheless, the findings suggest that the risk-benefit of amisulpride augmentation of clozapine for schizophrenia that has shown an insufficient

response to a trial of clozapine monotherapy may still be worthy of further investigation in larger studies.

Future trials of such a treatment strategy should have a sample size that provides adequate statistical power and be of sufficient duration, taking into account that a clinical response may not be evident within the 4-6 week follow-up period usually considered adequate in studies of antipsychotic treatment of acute psychotic episodes. Whether such trials are feasible remains uncertain, given the continuing challenge of recruitment in mental health studies in the NHS (Rendell et al 2007, Leeson & Tyrer 2013, Barnes et al 2016).

ACKNOWLEDGEMENTS

We would like to thank all the patients who agreed to be interviewed as part of this trial and extend special thanks to all those who agreed to participate. We thank the AMICUS research staff at the study sites, many of whom worked extremely hard to support the study. We would also like to extend our gratitude to all the mental health professionals at the study sites who supported the study, finding time for us in their busy schedules. Our thanks also to the members of the Trial Steering Committee (Professor Stefan Priebe, Professor Eileen Joyce, Ms Jenny Trite, Professor Tom Jamieson-Craig and Professor David Osborn), Data Monitoring and Ethics Committee (Professor Mohammed Abou-Saleh, Dr Stuart Cox, Dr Louise Marston and Ms Ulrike Naumann) and Trial Management Committee (aside from co-authors: Mr Kavi Gakhal, Ms Megan Lawrence, Mr Roger Oliver, Mr George Salaminios and Dr Dilveer Sually). Thanks are also due to other colleagues who co-wrote the original grant application, Dr Andrew Proctor and Professor Michael King, the helpful and friendly staff at the University of Sheffield Clinical Trials Research Unit who provided the trial database and randomisation service, and the staff at the Medical Toxicology and Information Services Ltd who provided a professional and reliable emergency unblinding service for the trial.

This project was funded by the National Institute for Health Research (Health Technology Assessment programme: project number 08/116/12). The full study protocol, may be accessed on the HTA website. The views and opinions expressed in this paper are those of the authors and do not necessarily reflect those of the Health Technology Assessment programme, NIHR, NHS or the Department of Health.

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