Augmentation Strategies in Patients with Schizophrenia Who Show Partial Response to Clozapine Treatment: A Systematic Review

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SUMMARY

A significant proportion of patients with schizophrenia that receive clozapine remain desensitized with only a partial response. In this group of patients, the outcomes regarding the addition of various psychotropics in combination with clozapine treatment for augmentation are controversial. In this review, literature regarding the efficacy and safety of adjunctive agents in clozapine resistant schizophrenic patients is examined. Augmentation agents added to clozapine in treatment resistant schizophrenic patients consist of antipsychotics, antidepressants, mood stabilizers, other agents (eg. omega-3 fatty acids and glutamatergic agents), and electroconvulsive therapy (ECT) are highlighted in this review. The number of controlled studies evaluating augmentation of clozapine in schizophrenia patients is highest for risperidone and lamotrigine add-on treatments. However, the results of recent meta-analyses studies do not support any benefit of either agent combined with clozapine treatment. Some evidence regarding the success of clozapine augmentation with amisulpride, aripiprazole, mirtazapine, omega-3 fatty acids, and ECT have been obtained and ultimately needs further clinical investigation. Current findings from relevant clinical investigations have determined that these studies have limitations consisting of small sample size, variable definitions of clozapine resistance, heterogeneity of outcome measures, and methodological designs. In addition, sufficient evidence does not yet exist regarding the success of various adjunctive treatments for clozapine resistant patients.

Key Words: Schizophrenia, clozapine, treatment resistance, augmentation treatment

INTRODUCTION

Clozapine is the only antipsychotic where its effectiveness has been demonstrated by certain evidence in treatment resistant schizophrenia (Lindström et al., 1988; Meltzer et al., 1994, 1995; Coşar et al., 1998; Soylu et al., 1999). However, a significant proportion of these patients (40%-70%) achieve only poor or partial response with clozapine (Kane et al., 1988; Tollefson et al., 2001; Anıl Yağcıoğlu et al., 2005; Tiihonen et al., 2009). In our country, studies examining clozapine augmentation in different treatment units are conspicuous (Coşar et al., 1997; Taner et al., 1998; Soylu et al., 1999; Uzun et al., 2000; Anıl et al., 2002). Recent reports conducted on clozapine treatment response rates in Turkey indicated that patients who show partial or no response to clozapine treatment constitute at least 30-40% of the sample size (Coşar et al. 1997; Soylu et al. 1999; Anıl et al. 2002). These patients have been termed 'clozapine resistant' or Super Refractory Schizophrenics (Buckley et al., 2001; William et al., 2002). Therefore, psychotropic drugs including different kinds of antipsychotics and anticonvulsants are used in combination with clozapine in order to augment treatment in schizophrenic patients with a partial response to clozapine. When an adequate trial using clozapine fails to result in clinical improvement, augmentation of clozapine with a second antipsychotic is relatively common in clinical practice. However, positive results supporting this practice with placebo controlled trials has not determined (Davis, 2006; Honer et al., 2006; Anıl Yağcıoğlu et al., 2005; Kıvırcık Akdede et al., 2006; Freudenreich et al., 2007; Paton et al., 2007). Although it seems less common as adding antidepressants, mood stabilizers, and ECT than antipsychotics on clozapine augmentation

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treatment, these applications are common in clinical practice (18-44%). Many other augmentation strategies have been investigated so far, but for most of these, clinical practice seems to be driven by case reports without any evidence supporting these clozapin augmentations (Remington et al., 2005). In our country, there are a limited number of studies which investigate clozapine augmentation treatment. One of the first studies examining this augmentation was performed in Hacettepe University Faculty of Medicine Department of Psychiatry. Atypical (11.6%) and typical (7%) antipsychotic adjunct agents were most effective in augmenting the antipsychotic effect of clozapine, while mood stabilizers (5.8%) and ECT (4.7%) were found to follow first group (Anil et al., 2002). However, in our country time course variability in the treatment of schizophrenia using the augmentation methods should be considered. In this study, additional treatments which were used for clozapine augmentation were grouped as antipsychotics, antidepressants, mood stabilizers, other pharmacologic agents (omega-3 fatty acids and glutamatergic agents) and ECT. The review of the added treatments' effectiveness based on double-blind, randomized, placebo controlled trials includes current meta-analysis study findings related to the sufficient number of additional controlled study methods. Examination of open studies and case series for additional treatment methods which have no controlled studies were also planned.

METHOD

The Pubmed database was searched for this review. English was used as language and there was not any limitation for years. "Schizophrenia", "clozapine", "resistance to treatment" and each augmentation agent and method were used key words.

Randomized, double-blind, placebo controlled trials, open studies, and case reports were included to review. Findings of recent meta-analysis studies were ranked. Patients included in this study were diagnosed with schizophrenia or schizoaffective disorder according to diagnostic criteria of DSM-III, DSM-IV, DSM-IV TR or ICD-9 or 10.

FINDINGS

Augmentation Clozapine treatment with antipsychotics

Adding other antipsychotics to clozapine treatment in clozapine resistant schizophrenic patients is the most effective augmentation method. It is assumed that efficacy of clozapine, an agent with relatively weak dopamine-D2 antagonist properties, might be enhanced by augmentation with an antipsychotic drug that provides high potency D2 blockade (Freudenreich et Goff 2002; Kontaxakis et al., 2005). When we analyzed the controlled studies, risperidone was determined as the most widely reported antipsychotic drug augmentation strategy for schizophrenia patients showing partial response to clozapine. But in two of three placebo controlled studies (which are ranged from 6-12 weeks), the addition of risperidone treatment was shown to provide no additional augmentation benefit (Anıl Yağcıoğlu et al. 2005 ; Honer et al. 2006). One study demonstrated that the addition of risperidon improved the overall positive and negative symptoms of schizophrenia (Table 1) (Josiassen et al., 2005). In a study conducted in Turkey, a less grade response was achieved in verbal memory in the risperidone augmentation group compared to placebo controlled group (Kıvırcık Akdede et al., 2006). However, in these studies the general safety profile was found good, in one of those rate of glucose plasma level increase was higher than the others (Honer et al., 2006). Two new meta-analysis studies that compared the efficacy of risperidone and placebo added to clozapine treatment (Porcelli et al. 2012; Sommer et al. 2012) found no significant difference between the effect size of risperidone and placebo (respectively Z: 0.14 and Hedge's g: 0.18). The meta-analysis study, which is conducted by Sommer et al., showed that heterogeneity among the studies was high for positive symptoms and moderate for negative symptoms. Comparability of augmentation studies with risperidone is low due to differences between samples and study designs (drug dose and duration of treatment).

The 2 randomized controlled trials (Chang et al., 2008; Fleischhacker et al., 2010) yielded no significant difference between aripiprazole and placebo for clinical effectiveness (Table 2). But in open designed trials, this method was determined to be effective, especially for negative symptoms and for reversing metabolic side effects of clozapine. Aripiprazole does not seem to interact with clozapine serum levels (this statement indicates that advantage of aripiprazole is independent from pharmacokinetic effect) (Ziegenbein et al., 2006; Mitsonis et al., 2007; Bachmann et al., 2009; Benedetti et al., 2010). The current meta-analysis of these two studies showed that severity of symptoms was similar to each other for the assessment of positive symptoms. Conversely, the degree of heterogeneity for the negative symptoms was high and there was no significant difference for effect size between aripiprazole and placebo (Hedge's g: 0.12) (Sommer et al. 2012).

Positive results were found in small number of open and controlled studies which examined the clozapine augmentation with amisülpiride in schizophrenic patients. One study on the efficacy of amisülpiride in augmenting clozapine yielded no significant difference between amisulpride and placebo regarding positive, negative, and total symptom severity. In addition, high rates of relevant side effects including bradykinesia, akathisia, tremor, and increase of prolactin serum levels were also reported (Assion et al., 2008) (Table 2).

Table 1. Placebo controlled studies of risperidone augmentation in patients with schizophrenia who show partial response to clozapine

Sample size, clinical features, study duration and outcome of study	**Anıl Yağcıoğlu et al. 2005, Kıvırcık Akdede et al. 2006**		**Josiassen et al. 2005**		**Honer et al. 2006**	
Total (n)	30		40		68	
Study duration (week)	6		12		8	
	Risperidone	**Placebo**	**Risperidone**	**Placebo**	**Risperidone**	**Placebo**
			Mean±SD			
Age (year)	35,3±10,8	31,2±6,9	40,8±6,9	39,9±10,8	39,4±11,0	34,9±8,5
Duration of illness (year)	14,4±9,1	9,8±5,9	21,8±7,0	22,4±11,6	16,9±11,2	13,0±9,0
Clozapine dose (mg/day)	515,6±138,7	414,3±96,9	528,8±166,7	402,5±102,9	494±168	487±135
Dose of add on treatment (mg/day)	5,1±1,3		4,43±1,5		2,94±0,2	
Baseline severity of illness	4,5 (0,12)[*3] 77,4(1,65)[*5]	4,5(0,13)[*3] 77,4(1,78)[*5]	48,8±9,2[1] 68,4±27,5[2] 5,2±1,1[3]	47,1±13,3[1] 71,5±30,9[2] 5,2±1,7[3]	5,44±0,82[3] 32,2±7,4[4] 102,5±14,6[5]	4,91±0,75[3] 35,0±7,5[4] 97,8±12,4[5]
Outcome	No difference between groups in terms of the change in positive, negative and total symptoms More improvement in verbal memory in the placebo group		Improvement in total, positive and negative symptoms in the risperidone group		No difference between groups in terms of the change in positive, negative and total symptoms Worsening in verbal working memory in the risperidone group	

n: Number
*: The least square mean (Standard Error)
[1]BPRS: Brief Psychiatric Rating Scale
[2]SANS: Scale for the Assesment of Negative Symptoms
[3]CGI: Clinical Global Impression Scale
[4]SOFAS: Social and Occupational Functioning Assesment Scale
[5]PANSS: Positive and Negative Syndrome Scale

Table 2. Placebo controlled studies of aripiprazole and amisulpride augmentation in patients with schizophrenia who show partial response to clozapine

Sample size, clinical features, study duration and outcome of study	**Chang et al. 2008**		**Fleischhacker et al. 2010**		**Assion et al. 2008**		
Total (n)	62		207		16		
Study duration (week)	8		16		6		
	Aripiprazole	**Placebo**	**Aripiprazole**	**Placebo**	**Amisulpride 400 mg/gün**	**Amisulpride 600 mg/gün**	**Placebo**
				Mean±SD			
Age (year)	33,2±8,2	31,7±7,4	37,6±10,9	40,5±9,9	43	41,5	46,3
Duration of illness (year)	--	--	12,6±9,3	14,4±9,1	>10		
Clozapine dose (mg/day)	304,3±104,8	290,6±101,9	383,8±158,2	362,6±158,7	256±38,4	268,8±41,3	285±23,9
Dose of add on treatment (mg/day)	15,5±7,1		11,1		400	600	
Baseline severity of illness	47,6±9,3[2] 14,0±6,6[4] 4,2±0,7[5]	48,5±10,5[2] 14,6±6,7[4] 4,0±0,6[5]	72,2±16,6[1]	70,7±16,5[1]	4,14[2*] 10,71[3*] 5,29[4*] 0,71[5*]	18,33[2*] 20,67[3*] 13,5[4*] 2,17[5*]	6,67[2*] 5[3*] 1,67[4*] 0[5*]
Outcome	Improvement in negative symptoms in the aripiprazole group	No difference between groups in terms of the change in positive, negative and total symptoms Improvement in metabolic parameters in the aripiprazole group		Improvement in global functioning, severity of illness and depressive symptoms in the amisulpride 600 mg/day group			

n: Number
*:Adjusted mean change in outcome measures
[1]PANSS: Positive and Negative Syndrome Scale
[2]BPRS: Brief Psychiatric Rating Scale
[3]GAF: Global Assesment of Functioning
[4]MADRS: Montgomery Asberg Depression Rating Scale
[5]CGI: Clinical Global Impression Scale

Whether there is only a randomized controlled study which examined clozapine augmentation with sulpride in patients who show partial response to clozapine, addition of sulpride to clozapine treatment exhibited substantially greater and significant improvements in positive and negative symptoms (Shiloh et al.,1997).

Clozapine augmentation with sertindole showed no benefit in a double-blind, randomized, placebo controlled study. Sertindole was associated with a 12 millisecond QTc prolongation compared with the placebo group (Nielsen et al., 2012). Furthermore, a double-blind clinical trial of pimozide augmentation in clozapine nonresponders reported negative results (Friedman et al., 2011). Similar to this finding, a randomized, double-blind, placebo controlled study (which was designed currently) showed that there was no beneficial effect in pimozide group compared with placebo (Gunduz Bruce et al., 2012).

In open designed studies, positive results were achieved in clozapine augmentation with ziprasidone. It has been demonstrated that in the course of time clozapine dose can be reduced and weight loss can be achieved (Kaye, 2003; Ziegenbein et al., 2006). An additional two studies compared ziprasidone and risperidone as augmentation strategies. Both agents were shown to have comparable clinical efficacy but, different side effects (Zink et al., 2009; Kuwilsky et al., 2010). Patients with risperidone were more prone to hyperprolactinemia, extrapyramidal symptoms, and weight gain. Patients with ziprasidone were instead observed to have an increased risk of QTc interval prolongation. However, these studies have limitations due to the drop out of many patients in the course of treatment, small sample size, brief observation time, and absence of comparable placebo groups and poor statistical analyses. The efficacy of ziprasidone augmentation remains unclear because of the mentioned limitations and lack of randomized controlled studies.

There are case reports and small sample sized open trials which shows clinical efficacy of clozapine augmentation with haloperidol, pimozide, loksapin, olanzapine, and quetiapine (Mowerman and Siris, 1996; Flynn et al., 1997; Friedman et al., 1997; Gupta et al., 1998; Reinstein et al., 1999; Rajarethinam et al., 2003). Placebo controlled studies which examine the augmentation with these drugs is needed. Concomitant medication of clozapine and olanzapine has high risk for metabolic side effects (Rummel-Kluge et al., 2010).

Clozapine Augmentation with Antidepressants

With regard placebo controlled studies which are intended to investigate clozapine augmentation with antidepressants, variable results were obtained (Table 3). While fluoxetine does not seem to have any clinical effect on clozapine augmentation (Buchanan et al., 1996), mirtazapine improved clozapine treatment by ameliorating negative symptoms (Zoccali et al., 2004). A high mean weighted effect size was obtained in current meta-analysis of augmentation studies with addition of mirtazapine, but no significant difference was found between mirtazapine and placebo (Hedges's g:2.91) even though there was very high heterogeneity among these studies (Sommer et al., 2012).

Table 3. Placebo controlled studies of antidepressant augmentation in patients with schizophrenia who show partial response to clozapine

Sample size, clinical features, study duration and outcome of study	**Buchanan et al. 1996**		**Zoccali et al. 2004**	
Total (n)	33		24	
Study duration (week)	8		8	
	Fluoxetine	**Placebo**	**Mirtazapine**	**Placebo**
		Mean±SD		
Age (year)	36,8±6,4	32,8±6,0	30,7±6,5	33,4±9,0
Duration of illness (year)	16,2±4,3	15,6±6,4	9,6±4,9	13,6±7,2
Clozapine dose (mg/day)	457,4±89,0	511,7±109,3	320±151,2	325±131,7
Dose of add on treatment (mg/day)	48,9		30	
Baseline severity of illness	10,3±4,7[1] 29,5±15,3[2] 13,3±10,0[4]	10,3±3,7[1] 23,9±10,9[2] 12,6±9,0[4]	45,5±4,1[1] 48,9±6,9[2] 6,9±3,6[3]	45,3±3,8[1] 51±5,3[2] 7,9±3,3[3]
Outcome	No difference between groups in terms of the change in total, positive, negative, depressive and obsessive-compulsive symptoms		Improvement in total and negative symptoms in the mirtazapine group	

n: Number
[1]BPRS: Brief Psychiatric Rating Scale
[2]SANS:Scale for the Assesment of Negative Symptoms
[3]SAPS:Scale for the Assesment of Positive Symptoms
[4]HDS: Hamilton Depression Scale

Augmentation with Selective Serotonin Reuptake Inhibitors (SSRI) is typically employed when depressive or negative symptoms are prominent and/or the presence of relevant anxiety and obsessive-compulsive symptoms are observed. Evidence of the efficacy of augmentation with antidepressants has been reported. Fluvoxamine seems effective on global symptomatology (Silver et al., 1996; Lu et al., 2000). Since it is a potent CYP1A2 inhibitor, it may decrease clozapine metabolism and increase the risk of side effects. This increase of clozapine plasma levels might also explain the positive effects reported with fluvoxamine augmentation, at least partially. On the other hand, fluvoxamine decreases plasma levels of norclozapine, a toxic metabolite of clozapine, which has been reported to contribute to weight gain, hyperglycemia, and lipid abnormalities in clozapine-treated patients (Lu et al., 2004). Therefore, this strategy could be useful by a close monitoring of drug doses. Fluoxetine also increases clozapine levels but it does not seem to have any clinical effect (Buchanan et al., 1996; Spina et al., 1998). Paroxetine, mirtazapine, and sertraline seem to improve clozapine treatment, mainly concerning negative and obsessive symptoms without affecting clozapine plasma levels (Allen et al., 1994; Rahman et al., 1998; Wetzel et al., 1998; Zoccali et al., 2004; Delle Chiaie et al., 2007).

Taking in account these data, we hypothesize that the positive effect observed with fluvoxamine augmentation may be due to its characteristic pharmacological profile, in particular to its ability to block sigma receptors (Hindmarch and Hashimoto, 2010). In the same way, the positive effect obtained by adding mirtazapine may be due its peculiar pharmacological profile. Drugs with predominant serotoninergic effects (e.g. fluoxetine) seem to be ineffective, thus we could make an inference that the effectiveness of adding fluvoxamine or mirtazapine could be due to their effects on other systems (Porcelli ve ark., 2012).

Clozapine Augmentation with Mood Stabilizers

With regard to placebo controlled augmentation studies concerning mood stabilizers (lithium, valproate, topiramate), lithium treatment seems to be ineffective (Small et al., 2003). The studies which assess the effectiveness of lithium-clozapine combination in schizophrenic patients, provide no clinical benefit except increased side effects (especially neurologic side effects) (Small et al., 2003; Bender et al., 2004; Kelly et al., 2006). One retrospective study which compared the valproate treatment to clozapine monotherapy and clozapine associated with lithium determined that valproate seems to be effective in the treatment of hostility, anxiety, and depressive symptoms (Kelly et al., 2006).

To date, data on topiramate augmentation of clozapine are scarce and controversial. A randomized, double-blind, placebo controlled study, which investigated several second generation antipsychotic drug combinations (clozapine, olanzapine, risperidone or quetiapine) with topiramate and did not analyze clozapine augmentation separately and reported a positive effect (effect size=0.7, p=0.021) on PANSS general psychopathology subscale compared to placebo (Tiihonen et al., 2005). In another randomized, double-blind, placebo controlled study topiramate had a beneficial effect on PANSS positive, negative, and general psychopathology symptoms and established control on antipsychotic associated weight gain (Afshar et al., 2009). In a more recent double-blind, placebo controlled study topiramate was found to be scarcely effective in all outcome measures (Muscatello ve ark., 2011). Add-on topiramate as a clozapine augmentation strategy showed a trend toward superior effect over placebo in reducing total symptom severity (Hedges's g:0.53, p=0.04), In particular, the trends regarding the positive symptoms in effect by topiramate was superior to the placebo, whereas the negative symptom data was not significant albeit heterogeneous (Sommer et al., 2012). The study by Afshar et al. 2009 was considered an outlier after exclusion of the trend for total symptom severity and the significant effect for positive symptoms disappeared.

Although positive results were observed in case reports which included clozapine augmentation with other anticonvulsants, such as pregabalin and gabapentin, no controlled studies were shown (Usiskin et al., 2000; Englisch et al., 2010).

Lamotrigine, which is a phenyltriazine derived anticonvulsant drug (Cousin et al., 1993; Grunze et al., 1998; Leach et al., 1991; Tiihonen et al., 2009), has been considered as a potential treatment option in schizophrenia since there is evidence that implies a dysfuctional glutamatergic neurotransmission in the pathophysiology of schizophrenia (Goff and Coyle, 2001; Tiihonen et al., 2009). In a meta-analysis, which aimed to investigate schizophrenic patients who receive only clozapine treatment, cases with clozapin augmentation and lamotrigine were selected (n=161). In this meta-analysis, Tiihonen et al showed that lamotrigine was more efficient than the placebo and effect size (0.57) was medium. It was emphasized that further trials with a duration of longer than 12 weeks should be done. In one of the recent two series of meta-analysis, which published in the past year, lamotrigine showed superior efficacy to placebo for total symptom severity (Sommer et al., 2012). But the study by Zoccali et al. (2007) was considered an outlier and then excluded from analysis. After exclusion, the mean weighted effect size was no longer significant and studies were homogeneous. Regarding negative symptom scores, the meta-analysis showed no significant difference between lamotrigine and placebo, while heterogeneity was shown to be high. Other recent meta-analysis, which included 3 randomized controlled trials (Tiihonen et al., 2003; Goff et al., 2007) identified in literature comparing lamotrigine to placebo, showed that lamotrigine was found to be

Table 4. Placebo controlled studies of lamotrigine augmentation in patients with schizophrenia who show partial response to clozapine

Sample size, clinical features, study duration and outcome of study	**Tiihonen et al. 2003**		**Kremer et al. 2004**		**Zoccali et al. 2007**		**Goff et al. 2007**				**Vayısoğlu et al. 2013**	
Total (n)	34		38		60		212		217		34	
Study duration (week)	14		10		24		12				12	
	Lamotrigine-Placebo Whole group		Lamotrigine	Placebo	Lamotrigine	Placebo	Study 1 Whole group		Study 2 Whole group		Lamotrigine	Placebo
						Mean±SD						
Age (year)	38,3±9,1		44,1±9,5	42,3±10,3	32,5±6,9	30,2±7,8	41,0±9,8		41,6±10,6		40,5±9,9	41,2±10,9
Duration of illness (year)	13,6±9,0				9,3±3,3	10,4±4,3	--		--		17,8±7,0	18,7±10,7
Onset age of illness (year)	24,7±5,7		20,1±6,8	22,5±8,9			--		--		--	--
Closapine dose (mg/day)	558±162		400,0±282,8	350,0±70,7	300±128,1	335±128,5	--		--		514,7±201,3	426,4±192,9
Dose of add on treatment (mg/day)	200		400		200		100-400				200	
	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo	Lamotrigine	Placebo
Baseline severity of illness	69,2±23,0[1]	78,2±20,9[1]	103,5±14,3[1] 43,7±9,5[2]	107,4±26,0[1] 41,7±13,8[2]	32,6±6,1[2]	30,2±11,3[2]	77,6±14,2[1]	75,5±15,7[1]	81,6±14,5[1]	80,9±14,0[1]	71,6±3,9[1]	71,8±2,2[1]
Outcome	Improvement in positive and general psychopathology symptoms in the lamotrigine group		Improvement in positive and general psychopathology symptoms in the lamotrigine group		Improvement in positive, negative and general psychopathology symptoms in the lamotrigine group Improvement in verbal fluency in the lamotrigine group		No difference between groups in terms of the change in total, positive and negative symptoms Improvement in cognitive functions (composite cognitive scores) in the lamotrigine group		No difference between groups in terms of the change in total, positive, negative symptoms and cognitive functions		No difference between groups in terms of the change in total, positive, negative symptoms and cognitive functions	

n: Number
[1]PANSS: Positive and Negative Syndrome Scale
[2]BPRS: Brief Psychiatric Rating Scale

not superior to placebo augmentation (Porcelli et al., 2012) . Following these meta-analyses, in our country a duration of a 12 week, randomized, placebo controlled, prospective, phase 3 clinical study, was conducted and showed that there was no difference between lamotrigine and placebo groups in terms of psychopathology, functional level, and change in cognitive functions (Vayısoğlu et al., 2013) (Table 4).

Clozapine Augmentation with Other Agents

Consistently with the NMDA receptor hypofunction hypothesis of schizophrenia (Farber et al., 1999), glutamatergic agents (glycine, D-serine, D-cycloserine, ampakine CX516, memantine, N-methylgylcine) were investigated in several randomized controlled trials, which overall showed different results. Although all these agents are glutamatergic, they attach different kind of glutamate receptors and their effect mechanisms are various (D-serine, glycine, D-cycloserine are agonists at the glycine site on the NMDA receptor, N-methylglycine is a glycine transporter-1 (Gly-T 1) inhibitor, memantine is a weak NMDA antagonist, ampakine CX-516 binds to an allosteric site of the AMPA receptor and enhances depolarization by prolonging the channel opening in response to glutamate, so the stimulus is reinforced). Nevertheless, the glutamatergic system is promising in the treatment, sort of receptors and effect mechanisms are different and complex and therefore, a need for new studies.

Adding glycine full or partial agonists (D-cycloserine, D-serine) ongoing clozapine treatment provided negative results. In a placebo controlled, randomized trial, addition of high dose glycine (30 g/day) to clozapine treatment was not

Table 5. Placebo controlled studies of glycine full or partial agonists (D-serine, D-cycloserine) augmentation in patients with schizophrenia who show partial response to clozapine

Sample size, clinical features, study duration and outcome of study	**Goff et al. 1996**		**Goff et al. 1999**	**Potkin et al. 1999**		**Evins et al. 2000**		**Diaz et al. 2005**	
Number (n)	10		11	19		27		12 28	
Study duration (week)	6		13	12		8			
	D-serine	**Placebo**	**D-Cycloserine-Placebo Whole group**	**Glycine**	**Placebo**	**Glycine**	**Placebo**	**Glycine**	**Placebo**
				Mean±SD or (SE)					
Age (year)	42,6±3,6	39,5±5,5	36,6±9,6	35,3±5,26	34,4±4,75	39±7		39,5±12,44	
Duration of illness (year)	20,6±6,1	19,9±5,7	14,8±8,4	---		16±7		---	
Clozapine dose (mg/day* or nmol/L**)	363±128	315±146	490,9±141,1	589±172	635±232	455±116		3103,7±1310,3**	
Dose of add on treatment (mg/kg/day* , g/day** or nmol/L***)	30*		50*	30**		60**		2832,75±1559,6***	
Baseline severity of illness	56,3±7,7[1] 5,3±0,8[2]	61,4±5,2[1] 5,3±0,5[2]	----	13,7±6,1[1] 40,4±12,2[3]	13,7±3,6[1] 45,9±9,9[3]	52±16[1] 39±7[3] 70±10[4]	58±14[1] 44±7[3] 75±11[4]	35,71 (1,14)[3] 61,32 (1,9)[4]	36,31 (1,19)[3] 61,04 (1,79)[4]
Outcome	No difference between groups in terms of the change in total and negative symptoms		No difference between groups in terms of the change in total and negative symptoms	Improvement in positive symptoms in the placebo group		No difference between groups in terms of the change in positive and negative symptoms		No difference between groups in terms of the change in positive and negative symptoms	

n: Number
[1]SANS:Scale for the Assesment of Negative Symptoms
[2]CGI: Clinical Global Impression Scale
[3]BPRS: Brief Psychiatric Rating Scale
[4]PANSS: Positive and Negative Syndrome Scale

effective (Potkin et al., 1999). Similarly another double-blind, placebo controlled, randomized trial showed that glycine augmentation of clozapine produced no significant change in positive and negative symptoms as well as cognitive functioning (Evins et al., 2000). A study by Diaz et al. (2005), which was a double-blind, placebo controlled, randomized trial aiming clozapine augmentation with glycine, showed no clinical benefit once again. Recent meta-analysis, which included the abovementioned three placebo controlled studies (Potkin et al., 1999; Evins et al., 2000; Diaz et al., 2005) were relevant to clozapine augmentation with glycine. These studies were shown to be homogeneous but there was no difference between placebo and glycine (Hedge's g:-0.16 for total symptom severity) in terms of the effect size of change in total, positive and negative symptoms (Sommer et al., 2012). Clinical worsening was shown in open and double-blind controlled studies which included addition of D-serine and D-cycloserine on clozapine treatment (Goff et al., 1996; 1999) (Table 5). Adding glycine and D-serine on clozapine treatment provided no benefit in negative symptoms. Clozapine augmentation

with NMDA agonists seemed to be ineffective. Relevance to clozapine as an NMDA agonist and other drugs, which have a similar effect profile, provide no clinical benefit (Tsai et al., 1999; Evins et al., 2000). The addition of glycine and D-serine could not further enhance the NMDA neurotransmission already influenced by clozapine (Tsai et al., 1999; Goff et al., 2001).

The membrane phospholipid hypothesis (Horrobin, 1998) of schizophrenia supported controlled studies of ethyl-eicosapentaenoic acid (E-EPA, also named omega-3 fatty acid) augmentation in schizophrenic patients. In two of these studies (Peet et Horrobin, 2002; Emsley et al., 2002), it was shown that a there was a significant decrease in PANSS total score, while one of those (Fenton et al., 2001) failed to show any significant benefit.

The small number of studies performed with modafinil, mazindol and donepezil, as clozapin augmentation strategies, reported negative results (Carpenter et al., 2000; Stryjer et al., 2004; Freudenreich et al., 2009). A double-blind, placebo controlled clozapine augmentation study with tetrabenazine, a presynaptic vesicular monoamine transporter inhibitor, provided no clinical benefit (Remington et al., 2012).

Clozapine Augmentation with Electroconvulsive Therapy (ECT)

Three open studies including clozapin augmentation with ECT provided clinical benefit (Frakenburg et al., 1993; Kho et al., 2004; Masoudzadeh et Khalilian, 2007). Nevertheless, these studies have relevant limitations. Data about clozapine and ECT dosages were not clearly reported, psychopathology measures were lacking and clozapine serum levels were not reported. A synergistic effect of the combined ECT-clozapine treatment on various neurotransmitter systems may contribute to their therapeutic effect (Newman et al., 1998). Furthermore, ECT enhancing the permeability of blood-brain barrier may allow greater amounts of clozapine to enter into the brain. This mechanism may encourage robust central nervous system effects of clozapine without worsening the adverse systemic effects (Fink, 1998). Therefore, clozapin augmentation with ECT could be a useful strategy.

In another study, 18 treatment-resistant schizophrenic patients were assigned to three equal groups: one group was given clozapine, one group was treated with ECT, and one group was treated with the combination of clozapine and ECT. This study showed that patients had a quick response to combination therapy proving that the combination therapy was superior (71%) to other single modality therapies (Masoudzadeh and Khalilian, 2007).

A systematic review which assessed open study and case series relevant to clozapine augmentation with ECT, stated that 16 patients (72.7%) showed marked improvement, 5 patients (22.7%) persisted substantial improvement beyond four months and side effects like nausea, tachycardia, hypertension, confusion and amnesia were reported during follow-up (Havaki-Kontaxaki et al., 2006). Although it has been hypothesized that clozapine and ECT association could increase the risk of status epilepticus (Bloch et al., 1996), , there is only one case report of tardive grand mal seizures seemingly related to ECT in a patient previously treated with clozapine (Masiar and Johns, 1991). Further, a review on 36 cases of clozapine and ECT combination suggested this strategy as safe and well tolerated (Kupchik et al., 2000).

DISCUSSION

When the data about clozapine augmentation with antipsychotics was evaluated together, clozapine augmentation with risperidone, a second generation antipsychotic which has a high degree D2 blockade, provided no clinical benefit. The assumption that clozapine resistant patients have a more complex pathophysiology compared to schizophrenic patients who respond to first generation antipsychotics or to other second generation antipsychotics except clozapine has been suggested. Clozapine D2 blockade is sufficient in these patients and increasing the D2 occupation might be deleterious rather than beneficial (Giegling et al., 2010). Under these circumstances, adding drugs with different profiles such as amisulpride (a potent D3 antagonist) and aripiprazole (a partial D2 agonist) is important. Other systems beyond the dopaminergic one are likely involved in the pathophysiology of clozapine resistant patients and may represent the target of augmentation strategies (Porcelli et al., 2012).

In order to interpret outcomes of these studies mentioned in this review, variable methodological differences, especially drug doses in study designs, duration of treatment, inclusion to research criteria and the differences of the initial psychopathological measures should be considered. Psychopathology in particular can vary tremendously in terms of resistance from predominantly positive, negative, or behavioral symptomatology. Most studies, were limited by small sample size, short follow-up period and the open trial design. Further, clozapine plasma levels were not always reported, a critical point that should be taken into consideration to ascertain the patient's compliance and assessment of changes in plasma clozapine levels due to the pharmacokinetic interaction with concurrent medication. More importantly, there are no well-established and defined homogeneous criteria for resistance to clozapine. Some patients showed delayed responses occurring after 6 months to a year of treatment (Meltzer et al., 1989; Rosenheck et al., 1999) that may explain, at least partially, the placebo response observed in some trials. Moreover, outcome measures are often heterogeneous because different drugs are used for different purposes (mood stabilizers are

often proposed for mood shifts, antidepressants are employed to control depressive and obsessive-compulsive symptoms). Some studies investigated only specific symptomatic domains without a global psychopathological assessment. Several studies included both schizophrenic and schizoaffective patients, making it difficult to determine if a treatment is more effective in a group rather than in the other (Porcelli et al., 2012).

In conclusion, some strategies seem to be promising and relatively safe. No one showed a strong evidence-based support in clozapine resistant patients. All positive effects, which were shown in recent meta-analysis, were either based on one outlying study or derived from a single randomized controlled trial (Sommer et al., 2012). As required, the number of placebo controlled studies, which investigate pharmacological augmentation strategies, should be enhanced and is necessary to investigate the other augmentation strategies (notably ECT) which have been examined and seem to be promising.

When the risk of multi drug use in long term and serious health problems are considered in this patient group, the necessity of additional studies far overweigh. Considering difficulties in recruitment of these patients, multi-center studies could be arranged to overcome the small sample problem. Thus, further studies are required in order to better understand the complex pathophysiology of clozapine resistant patients and to develop pharmacological strategies for this condition.

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