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Clozapine augmentation strategies

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Abstract

Clozapine is established as the gold standard for antipsychotic treatment of patients suffering from treatment-resistant schizophrenia. Over virtually 3 decades, the level of inadequate response to clozapine was found to range from 40% to 60%. A heightened interest developed in the augmentation of clozapine to try to achieve response or maximize partial response. A large variety of drug groups have been investigated. This article focuses on the meta-analyses of these trials to discover reasonable evidence-based approaches to the management of patients not responding to clozapine.

Keywords: clozapine, augmentation, antipsychotics, schizophrenia, treatment resistance, refractory, ECT, mood stabilizers

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Introduction

Clozapine was approved by the US Food and Drug Administration (FDA) in 1989 and marketed in 1990 in the United States for the treatment of treatment-resistant schizophrenia (TRS) defined as at least 2 trials[1,2] of nonclozapine antipsychotics at an adequate dose (400 to 600 mg chlorpromazine equivalent per day) unless prohibited by side effects and duration (≥6 weeks) without benefit. Twenty to thirty percent of patients with the diagnosis of schizophrenia display treatment resistance.[3] The annual costs for TRS, which include antipsychotic drug costs, hospitalization, and total health resource use are 3- to 11-fold higher compared to costs for schizophrenia in general.[4] Clozapine currently carries FDA indications for use in TRS and for suicidal behavior in schizophrenia or schizoaffective disorder.[5] Off-label uses of clozapine include treatment of violent, aggressive patients, patients with tardive dyskinesia, and treatment-resistant bipolar disorder and in psychosis associated with Parkinson disease.[6-12] The efficacy of clozapine has been repeatedly demonstrated. Regarding tolerability, clozapine imparts a low risk of extrapyramidal side effects.[13] It is now recognized as the gold standard for treatment of TRS.[4] However, 40% to 60% of TRS patients do not have an efficacious outcome or only have a partial response to clozapine treatment.[14,15]

Treatment-resistant schizophrenia is divided into 3 types or presentations. First is pseudo-TRS, which represents 25% to 30% of TRS patients. Their lack of improvement in symptoms is due to not receiving an appropriate dose/plasma concentration and duration of antipsychotic treatment. With dose/plasma concentration optimization, these patients would have a reasonable chance for response. Second is TRS patients, 20% to 30% of patients, who respond to clozapine. Third is ultra-TRS, which

represents 40% to 60% of clozapine patients who failed or had only a partial response to an adequate clozapine trial.[16-18] An adequate trial of clozapine is defined by 2 factors: an adequate steady-state plasma concentration and an adequate duration of treatment. The minimum steady-state plasma concentration for response has been reported as >350 ng/mL. Unfortunately, the upper end of the plasma concentration range is unclear. Hence, it is suggested to increase plasma concentrations if there is no response, guided by the patient's tolerability. Concentrations above 1000 ng/mL rarely are associated with response.[19,20] Historically, the duration of treatment was thought to be between 3 and 6 months. However, current recommendations suggest that a duration of 2 to 3 weeks after a dose increase is sufficient time to determine response.[19]

Take Home Points

1. Forty to sixty percent of treatment refractory schizophrenia patients do not fully respond to clozapine.
2. Prior to considering augmentation, patient cases should be reviewed regarding diagnosis, comorbidities, level of compliance, clozapine/norclozapine plasma concentration, and continuous stressors.
3. Little data support adding another antipsychotic at this time.
4. Of the mood stabilizers, only sodium valproate has positive data supporting its use and tolerability.
5. Data indicate the augmenter with the most evidence of efficacy is electroconvulsive therapy.

Methods

An exhaustive literature search was conducted through the PubMed/MEDLINE database. Search terms included clozapine, augmentation, antipsychotics, schizophrenia, treatment resistance, ultra-treatment resistance, refractory, electroconvulsive therapy (ECT), and mood stabilizers. All meta-analyses were reviewed; selection of individual studies included those involving clozapine treatment-resistant studies. Several individual studies were explored of agents found to be efficacious in meta-analyses. The patient populations consisted of patients receiving clozapine without response (as measured via symptom-assessment scales) or those with partial response as determined by the individual studies. Outcome criteria included validated symptom-assessment scales including the Positive and Negative Symptom Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) as well as their subscales. Several studies used specific negative symptom scales. Assessments occurred at baseline and at various time points over weeks to months after the initiation of the augmentation agent.

Meta-Analyses

A large number of individual studies have explored augmentation strategies to bring about symptom reduction in patients who have not responded to an adequate trial of clozapine. However, the quality of these studies varies considerably. Few of the studies are double-blind randomized controlled trials (RCTs). Many are case reports, small case series, or small open-label studies. With this in mind, the more informative review of the literature resides in exploring the meta-analyses of reports of clozapine augmentation. Meta-analyses are statistical assessments of data to provide a single best estimate of effect.[21] The data sources are studies that meet a priori inclusion criteria set up to determine which studies to include in the review. This enables a statistical pooling of results from different studies, which improves the precision of the data, allowing a more accurate estimation of the effect. However, the quality of meta-analysis is dictated by the quality of studies included. Meta-analyses can be inaccurate due to reporting bias, publication bias, and heterogeneity of the studies included.

Although meta-analyses provide an estimation of effect, other factors also have influence on the feasibility of the augmentation strategy. As is pointed out, side-effect burden can limit the application of a meta-analysis to suggest treatment.

Approach to Clozapine-Resistant Patients

Prior to the consideration of augmenting strategies, the patient's status should be reviewed using the five "C"s[16]: correct diagnosis, comorbid conditions, compliance, concentration of antipsychotics, continuous psychosocial stressors (Table 1). This assessment allows a determination of factors or conditions that, if addressed, may reduce the need of an augmentation trial. Following this assessment, consideration of augmentation strategies may still be warranted, and the provider would consider the following agents.

Antipsychotics

Five[22-26] of the 12 medication meta-analyses reported on antipsychotic augmentation of clozapine exclusively (Table 2). The remaining analyses reviewed augmentation of a variety of agents, including antipsychotics. Barbui et al[22] reviewed 21 randomized studies (n = 1480) evaluating chlorpromazine and risperidone as well as agents not available in the United States, such as pipothiazine and sulpiride. The trials consisted of 14 open and 6 double-

TABLE 1: The 5 "Cs" assessment (correct diagnosis, comorbid conditions, compliance, concentration of antipsychotics, continuous psychosocial stressors)

Correct diagnosis	Ruling out pseudoresistance conditions, such as severe personality disorders, mania, or depressive disorders with psychotic features, and other brain diseases, such as anti-NMDA receptor encephalitis,[61,62] will allow the determination of other treatable causes of the patient's condition.
Comorbid conditions	Determining the presence of substance abuse, affective disorders, and obsessive-compulsive disorder or personality disorders[61] allows for the incorporation of additional therapeutic modalities that may be synergistic with the augmentation trial.
Compliance	Assessment of the patient's ability to comply with treatment is essential. Poor compliance has been associated with substance abuse, greater hostility, and lack of insight.[63] If the patient is determined to have questionable compliance, it may be necessary to delay the augmentation trial until the compliance issues are resolved.
Concentration of antipsychotics	Determination of the clozapine and norclozapine plasma concentration is recommended prior to initiating an augmentation trial. In a study by McCutcheon et al,[17] a third of treatment-resistant patients were found to have subtherapeutic plasma concentrations. In general, plasma concentrations of clozapine should be at a minimum of 350 to 600 ng/mL.[64] An upper limit for the range is unclear at this time. In the case of low plasma concentration of clozapine, the concentration should be increased to the minimum therapeutic threshold for an appropriate duration of time to assess the effect on the patient's symptoms. In general, a trial of 3 to 6 mo at a therapeutic plasma concentration should occur prior to initiating an augmentation trial[65-71]
Continuous psychosocial stressors	Factors such as poor housing, little social support, isolation, and poverty may contribute to the appearance of a treatment refractory condition in patients with schizophrenia.[71]

NMDA = N-methyl-D-aspartate.

blind trials. The majority of randomized trials (15/21) were conducted in China. Upon separate analysis, the open trials were found to significantly favor the augmentation group. However, the analysis of the double blind trials revealed no significant difference between placebo and augmenter. Risperidone was the augmenter in 10 trials with 4 of the 10 having a double-blind design. The authors felt there was no support for antipsychotic augmentation of clozapine.

Taylor et al[23] evaluated 14 trials consisting of 734 subjects. Augmenters included the second-generation antipsychotics (SGAs) aripiprazole and risperidone and first-generation antipsychotics chlorpromazine, haloperidol, and pimozide as well as agents not available in the United States: amisulpride, sertindole, and sulpiride. Unlike the Barbui et al[22] report, this analysis consisted of only randomized, placebo-controlled trials. The results showed a small benefit of the augmenter over placebo, effect size –0.239 (95% confidence interval [CI]: –0.452, –0.026); $P = .028$. Meta-regression did not find a relationship between treatment duration and symptom reduction. The data do not allow for a recommendation of any particular augmentation agent.

Galling et al[24] reviewed augmentation of antipsychotic therapy with a second antipsychotic versus continued monotherapy. Thirty-one studies were reviewed, of which 20 trials (n = 1112) involved clozapine. Augmenters included fluoxetine, pimozide, risperidone, paliperidone, aripiprazole, ziprasidone, sulpiride, and sertindole. Double-blind and higher quality studies found no significant difference between groups.

A recent meta-analysis[25] evaluated 12 double-blind randomized clinical trials involving the addition of a SGA to clozapine treatment. Five studies investigated risperidone, and 3 trials investigated aripiprazole. The remaining agents (amisulpride, sertindole, sulpiride, and ziprasidone) had only 1 trial each. Results of the analysis found no significant benefit of augmentation for positive symptoms. A small effect was seen for negative (standardized mean difference [SMD] = –0.38; $P = .005$; $I^2 = 62.7\%$) and depressive symptoms (SMD = –0.35; $P = .003$; $I^2 = 4.9\%$). The authors[25] suggested the statistically significant effects may not be clinically significant. In addition, the quality of evidence for the effect on negative and depressive symptoms was low.

A nationwide cohort study in Sweden was report by Tiihonen et al.[26] The study explored the risk of psychiatric rehospitalization in 62 250 patients with schizophrenia during the use of 29 different antipsychotic monotherapy and polypharmacy treatments. The data reported were from April 24 to June 15, 2018. Risks were determined using within-individual analyses to minimize selection bias. The authors reported the lowest risk of psychiatric rehospitalization was found for the combination of clozapine plus aripiprazole (hazard ratio [HR], 0.86; 95% CI: 0.79, 0.94) and was superior to clozapine monotherapy. The risk was lower in the subgroup of patients experiencing their first psychotic break (HR, 0.78; 95% CI: 0.63, 0.96). This population was assumed to be poor responders to monotherapy, but treatment refractory status was not determined. Also, confounding by indication bias could not be ruled out.

TABLE 2: Pharmacological agents discussed

Reference	Type of Studies Reviewed	Augmenters	Outcomes	Comment
Antipsychotics				
Barbui et al[22] (2009)	21 Randomized studies (n = 1480): 6 studies were double-blind, placebo-controlled trials	Amis, CPZ, Pipo, Risp, Sulp	• 14 Randomized open studies significantly favored aug: SMD = −0.80; 95% CI: −1.14, −0.46 • 6 RCT found no statistically significant positive effect: SMD = −0.12; 95% CI: −0.57, 0.32	Mix of co-initiation (cloz + aug started at same time) and augmentation (Aug added) studies together. Authors concluded the evidence supporting the addition of an antipsychotic was weak.
Taylor et al[23] (2012)	14 Studies (n = 734): combination of open-label and double-blind studies	Amis, Arip, CPZ, Hal, Pim, Risp, Sert, Sulp	Aug with an antipsychotic conferred a small benefit over plac: effect size −0.239 (95% CI: −0.452, −0.026); *P* = .028	Focused only on symptom reduction, not response rates. Did not analyze open-label vs double-blind separately. Authors concluded augmentation with a second antipsychotic is modestly beneficial.
Galling et al[24] (2017)	20 Clozapine trials (n = 1112) compared randomized trials augmentation with a second antipsychotic vs continued antipsychotic monotherapy	Ari, Flu, Pal, Pim, Risp, Sert, Sul, Zip	• Total symptom reduction—Aug superior to mono only in open-label and low-quality trials (*P* < .001) • Double-blind and high-quality trials found no significant difference (*P* = .120 and .226, respectively) • Study-defined response found no difference in low- or high-quality studies	Evidence regarding symptom improvement lacking for augmentation of either clozapine or nonclozapine antipsychotics. Negative symptoms improved more with augmentation only with aripiprazole (8 studies, N = 532; SMD = −0.41; 95% CI: 20.79, 20.03; *P* = .036).

Anticonvulsants

Lamotrigine is of interest as an augmenter of clozapine due to its ability to inhibit excess glutamate release.[27] Glutamate activity has been put forward as dysfunctional in the pathophysiology of schizophrenia.[28] A meta-analysis[29] was performed on studies of lamotrigine augmentation of clozapine. Five randomized, placebo-controlled studies were reviewed (Table 2). However, in 3 of the trials,[30,31] the majority of subjects were not receiving clozapine but other SGAs. The 2 studies by Goff et al[30] had only 20.6% and 10%, respectively, treated with clozapine. The report by Kremer et al[31] of study completers (n = 21) had only 1 subject receiving clozapine. The duration of the trials ranged from 10 to 24 weeks, and 161 subjects were included. The primary outcome measure was the PANSS or BPRS total score; the secondary outcome measures consisted of positive and negative symptom ratings. Individually, none of the 5 trials reported a significant difference between lamotrigine and placebo using intent to treat analysis. The results of the meta-analysis found lamotrigine was significantly different from placebo on the primary and secondary outcome variables.

Zheng et al[32] evaluated 22 RCTs (n = 1227) published in English and Chinese languages. A variety of anticonvulsants were used, including topiramate (5, n = 270), lamotrigine (8, n = 299), sodium valproate (6, n = 430), and magnesium valproate (3, n = 228). Significant superiority of augmentation was found for studies utilizing topiramate, lamotrigine, and sodium valproate. Topiramate showed significant results for total psychopathology score as well as positive, negative, and general psychopathology symptoms. The all-cause discontinuation for the topiramate trials indicated a high

TABLE 2: Pharmacological agents discussed (continued)

Reference	Type of Studies Reviewed	Augmenters	Outcomes	Comment
Bartoli et al[25] (2019)	12 Double-blind RCTs of adjunctive SGAs (n = 762)	Amis, Arip, Risp, Sert, Sulp, Zip	No difference between SGAs and placebo: • Positive symptoms: o SMD = −0.21; P = .170, I^2 = 68.0%, measure of heterogeneity • Low-moderate effects • Negative symptoms: o SMD = −0.38; P = .005, I^2 = 62.7% • Depressive symptoms: o SMD = −0.35; P = .003, I^2 = 4.9%	No demonstrable efficacy for positive symptoms. Small improvement for negative and depressive symptoms.
Tiihonen et al[26] (2019)	Cohort study (n = 62 250) patients with schizophrenia: 29 different antipsychotic mono and poly	Arip, LAI, Olan, Quet, Risp	• Lowest risk of psychiatric rehospitalization (poly vs mono with cloz) • Poly-cloz + arip (HR, 0.86; 95% CI: 0.79, 0.94)	Analyzing only first episode patients Poly-cloz + arip (0.78; 95% CI: 0.63, 0.96)
Anticonvulsants				
Tiihonen et al[29] (2009)	RCTs, 5 trials 10- to 24-wk duration (n = 161)	Lamot	• Total score for psychosis: o SMD = 0.57; 95% CI: 0.25, 0.89; P < .001 o OR 0.19; 95% CI: 0.09, 0.43 o P < .001; NNT 4; 95% CI: 3, 6 • Positive symptoms: SMD = 0.34; 95% CI: 0.02, 0.65; P = .04 • Negative symptoms: SMD = 0.43; 95% CI: 0.11, 0.75; P = .008	Authors suggest that 20% to 30% of clozapine-resistant patients may obtain clinical benefit from lamotrigine augmentation.
Zheng et al[32] (2017)	22 RCTs (n = 1227) for adjunctive antiepileptic agents: Topiramate: 5 Lamotrigine: 8 Sodium valproate: 6 Magnesium valproate: 3	Lamot, MgVal, NaVal, Top,	Significant superiority in total psychopathology over clozapine monotherapy: • Topiramate P < .0001 • Lamotrigine P = .05 • Sodium valproate P = .002	English and Chinese databases reviewed. After removal of outliers Lamotrigine lost significance. Topiramate had high dropout rate, NNH = 7. Only 3 of the 22 RCTs established that the clozapine plasma concentration was >350 ng/mL.

TABLE 2: Pharmacological agents discussed (continued)

Reference	Type of Studies Reviewed	Augmenters	Outcomes	Comment
Antidepressants and mixed agents				
Sommer et al[33] (2012)	Double-blind RCTs: 29 studies reporting on 15 different aug (n = 1066)	Amis, Arip, Cit, CX516, D-cycl, D-ser, Fluox, Gly, Hal, Lamot, Mir, Risp, Sar, Sulp, Top, Val	• Lamot and top were dependent on single studies with deviating findings • Cit, sulp, and CX516 based on single studies	Analyzed only individual drug combinations. Not limited to participants with cloz resistance. Authors concluded that pharmacological augmentation of cloz not demonstrated to be better than plac.
Porcelli et al[34] (2012)	62 Studies (n = 1556): only 8 RCTs (5 risp and 3 lamot, used for meta-analysis)	Amis, Arip, Risp, Sulp, Zip Fluox, Fluv, Mirt, Lamot, Top, Li, CX516, D-cycl, D-ser, E-EPA, Gly, Maz, Mem, Mod, N-MG, ECT	Evidence for augmentation with: • Amis and arip • Mirt • E-EPA	Meta-analyses did not support either the use of risp or lamot as cloz adjunct.
Correll et al[35] (2017)	9 Meta-analyses of 42 combination strategies 381 individual trials (n = 19 833) • 5 strategies that augmented cloz	Amis, Arip, Hal, Pim, Risp, Sulp, Cit, Dul, Fluox, Mirt, E-EPA, Gly, Lamot, Top,	• No combination strategies with cloz outperformed controls • Glycine efficacy for positive symptoms	Effect sizes were inversely correlated with study quality (correlation coefficient, −0.06; 95% CI: 0.01, −0.12; *P* = .02).
Siskind et al[36] (2018)	46 Studies (n = 2182; 16 in Chinese database) of 25 interventions RCTs: • Cloz + aug vs Cloz + plac • Cloz + aug-1 vs Cloz + aug-2	Arip, Flu, Val, Mem	• Total symptoms: o Arip (SMD = 0.48; 95% CI: −0.89, −0.07) o Flu (SMD = 0.73; 95% CI: −0.97, −0.50) o Val (SMD = 2.36 95% CI: −3.96, −0.75) • Negative symptoms: o Mem (SMD = −0.56; 95% CI: −0.93, −0.20)	Not limited to the English language. All the Chinese studies were deemed to be of low quality. When low-quality studies were excluded arip and flu lost statistical significance. ECT, highly promising.

dropout rate (relative risk = 1.99; 95% CI: 1.16, 3.39; $P = .01$; $I^2 = 0\%$; number needed to harm [NNH] = 7. Lamotrigine showed marginally significant improvement in total rating scale score. After removal of outliers (2 studies with SMD < –1.0), lamotrigine lost significance. In addition, lamotrigine did not show significant effects for positive, negative, or general psychopathology symptoms. Sodium valproate demonstrated significant reduction in PANSS total score (SMD = –1.26; 95% CI: –2.05, –0.47; $P = .002$; $I^2 = 91\%$). The results remained significant with the removal of outliers. The subscales of positive and general psychopathology symptoms showed significant effect, but the negative symptoms demonstrated no change between groups. Study defined response was not different between the valproate-clozapine group and the clozapine-alone group. Lastly, only 3/22 trials included clozapine plasma concentrations to assure the concentration was >350 ng/mL.

Antidepressants and Miscellaneous Agents

Twenty-nine studies evaluating 15 different augmenters were reported by Sommer et al.[33] All were double-blind trials (Table 2). The primary outcome was total symptom severity, and secondary outcomes were subscores for positive and negative symptoms. Sulpiride had significant effects for total, positive, and negative symptoms. Lamotrigine showed significant efficacy for total symptoms; however, the effect disappeared after an outlier was

TABLE 2: Pharmacological agents discussed (continued)

Reference	Type of Studies Reviewed	Augmenters	Outcomes	Comment
ECT				
Lally et al[37] (2016)	5 Trials (n = 71): • 4 open label • 1 RCT Case series and case reports (52 patients)	ECT	• 5 trials proportion of response • Cloz + ECT = 54% (95% CI: 21.8%, 83.6%) • 4 open label studies = 56% (95% CI: 19.4%, 87.2%) • 1 RCT = 48.7% (95% CI: 33.6%, 64.0%) • Case series and case reports clinical response rate = 76%	Data from retrospective chart reviews, case series, and case reports were added to the 5 trials resulting in a total of 192 subjects with a response to Cloz + ECT of 66% (95% CI: 57.5%, 74.3%). Mean number of ECT treatments = 11.3. 32% of cases (20 out of 62 patients) relapsed following cessation of ECT.
Ahmed et al[38] (2017)	23 Studies (n = 1179): • 9 studies Cloz augmented ECT (95 patients) • 14 studies other APs – aug ECT (1084 patients)	ECT	• Non-cloz studies: SMD = 0.891 • Cloz studies: SMD = 1.504	Nonclozapine APs: flup, cpz, risp, sulp, olanz, and lox.
Wang et al[39] (2018)	18 RCTs (n = 1769), 17 studies published in China and 1 study in the United States • Mean sample size = 88.5 ± 41.7 (range = 39–246, median = 79) subjects • Duration = 9.2 ± 2.6 (range = 4–12, median = 8) wk	ECT	• Post-ECT assessment: o SMD = −0.88; 95% CI: −1.33, −0.44; I^2 = 86%, P = .0001 o Response NNT = 3 o Remission NNT = 13 • End point assessment: o SMD = −1.44; 95% CI: −2.05, −0.84; I^2 = 95%, P < .00001 o Response NNT = 4 o Remission NNT = 14 o Memory impairment NNH = 4 o Headache NNH = 8	Significant separation occurring at wk 1–2.

Amis = amisulpride; Arip = aripiprazole; Aug = augmenter; Cit = citalopram; CPZ = chlorpromazine; Cloz = clozapine; CI = confidence interval; CX516 = glutamatergic agonist; D-cycl = D-cycloserine; D-ser = D-serine; Dul = duloxetine; ECT = electroconvulsive therapy; E-EPA = ethyl eicosapentaenoic acid; Fluox = fluoxetine; Flu = fluphenazine; Flup = flupenthixol; Fluv = fluvoxamine; Gly = glycine; Hal = haloperidol; I^2 = measure of heterogeneity; Lamot = lamotrigine; LAI = long-acting injection; Li = lithium; Lox = loxapine; MgVal = magnesium valproate; Maz = mazindol; Mem = memantine; Mirt = mirtazapine; Mod = modafinil; Mono = monotherapy; N-MG = N-methylglycine; NaVal = sodium valproate; NNT = number needed to treat; NNH = number needed to harm; Olan = olanzapine; Pal = paliperidone; Pim = pimozide; Pipo = pipothiazine; Plac = placebo; Poly = polypharmacy; Quet = quetiapine; RCT = randomized controlled trial; Risp = risperidone; Sar = sarcosine; Sert = sertindole; SGAs = second-generation antipsychotics; SMD = standard mean difference; Sulp = sulpiride; Top = topiramate; Val = valproate; Zip = ziprasidone.

removed. A significant improvement for positive symptoms was found for topiramate; however, similar to lamotrigine, the effect was lost with the removal of an outlier. Citalopram was found to have significant effect for total and negative symptoms. CX516 (a glutamate agonist) showed significant effect on total and negative symptoms. All of the positive results, other than those with lamotrigine, were based on only 1 trial. Mirtazapine and fluoxetine did not show significant changes. The remaining antipsychotics, amisulpride, aripiprazole, haloperidol, and risperidone showed no effect. Of the remaining glutamatergic agents, D-cycloserine, D-serine, glycine, and sarcosine did not show an effect.

Porcelli et al[34] evaluated 62 trials (n = 1556). The primary outcome criterion was the mean change in total score on the PANSS or the BPRS. Only 8 RCTs were used for the meta-analysis. These included 5 risperidone studies and 3 lamotrigine trials. The meta-analyses did not support either the use of risperidone or lamotrigine as augmenters of clozapine. Open-label trials of amisulpride, aripiprazole, mirtazapine, and ethyl eicosapentaenoic acid showed evidence for augmentation effects. The ECT augmentation required further evaluation. Tolerability was found to be a problem with risperidone (cognition and glucose control, hyperprolactinemia, extrapyramidal symptoms, and weight gain) and amisulpride (bradykinesia, akathisia, tremor, and increased prolactin serum concentrations).

Correll et al[35] conducted a systematic review of meta-analyses of pharmacologic treatment strategies added to antipsychotic drug treatments and compared these to antipsychotic monotherapy. Clozapine combinations were compared separately. The primary outcome was total symptom reduction. Secondary outcomes included positive and negative symptoms. There were 5 strategies that augmented clozapine (antidepressants, antipsychotics, glycine, lamotrigine, topiramate). None of the combination strategies evaluating total psychopathology with clozapine outperformed controls. The authors also reported, when considering the quality of the studies in the meta-analysis, the effect sizes were inversely correlated with study quality. The authors concluded that patients not responding to clozapine are unlikely to have a response to an augmentation treatment.

Siskind et al[36] reviewed 46 studies, 16 from a Chinese database, consisting of 25 interventions. Outcome criteria included total psychosis symptom scores, PANSS and BPRS, negative symptoms (Scale for the Assessment of Negative Symptoms and PANSS negative symptom subscale and positive symptoms Scale for the Assessment of Positive Symptoms). Studies consisted of RCTs with clozapine plus augmenter versus placebo or another augmenter. Interventions included antipsychotics (aripiprazole, risperidone, sulpiride/amisulpride, sertindole, haloperidol, penfluridol, olanzapine, pimozide quetiapine, and ziprasidone), antidepressants (fluoxetine, paroxetine, duloxetine, and mirtazapine), and mood stabilizers (sodium valproate, topiramate, lamotrigine, and lithium). Other pharmacologic agents consisted of memantine, glycine, sarcosine, minocycline, and ginkgo biloba. Non-pharmacologic interventions included cognitive behavioral therapy, ECT, and transcranial magnetic stimulation. Four interventions showed significant response: aripiprazole, fluoxetine, and sodium valproate for total symptom reduction and memantine for negative symptoms. However, when only high-quality studies and studies that used rating scales were analyzed, aripiprazole lost significance of all psychosis outcomes. Fluoxetine had 1 high-quality study and 5 low-quality studies. The exclusion of the low-quality studies resulted in the loss of significance for positive and negative symptoms.

Electroconvulsive Therapy

Three recent meta-analyses[37-39] were performed to determine the effect of ECT as an augmenter in clozapine-resistant patients (Table 2). In addition, there are many literature reviews and case series that explore this question that are not reviewed here. Response definitions ranged from 25% to 50% reduction in total PANSS or BPRS and remission is defined as $\geq$75% reduction in total PANSS or BPRS in the studies.

Lally et al[37] reviewed five trials (n = 71), 4 of which were open trials. Response was defined as a $>$40% reduction in BPRS scores. They found the proportion of subjects who responded was 54% (95% CI: 21.8%, 83.6%) for all 5 trials. The response rate in open-label trials (n = 32) was 56% (95% CI: 19.4%, 87.2%), and in the RCT (n = 39), it was 48.7% (95% CI: 33.6%, 64.0%).

Ahmed et al[38] reviewed 23 studies (n = 1179) comparing ECT augmentation of clozapine versus ECT augmentation of other antipsychotics. The outcome criteria was total psychopathology measured by the PANSS or BPRS. The ECT-clozapine group had an SMD = 1.504, and the ECT-other antipsychotic group had an SMD = 0.891. The authors speculated there may be a synergistic effect of ECT with clozapine versus other antipsychotics.

Wang et al[39] reported on 18 RCTs (n = 1769) evaluating ECT augmentation of clozapine treatment. Seventeen studies were published in China and 1 in the United States. Prior meta-analyses have not included studies published in Chinese as they were not accessible until now. Post-ECT and end-point assessments revealed a significant improvement in symptoms. Response was associate with a number needed to treat [NNT] = 4 and remission had an NNT = 14. Subject-reported adverse events included memory impairment (NNH = 4) and headache (NNH = 8). This study represents the largest meta-analysis to date of ECT augmentation of clozapine treatment.

Significant improvement was evident 1 to 2 weeks after the initiation of the ECT treatments. A sensitivity analysis indicated that the improvement was not driven by outlier studies. Overall, ECT augmentation of clozapine was generally safe and well tolerated.

Individual Studies

There are several agents that have additional data that warrants discussion regarding use in ultra-TRS patients.

Memantine

Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist.[40] It carries an FDA indication for the treatment of moderate-to-severe Alzheimer disease. The rationale for use in the treatment of schizophrenia focuses on glutamatergic system dysfunction via the NMDA receptors. Agents that block NMDA receptors, such as phencyclidine, produce symptoms similar to those in schizophrenia. Hypofunctioning of the NMDA system reduces stimulation of GABAergic neurons

resulting in an excess of glutamate in the synapse resulting in cell death. Memantine may modulate the neurotoxic glutamate activity while allowing normal activation of the receptor system.[41-47]

Siskind et al[48] found memantine effective in the treatment of negative symptoms (PANSS, BPRS) SMD = -0.56; 95% CI: –0.93, –0.20). Single studies have explored the use of memantine in the treatment of schizophrenia and as an augmenter of clozapine treatment. However, memantine did not show effect as an adjunct to nonclozapine antipsychotics.[49]

De Lucena et al[50] reported a 12-week, double-blind, randomized, placebo-controlled trial comparing the addition of memantine 20 mg/d to ongoing clozapine treatment. Subjects were individuals who received clozapine for at least 10 years with partial response of negative symptoms. The primary outcome measure was the total score on the BPRS as well as subscales for negative and positive symptoms. Secondary outcomes included the Clinical Global Impression (CGI) and the Mini Mental State Examination (MMSE) as well as extrapyramidal side effects (EPSE) and weight gain. Twenty-two subjects were randomized, and 21 subjects completed the trial. A significant improvement was observed for the BPRS total, positive, and negative symptom scores as well as the CGI and MMSE. No differences were found in EPSE or weight. In light of the effect of memantine on all 3 scales, its overall benefit may be broader than treating only negative symptoms.

Veerman et al[51] conducted a 12-week, randomized, double-blind, placebo-controlled crossover study of memantine 20 mg/d added to current clozapine therapy. The primary end points were changes in memory and executive function assessed via the Cambridge Neuropsychological Test Automated Battery (CANTAB) as well as the PANSS and CGI-severity scale. Assessments included the change from baseline to week 12 and, after the crossover, weeks 14 to 26. All subjects were treated with clozapine for at least 6 months and had a minimum of 12 weeks with the clozapine plasma concentration above 350 ng/mL. Fifty-two subjects with ultra-TRS were randomized to the 2 groups. Compared with placebo, memantine improved the composite memory score (verbal recognition memory and paired associates learning task) on the CANTAB (effect size = 0.30) and PANSS negative subscale score (effect size = 0.29). Diminished expression was affected more than social amotivation.

Veerman et al[52] subsequently published the results of an open-label 1-year extension study. Subjects completed the first trial, and those who experienced beneficial effects continued open-label memantine treatment for an additional year. Again, the primary end points were memory and executive function using the CANTAB, PANSS, and the CGI-S. Twenty-four subjects received memantine for 1 year. The small improvement in memory realized in the 12-week trial was maintained through the 1-year extension. At the end of 24 weeks, the PANSS negative, positive, and total symptoms significantly improved. Significant improvement continued in all these measures between 26 and 52 weeks of memantine treatment. The effect sizes varied from 0.39 to 0.51. The CGI-S showed a nonsignificant improvement at 26 and 52 weeks. No effects were seen on executive function at 12 weeks in the placebo-controlled trial or at 26 or 52 weeks of the extension trial. The effect size associated with negative symptoms became larger over the 1-year extension. In addition, the effect on diminished expression that was found after 12 weeks expanded to include an equal and moderate effect on expressive deficits and social amotivation. There was no effect on positive and overall symptoms of schizophrenia in the placebo-controlled trial; however, these symptoms showed substantial significant improvement after 26 weeks of memantine and further improvement at 52 weeks with the effect sizes ranging from moderate to large. All available studies dosed memantine at 20 mg/d; the authors speculate as to the possibility of more improvement at doses of 30 or 40 mg/d.

Fluvoxamine

Clozapine undergoes oxidative metabolism primarily by the P450 1A2 (CYP1A2) enzyme with minor pathways involving CYP2D6 and CYP3A4 enzymes.[53] Fluvoxamine is a selective serotonin reuptake inhibitor that possesses potent inhibitor effects of CYP1A2. The addition of 50 mg of fluvoxamine is reported to increase clozapine plasma concentrations by 120%, and the combination increases the ratio of clozapine to N-desmethylclozapine (NDMC or norclozapine), the primary metabolite.[54] It was reported that a larger clozapine/norclozapine ratio may be more predictive for response than the clozapine plasma concentration.[55] In addition, norclozapine is a more potent serotonin 5-HT2C antagonist, which may contribute to seizure risk and weight gain.[56] However, intolerance has been reported with increased plasma concentrations and subsequent toxic symptoms, including constipation, hypersalivation, nausea, and sedation.[57,58]

Polcwiartek and Nielsen[59] performed a systematic review of fluvoxamine as a clozapine augmenter to increase the ratio of clozapine to norclozapine. They graded the evidence A, B, C, or D depending on the quality of the data. They found 24 case reports/series, 7 cohort studies, and 2 RCTs (n = 241). Their review found A-level evidence supporting adjunctive fluvoxamine increasing clozapine plasma concentrations and increasing the clozapine/norclozapine ratio. B-level evidence supported reduced metabolic adverse effects of clozapine and found B-level evidence for not reducing agranulocytosis risk. Depressive or obsessive-compulsive symptoms may improve with a C-level of evidence. No studies investigated the effect of adjunctive fluvoxamine to minimize clozapine rebound psychosis or to reduce the effects of smoking on clozapine plasma concentrations.

Lu et al[60] conducted a 12-week, randomized, double-blind, placebo-controlled study to evaluate the effects of fluvoxamine on metabolic parameters and psychopathology in subjects being started on clozapine (n = 85). Subjects were randomized to receive combination therapy of fluvoxamine 50 mg/d plus clozapine 100 mg/d or monotherapy of clozapine 300 mg/d. Subject's previous antipsychotics were tapered and discontinued. Assessments were done at baseline and 4, 8, and 12 weeks. Clozapine plus fluvoxamine significantly attenuated body weight and the following metabolic parameters compared with clozapine monotherapy: insulin resistance and concentrations of insulin, glucose, and triglycerides. The combined treatment group showed significant reduction in the PANSS general psychopathology scores compared with the monotherapy group. However, both groups exhibited significant improvements in the PANSS total and negative scores. In light of the dosing differences between groups, no difference was observed in the plasma clozapine level. Predictably, the monotherapy group showed higher levels of norclozapine and clozapine N-oxide than the combined group. The ratio of clozapine to norclozapine was significantly different between the two groups (monotherapy ratio = 3.9 [2.2], combination group ratio = 6.8 [4.0], $P \leq .0001$.

Case

Part 1

Patient AB developed schizophrenia at approximately age 20 and is now age 50.

AB experienced persistent auditory hallucinations, which took the form of voices making comments about him. The content of the hallucinations revolved around negative themes, such as "you will be alone when mother dies," "no one will help you," "you shouldn't be in your apartment." In addition, AB presents with negative symptoms involving lack of motivation to carry out tasks, little interest in any activities, and isolation in the apartment. The patient is obese with a weight of 300 lbs. AB smokes and gets little, if any, exercise.

AB had been treated with a variety of antipsychotics over the years with little effect. Most of the trials had adequate dose and duration.

AB met criteria for a clozapine trial in that he fulfilled the criteria for treatment refractory schizophrenia of at least 2 trials of antipsychotic treatments at appropriate doses and duration. Clozapine was titrated to 300 mg/d. Additional medication included bupropion extended release 300 mg at bedtime and topiramate 50 mg at bedtime to reduce appetite. The clozapine trough plasma concentration was drawn at steady state and was found to be 318 ng/mL.

Part 2

Due to persistent symptoms, the clozapine dose was gradually increased to 700 mg/d over 15 months, ultimately achieving a clozapine plasma concentration = 828 ng/mL and norclozapine = 444 ng/mL. Over this period, the patient's symptoms improved with a reduction in paranoia and auditory hallucinations. AB continued to report low motivation and low energy.

Bupropion extended release was tapered and discontinued due to unclear indication, potential seizure risk, and potential stimulation of positive symptoms. No emergence of depressive symptoms occurred. AB's mother reported the clozapine has been quite helpful with the paranoia and voices over the past 6 months. AB still suffers from amotivation, does not leave the apartment, and does not get any exercise.

Part 3

In light of the persistence of negative symptoms, AB's case was reviewed to determine if an augmentation strategy would be indicated. Applying the 5Cs assessment, the diagnosis was verified as schizophrenia; no comorbid depression was found. AB was compliant with medication. Clozapine plasma concentrations were found to be above the therapeutic threshold. AB had positive support from the mother and did not have any other stressors present. Target symptoms were identified to include amotivation, lack of interest in activities, and isolating in the apartment. A review of the literature investigating treatments for negative symptoms was conducted. Memantine studies indicated effects in treating negative symptoms with good tolerability. The report of 52-week data showing improvement in cognition and psychopathology supported the use of memantine.[47] The plan was discussed with AB and the mother. They were accepting of the plan. Memantine was initiated at 10 mg/d for 1 week, then increased to 20 mg/d.

Part 4

One month later, AB presented with stable symptoms and a low occurrence of voices. At the 2-month visit, AB reported interest in doing some art projects, which used to be a preferred activity in the past. At the 3-month visit, AB described going to the apartment's exercise room riding the stationary bike on 3 occasions.

Although these changes appear quite minimal, for this patient, they represent a potential beginning of improvement in negative symptoms. The data available suggest continued improvement over 52 weeks. For these gains to be viewed as successful, the improvement will have to continue and expand over the next 9 months.

Conclusion

In summary, a substantial group of treatment refractory patients with schizophrenia do not respond to clozapine. Switching to another antipsychotic appears to be futile as nonresponse was what brought them to clozapine treatment. As such, consideration of augmenting interventions needs to be undertaken to benefit these patients. However, little data support the attempts to augment

clozapine. The largest data set suggests ECT augmentation as an effective augmentation strategy. Sodium valproate has data supporting its use. In a recent observational cohort study, aripiprazole combined with clozapine appeared to be associated with a lower rehospitalization rate. Although the memantine data set is smaller, memantine appears to be associated with significant improvement in PANSS negative symptoms, positive symptoms, and total score in a 1-year open-label extension trial. Lastly, fluvoxamine requires further study to determine its safety and efficacy as an augmentation strategy.

This article has reviewed data concerning augmentation of clozapine in patients who are nonresponders or partial responders to treatment. A great number of reports on a complex group of drugs have led to little reliable evidence for augmentation. In the future, investigations of augmenting strategies need to be rigorous, high-quality trials that can give definitive answers for efficacy and safety questions.

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