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Review

New therapeutic approaches for treatment-resistant schizophrenia: A look to the future

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ABSTRACT

Schizophrenia for many patients is a lifelong mental disorder with significant consequences on most functional domains. One fifth to one third of patients with schizophrenia experience persistent psychotic symptoms despite adequate trials of antipsychotic treatment, and are considered to have treatment-resistant schizophrenia (TRS). Clozapine is the only medication to demonstrate efficacy for psychotic symptoms in such patients. However, clozapine is not effective in 40%–70% of patients with TRS and it has significant limitations in terms of potentially life-threatening side effects and the associated monitoring. Accordingly, a number of pharmacological and non-pharmacological biological approaches for clozapine-resistant TRS have emerged. This article provides a brief updated critical review of recent therapeutic strategies for TRS, particularly for clozapine-resistant TRS, which include pharmacotherapy, electroconvulsive therapy, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation.

1. Introduction

Schizophrenia for many patients is a lifelong mental disorder which affects approximately 0.4%–1% of the population worldwide (Saha et al., 2005). Symptoms of schizophrenia consist of positive, negative, affective, and cognitive symptoms (Insel, 2010). Despite advances in the pharmacotherapy for the illness, many patients continue to be plagued by impairments in social and occupational functioning (Miyamoto et al., 2012). Moreover, one fifth to one third of patients with schizophrenia experience persistent psychotic symptoms despite two or more adequate trials of antipsychotic treatment, defined as "treatment-resistant schizophrenia (TRS)" (Lieberman, 1999). Treatment of these patients has remained a persistent public health challenge, since they often have a low quality of life (QOL) and social dysfunction.

Clozapine is the only medication to consistently demonstrate efficacy for psychotic symptoms in well-defined patient populations with TRS (Conley and Kelly, 2001; Kane et al., 1988). However, clozapine is not effective in 40%–70% of patients with TRS, even with adequate blood levels of clozapine, and it has significant limitations in terms of potentially life-threatening side effects and the related strict monitoring requirements (Porcelli et al., 2012; Sommer et al., 2012a). Accordingly, a number of pharmacological and non-pharmacological approaches for clozapine-resistant TRS or super refractory schizophrenia have emerged (McIlwain et al., 2011; Porcelli et al., 2012). This article provides a brief updated critical review of recent therapeutic strategies for TRS, particularly for clozapine-resistant TRS, which include pharmacotherapy, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS).

2. Augmentation of clozapine with a second antipsychotic

Augmentation of clozapine with a second antipsychotic drug is the most frequently employed and tested strategy for the management of clozapine-resistant schizophrenia (Porcelli et al., 2012). Recently, Taylor et al. (2012) conducted a meta-analysis of 14 randomized, placebo-controlled, double-blind studies (n = 734) of

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antipsychotic augmentation of clozapine treatment in patients with schizophrenia who show partial response to clozapine. In 5 trials, clozapine was combined with risperidone, in 3 trials with aripiprazole, and 6 studies with amisulpride, chlorpromazine, haloperidol, pimozide, sertindole, or sulpiride. Augmentation with a second antipsychotic was modestly superior to placebo (effect size = 0.239, $p = 0.028$) and equally well tolerated. Six weeks may be sufficient time to assess the therapeutic effect of augmentation with a second antipsychotic. Porcelli et al. (2012) also performed a meta-analysis of 5 studies ($n = 116$) comparing the efficacy of risperidone and placebo, when added to clozapine, and found that risperidone was not superior to placebo augmentation (effect size = 0.14, $p = 0.89$). Another meta-analysis by Barbui et al. (2009) examining 14 randomized open trials ($n = 1064$) and 6 randomized double-blind trials ($n = 227$) of clozapine augmentation with a second antipsychotic, also reported that there was no statistically significant positive effect of augmentation. Despite these negative results, there may be subgroups of patients that demonstrate meaningful improvement after the addition of a second antipsychotic. However, it remains unclear which combination of patient characteristics will match most effectively with a specific augmentation antipsychotic for clozapine-treated individuals with TRS (Taylor et al., 2012). It should also be noted that some patients may even experience worsening of psychotic symptoms during clozapine augmentation with sertindole, although the mechanism of this finding remains unknown (Nielsen et al., 2012).

3. Augmentation of clozapine with mood stabilizers

The ability of non-competitive N-methyl-D-aspartate receptor (NMDA-R) antagonists, such as phencyclidine and ketamine, to induce schizophrenia-like symptoms has led to the hypothesis that NMDA-R hypofunction can contribute to the pathophysiology of schizophrenia (Coyle, 1996; Javitt and Zukin, 1991; Krystal et al., 1994). It has also been proposed that NMDA-R antagonists can cause an excess compensatory release of glutamate that can overactivate other non-NMDA receptors, including α-amino-3-hydroxy-5-methy-isoxazole-4-propionic acid (AMPA) and kainate receptors, which are not being antagonized and remain functionally active (Miyamoto et al., 2003). The increase in glutamate release induced by NMDA-R antagonists might be in part responsible for their behavioral effects.

Lamotrigine, an anticonvulsant drug that inhibits excessive cortical glutamate release at presynaptic sites by antagonism of sodium channels and by increasing gamma-aminobutyric acid (GABA) release (Cunningham and Jones, 2000), has been studied as a potential augmenting treatment for TRS. Tiihonen et al. (2009) performed a meta-analysis of 5 randomized, placebo-controlled, double-blind studies (total $n = 161$), investigating the effect of augmenting clozapine treatment with lamotrigine, and found that lamotrigine was superior to placebo augmentation in total score for symptoms of psychosis (effect size = 0.57, $p < 0.001$), a positive (effect size = 0.34, $p = 0.04$) and negative (effect size = 0.43, $p = 0.008$) symptoms of schizophrenia. However, two recent meta-analyses, in which the study by Zoccali et al. (2007) was excluded because it was considered an outlier, found that augmentation of clozapine with lamotrigine was not superior to placebo (Porcelli et al., 2012; Sommer et al., 2012a). In accordance with this result, Vayısoğlu et al. (2013) recently found no beneficial effects of lamotrigine augmentation on psychopathology or cognitive functions in 34 patients with partial response to clozapine.

Topiramate, an anticonvulsant drug, has AMPA receptor antagonist properties and a GABA potentiating action (Arnone, 2005; Shank et al., 2000). Topiramate has been studied in patients with schizophrenia for its potential ability to modulate glutamatergic signaling (McIlwain et al., 2011). Four randomized, placebo-controlled, double-blind studies have examined the use of topiramate as an adjunct to treatment to clozapine, with discrepant results (Afshar et al., 2009; Behdani et al., 2011; Muscatello et al., 2011; Tiihonen et al., 2005). Tiihonen et al. (2005) reported that topiramate was more effective than placebo in reducing Positive and Negative Syndrome Scale (PANSS) general psychopathologic symptoms (effect size = 0.7, $p = 0.021$), but no significant improvement was observed in positive or negative symptoms in patients with schizophrenia resistant to treatment with second-generation antipsychotics. Subsequently, Afshar et al. (2009) demonstrated that topiramate was superior to placebo in reducing all PANSS subscales. Although the results of this small study ($n = 32$) appear to favor topiramate augmentation, the follow-up period is relatively short (8 weeks) (McIlwain et al., 2011). In 2011, Muscatello et al. (2011) conducted a 24-week trial in 43 patients and found no benefits of topiramate add-on pharmacotherapy. Similar results were obtained by Behdani et al. (2011) in a 17-week study in 80 patients. Topiramate augmentation of clozapine did not significantly reduce any of the three PANSS subscales compared with placebo. Sommer et al. (2012a) have recently performed a meta-analysis of 3 trials (Afshar et al., 2009; Muscatello et al., 2011; Tiihonen et al., 2005) on topiramate as a clozapine augmentation strategy ($n = 89$) and found a trend towards a superior effect over placebo in reducing total symptom severity (effect size = 0.75, $p = 0.07$). However, after exclusion of the study by Afshar et al. (2009), which was considered an outlier, the trend disappeared. Interestingly, a growing body of evidence suggests that topiramate may have beneficial effects on weight gain induced by new-generation antipsychotics, including clozapine (Hahn et al., 2013; Mizuno et al., 2014).

In summary, for both lamotrigine and topiramate, there is currently not enough evidence to regard these agents as effective augmentation strategies for patients with insufficient response to clozapine (Sommer et al., 2012a).

4. Augmentation of clozapine with other agents

Tetrabenazine (TBZ) is a presynaptic vesicular monoamine transporter (VMAT2) inhibitor that preferentially depletes dopamine over serotonin and norepinephrine in the brain (Fasano and Bentivoglio, 2009). Several researchers have proposed that a presynaptic dopamine dysfunction may occur over repeated psychotic episodes and schizophrenia may be associated with a process of "endogenous sensitization" (Laruelle, 2000; Lieberman et al., 1997; Lyon et al., 2011). In fact, TBZ itself was evaluated as an antipsychotic with a diminished risk of extrapyramidal symptoms during the 1960s (Lingjaerde, 1963). Remington et al. (2012) recently performed a 12-week, double-blind, placebo-controlled trial to establish whether augmentation with TBZ in combination with either clozapine (73%) or other antipsychotics can enhance response in 41 patients with TRS. Tetrabenazine was well tolerated, but there was no significant improvement in symptoms (total, positive, and negative), overall severity of illness, or level of functioning.

Augmentation of clozapine with 5 glutamatergic drugs, including CX516, D-cycloserine, D-serine, glycine, and sarcosine, was investigated in 7 randomized, double-blind, controlled studies in patients with TRS (Sommer et al., 2012a). Among them, only CX516, a positive modulator of the AMPA receptor, showed better efficacy for total symptom severity (effect size = 1.35) and negative symptom severity (effect size = 1.43) than placebo (Goff et al., 2001; Sommer et al., 2012a). However, the sample size of this study was very small ($n = 18$) and the large improvement in negative symptoms with CX516 compared with placebo might