Psychiatria Danubina, 2019; Vol. 31, Suppl. 3, pp 574-578 *Conference paper*
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CLOZAPINE: PROMISING TREATMENT FOR SUICIDALITY IN BIPOLAR DISORDER

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SUMMARY

Bipolar disorder is associated with the highest risk of completed suicide of all mental disorders. The suicide mortality of people with bipolar disorder is approximately 25 times higher than the general population. No approved pharmacological strategies for suicidality in bipolar disorder have been introduced so far. There is evidence for anti-suicidal effect of clozapine in schizophrenia. Clozapine with its unique pharmacology, anti-aggressive and anti-impulsive properties is potentially an effective strategy for suicidality in bipolar disorder.

Key words: *clozapine - bipolar disorder - suicidality - treatment resistance*

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INTRODUCTION

Suicidality in bipolar disorder is a major issue (Schaffer et al. 2015, Carter et al. 2003). Suicide accounts for 15% to 20% of deaths among bipolar disorder patients (Baldessarini et al. 2006, Goodwin &J amison 1990). Absolute rates of suicide in bipolar disorder are about 0.4% per year. This is 20 fold greater than population rates and translates into risks at long term follow-up between 3-6% (Baldessarini et al. 2006).

Naturalistic studies suggest that suicide rates are lower in patients who receive long-term treatment (Angst et al. 2002). Especially lithium may have particular efficacy. The findings from different centres are consistent and the treatment effect is large Tondo et al. 2001, Toffol et al. 2015). A study of a large Swedish data base has confirmed lithium effect in reducing suicide attempts by 30%; the same effect was not seen with valproate (Song et al. 2015). Both lithium and valproate treatment were associated with 90% reduction in completed suicide.

The key issue in pharmacotherapy of suicidality is its potential effect not only as a syndromolitic intervention, but also as symptom-domain treatment regardless the diagnosis. Although there are no approved interventions for suicidality in bipolar disorder, there is body of evidence on anti-suicidal effect of clozapine in patients with schizophrenia and it is suggested that this strategy can also be useful in patients with bipolar disorder.

CLOZAPINE AS MOOD STABILIZER

Although clozapine lacks regulatory approval for use in any phase of bipolar disorder it is used in treatment resistant bipolar disorder (TRBD) in US since 1989 (Nielsen et al. 2012). It reduces symptom severity in manic and mixed episodes and decreases the need for use of concomitant psychotropic drugs (Nielsen et al. 2012, Chang et al. 2006). There is some evidence to support efficacy in rapid cycling bipolar disorder when standard treatments have failed.(Calabrese et al. 1991, Chen et al. 2005).

Use of clozapine in bipolar disorder is significantly associated with a reduction in psychiatric admissions, psychotropic comedications, and hospital contact for self-harm and overdose (Nielsen et al. 2012), which suggests that clozapine has strong mood-stabilizing properties. Clozapine has been shown to be useful in treatment of TRBD, decreasing the number of hospitalizations and improving symptomatic and functional improvement (Li et al. 2015). It has anti-manic and possibly an antidepressant effect described in one case report (Green et al. 2000, Banov et al. 1994, Calabrese et al. 1996). There is also evidence for use of clozapine in rapid cycling bipolar disorder (Calabrese et al. 1991, Chen et al. 2005).

According to British guidelines, clozapine is worth considering as a treatment option in cases of resistant bipolar I disorder, including rapid cycling (Goodwin et al. 2016). It is also recommended for treatment-resistant bipolar disorder in the latest version of The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders (Grunze et al. 2013) . The latest Canadian guidelines for the treatment of BD suggest using clozapine as the third-line treatment for acute mania and as an additional agent for the maintenance treatment of bipolar I, treatment-resistant mania (Yatham et al. 2009).

SAFETY ISSUES

The risk-benefit profile in long term clozapine treatment of bipolar disorder needs to be assessed carefully. Most common side-effects of clozapine are sedation, hypersalivation, constipation, postural hypotension, hypertension, tachycardia, weight gain, fever, seizures, nausea, nocturnal enuresis, gastro-oesophageal reflux disease. It can also increase triglyceride and cholesterol

levels. Clozapine is strongly linked to hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis. The risk of diabetes appears to be higher with clozapine than with other SGAs and conventional drugs, especially in younger patients. Clozapine appears to increase plasma levels of insulin in a clozapine level-dependent fashion. Patients on clozapine should be closely observed for signs or symptoms of myocarditis, particularly during the first 2 months of treatment. Clozapine is also linked to cardiomyopathy. Anticholinergic effect of clozapine can worsen cognitive functions (Abel et al. 2018)

Clozapine can cause serious, life-threatening adverse effects, of which agranulocytosis is the best known. Early US data suggested a mortality rate of 0.012%. Risk can be well managed by the approved clozapine monitoring systems. Risk of fatal agranulocytosis is less than 1 in 8000 patients treated. Other uncommon adverse effects are colitis, delirium, eosinophilia, heat stroke, liver enzymes abnormalities, interstitial nephritis, pancreatitis, parotid gland swelling, pericardial effusion, pneumonia, stuttering, thromboembolism, skin reactions and thrombocytopenia. It is worth noticing that overall mortality of patients with schizophrenia is lower for those on clozapine than in schizophrenia as a whole. Risk of fatal pulmonary embolism is estimated to be around 1 in 4500 patients treated. Careful monitoring (full blood count, lipids, weight, glucose, blood pressure, ECG) can help avoiding most of adverse effects. Many of the adverse effects of clozapine are dose dependent and associated with speed of titration. Adverse effects also tend to be more common and severe at the beginning of therapy. To minimize these problems it is important to start treatment at a low dose and to increase dosage slowly (Abel et al. 2018).

There is some evidence that clozapine improves treatment adherence in comparison to FG drugs (Rozenheck et al. 2000), through greater and more regular clinical supervision coinciding with mandatory blood testing.

CLOZAPINE AS AN ANTI-SUICIDAL AGENT

Suicide accounts for 15% to 20% of deaths among bipolar disorder patients (Baldessarinie et al. 2006, Goodwin et al. 1990). The ratio of suicidal attempts among bipolar disorder patients is much lower (~ -3:1) than in the general population (~30:1); however, the attempts are highly lethal (Baldessarini et al. 2006). Suicidal acts appear mostly in association with severe depressive or mixed states. Independent associations have been found for female gender, previous criminality, parental psychiatric disorders and low family income (Webb et al. 2014) Aggression and impulsivity may also be associated with suicide attempts (Oquendo et al. 2000, Oquendo et al. 2004).

For today there are no approved pharmacological interventions for suicidality in bipolar disorder. Clozapine has been shown to have specific anti-suicidal properties in patients with schizophrenia (Meltzer et al. 2003, Hennen et al. 2005, Ciapperelli et al. 2000). Some authors have suggested that clozapine's anti-suicidal properties could extend beyond schizophrenia to bipolar disorder (Carter et al. 2003, Meltzer et al. 2000). This effect was described in one case report (Vangala et al. 1999). Anti-suicidal effect seems to be independent of that which provides psychotic symptom relief. Interestingly, psychotic symptoms do not predict a better response to clozapine in bipolar patients compared to schizophrenic patients Ciapperelli et al. 2000) and the doses required for optimal effect in bipolar disorder may be less than those used for treatment-resistant schizophrenia (Fehr et al. 2005) although it demands further study.

There is also some evidence that clozapine reduces suicidal behaviours in severe borderline personality disorder (Benedetti et al. 1998). Possible mechanisms of reducing suicidality with clozapine probably involve the simultaneous modulation of dopamine, norepinephrine, and serotonin (Meltzer et al. 2000), regulation of the hormone system (pregnenolone, cortisol) (Marx et al. 2006) and intracellular systems – dependent modulation of N-methyl-D-aspartate (NMDA) receptor expression, brain-derived neurotrophic factor up-regulation, and regulation of the arachidonic acid cascade (Leveque et al. 2000, Spivak et al. 2003). According to Youssef, pregnenolone alterations may be relevant to the neurobiology of suicide in schizophrenia and bipolar disorder and may constitute a common path for the anti-suicidal effect for clozapine and lithium (Youssef et al. 2015).

Despite being the first drug to demonstrate a reduction in suicidal behavior in a large RCT, clozapine is used with only 1.5% of bipolar patients (Nielsen et al. 2010), suggesting a substantial underutilization of this valuable drug.

ANTI-IMPULSIVE AND ANTI-AGGRESSIVE PROPERTIES OF CLOZAPINE.

Clozapine reduces violence and aggression in patients with schizophrenia and other psychiatric disorders (Frogley et al. 2012). There is also evidence that clozapine can reduce aggressive behavior in patients with bipolar disorder with psychotic symptoms (Kowatch et al. 1995) Clozapine's anti-aggressive effect seems to be specificand greater than both: antipsychotic and sedative effects, although definitely more studies are needed in this field (Frogley et al. 2012). Clozapine effectively reduces aggression against self, including physical mutilation (Chengappa et al. 1999, Swinton 2001) in severe cases of BPD. Many of these patients may have experienced psychotic or quasi-psychotic symptoms; however, (Parker 2002) has shown that clozapine reduces aggression whether directed at self or others in BPD patients, independently of changes in psychotic-type symptoms. The patients' aggression also rapidly reoccurred if clozapine

was discontinued and improved when reinstated. There is also evidence for reduction of aggression in post-traumatic stress disorder with psychotic symptoms (Wheatley et al. 2004).

Clozapine has complex receptor-binding affinities for D_2 and D_4, but also 5-HT_2A, receptors could underpin its anti-aggressive effects which may in part be mediated by an anxiolytic as opposed to an exclusively antipsychotic effect (Becker et al. 2003, Gallitano-Mendel et al. 2008). Elevated plasma noradrenalin (NE) levels in patients treated with clozapine may also play a role in its anti-aggressive and anti-suicidal properties (Nielsen at al. 2010) Probably a number of pathways are involved and might include reduced substance misuse and impulsivity, increased monitoring and surveillance compliance, increased treatment concordance, and a generally better outcome (Volavka & Citrome 2008).

ROLE OF CLOZAPINE IN SUBSTANCE USE DISORDERS

As mentioned before there is evidence for clozapine reducing substance abuse. It may limit the use of cannabis (Brunette et al. 2011), alcohol (Chau et al. 2010), both combined (Green et al. 2003) and poly-substance abuse including cocaine (Zimmet et al. 2000) in comparison to FG and other SG antipsychotics. It even appears that clozapine treatment is associated with reduced cigarette smoking (Mc Evoy et al. 1999), although this remains contentious (de Leon et al. 2005). Some authors suggest that clozapine should be evaluated for reducing abuse of alcohol and other substances in bipolar disorder patients (Zhornitski et al. 2010).

TITRATION RATE

An interesting aspect of clozapine use in TRBD is the titration rate. According to clinical guidelines and drug information the rate of 12.5-25 mg/d is optimal. Following this regimen, it takes 2-3 weeks until reaching the target dose. Ifteni et al. based on their study suggest that rapid titration max 100 mg/day is safe, corelates with shorter hospitalization and smaller doses of benzodiazepines used in this group of patients (Ifteni et al. 2014).

One study reported ultra-rapid titration of clozapine (max 150 mg on the first day) in four patients with treatment-refractory mania with psychotic features. The authors observed very rapid antimanic and antipsychotic effect during the first week of treatment. The dose of clozapine on discharge was relatively low (100 mg/d, 150 mg/d, 300 and 400 mg). None of the patients developed life-threatening adverse effects such as neutropenia, symptoms suggestive of myocarditis, neuroleptic malignant syndrome, or delirium. The authors recommend rapid titration of clozapine, after an initial test dose of 25 mg, if this is well tolerated, especially in young patients in whom adequate control of symptoms is urgent, particularly for inpatients having severely agitated mania with psychotic symptoms requiring physical restraints and seclusion, with no response to high doses of antipsychotics generally given in parenteral form or ECT (Aksoy et al. 2015).

Chengappa et al. 2002 suggest that the rapid mood-stabilizing effect of clozapine might be connected with its anti-aggressive effect and that anti-aggressive benefits of clozapine continues to occur for months after the rapid titration phase. The benefits of rapid clozapine titration should be always balanced against the potential for an increased risk of hypotension, seizures, myocarditis and delirium (Abel et al. 2018).

CONCLUSION

Although no approved drug for suicidality in bipolar disorder is available, there is a body of evidence for clozapine as a mood stabilizer and it should be considered as a treatment strategy especially in treatment resistant patients with suicidality.

Acknowledgements:

This paper was granted by the Medical University of Gdańsk, Poland (Grant No. ST-02-0039/07/221).

Conflict of interest: *None to declare.*

Contribution of individual authors:

Alina Wilkowska: literature searches and analyses, manuscript writing.

Mariusz S Wiglusz: literature searches and analyses, manuscript correction.

Wiesław J Cubała: design of the paper, literature searches and analyses, manuscript correction.

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