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BENZODIAZEPINES AS ADJUNCTIVE THERAPY IN TREATMENT REFRACTORY SYMPTOMS OF SCHIZOPHRENIA

Joanna Szarmach, Adam Włodarczyk, Wiesław Jerzy Cubała & Mariusz Stanisław Wiglusz

Department of Psychiatry, Medical University of Gdańsk, Poland

SUMMARY

Antipsychotics are a key intervention strategy in pharmacotherapy in schizophrenia. However, the benzodiazepines are often prescribed to control sleep disturbances, anxiety or hostile behaviour.

There is some evidence supporting the combination therapy with antipsychotics and benzodiazepines providing beneficiary treatment effect to the psychosis in positive and negative symptom domains as well as catatonia or adverse reactions to antipsychotic drugs. In particular, in a population suffering from residual symptoms of schizophrenia, in particular anxiety, emotional flattening, being refractory to approved treatment strategies, benzodiazepines as add-on to antipsychotics seem to be an option. There is rationale for the therapeutic use for long-acting benzodiazepines as the treatment of option with limited literature indicating the use of chlordiazepoxide, and diazepam. The paper reviews the best clinical practice indications for benzodiazepines as the add-on treatment to antipsychotics in schizophrenia.

Key words: *schizophrenia - pharmacotherapy - antipsychotics - benzodiazepines - anxiety - residual symptoms*

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Introduction

Schizophrenia is one of the most debilitating mental disorders characterized by thinking disruptions, affecting sense of self, language and perception of the sick person. It is chronic and persistent with some proportion of patients exhibiting drug resistance with residual symptomatology. There are unmet needs as contemporary antipsychotics, both 1st and 2nd generation do not fully address the burden of the disease.

At present the standard in the treatment of schizophrenia are second generation antipsychotics with predominant action exerted through dopaminergic activity. Dopamine receptors, of which there are at least five subtypes: D1, D2, D3, D4, and D5, play an important role in the reward system, incentive salience, cognition, prolactin release, emesis and motor function. Schizophrenia is also characterized by loss of brain volume which may represent an ongoing pathophysiological process. A possible mechanism is hypofunction of the NMDA-type of glutamate receptor, which reduces the excitation of inhibitory GABAergic interneurons, resulting in a disinhibition of glutamatergic pyramidal neurons. Disinhibition of pyramidal cells may result in excessive stimulation by glutamate, which in turn could cause neuronal damage or death through excitotoxicity (Marsman 2014). The disturbances in cortical GABA neurons may strongly contribute to symptoms like overinclusivness or thought disorganization. In limbic system it may contribute on the other hand to the observed pale or parathymic affect in schizophrenia being associated with the limbic system and the role it plays in emotion processing. It also may account for neurocognitive decline (Hashimoto 2010).

Glutamate is the main excitatory neurotransmitter in the brain and is linked to another model of schizophrenia. The glutamate hypothesis proposes the hypofunction of NMDA receptors preventing glutamate from binding to the receptor increasing excitotoxicity glutamate levels, which induce schizophrenia symptoms. Blockade of NMDA receptors in the anterior thalamus could be the main site leading to cortical glutamate release, and cortical excitotoxicity (Graham 2016).

The tracts formed by GABA-contatining neurons in the brain modify dopaminergic function decreasing presynaptic dopamine release and the inhibition of GABA input to dopamine neurons in the ventral tegmental area results in increased dopamine activity in the nucleus accumbens and olfactory tubercule (Wolkowitz, 1996). GABAergic dysfunction in schiophrenia is among other proposed mechanisms to be considered. As GABAergic transmission is vital in modulating cortical activity, the altered receptor activity and pharmacology would disrupt normal neural processing, resulting in an imbalance in other systems, and symptoms of schizophrenia (Hinton 2008).

The interplay between GABA-ergic and dopaminergic systems modulated with benzodiazepines seem to explain certain beneficial, long-term effect of benzodiazepine use in patients with schizophrenia. Benzodiazepines are commonly used worldwide in the treatment of schizophrenia as rescue medication. However there is some clinical evidence for clinical efficacy for these drugs in certain subpopulations of patients. Benzodiazepines act primarily through the GABA-A receptor complex. As for GABA, the chief inhibitory neurotransmitter, is common and widespread in the whole central nervous system. It plays the principal role in reducing neuronal excitability throughout the nervous system.

As GABA neurons carry inhibitory signals that help keep brain activity at optimal levels of operation, glutamate, on the other hand, carries excitatory signals. As the interplay between these two exists they are

keeping the dopamine levels in the average levels. But, as other studies indicate, GABA disruption in schizophrenia may lead to fluctuation of dopamine levels bypassing the glutamate action inducing the dopamine levels to rise which may result in psychosis. Affecting the GABA neurons with benzodiazepines may restore the balance in the main neurotransmitter in the schizophrenia onset, having favorable way in treating both positive and negative symptoms of schizophrenia. Augmentation of benzodiazepines causes drug-induced dopamine decrease in prefrontal cortex of the brain which gives a synergistic effect with antipsychotic action in mesolimbic-cortical-striatal mechanism.

Rationale for benzodiazepine use as add-on treatment to antipsychotics in schizophrenia

Several studies showed that BDZs alone may have beneficial effect, even on purely psychotic symptoms. However, it has not been convincingly demonstrated in controlled trials. The safe and efficient way is to consider the combination treatment with BDZ and antipsychotics. Although some studies were negative on BDZ-antipsychotics combination, there seems to be more solid evidence for beneficial effect of BDZs when given in addition to antipsychotics (Wolkowitz 1996). Type and course of schizophrenia might be another variable. The most positive results in studies obtained were in chronic schizophrenics. Still, the majority of results were reported in open-label studies or case series and the conclusions drawn must be approached with caution (Table 1).

Negative symptom domain in schizophrenia as the target for benzodiazepine use

Although newer atypical antipsychotics have less affinity for dopamine receptors and well reduce positive symptoms they do not adequately reduce negative symptoms. The disturbances in cortical GABA neurons in the limbic system may correspond with pale or parathymic affect or neurocognitive decline. By affecting the GABA neurons, the balance in the dopamine pathways may hypothetically be restored having favorable way in treating negative symptoms of schizophrenia.

Several authors commented on the beneficial effects of benzodiazepines on negative symptoms, such as lack of spontaneity, emotional withdrawal, blunted affect, passivity, apathy and negativism. Wolkowitz et al. and others have noted rapid (within 1-2 weeks) and occasionally striking improvements in social relatedness, affability, spontaneity, humor, and interest in family and social life in some benzodiazepine-treated schizophrenic patients with drugs such as alprazolam or diazepam (Wolkowitz 1996).

Benzodiazepines were primarily used asadjunctive therapy with antipsychotics. There have been some studies, many of which reported significant improvement compared to placebo. Studies, which showed positive outcome, investigated diazepam, alprazolam, and estazolam. Doses ranged from as low as 15 mg of diazepam to 4 mg of alprazolam. Improvement was seen both inpositive and negative symptoms. This improvement can be substantiated logically on postulates that schizophrenic patients may have decreased GABA activity (Prakash 2008)

Benzodiazepines and anxiety symptoms in schizophrenia

Anxiety symptoms accompany patients with schizophrenia as a part of the disease, comorbid condition or residual symptomatology. Anxiety may be considered as a major symptom of schizophrenia with a sense of insecurity and the perception that most events are threatening are frequent in the processes The anxious phenomena in the schizophrenic patients, however, are underestimated. Several factors may explain this undervaluation including the florid picture of positive symptoms masking anxious manifestations. On the other hand, in patients treated with antipsychotics symptoms are attributed to adverse effects of antipsychotics and not related to anxious manifestations. Many studies on the activity of benzodiazepine anxiolytics in patients with schizophrenia demonstrated moderate effectiveness. Only one study evaluated the efficacy of benzodiazepines in schizophrenic patients with panic attacks and the same study team suggested that panic anxiety may contribute to the exacerbation of schizophrenic symptoms, which could explain and predict the efficacy of alprazolam on them. In an open study, these authors treated seven patients who responded to the DSM III criteria for schizophrenia and panic disorder. The results demonstrated a significant improvement in positive and negative symptomatology and a disappearance of panic attacks, but there was an upsurge of symptomatology after discontinuation of alprazolam (Gaillard 2006) (Table 2).

Benzodiazepines and catatonia

Catatonia is a psychomotor syndrome characterized by concomitant emotional, behavioral and motor symptoms. In many cases clinical symptoms disappear almost immediately with administration of high doses of lorazepam, which acts on GABA-A receptors (Richter 2010).

Since the early 1980s, numerous reports of clinical cases have highlighted the interest of benzodiazepines in the treatment of catatonia. This therapeutic effect relates essentially to lorazepam, a benzodiazepine of short half-life used at small doses, between 1 and 3 mg. Rosebush et al. also demonstrated that lorazepam can be used in 80% of the cases within 24 hours after administration of a small dose. Other controlled studies found a rapid and complete improvement in 60 to 85% of the patients. Administration of high doses (>5 mg/day) does not improve efficacy. The effect seems to be specific to dulorazepam: a double-blind, randomized, double-blind trial results in a higher efficacy of lorazepam compared to oxazepam. This specific effect should be compared with that of a hypnotic, zolpidem,

Table 1. Benzodiazepines add-on to antipsychotics in schizophrenia

Benzodiazepine half-life		Daily dose	Evidence
Short-acting	No significant studies found		
Medium-acting	alprazolam	3-4 mg	Improvement seen in both positive and negative symptoms
	lorazepam	2-6 mg	Significantly more improvement than placebo in anxiety, insomnia, delusions, hallucinations, behavior, fear, agitation, and global clinical assessment and nonsignificantly more improvement in Hamilton anxiety score
Long-acting	clonazepam	1-3 mg	Improvement mainly in anxiety, tension and excitement
	diazepam	5-15 mg	Improvement seen in both positive and negative symptoms
	chloriazepoxide	30 mg	Significantly worse for schizophrenic disorganization, especially in women, but superior for thought disorder and ward behavior

Table 2. Indication for best practice when benzodiazepines add-on to antipsychotics in schizophrenia should be considered

Antipsychotic-resistant psychosis
Persistent negative symptoms
Anxiety
Catatonia
Antipsychotic drugs induced akathysia or Parkinsonian syndrome

in the same indication. The heterogeneity of the cases and of the clinical forms grouped under the concept of catatonia is a possible one in these studies. Chronic catatonia associated with schizophrenia does not seem to have the same sensitivity to these therapies. A double-blind, double-blind, placebo-controlled study in 18 chronic schizophrenic catatonic subjects was therefore not effective with lorazepam (Gaillard 2006).

Patients with past or present catatonic symptoms are particularly vulnerable to Neuroleptic Malignant Syndrome, and treatment of catatonia requires avoidance of antipsychotics and the use of benzodiazepines or electroconvulsive therapy (ECT). The extreme negativism and constriction of consciousness in catatonia suggest a primary role of the frontal lobes, with secondary involvement of the extrapyramidal system and its movement disorders (Blumer 1997). Using functional magnetic resonance imaging (fMRI) negative emotional pictures lorazepam induced higher signal decreases in the orbitofrontal cortex (OFC) in catatonic patients than in healthy subjects resulting in a regularization of activity patterns comparable to healthy subjects with placebo. Results indicate disturbances in the functioning of OFC in catatonia. GABAergic modified emotion regulation with decreased inhibition of affective stimuli could lead to the intense emotions reported by many catatonic patients (Richter 2010).

Benzodiazepines and adverse effects of antipsychotics

Benzodiazepines have been proposed as a treatment for the adverse effects of antipsychotics. Their efficacy on late dyskinesias, secondary to hypersensitivity to dopamine resulting from prolonged dopamine deprivation, is not evident. Jordan et al., report a case of tardive dyskinesia treated effectively with alprazolam. Cochrane analysis found only two studies that met the usual inclusion criteria for a meta-analysis (blinded versus placebo controlled studies): benzodiazepines did not demonstrate superior efficacy to placebo. Nevertheless, the decrease in the dosage of antipsychotics when combined with benzodiazepines may lead to a reduction in the incidence of late dyskinesias. Horiguchi et al. carried out a double-blind study on the efficacy of clonazepam on akathisia and parkinsonian syndrome induced by antipsychotics at the discontinuation of anti-parkinsonian correctors in patients with chronic schizophrenia. Out of 117 cases, 78 did not have akathisis or parskinsonian syndrome 6 weeks after discontinuation of anti-Parkinsonian correctors. In other patients, clonazepam showed a 100% efficacy on akathisia and 75% on parkinsonian syndrome. An open-label study in 18 patients also demonstrates the efficacy of intravenous diazepam on akathisia. Stopping benzodiazepines, when used in combination with antipsychotics, may alleviate adverse effects attributed to antipsychotics. Lane et al. report a case of convulsions at the gradual cessation of lorazepam in patients with clozapine (Gaillard 2006).

Benzodiazepines treatment safety

The combination of benzodiazepines and antipsychotics may lead to combined adverse effects, especially when clozapine is used. Grohman et al. reported 4 cases of severe cardio-vascular or respiratory accidents in 189 patients exposed to clozapine-benzodiazepine, a risk of 2.1%. Benzodiazepines may be the cause of disinhibition and dysphoria, which involves close clinical monitoring. The discontinuation of benzodiazepines may also be the cause of clinical aggravation (ripple effect). Patients with poor observation of treatments with frequent breaks in care are therefore poor candidates for benzodiazepine treatment. Finally, the prescription of benzodiazepines must always be accompanied by a reflection on the risks of dependence. The literature on benzodiazepine dependence in schizo-

phrenic patients is rather poor. A prospective German study shows a low prevalence of benzodiazepine dependence in schizophrenia. Of the 15.000 patients received in psychiatric hospitals in Munich and Berlin between 1980 and 1985, 726, or 4.7%, were dependent on benzodiazepines. The prevalence of benzodiazepine dependence in this population was 9.3% in non-psychotic patients versus 0.9% in psychotic patients (chronic psychosis, schizophrenia and manic-depressive illness). On the other hand, several authors suggest the idea that benzodiazepines could improve the prognosis of schizophrenia by decreasing dependency behaviors. A recent review on addictions in schizophrenia also discusses the potential value of prescribing benzodiazepines in the treatment of addictions (Gaillard 2006).

Conclusions

A full remission is the major challenge in the treatment of patients with schizophrenia, and this is often hard to achieve. As the approved treatment with antipsychotics has certain limitations evidence based and safe treatment strategies should be employed each time focusing on treatment response.

Although there is limited data for benzodiazepine use in treatment-resistant patients with schizophrenia with persistent symptoms in the domain of anxiety and negative dimension, benzodiazepines seems to be an option. Safety precautions must be considered each time benzodiazepine is used with particular patients icluding education regarding of drug use. Further research is needed, having in mind that as the ultimate goal in schizophrenia treatment to full remission should be considered. It seems that long-acting benzodiazepines are a treatment of option with the limited literature indicating chlordiazepoxide and diazepam.

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Correspondence:
Mariusz S. Wiglusz, MD, PhD
Department of Psychiatry, Medical University of Gdańsk
Dębinki St. 7 build. 25, 80-952 Gdańsk, Poland
E-mail: mwiglusz@gumed.edu.pl