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Augmentation of antipsychotics with glycine may ameliorate depressive and extrapyramidal symptoms in schizophrenic patients: a preliminary 10-week open-label study

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Summary

Aim. The objective of this study was to analyze the changes in depressive and extrapyramidal symptomatology during glycine augmentation of antipsychotic treatment in patients with schizophrenia.

Materials and methods. Twenty-nine schizophrenic patients (ICD-10) with predominant negative symptoms in stable mental state participated in a 10-week open-label prospective study. Patients received stable doses of antipsychotic drugs for at least 3 months before glycine application. During the next 6 weeks patients received augmentation of antipsychotic treatment with glycine (up to 60 g per day). The first and last two weeks of observation were used to assess stability of mental state. Symptom severity was assessed using the Hamilton Depression Rating Scale (HDRS), the Positive and Negative Syndrome Scale (PANSS), and the Simpson-Angus Extrapyramidal Symptom Rating Scale (SAS).

Results. In the studied group after 6 weeks of administration of glycine a significant improvement in depressive symptoms (reduced scores by 25.8% in HDRS, $p < 0.001$) and reduced scoring in mood symptoms of PANSS were observed. In SAS a reduction of extrapyramidal symptoms' severity ($p < 0.05$) was also noted. Two weeks after the glycine augmentation the symptom severity in the HDRS, PANSS, and SAS remained at similar levels.

Conclusions. Glycine augmentation of antipsychotic treatment may reduce the severity of depressive and extrapyramidal symptoms. Glycine use was safe and well tolerated.

Key words: schizophrenia, glycine, NMDA receptor, glutamatergic system, affective symptoms, extrapyramidal symptoms

Introduction

Depressive symptoms in schizophrenic patients have been subject of serious interest for a relatively short time, although these symptoms are very often associated

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with schizophrenic psychosis – they are present both in the acute (up to 50% patients), and in the chronic phase (4-25%) [1, 2]. Similarly as in other disorders, depressive symptoms cause important consequences: increased risk of suicide and drug dependency, worsening of everyday functioning and quality of life, poorer compliance [3-7]. Functional remission comprises the amelioration of positive and negative symptoms, efficient cognitive functioning but also the presence of depressive symptoms - often difficult to distinguish from primary negative symptoms. General functioning and quality of life also improve with the reduction of the extrapyramidal symptoms severity [8]. „Glutamatergic" substances such as NMDA receptor co-agonists have the antidepressive potential [9-11], but interestingly also NMDA receptor antagonists (ketamine, memantine) exhibit some antidepressive properties [12-14]. Other substances modifying the glutamatergic system function such as modulators of metabotropic glutamate receptors [15] and ampakines (CX516) are under investigation [16]. Mood stabilizers – lithium and lamotrigine prevent depressive episodes in bipolar disorder secondarily influencing the release of glutamate [17].

Study group

The study included thirty-two patients who signed the informed consent and met the following criteria:

1. Diagnosis of schizophrenia with predominant negative symptoms (according to ICD-10 and Positive and Negative Syndrome Scale - PANSS),
2. age 18-55 years,
3. stable doses of antipsychotics (first or second generation) for at least 3 months prior to inclusion in the study,
4. lack of co-existing severe somatic and neurological disorders,
5. exclusion of alcohol or drug dependence and intoxication in the last 3 months (including opiates, cocaine, hallucinogens, amphetamine, cannabis)
6. exclusion of pregnancy and breastfeeding.

Women enrolled in the study were informed of the need for taking oral contraceptives or use the „double barrier" method (e.g. condom and cap). Study participants were mostly outpatients, at the beginning weeks of the study 3 patients were hospitalized at the Central Clinical Hospital, Medical University of Łódź.

The Research Ethics Committee of the Medical University of Łódź accepted the research project (Ethics Committee Decision No. RNN/1121/99).

Twenty-nine individuals (13 women and 16 men) completed the study and were the subject of further analysis. Mean parameters of study group were: age – 32 years, duration of the illness – 8,4 years, number of hospitalizations – 2. The severity of the negative symptoms was moderate, and mild in positive and affective symptoms and general psychopathology (Tab. 1).

Table 1. **PANSS scores**

Parameter	Visit 2		Visit 6		Change			p (Wilcoxon)
	Mean	SD	Mean	SD	Mean	SD	%	
PANSS_P	12.00	4.192	11.069	4.026	-0.931	1.926	-7.8	p<0.05
PANSS_N	25.69	5.00	21.55	4.57	-4.14	1.75	-16.1	p<0.001
PANSS_G	36.14	6.15	31.72	5.51	-4.41	3.09	-12.2	p<0.001
PANSS_T	73.83	11.98	64.35	11.08	-9.48	5.55	-12.8	p<0.001

PANSS_P, PANSS_N, PANSS_G – score in positive, negative and general psychopathology PANSS subscales, PANSS_T – total PANSS score, SD – standard deviation

Seven patients were treated with typical neuroleptics (sulpiride – 2, perazine – 2, zuclopenthixol – 1, flupentixol – 1, perphenazine – 1), 14 patients with atypical antipsychotics (olanzapine – 5, risperidone – 5, clozapine – 4) and 7 patients with neuroleptics from both groups (olanzapine + sulpiride – 3, olanzapine + flupentixol - 2, olanzapine + perphenazine – 1, risperidone + haloperidol –1). No patients were taking any antidepressants or substances with anticholinergic properties (biperiden, pridinol). Only 3 patients have not completed the study.

Method

The study consisted of three parts: the first 2 weeks after enrollment the stability of mental state was assessed (visit V1 and V2) using the PANSS. During the next 6 weeks (V2-V6), patients received glycine at a dose of 0.8 g per kg of body mass, up to 60 g / day. The previous doses of antipsychotic drugs remained unchanged. On the last visit (V7) – two weeks after glycine termination - the mental state was assessed to evaluate the stability of the glycine effect and the possible clinical consequences of its withdrawal. Study visits were planned in the following order: 2 weeks after the enrollment visit (V1) on visit V2 the administration of glycine was started. Visits V3 and V4 were planned every week after V2, then visits V5 and V6 every 2 weeks. On V6 the glycine augmentation was discontinued. Two weeks after was the last visit V7. Scales used to assess the severity of schizophrenic symptomatology on each visits were the PANSS and the Hamilton Depression Rating Scale (HDRS). Previously we published papers on the assessment of changes in positive and negative symptoms, cognitive functions during augmentation glycine in this group [18,19]. Affective symptoms in schizophrenia may also be assessed using the Calgary Scale, but we decided to choose the HDRS, because most of similar studies preferred this tool. The HDRS is more detailed, observing broader spectrum of affective symptoms. Selected items of the PANSS describing affective symptoms were also analyzed. To assess the severity of extrapyramidal symptoms the popular Simpson Angus Scale (SAS) was used.

In all patients on visits V1 and V2 standard blood tests (complete blood count, biochemical tests, electrolytes) and ECG were carried out. The deviation from the planned visit date was up to 2 days.

Glycine (crystallizate) used in the study was bought at MERCK Germany KGaA (in 25 kg packages) and labelled with a symbol 5.00190 in the producer's catalogue [conforming to European pharmacopoeia standards (5th edition), British (2004) and American (27) requirements]. It was subsequently weighed and portioned according to each participant's body weight (0.8g/kg/24 h/3 doses). The patients were given the amino acid in small polyethylene bags and instructed on the time of drug intake and formula preparation (dissolution in approx. 1/2 glass of water or orange juice three times a day).

Statistical Methods

The distribution normality was examined using the Shapiro-Wilk test, the parameter changes were analyzed using the Wilcoxon test. The significance level $p<0,05$ was considered statistically significant.

Results

Depressive symptoms. The number and average severity of depressive symptoms was low in the group, none of the patients met criteria of even a mild depressive episode, but during the glycine augmentation we observed a consistent decrease in HDRS score. The HDRS scoring in shown in Tab. 2 and Fig. 1 – *next page* .

Table 2. **HDRS scores**

Visits	Mean	SD	Difference of change	SD	Change [%]	p
V1	9.41	3.82	0.45	1.40	5.0	ns
V2	8.97	3.52	0.00	0.00	0.0	-
V3	8.10	3.06	-0.86	1.38	-9.6	p<0.01
V4	7.28	2.91	-1.69	1.93	-18.8	p<0.001
V5	6.97	2.96	-2.00	2.07	-22.3	p<0.001
V6	6.66	2.48	-2.31	2.25	-25.8	p<0.001
V7	6.52	2.47	-2.45	2.29	-27.3	p<0.001

In comparison to V2 a statistically significant improvement in depressive symptoms was noted from V3 ($p<0,01$) and for the whole group score decreased by 25.8% on V6 ($p<0,001$).

After the glycine discontinuation the severity of depressive symptoms remained at similar levels. Comparing to V2, mean HDRS scores on V7 were by 27.3% lower ($p<0,001$). Figure 1. – *next page*

Analysis of PANSS affective scores (Tab. 3 – *next page*). The symptoms, which can be classified in the PANSS as depressive symptoms are: anxiety (G2) and depression (G6), but these symptoms may have psychotic provenance. Other symptoms exami-

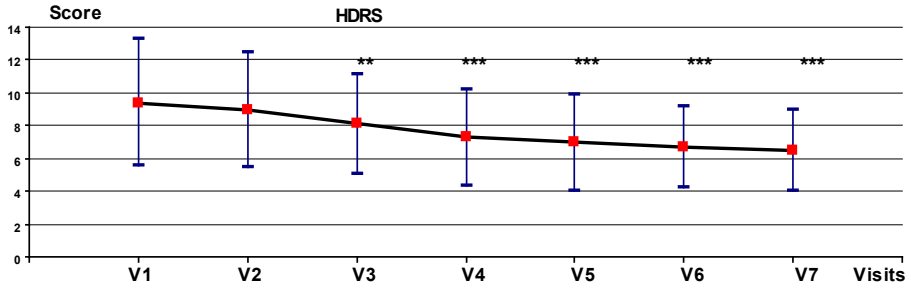

Figure 1**. HDRS scores.: **p<0,01; ***p<0,001 (comparing to V2). Whiskers show standard deviation (SD)**

Table 3. **PANSS affective items scores on V2 and V6**

Symptom	V2 Mean	SD	V6 Mean	SD	Change [%]	p
G1	2.10	1.15	1.93	1.00	-8.2	ns
G2	2.35	1.17	1.83	1.04	-22.1	p<0.01
G3	2.07	1.03	1.90	1.01	-8.3	ns
G4	2.35	1.08	1.79	0.98	-23.5	p<0.001
G6	2.28	1.13	1.79	1.05	-21.2	p<0.01
G7	2.55	1.12	1.97	0.94	-23.0	p<0.001
G11	3.07	0.75	2.59	0.68	-15.7	p<0.001
G13	2.86	0.88	2.72	0.80	-4.8	p<0.05

G1-somatic concern, G2-anxiety, G3-guilt feelings, G4-tension, G6-depression, G7-motor retardation, G11-poor attention, G13-disturbance of volition

ned here – G1, G3, G4, G7, G11, G13 – are also part of affective symptomatology in patients with schizophrenia. In comparison to V2 statistically significant improvement in anxiety (G2) was observed on V5 (p<0,05), mean score for the group decreased by 22.1% on V6 visit (p<0,01). After V6 visit the symptom severity remained at similar levels. The severity of depression (in terms of symptom, G6) comparing to V2 was significantly reduced beginning on V4 (p<0,05) and was reduced by 21.2% on visit V6 (p <0,01).

Extrapyramidal symptoms (EPS) Analysis of the SAS scores in the study group (Tab. 4 – next page)

In comparison to V2 a significant improvement in extrapyramidal symptoms was observed only at the V6 visit (p<0,05, 10% reduction). After the V6 visit and glycine discontinuation symptoms persisted on V7 at similar level.

Safety Issues Among 3 women who did not complete the study, one was withdrawn due to the spontaneous occurrence of positive symptoms before starting glycine treatment but after signing the informed consent form. The second patient on the second day of the glycine administration experienced severe vomiting, the third one after a few

Table 4. **SAS scores**

Visits	Mean	SD	Difference of change	SD	Change [%]	p
V1	2.93	3.40	0.17	0.54	6.3	ns
V2	2.76	3.31	0.00	0.00	0.0	-
V3	2.76	3.27	0.00	0.27	0.0	ns
V4	2.69	3.08	-0.07	0.37	-2.5	ns
V5	2.55	2.98	-0.21	0.73	-7.5	ns
V6	2.48	2.98	-0.28	0.70	-10.0	p<0.05
V7	2.48	2.98	-0.28	0.70	-10.0	p<0.05

doses of glycine began to experience excessive sedation. Both participants resigned from further participation in the study. Other patients reported no serious side effects. Four patients reported a feeling of fullness in the abdomen or a mild nausea, occurring during the first days of treatment, not causing the termination of study participation. Nausea disappeared within a week, often alleviated by modifying the way of taking glycine.

Discussion

Some studies and clinical experience show that some classical neuroleptics such as haloperidol, chlorpromazine and fluphenazine may induce depression, while others, such as sulpiride, levomepromazine, flupenthixol, chlorprothixen and most second-generation drugs may improve mood. In addition, most antipsychotic drugs reduce the level of anxiety and have a sedative effect.

If these antipsychotics are not effective enough and depressive symptoms persist, the current guidelines recommend cautious use of antidepressant drugs - mainly SSRI, SNRI (venlafaxine, milnacipran) or mirtazapine [20]. In addition to the drugs mentioned above, which have been in use for decades – we are still looking for new opportunities, the project discussed here is one of such attempts. Great importance of the glutamatergic system was the theoretical basis for attempts to modulate its function. It is assumed that the glutamatergic along with the dopaminergic dysfunctions are the functional and morphological substrates of negative and cognitive symptomatology. This is associated with early developmental damage and abnormal formation of inter-neuronal connections, cytoarchitecture and decrease in expression density of neurons, dendrites, dendritic spines and synapses [21, 22]. Currently several substances affecting the ionotropic (now mainly NMDA) and metabotropic glutamate receptors are under the process of verification for clinical use. Beneficial effects of NMDA co-agonists may be associated with the normalization of altered glutamatergic transmission, particularly in the prefrontal cortex and the limbic system. Perhaps glutamatergic drugs, in this case NMDA receptor glycine site co-agonists, amplify the action of antipsychotic drugs (with the dopaminergic and serotonergic activity). During their use, in addition to the

beneficial effects on negative and probably cognitive symptoms (although data on this subject are inconsistent), we observed a reduction of the severity of affective symptoms, which was noted in our group [23-25]. Observed improvement, although statistically significant, clinically is not large – the reduction of symptoms severity reached 25.8%, from 8.97 to 6.66 points in HDRS - but what may be worth emphasizing, 7 points and less means no depressive episode in a 17-item HDRS. The effect could be more pronounced at more severe depressive symptomatology in the study group.

The reported reduction in extrapyramidal symptoms should be interpreted rather as a sign of normalization of dopaminergic (and cholinergic?) transmission. No anticholinergic properties of glycine were noted in the study. It is noteworthy that in the previously observed groups the changes in extrapyramidal symptoms during the glycine use did not reach the statistical significance [26-28]. The use of glycine was safe, there was no increased risk of exacerbation of positive symptoms, which can occur during the use of antidepressants. This observations may indicate a benefit of a concurrent use of antipsychotic drugs together with glutamatergic modulators such as glycine, bettering negative symptoms [23, 24] and probably also the positive symptoms of the illness. The observed reduction of the extrapyramidal symptom severity in the study group during the application of glycine should improve overall quality of life and tolerability of antipsychotic treatment. Of course, due to the methodological weaknesses the study (a preliminary study without a control group), conclusions must be formulated carefully.

Conclusions

1. During the glycine augmentation of antipsychotic treatment in schizophrenic patients with predominant negative symptoms we observed a moderate improvement in depressive symptoms, which persisted also 2 weeks after its discontinuation. 2. The extrapyramidal symptoms' intensity was significantly lower after 6 weeks of glycine administration and 2 weeks after its discontinuation. 3. The use of glycine was safe and well tolerated by most patients.

References

1. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. *Psychiatric comorbidities and schizophrenia.* Schizophr. Bull. 2009; 35(2): 383–402.
2. Leff, J. *Depressive symptoms in the course of schizophrenia*. In: *Depression in Schizophrenia* (ed. L. E. DeLisi) 1990. Washington, DC: American Psychiatric Press.
3. Kasckow J, Felmet K, Zisook S. *Managing suicide risk in patients with schizophrenia*. CNS Drugs 2011; 25(2): 129–143.
4. Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. *The burden of depressive symptoms in the long-term treatment of patients with schizophrenia*. Schizophr. Res. 2007; 90(1-3): 186–197.
5. Reine G, Lançon C, Di Tucci S, Sapin C, Auquier P. *Depression and subjective quality of life in chronic phase schizophrenic patients*. Acta Psychiatr. Scand. 2003; 108(4): 297–303.

6. Mauriño J, Sanjúan J, Haro JM, Díez T, Ballesteros J. *Impact of depressive symptoms on subjective well-being: the importance of patient-reported outcomes in schizophrenia*. Patient Prefer. Adherence. 2011; 5: 471–474.
7. Schennach-Wolff R, Obermeier M, Seemüller F, Jäger M, Messer T i wsp. *Evaluating depressive symptoms and their impact on outcome in schizophrenia applying the Calgary Depression Scale.* Acta Psychiatr. Scand. 2011; 123(3): 228–238.
8. Hunter R, Barry S. *Negative symptoms and psychosocial functioning in schizophrenia: Neglected but important targets for treatment*. Eur. Psychiatry. 2011 in press.
9. Heresco-Levy U, Ermilov M, Shimoni J, Shapira B, Silipo G, Javitt DC. *Placebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine, or risperidone in schizophrenia*. Am. J. Psychiatry. 2002; 159: 480–482.
10. Heresco-Levy U, Javitt DC, Ermilov M, Silipo G, Shimoni J. *Double-blind, placebo-controlled, crossover trial of D-cycloserine adjuvant therapy for treatment-resistant schizophrenia*. Int. J. Neuropsychopharmacol. 1998; 1: 131–135.
11. Heresco-Levy U, Javitt DC, Ermilov M, Mordel C, Horowitz A, Kelly D. *Double-blind, placebo -controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia*. Br. J. Psychiatry. 1996; 169: 610–617.
12. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvadore G, Machado-Vieira R, Manji HK, Zarate CA Jr. *A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression*. Arch. Gen. Psychiatry. 2010; 67(8): 793–802.
13. Ferguson JM, Shingleton RN. *An open-label, flexible-dose study of memantine in major depressive disorder*. Clin. Neuropharmacol. 2007; 30: 136–144.
14. Muhonen LH, Lönnqvist J, Juva K, Alho H. *Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence*. J. Clin. Psychiatry. 2008; 69: 392–399.
15. Pilc A, Chaki S, Nowak G, Witkin JM. *Mood disorders: regulation by metabotropic glutamate receptors*. Biochem. Pharmacol. 2008; 75(5): 997-1006.
16. Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. *Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder*. Eur. Neuropsychopharmacol. 2012; 22(5): 339–346.
17. Arai AC, Kessler M. *Pharmacology of ampakine modulators: from AMPA receptors to synapses and behavior*. Curr. Drug Targets 2007; 8(5): 583–602.
18. Strzelecki D, Rabe-Jabłońska J. *Changes in positive and negative symptoms, general psychopathology in schizophrenic patients during augmentation of antipsychotics with glycine: a preliminary 10-week open-label study*. Psychiatr. Pol. 2011; 45(6): 825–837.
19. Strzelecki D, Rabe-Jabłońska J. *Wpływ augmentacji leczenia przeciwpsychotycznego glicyną na funkcje poznawcze u chorych na schizofrenię z dominującymi objawami negatywnymi*. Farmakoter. Psychiatr. Neurol. 2010; 1: 15-22.
20. Jarema M, Kiejna A, Landowski J, Meder J, Rabe-Jabłońska J, Rybakowski J. *Standardy leczenia farmakologicznego schizofrenii*. Psychiatr. Pol. 2006; 40(6): 1171–1205.
21. Marek GJ, Behl B, Bespalov AY, Gross G, Lee Y, Schoemaker H. *Glutamatergic (N-methyl-D-aspartate receptor) hypofrontality in schizophrenia: too little juice or a miswired brain?* Mol. Pharmacol. 2010; 77(3): 317–326.
22. Bennett M. *Positive and negative symptoms in schizophrenia: the NMDA receptor hypofunction hypothesis, neuregulin/ErbB4 and synapse regression*. Aust. N. Z. J. Psychiatry. 2009; 43(8): 711–721.
23. Tuominen HJ, Tiihonen J, Wahlbeck K. *Glutamatergic drugs for schizophrenia*. Cochrane Database Syst. Rev. 2006 19; (2): CD003730.

24. Singh S, Singh V. *Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia*. CNS Drugs. 2011; 10: 859–885.
25. Heresco-Levy U, Javitt DC, Ermilov M, Mordel C, Horowitz A, Kelly D. *Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia*. Br. J. Psychiatry. 1996; 169(5): 610–617.
26. Buchanan RW, Javitt DC, Marder SR, Schooler NR, Gold JM, McMahon RP, Heresco-Levy U, Carpenter WT. *The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments*. Am. J. Psychiatry. 2007; 164(10): 1593–1602.
27. Heresco-Levy U, Ermilov M, Lichtenberg P, Bar G, Javitt DC. *High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia*. Biol. Psychiatry. 2004; 55(2): 165–171.
28. Heresco-Levy U, Javitt DC, Ermilov M, Mordel C, Silipo G, Lichtenstein M. *Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia*. Arch. Gen. Psychiatry. 1999; 56(1): 29–36.

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