Archives of Psychiatry and Psychotherapy, 2011; 2 : 5–11

Initial glycine serum level is not a predictor of the recovery resulting from glycine augmentation of antipsychotic treatment

Dominik Strzelecki, Olga Kałużyńska, Olga Józefowicz,
Tomasz Pawełczyk, Jolanta Rabe-Jabłońska

Summary

Glycine is a non-competitive NMDA co-agonist of an ionotropic NMDA receptor in the glutamate system. Beneficial effects of this amino acid on primary negative symptoms of schizophrenia were revealed in the literature. The main research hypothesis assumes the existence of a relationship between negative symptoms of schizophrenia and serum glycine concentration.

Aim. The aim of the study is finding a relationship between the initial glycine serum concentrations together with changes in concentration of this compound and severity of schizophrenia symptoms (in PANSS) and selected cognitive functions as a result of application of glycine at a dose of 0.8g/kg/day orally added to the existing antipsychotic treatment.

Method. A group of 28 individuals with schizophrenia with predominantly negative symptoms completed a 6-week open-label prospective study. The patients received oral glycine (60g/day) in parallel with the existing antipsychotic treatment At the beginning and end of the study serum glycine levels were measured and the severity of the symptoms of schizophrenia using PANSS and cognitive functioning (using Wisconsin Card Sorting Test, Trail Making Test and Stroop Test) were assessed.

Results. From the data, obtained on two check-ups before and after the 6 weeks of glycine application, no significant correlations between serum glycine concentrations and either the PANSS score (subscales assessing positive and negative symptoms, general psychopathology and a total score) or the cognitive battery results were found excluding a correlation between the increase in the glycine concentration and the reduction in the number of errors in the second part of the Trail Making Test (TMT).

Conclusion. Measurements of serum amino acid concentrations do not allow direct assessment of severity of disease symptoms or resulting improvement. Unfortunately, the initial serum glycine concentration may not be used as a predictor of the improvement resulting from augmentation of antipsychotic treatment with glycine. The results obtained in the whole PANSS scale and in its subscales suggest beneficial effects of glycine in the applied dose on the psychopathology of schizophrenia.

schizophrenia / negative symptoms / glycine /NMDA / glutamic acid / glycine / serum concentration

Dominik Strzelecki[1], Olga Kałużyńska[2], Olga Józefowicz[1], Tomasz Pawełczyk[1], Jolanta Rabe-Jabłońska[1]: [1]Department of Affective and Psychotic Disorders, Medical University of Łódź, 8/10 Czechosłowacka Str., 92-216 Łódź, Poland. [2]Central Clinical Hospital, 8/10 Czechosłowacka Str., 92-216 Łódź, Poland. Correspondence address: Dominik Strzelecki, 2Central Clinical Hospital, 8/10 Czechosłowacka Str., 92-216 Łódź, Poland.

E-mail: dominik.strzelecki@umed.lodz.pl

Manuscripts submitted for publication have been reviewed by the Ethics Committee of Medical University of Łódź and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Source of financing: Department own sources, no potential conflict of interest.

INTRODUCTION

Glutamic acid is the largest excitatory neurotransmitter in the central nervous system (CNS), the population of glutamatergic neurones represents approximately 50% of all neurones in the brain. Being closely dependent on the inhibitory GABA system, the glutamate system is responsible for the transmission and modulation of the majority of brain signals, such as dopaminergic and serotonergic transmission. The glutamate system (relatively much is known about NMDA

receptors) plays an important role in the pathogenesis of schizophrenia [1, 2]. NMDA receptor antagonists, including phencyclidine, ketamine and MK-801, cause symptoms similar to those found in schizophrenia [3], as well as deterioration of mental state in patients with schizophrenia [4]. What is important, from a theoretical point of view NMDA agonists also cause negative symptoms which are not observed after amphetamine or other drugs intoxication. Based on these observations, it was assumed that normalization of glutamatergic transmission may result in an improvement in schizophrenia symptomatology. According to the assumptions of this hypothesis, attempts were made to stimulate transmission within this system. Due to the high risk of excitotoxic effects induction therapy with glutamic acid is not administered (hyperactivity of glutamatergic system, leading to nerve cell damage was observed in neurodegenerative diseases) [5]. Along with glutamic acid and voltage changes dependent on another glutamatergic receptor-AMPA, presence of glycine is necessary to stimulate the NMDA receptor [6]. This widely distributed amino acid, an important element of protein chains, is present in a daily diet (average consumption amounts to 2g/day). In addition to building properties, it is of paramount importance in the central nervous system. As a primary transmitter in glycinergic neurones it belongs to the class I of neurotransmitters. Moreover, it also plays a role as a co-agonist and a modulator, for example in the glutamatergic system.

Glutamic acid is released from nerve endings into the synaptic cleft, where it is re-uptaken and dispersed, which, in consequence, results in a rapid decline in its concentration in the vicinity of NMDA receptors. As a result, the time of receptor binding is short [7]. Intrasynaptic glycine turnover is different – it resides inside the synapses permanently, depending on the concentration and, to a greater or lesser extent, binds to a modulatory site [6, 8]. Glial cells, with identified glycine transport system (GlyT-1) [9, 10] are responsible for maintaining a stable level of glycine in neuronal junctions. New research on inhibitors of this transport system (GTI), which may have similar effects to glycine administration, have begun. Glycine does not bind to all the modulatory sites on NMDA receptor in vivo, and augmentation of this saturation intensifies glutamatergic transmission. This phenomenon is particularly observed in individuals with relatively low (not sufficient for maximum saturation of the receptor site) levels of synaptic glycine. Due to the poor penetration of glycine through the blood-brain barrier [11], other partial agonists of glycine site, such as D-cycloserine and D-serine, which more easily pass into brain tissue were used. The glycine content in an average diet (about 2g/day) does not increase levels of this amino acid in cerebrospinal fluid. Oral administration of high doses of glycine (up to several dozens of g/day) causes an increase in its concentration in the CSF [12]. Clinical studies confirmed the safety of this therapeutic method, even a maximum saturation of glycine does not cause the cytotoxic effect. Moreover, glycine which does not cause adverse effects more often than a placebo, is well tolerated even when used at high doses over time. There is fairly extensive literature on the use of NMDA receptor co-agonists (glycine, or substances with similar properties such as D-serine, D-cycloserine and D-alanine) and glycine transporter inhibitors GlyT-1 (sarcosine) [13, 14, 15]. The majority of these studies, although inconclusive, suggest beneficial effects of these substances used as augmentation of antipsychotic treatment, especially in terms of negative and cognitive symptoms. The meta-analysis, which includes most published studies, shows improvement in negative symptoms estimated to be moderate [16] and in cognitive symptoms reached statistical trend. The aim of the study described below is to assess whether serum glycine levels correlate with severity of schizophrenia symptoms (assessed with the subscales of negative and positive symptoms and PANSS total score), and whether changes in the glycine concentration resulting from the use of high oral doses of this substance correspond with clinical improvement. Earlier studies do not give a definite answer to these questions [17, 18, 19].

METHOD

Study group

Thirty-two patients with schizophrenia (according to ICD-10) with predominant negative

symptoms – mean 25.69 points in PANSS negative symptoms subscale – signed informed consent prior to their inclusion in the project and were qualified for the prospective open-label study. Twenty-nine individuals completed the study and were the subjects of further analysis. There were 13 women and 16 men, predominantly young (average age about 32 years), with a history of schizophrenia for several years and multiple hospitalizations (Tab. 1). The severity of positive and general psychopathology symptoms was considered benign, while intensity of negative symptoms was evaluated as moderate (Tab. 2). 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).

Table 1. Characteristics of the study group

Parameter	Mean	Median	Range	SD
Age (years)	32.32	29.50	20-50	8.82
Psychosis duration (years)	8.39	5.00	1.0-24.0	6.87
Hospitalisations	2.28	2.00	0.0-6.0	1.46

Patients' stable mental state and antipsychotic treatment, which had not been changed for at least 3 months (data confirmed by medical documentation) were the most important qualifying criteria (apart from a respective psychiatric diagnosis). For 6 weeks the patients were given glycine at a dose of 0.8 g/kg bm/3 doses orally. Glycine serum level tests were conducted twice - before glycine application and after 6 weeks of its administration. On both check-ups the patients were examined and evaluated with PANSS, including a negative symptoms subscale. One of three female patients who did not complete the study and were excluded had spontaneous relapse of psychosis (paranoid syndrome symptoms) after informed consent visit, before the treatment with glycine was started. Two other patients were excluded because of severe vomiting and excessive sedation respectively after glycine administration.

Psychological instruments used to assess cognitive function

Commonly used cognitive assessment instruments, such as: Wisconsin Card Sorting Test, Trail Making Test and Stroop Test were used in the study. Wisconsin Card Sorting Test (Wisconsin Card Sorting Test, WCST) is used to assess working memory and executive functions. In the computer version of the test 4 cards are placed at the top of the screen. Starting from the left side there is a card with a red triangle, then cards with two green stars, three yellow crosses, and four blue circles respectively. At the bottom of the screen cards with varying characteristics (i.e. color, number, shape, figure) appear one by one. The task is to arrange the cards according to similarity of particular characteristic. During the course of the test the matching rules are changed. The entire test consists of 6 series, with one criterion in force in each of series. The task ends when all six series are completed, or in case of failure, when 128 cards are arranged. The number of completed series (more series completed signifies better planning and reasoning processes), perseverative errors (evidence of difficulties in maintaining an appropriate criterion and switching to the new one, and reflect working memory disturbances) and non-perseverative errors (derivatives of attention deficits) are recorded. A computerised version of the WCST developed by Heaton was used in the study.

A Trail Making Test (TMT) consist of two parts: A and B. Both parts of the test consist of 25 circles distributed over a sheet of paper. In Part A the circles are numbered 1–25 and the patient should draw lines to connect the numbers in ascending order. This section allows to assess attention and psychomotor functions. In Part B the circles include both numbers (1–13) and letters (A–L); as in Part A, the patient draws lines to connect the circles in an ascending numerical pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). In section B ability to switch from one criterion to another as well as visuo-spatial coordination are evaluated. In both parts the time of test completion and correctness of the test results (quality and quantity of errors) are measured.

A Stroop Test (Stroop Color Interference Test, TS) consists of two (the version used in the study) or more rarely three parts. In the first section participants read words denoting color names and names of colors, which appear in black. In the second part names of colors appear in a different ink than the color named. The task is to say the color of the written words independently of the meaning of the written word. Reading a printed word is regarded as erroneous. In the expanded version of the test squares of different colors are placed among the words. Participants should say the colors of the letters and the squares. The time of test completion and number of errors are analysed.

Glycine formulation

Glycine (crystallizate) used in the study was bought at MERCK Germany KGaA (in 25kg 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 participants' body weight (0.8g/kg bm/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)

Determination of serum glycine concentration

lycine concentration was determined using high performance liquid chromatography (HPLC). Chromatography kit consisted of two pumps with a pulsation dampener (RF-535) and an integrator (RF-530). For chromatographic separation a column 25 x 0.4nm in size was used. It was filled with solid phase (Hypersil ODS) with a grain diameter of 5nm and protected by a 3 x 0.4 nm precolumn filled with the same material. The flow through the column was performed at 35°C. Samples were injected using an automatic injector with an installed loop of a capacity of 20ml. Measurements were made at an excitation wavelength of 340 nm and an emission wavelength of 445nm using a 12μL flow cell and a xenon lamp. A gradient system with one phase of 50mM Na-acetate and methanol (in ratio 78:22) and a second phase of the same compounds in ratio 25:75 was used. The flow rate of the liquid phase was 1.0ml/minute.

Analytical procedure

Blood samples were collected on EDTA (if necessary, frozen at -30°C) and deproteinized with methanol then, using OPA/3MPA (o-phthaldialdehyde/3-mercaptopropionic acid), the deproteinized filtrate and standard glycine at concentration of 10pM/20 ml were subjected to a two-stage derivation. Sample concentration was measured using the Eurochrom 2000' software by Knaller, which collected data automatically and integrated the chromatograms simultaneously with the sample injection. Determination of glycine concentration was performed in the Medical Analysis Laboratory of The Polish Mother's Memorial Hospital Research Institute in Łódź, Poland.

In addition to determination of serum glycine concentration standard blood tests (blood count, biochemical tests, serum electrolytes) and an electrocardiogram were performed in all patients on both visits.

Data was analysed statistically using description and inference methods. Normality of distributions was assessed using the Shapiro-Wilk test. Parameter changes were assessed using Wilcoxon signed-rank test. The significance of correlation coefficients was tested using U Mann Whitney test. Two-tailed p values were calculated: values $p>0.05$ were considered statistically not significant. Analyses were performed using statistical package (SPSS for Windows 12.0, Statistical Package for Social Science, Chicago Il. 1989-2003).

RESULTS

Serum glycine concentrations increased on average by 156% during the course of the study ($p<0.001$, Tab. 2). Moreover, significant reduction in severity of positive and negative symptoms, general psychopathology and PANSS total score were observed. The most evident change

was the reduction in severity of negative symptomatology. The effect was moderate (change by 16.1%). Studies with similar results – moderate, statistically significant improvement observed in the highest degree in the scale of negative symptoms predominate in the literature (including a meta-analysis in The Cochrane Collaboration Database [20]). Cognitive dysfunction, an important component of negative symptomatology, also results from malfunctions in the prefrontal lobes. Impairment of cognitive control and executive functions – memory, purposeful, intentional and volitional activity – are responsible for the inability to make use of new information and experience adequately. This, of course, also applies to patients' interactions with the environment and determines typical clinical picture. Tests conducted at the beginning of the study showed distinct cognitive dysfunctions in the study group. On the second check-up - after glycine intake – the patients needed fewer attempts to complete a higher number of test categories ($p<0.001$) and made fewer perseverative errors ($p<0.001$) in the WCST, which is particularly important in the assessment of working memory. A lower number of non-perseverative errors was also observed ($p<0.01$). In both parts of the Trail-Making Test ($p<0.01$) and the second part of the Stroop Test ($p<0.05$) significantly better memory performance, switching, and visuospatial functions after augmentation of antipsychotic treatment with glycine were confirmed. Analysis of correlations between initial and final glycine concentrations, changes in serum glycine concentration with PANSS score and cognitive function showed only a relationship between glycine concentrations with a reduction in the number of errors in the second part of the TMT ($p=0.02$). Tab. 2 (*next page*).

Analysis of hematological and biochemical parameters, electrolyte levels and ECG revealed no changes.

CONCLUSIONS

Use of glycine as augmentation of antipsychotic treatment in refractory schizophrenia has been approved by both American and Polish Psychiatric Associations. Determining of serum glycine concentration (e.g. low) before its contingent administration could be a convenient marker of clinical usefulness of glycine. If in the initial stage it was known whether one should use glycine, it would be possible to predict the scale of improvement and limit administration of glycine only to the indicated cases. A decision to introduce the glycine therapy for the first time would be based not only on the intuition of the investigator, symptom profile and adverse drug reactions. Unfortunately, the results of our study do not warrant the use of baseline glycine concentration as a prognostic factor, although it must be emphasized that methodological factors (an open-label study and a small study group) imply cautious interpretation of the results. The severity of symptoms of schizophrenia, as well as the results obtained in the tests evaluating cognitive functions prior to the introduction of glycine augmentation did not show correlations with the serum glycine concentrations. It is worth noting that several studies showed low levels of this amino acid in patients with severe negative symptoms, which, as suggested by the authors of these publications may be clinically useful [17, 18, 19].

Serum glycine concentration determined on the final check-up, although higher, did not correlate with improvement in the particular subscales or the PANSS total score. The demonstrated correlation between the increase in the glycine and the reduction in the number of errors in the second part of the TMT ($p=0.02$) supports the hypothesis of the involvement of glutamatergic system in cognitive functioning, but has minimal practical value – the key data was obtained in the final phase of the study. Average serum glycine concentrations (mean 0.125 mmol/ml at baseline and 0.321 mmol/ml at the end) reported by us correspond with the results described earlier [12]; however some authors observed much higher glycine concentrations (up to 1.4mmol/ml in 6th week of augmentation) due to the use of high oral doses of the amino acid [18]. Owing to poor pharmacokinetic properties of glycine (poorly penetrates the blood-brain barrier) high doses are required in the oral treatment. Therefore, determination of serum concentrations remains only an approximate method, its concentration in the brain tissue may be secondary to serum concentrations, but the relationship between them is not stable and can depend on dif-

Table 2. Analysis of the average plasma glycine concentrations and the parameters of mental state and cognitive functions (PANSS, TMT, Stroop Test, WCST) in patients on both checkups.

Parameter	Check-up 1		Check-up 2		Change			p (Wilcoxon)
	Mean	SD	Mean	SD	Mean	SD	%	
Gly [µmol/ml]	0.125	0.032	0.321	0.154	0.196	0.140	156.5	p<0.001
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
Pers_Err	23.21	16.16	12.52	11.16	-10.69	13.37	-46.1	p<0.001
Nonpers_Err	21.62	12.91	12.79	10.40	-8.83	13.40	-40.8	p<0.01
WCST_tat	4.17	1.75	5.41	1.32	1.24	1.48	29.8	p<0.001
TMT_1 [s]	52.1	23.2	38.3	14.2	-13.8	22.2	-26.5	p<0.01
TMT_2 [s]	112.0	75.8	75.3	31.1	-36.7*	69.8	-32.7	p<0.01
Stroop_1 [s]	28.7	12.6	25.6	7.2	-3.1	13.1	-10.8	ns
Stroop_2 [s]	68.4	21.3	60.0	15.6	-8.3	16.3	-12.2	p<0.05

Gly – glycine plasma levels, PANSS_P, PANSS_N, PANSS_G – scores in the subscales of positive symptoms, negative symptoms, general psychopathology in PANSS and total PANSS score – PANSS T, Pers Err – number of perseverative errors in WCST, Nonpers Err – number of nonperseverative errors in the WCST, WCST Cat – number of completed categories in the WCST, TMT_1 [s] and TMT_2 [s] - time needed to complete the Trail Making Test (parts 1 and 2), TS_1 [s] TS_2 [s] – time needed to complete the Stroop Test (parts 1 and 2), * – correlation between increased plasma glycine levels and shortening of the time needed to complete the second part of the TMT (p=0.02, Mann-Whitney U)

ferent variables. It seems, thus, that it would be more appropriate, though not acceptable in clinical practice, to determine glycine concentration in the cerebrospinal fluid (which was performed by D'Souza [12]) or in brain regions relevant to the pathogenesis of schizophrenia by the use of imaging methods, e.g. magnetic resonance spectroscopy. Using more accurate methods of determination of glycine concentration could also have greater prognostic and clinical value. For example, this would help to designate groups of patients with low concentrations of glycine who require supplementation. Increase in the transmission associated with NMDA receptor could lead to the improvement of mental state, especially in negative symptomatology. Glycine may improve symptomatology of schizophrenia, which is confirmed by PANSS scores and the results of cognitive function tests. However, determination of its concentration in serum does not enable direct assessment of the severity of symptoms. In addition, initial serum glycine concentration failed to serve as a prognostic factor of improvement resulting from the augmentation of antipsychotic treatment with glycine.

REFERENCES

1. Carlsson A, Waters N, Waters S, Carlsson ML. Network interactions in schizophrenia - therapeutic implications. Brain Res Brain Res Rev. 2000, 31: 342–349.
2. Olney JW, Newcomer JW, Farber NB. NMDA receptor hypofunction model of schizophrenia. J Psychiatr Res. 1999, 33: 523–533.
3. Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA. Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacol. 2001, 25: 455–467.
4. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacol. 1995, 13: 9–19.
5. Lawlor BA, Davis KL. Does modulation of glutamatergic function represent a viable therapeutic strategy in Alzheimer's disease? Biol Psychiat. 1992, 31: 337–350.
6. Mayer ML, Westbrook GL. The physiology of excitatory amino acids in the vertebrate central neurous system. Prog Neurobiol. 1987, 28: 197–276.
7. Lester RA, Clements JD, Westbrook GL, Jahr CE. Channel kinetics determines the time course of NMDA receptor-mediated synaptic currents. Nature. 1990, 346: 565–567
8. McBain CJ, Mayer ML. N-methyl-D-aspartic acid receptor structure and function. Physiol Rev. 1994, 74: 723–760.

9. Gadea A, Lopez-Colome AM. Glial transporters for glutamate, glycine, and GABA III. Glycine transporters. J Neurosci Res. 2001, 64: 218–222.
10. Supplison S, Bergman C. Control of NMDA receptor activation by a glycine transporter coexpressed in xenopus oocytes. J Neurosci. 1997, 17: 2921–2927.
11. Oldendorph WH. Brain uptake of radio labelled amino acids, amines, and hexoses after arterial injecton. Am J Physiol. 1971, 221: 1629–1639.
12. D'Souza DC, Gil R, Cassello K, Morrissey K, Abi-Saab D, White J, Sturwold R, Bennett A et al. IV glycine and oral D-cycloserine effects on plasma and CSF amino acids in healthy humans. Biol Psychiat. 2000, 47: 450–462.
13. Strzelecki D, Rabe-Jabłońska J. Glutamatergic transmission alterations in schizophrenia. Post Psych Neurol. 2003, 12: 183–192.
14. Strzelecki D, Rabe-Jabłońska J. Glycine and its role in treatment of schizophrenia. Post Psych Neurol. 2003, 12: 193–200.
15. Strzelecki D, Rabe-Jabłońska J. Glycine transporters – potential target of pharmacologic intervention in schizophrenia treatment. Post Psych Neurol. 2006, 15: 117–120.
16. Tuominen HJ, Tiihonen J, Wahlbeck K. Glutamatergic drugs for schizofrenia: a systematic review and meta-analysis. Schizophr Res. 2005, 72: 225–234.
17. Neeman G, Blanaru M, Bloch B, Kremer I, Ermilov M, Javitt DC, Heresco-Levy U. Relation of plasma glycine, serine, and homocysteine levels to schizophrenia symptoms and medication type. Am J Psychiat. 2005, 162: 1738–1740.
18. Leiderman E, Zylberman I, Zuckin SR, Cooper TB, Javitt DC. Preliminary investigation of high-dose oral glycine on serum levels and negative symptoms in schizophrenia: an open-label trial. Biol Psychiat. 1996, 39: 213–215.
19. Sumiyoshi T, Anil Elif A, Yin D, Jayathialke K, Lee M, Meltzer HY. Plasma glycine and serine levels in schizophrenia compared to normal controls and major depression: relation to negative symptoms. Int J Neuropsychopharmacol. 2004, 7: 1–7.
20. Tuominen HJ, Tiihonen J, Wahlbeck K. Glutamatergic drugs for schizophrenia. Cochrane Database Syst Rev. 2006, 19(2): CD003730.

Next issue

ARCHIVES OF PSYCHIATRY AND PSYCHOTHERAPY

Volume 13 Issue 3 September 2011

In the next issue of the „Archives of Psychiatry and Psychotherapy"

you will find among others:

- *Family constellation method of Bert Hellinger in the context of the Code of Ethics for Psychotherapists* Małgorzata Talarczyk
- *Concept of reliable change in the usage of the KON-2006 neurotic personality questionnaire* Rafał Styła
- *Various ways of understanding compliance: a psychiatrist's view* Rafał Jaeschke, Marcin Siwek, Dominika Dudek

---

Archives of Psychiatry and Psychotherapy
31-138 Krakow, 14 Lenartowicza St., Poland
e-mail: archives@psychiatriapolska.pl
www.archivespp.pl/