



# CAN WE INFLUENCE THE NEGATIVE DRUG ATTITUDE? INTERPRETATION OF THE REJECTION OF COVID-19 VACCINE IN THE LIGHT OF RESULTS OF A PILOT STUDY

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## BEFOLYÁSOLHATÓ-E A NEGATÍV GYÓGYSZERSZEDÉSI ATTITÚD? A COVID-19-VAKCINÁT ELUTASÍTÓ MAGATARTÁS INTERPRETÁCIÓJA EGY ELŐKÉSZÍTŐ VIZSGÁLAT EREDMÉNYEINEK TÜKRÉBEN

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**Background and purpose** – Vaccination refusal is a serious obstacle to minimizing the spread of COVID-19. Nevertheless, the rejection of vaccine can be considered the result of a negative attitude towards medical treatment, and according to our previously published data, it can be influenced by the underlying affective state.

Increased incidence of affective disorders and anxiety could be observed globally during the pandemic, which may have a significant impact on vaccination acceptance. The aim of our pilot study was to determine the association between clinical improvement of affective and neurocognitive symptoms and change of drug attitude and health control beliefs in a sample of psychiatric patients.

**Methods** – A data set of 85 patients with psychiatric disorder has been analysed with the use of Patient's Health Belief Questionnaire on Psychiatric Treatment (PHBQPT) with 5 subscales (Negative Aspect of Medication – NA; Positive Aspect of Medication – PA; Doctor health locus of control- Doctor HLOC; Internal HLOC; Psychological Reactance – PR); Hospital Anxiety Depression Scale (HADS-Anx; HADS-Dep) and neurocognitive tests, such as the Stroop test and the Trail Making Tests. All the tests were performed before and after a 14 days treatment. Paired t-tests and generalized linear models were performed to assess the associations between the variables.

**Results** – The baseline scores of NA and HADS-Anx correlated significantly ( $p=0.001$ ) and after two weeks of treatment NA decreased ( $p=0.001$ ), while Doctor HLOC and Internal HLOC increased ( $p=0.001$  and  $p=0.006$ ). The patients performance of the neurocognitive tests improved (all  $p<0.05$ ). The reduction of HADS-Anx ( $p=0.002$ ) and HADS-Dep ( $p=0.006$ ) scores showed significant associations with the decrease of NA. Increase of the PA score

**Háttér és célkitűzés** – A vakcina elutasítása komoly kihívást jelent a pandémia elleni harcban. Ugyanakkor a vakcinaelutasítás negatív gyógyszereszedési attitűdként is értelmezhető, amit korábbi eredményeink szerint az affektív tünetek is jelentősen befolyásolhatnak. Tekintettel arra, hogy az affektív zavarok száma világszerte drámaian megemelkedett a pandémia következtében, a depressziós és szorongásos tünetek hatása a vakcinával szembeni negatív attitűdre meghatározó lehet. Vizsgálatunk célja az volt, hogy meghatározzuk az affektív tünetek és a neurokognitív funkció javulása és a gyógyszereszedési attitűd, valamint az egészségkontrollhit változása közötti összefüggéseket pszichiátriai betegek csoportjában.

**Módszerek** – A vizsgálatban 85 pszichiátriai beteg adatait dolgoztuk fel, akik az Egészségkontrollhit Kérdőív (Patient's Health Belief Questionnaire on Psychiatric Treatment, PHBQPT) 5 alszállját (a gyógyszerek negatív aspektusa, NA; a gyógyszerek pozitív aspektusa, PA; Orvos-egészségkontrollhely, Doctor HLOC; Belső egészségkontrollhely, Internal HLOC; Pszichológiai reaktancia, PR) és a Kórházi Szorongás és Depresszió Skálát (Hospital Anxiety Depression Scale: HADS-Anx, HADS-Dep) töltötték ki, valamint neurokognitív tesztek végeztek (Stroop teszt és Trail Making teszt). A kérdőíveket és tesztek a kezelés első napján és az adott kórképnek megfelelő 14 napos kezelést követően vettük fel a betegekkel. Páros t-tesztel és generalizált lineáris modellel elemeztük a változók közötti összefüggéseket.

**Eredmények** – A kiindulási NA- és HADS-Anx-értékek szignifikánsan korreláltak ( $p=0,001$ ), és 14 napos kezelés után az NA-pontszám csökkent ( $p = 0,001$ ), míg a Doctor HLOC- és az Internal HLOC-pontszám emelkedett ( $p = 0,001$  és  $p = 0,006$ ). A neurokognitív teljesíté-

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was associated with reduction of HADS-Dep ( $p=0.028$ ). Improvement of neurocognitive functions had no effect on PHBQPT scores.

**Conclusion** – Important conclusions can be drawn regarding the rejection of the COVID-19 vaccine based on the associations found between the intensity of affective and anxiety symptoms and the attitude towards treatment. Our findings suggest that affective symptoms have a negative influence on the attitude towards treatment and that the improvement of these symptoms can facilitate the acceptance of the therapy, regardless of diagnosis. The modest effect of the improvement of neurocognitive functioning on the attitude towards drugs and the significant role of affective-emotional factors suggest that the acceptance of vaccination probably cannot be facilitated solely with the aid of educational programs. Considering the increasing incidence of affective disorders during the COVID-19 pandemic, the screening of affective and anxiety symptoms and treatment of these disorders could be an important step towards the acceptance of the vaccine. Although psychiatry is not considered as a frontline care unit of the COVID cases, more attention is needed to pay on the availability of mental health services because refuse of vaccine can develop due to affective disorders too.

**Keywords:** anti-vax behavior, rejection of vaccination, drug attitude, health beliefs, psychological reactance

mény szignifikánsan javult a kezelés 2. hetének végére ( $p < 0,005$ ). A HADS-Anx- és HADS-Dep-pontszám csökkenése és az NA alskála pontszámának csökkenése szignifikáns összefüggést mutatott ( $p = 0,002$  és  $p = 0,006$ ). A PA emelkedése a HADS-Dep-pontszám csökkenésével korrelált ( $p = 0,028$ ). A neurokognitív funkció javulása nem volt hatással a PHBQPT alskála pontszámainak változására.

**Következtetés** – A gyógyszeres kezeléssel szembeni attitűd és az affektív tünetek összefüggései alapján fontos következtetéseket vonhatunk le a vakcinát elutasító magatartással kapcsolatban is. Eredményeink arra utalnak, hogy az affektív tünetek negatív hatással bírnak a kezeléssel szembeni attitűdre, és a tünetek javulása a terápia elfogadását is segíti, függetlenül a kezelést indokló diagnózistól. A neurokognitív funkciók ilyen irányú hatását nem tudtuk kimutatni, ami arra utalhat, hogy ezeknél a pácienseknél a vakcinával kapcsolatos edukációs programok hatástalanok lehetnek. Tekintettel arra, hogy az affektív zavarok előfordulása a pandémia során jelentősen megnőtt, a negatív érzelmi állapotok kiszűrése és kezelése kulcs lépés lehet a vakcina elfogadásának javításában. Annak ellenére, hogy a pszichiátriát a Covid-ellátás frontvonalán kívüli ellátásként tartják számon, nagyobb figyelmet kellene fordítani a mentálhigiénés szolgálatok elérhetőségére a pandémia idején is, mivel a vakcinát elutasító magatartás mögött pszichés zavarok is húzódnak.

**Kulcsszavak:** antivakcina mozgalom, vakcinaelutasítás, gyógyszereszedési attitűd, egészségkontrollhit, pszichológiai reaktancia

The attitude towards drug treatment has a major influence on the effectiveness of the therapy and the long-term outcome. Patients' mistrust, fears, beliefs related to the treatment constitute an important challenge on every field of medicine<sup>1, 2</sup>. This issue has become even more important during the COVID pandemic due to the rising number of people who refuse to be vaccinated (anti-vaxxers). This has become a problem beyond the fate of the individual, it is an issue which endangers the whole population. The difficulty lies in the fact that the modification of negative attitude towards vaccination requires serious efforts, in addition to this, the factors which could be used for influencing this attitude has not been thoroughly analyzed yet. The majority of medical professionals who are dealing with this problem are not familiar with the techniques used in the routine psychiatric care for influencing the negative attitude towards drug treatment and improving adherence. Since the beginning of the pandemic, psychiatrists had to deal with the psychological consequences of the COVID-19 situ-

ation, as depressive symptoms, anxiety, grief, post-traumatic stress disorder, burnout, etc. Besides these, many professionals made efforts to understand and explain the psychological background of the anti-vaccine attitude arising in the society. According to *Joseph F. Goldberg*, in the background of vaccine hesitancy behavior several psychological factors can be identified<sup>3</sup>. Some people decide to avoid vaccination due to their wrong overestimation of their ability to assess their own medical safety, which is a misperception of higher-than-actual competence by people who are unaware of their lack of knowledge and expertise, a phenomenon called in social psychology Dunning-Kruger effect. Vaccines can serve as an object of projection as well, uncertainties can intensify and transform into paranoid thoughts, or later can give way to magical thinking and implausible or bizarre ideas. Paranoia can lead to aggressive behavior when the perception of the threat intensifies. The author suggests that past negative medical experiences of the vaccine-hesitant patients need to be explored,

efforts should be done to determine the reasons of their mistrust and psychiatrists should work with the patients to help overcome the barriers of their mistrust. On a public health level, psychiatrists can share opinions, raise awareness, correct misinformation and encourage dialog. Psychiatrists can also provide support to colleagues working on other fields of medicine, who have to cope with the anti-vaccine attitudes of their patients<sup>3</sup>.

The patients' willingness of medication taking is influenced among others by factors like attitude towards treatment, health locus of control and psychological reactance<sup>1, 2</sup>. In the case of patients requiring treatment for psychiatric disorders the negative attitude towards medication, the overestimation of own control over health status, mistrust in medical professionals and high psychological reactance are important factors which lead to poor long-term adherence<sup>4</sup>. The health locus of control (HLOC) is one of the important determining factors of health behavior and as a result, has influence on the individual's health status. At the same time, health status can also influence the individual's HLOC<sup>4</sup>. Originally, the health control belief was considered to be stable over time, as a component that belongs to one's personality. Later it was proved that it can be changed, moreover, it can be one of the important targets of therapeutic interventions<sup>5</sup>.

On the other hand, besides mistrust and preconceptions, affective symptoms may have an impact on patients' decisions regarding the acceptance of treatment<sup>2</sup>. Despite of the importance of these aspects, there is a scarcity of data on the relationship between affective symptoms, health control beliefs and the attitude towards drugs. In this study we intended to assess the possible correlations between the improvement in affective and cognitive symptoms and the changes of attitude towards treatment, health control beliefs and psychological reactance of the patients.

## Methods

Eighty-five psychiatric inpatients (45 women and 40 men; mean age: 42.9±13.5 years) were enrolled in the study between May 2020 and May 2021 from the Department of General Psychiatry B of the National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary. We enrolled patients treated for psychotic disorders (F2.0), mood disorders (F3.0), anxiety disorders (F4.0) and personality disorders (F6.0) who were in a stable state and decided to participate voluntarily in the study

**Table 1.** Frequencies of the categories of disorders in the sample

ICD	Frequency
F2.0	40.5%
F3.0	37.9%
F4.0	16.2%
F6.0	5.4%

ICD: International Classification of Diseases

(**Table 1**). Patients treated for addictions, mental retardation and neurocognitive disorders were excluded. The enrolled patients received pharmacological treatment, supportive therapy and participated in different group therapies. Attitude towards treatment, health locus of control and psychological reactance was assessed with the Hungarian version of the Patient's Health Beliefs Questionnaire on Psychiatric Treatment (PHBQPT), which was validated in Hungarian sample by our group<sup>6</sup>. The PHBQPT is composed of five subscales (Negative Aspect of Medication – NA; Positive Aspect of Medication – PA; Doctor health locus of control-Doctor HLOC; Internal HLOC; Psychological Reactance – PR). Anxiety and depressive symptoms were evaluated with the Hospital Anxiety and Depression Scale by two subscales (HADS-Anx and HADS-Dep)<sup>7</sup>. Neurocognitive performance was assessed with the Trail Making Test (TMT-A and TMT-B)<sup>8</sup> and Stroop test<sup>9</sup>. The patients filled the PHBQPT and HADS questionnaires, the neurocognitive tests were also performed on the day of their admission to the department (visit<sub>1</sub>). After two weeks of treatment all assessments performed initially were repeated (visit<sub>2</sub>). The study was approved by the Hungarian Central Ethical Committee, Budapest, Hungary (number of approval: 45735-5/2020). Signed informed consent was obtained from all subjects. The study was conducted according to the Declaration of Helsinki. The score changes of the scales were tested with paired t-test, the correlation of the score changes was tested with the help of the generalized linear model (GLM).

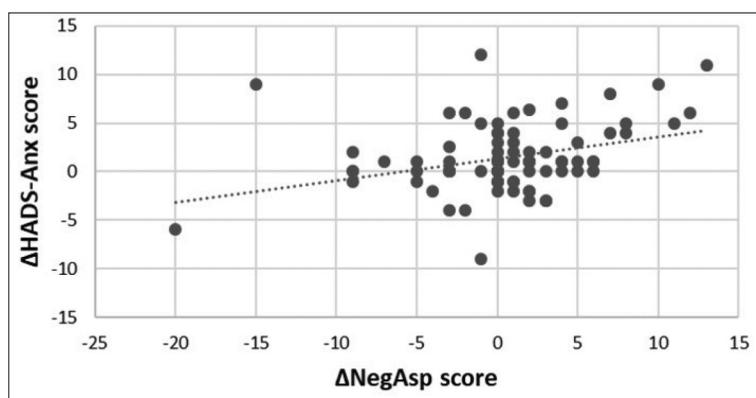
## Results

The Negative Aspect subscale score at the baseline showed a significant correlation with the HADS-Anx score (p=0.015). The Negative Aspect score decreased significantly (p=0.001), while the Doctor HLOC (p=0.001) and the Internal HLOC subscale

**Table 2.** Mean scores of the PHBQPT subscales, the HADS and the neurocognitive tests at visit<sub>1</sub> and visit<sub>2</sub>

	Visit <sub>1</sub>	Visit <sub>2</sub>	Sig.*
Positive attitude	20.04±6.2	20.45±6.05	0.45
Negative attitude	11.02±4.03	9.64±3.68	0.001
Doctor HLOC	14.78±3.16	16.09±2.47	0.001
Internal HLOC	13.13±3.42	14.13±3.07	0.006
Psychological Reactance	11.60±2.89	11.49±3.07	0.71
HADS Anx	10.15±4.95	9.69±5.34	0.42
HADS Dep	7.99±5.52	7.58±5.13	0.42
TMT-A time	49.31±20.53	40.31±19.03	0.001
TMT-B time	134.28±84.79	94.03±64.12	0.002
Stroop 1 time	60.06±20.53	51.83±15.42	0.004
Stroop 2 time	80.83±33.24	74.46±23.26	0.16
Stroop 3 time	143.69±73.58	122.86±45.43	0.034
Stroop 1 error	2.86±12.68	0.03±0.17	0.19
Stroop 2 error	4.54±19.32	0.77±1.21	0.25
Stroop 3 error	3.85±5.91	2.09±2.31	0.044

\*p-value of the paired sample t-tests



**Figure 1.** Association between change of HADS-Anx subscale score and change of Negative Aspect subscale score

Scatter plot presents the results of the generalized linear model. The greater the decrease of HADS-Anx, the greater the decrease of the Negative Aspect ( $p=0.002$ ).

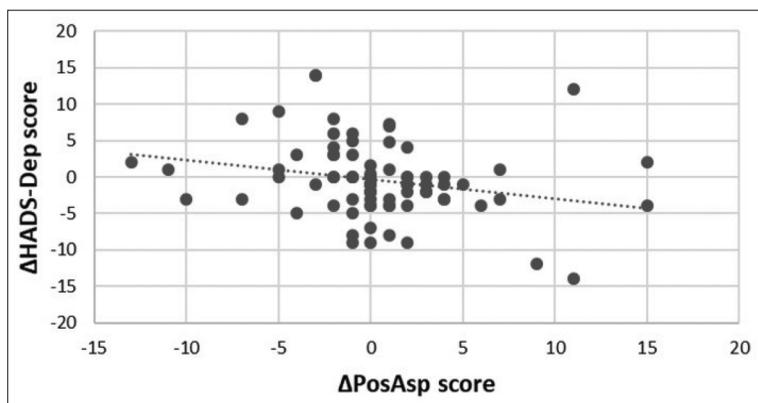
HADS-Anx: Anxiety subscale of the Hospital Anxiety Depression Scale, NegAsp: Negative Aspect of Medication of the Patient's Health Beliefs Questionnaire on Psychiatric Treatment

scores increased significantly during the two-week treatment period. Regarding the neurocognitive tests, the time required to perform the TMT-A ( $p=0.001$ ) and the TMT-B ( $p=0.002$ ) decreased as well. The speed of performance of the Stroop test increased, the time needed to perform the tasks became shorter ( $p_{\text{Stroop1}}=0.004$ ;  $p_{\text{Stroop3}}=0.034$ ) and the number of errors was lower at visit<sub>2</sub> compared to visit<sub>1</sub> ( $p_{\text{Stroop3}}=0.044$ ). However, there was no difference between the two visits regarding the number of errors at the first task and at the second task, neither the time, nor the number of errors changed significantly (Table 2).

According to the results of the GLM tests, there was a strong correlation between the decreasing NA subscale scores and the decrease of the HADS-Anx ( $p=0.002$ ) and HADS-Dep scores ( $p=0.006$ ) as well (Figure 1 and Figure 2). Besides these, correlation could be found between the increasing scores of the PA subscale and the decrease of HADS-Dep ( $p=0.028$ ) (Table 3). No correlation could be found between the improvement of neurocognitive functioning and the changes of scores related to the attitude towards drug treatment. No significant influencing effect of age and sex on attitude towards drug treatment could be found.

## Discussion

According to the results of our pilot study, the Negative Aspect of drug treatment decreased and the Doctor HLOC and Internal HLOC scores increased significantly during treatment. These favorable changes were regardless of the nature of the disorder for which the patients required psychiatric care. The results of the regression analysis have shown that there is correlation between the extent of decrease of the Negative Aspect subscale scores and the decrease of anxiety and depressive symptom scores. Besides this, there is also correlation between the extent of decrease of depressive symptom scores and the increase of scores of the



**Figure 2.** Association between change of HADS-Dep subscale score and change of Positive Aspect subscale score

Scatter plot presents the results of the generalized linear model. The greater the decrease of HADS-Dep, the greater the increase of the Positive Aspect ( $p=0.006$ ). HADS-Dep: Depression subscale of the Hospital Anxiety Depression Scale, PosAsp: Positive Aspect of Medication subscale of the Patient's Health Beliefs Questionnaire on Psychiatric Treatment

Positive Aspect of drugs subscale. It is important to mention, that although the neurocognitive functioning of the patients improved during their treatment, this improvement did not have a significant influence on their attitude towards drug treatment, health locus of control and psychological reactance. The results of our previous research have shown that no significant difference could be found between the attitude towards drug treatment of patients treated for somatic illnesses and those who required treatment for psychiatric disorders<sup>10</sup>. The decreasing Negative Aspect scores and increasing Positive Aspect scores followed by the concomitant improvement of affective symptoms can be observed in the group of somatic and psychiatric patients as well. The effective treatment of anxiety and depressive symptoms may influence favorably the attitude towards treatment regardless of the

nature of the therapy. Accordingly, it may facilitate the acceptance of COVID-19 vaccination, too.

The results of a large number of studies have shown that the incidence of anxiety and depressive symptoms increased significantly in the general population since the onset of the COVID-19 pandemic. According to the results of a survey involving more than 71000 people, 31% of this population presented anxiety symptoms while the occurrence of depressive symptoms was 28%. In the case of subjects with confirmed COVID-19 and their family members the risk of depression and anxiety was higher than the risk of non-affected persons (depression: adjusted odds ratios: 3.27 for patients; 1.53 for family members, anxiety: adjusted odds ratios: 2.48 for patients; 1.53 for

family members)<sup>11</sup>. According to the results of an international survey, 25% of the participants presented anxiety symptoms and 23% of the respondents could be diagnosed with depression<sup>12</sup>. The results of a Libyan online survey have shown that depressive symptoms could be identified in the 46% of respondents, while the anxiety symptoms were present in 19% of them in the summer of 2020<sup>13</sup>. According to the results of a Canadian study, the occurrence of affective disorders among young adults did not change during the first wave of the pandemic compared to the previous period, but the incidence of severe cases increased significantly<sup>14</sup>. An increasing occurrence of severe affective symptoms can be expected in the upcoming period as a result of the social and economic impacts of the pandemic. For this reason, the assessment of affective symptoms as a part of the evaluation of the atti-

**Table 3.** Associations of the delta scores of PHBQPT subscales, HADS scores and neurocognitive tests

	$\Delta$ Positive Aspect	$\Delta$ Negative Aspect	$\Delta$ Doctor HLOC	$\Delta$ Internal HLOC	$\Delta$ Psychological Reactance
$\Delta$ HADS-Anx	ns	0.002	ns	ns	ns
$\Delta$ HADS-Dep	0.028	0.006	ns	ns	ns
$\Delta$ TMT-A	ns	ns	ns	ns	ns
$\Delta$ TMT-B	ns	ns	ns	ns	ns
$\Delta$ Stroop 1 time	ns	ns	0.012	ns	ns
$\Delta$ Stroop 2 time	ns	ns	ns	ns	ns
$\Delta$ Stroop 3 time	ns	ns	ns	ns	ns
$\Delta$ Stroop 1 error	ns	ns	ns	ns	ns
$\Delta$ Stroop 2 error	ns	ns	ns	0.038	ns
$\Delta$ Stroop 3 error	ns	ns	ns	ns	ns

p-values of the GLM tests are presented.

tude towards vaccination has become more and more important.

Our results can be regarded with some limitations due to small sample size. Further studies are needed to confirm these data.

Taking these data into consideration, the screening of affective symptoms of persons who reject the vaccine should be considered. In this program could participate consultation-liaison psychiatrists and general practitioners as well. According to our results, there is a stronger correlation between the emotional state of patients and their attitude towards treatment than between the latter and the level of their neurocognitive functioning. These results show that the educational efforts regarding the vaccination are less efficient in the case of

patients presenting affective symptoms, of whose number is growing as a result of the negative psychological consequences of the pandemic. The treatment of anxiety and depressive symptoms (using cognitive behavioral therapy, relaxation techniques and medications) would influence their attitude towards treatment and health locus of control in a positive manner, and as a result, the acceptance of the vaccine, which would lead at population level to a more efficient control of the disease.

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