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The effect of two predictors' interaction on short- and long-term treatment outcomes of schizophrenia

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Summary

Objectives: To monitor the effect of interaction of duration of untreated psychosis (DUP) and expressed emotion (EE) on treatment outcomes in schizophrenia.

Methods: 56 individuals diagnosed with schizophrenia were assessed at 4 time points. The number of relapses, the number and duration of rehospitalizations and the severity of symptoms were assessed at index hospitalization and at 3, 7 and 12-year follow-ups.

Results: No correlation was found between DUP and EE measured at index hospitalization. Over the 12-year period the number of rehospitalizations for individuals with short DUP and low EE did not increase, as opposed to those with short DUP and with high EE. In the group with long DUP, the number of rehospitalizations increased irrespectively of EE level. The positive syndrome in the group with short DUP and high EE was less severe than in individuals with long DUP and high EE. Analogous differences appeared in the group with low EE.

Conclusions: 1) No correlation was found between DUP and EE at index hospitalization. 2) Number of rehospitalizations and intensity of positive symptoms proved to be associated over time with the interaction of DUP and EE. 3) Long-time observation and multiple assessments allow to obtain more reliable results

Key words: schizophrenia, treatment outcome, expressed emotions

Introduction

The effects of various predictors on the circumstances of index hospitalization and the course, as well as the ultimate outcome of schizophrenia have been assessed in numerous studies [1-23]. Such studies indicate that at present nearly half of schizophrenia patients are able to avoid negative treatment outcomes, although this depends on the context and type of therapeutic interventions [8, 15]. The potential differences in prognosis for the illness justify the search for protective factors to reinforce the tre-

atment process. In analyses of predictors of the course of schizophrenia, researchers have noted the significance of issues within the family, as described by the expressed emotions indicator (EE) [18-24], as well as the effect of the duration of untreated psychosis (DUP) [5, 9-16].

An understanding of the patient's family environment greatly influences both the patient as well as the treatment process [21-26]. During the course of a mental illness, numerous complicated, multifaceted relationships come into play between the patient's psychopathological state and their social environment. Since the 1960s researchers describing the role of the family environment, e.g. Brown et al.[22], and Vaughn and Leff [23], have highlighted certain aspects of the family dynamics which they describe as the indicator of expressed emotions (EE) evinced by close relatives towards the sick family member. Numerous studies in various cultural and social contexts [19, 21, 24] have proved that the level of EE is associated with the number of patient relapses [7-8, 18-23]. High levels of EE were found in more than half of interactions between patients and their caregivers; furthermore, the relationship between the EE indicator and number of relapses may be more pronounced in patients with a more chronic course of the schizophrenia [24]. Moreover, Berry et al. [25] made a review of 27 studies which employed CFI and Five Minute Speech Sample to assess EE indicator among professional personnel taking care of the severely mentally ill. The results indicate to a relationship between higher criticism on the part of the personnel and deficits in social functioning of their patients, as well as a relationship between low EE indicator with discharge from hospital due to improvement in mental health. There is no evidence, however, that a high EE indicator in personnel is related to higher number of relapses, as opposed to the results of family studies [25].

Another important factor, which has been the subject of numerous studies, is the duration of untreated psychosis (DUP). A meta-analysis by Perkins et al. [14] indicated that a shorter length of time during which patients experiencing psychosis without therapeutic intervention is associated with longer and stronger remission of general, fewer relapses, and overall better functioning (GAF, GAS) [14]. Other studies, such as Johannssen et al., Kallaet al., and Peralta et al. [15-17], stress the association between DUP and social functioning. Patients with a longer DUP had a lower employment indicator, lived alone (mainly males), and had fewer professional skills, weaker social bonds and overall worse social functioning. A study conducted in Cracow by Cechnicki et al. also found an association between a longer duration of untreated psychosis on the one hand and more intense general and positive symptoms and a higher number of relapses [5] on the other.

No studies assessing directly the interaction of EE indicator and the duration of untreated psychosis with the course of schizophrenia were found in the literature. However, there were some studies which included both of those factors, whose effect on the course of illness seems clinically important. Ross et al. [27] studied the relationship between a family history with no prior experience of psychosis, and the duration of untreated psychosis (DUP) and untreated illness (DUI). The study encompassed 169 patients after their first psychotic episode. Results showed no association between a family history with no previous mental illness and the length of the DUP, but there

was an association with a longer DUP, with early anxiety, depressive and negative symptoms not being identified as prodromes of impending psychosis. Families that did have a prior history of mental disturbance, on the other hand, sought help earlier. Similar associations between family history with prior mental illness and a shorter DUP were found by Chen et al. [28], while Compton et al. confirmed that a shorter DUP is associated with the family's involvement in seeking help [29], a behavior that is observed in families with low EE indicator.

The aims of this study were: 1) to assess the relationship between EE and DUP at the index psychiatric hospitalization, 2) to assess of the relationship between short- and long-term treatment outcomes spanning 12 years and the interaction between DUP and the EE as measured at the index psychiatric hospitalization.

Subjects

The analyzed group comprised of 56 individuals with a DSM III diagnosis of schizophrenia and a subsequent rediagnosis according to DSM IV – TR who underwent all the follow-up assessments. This was 70% of the original group participating in the study. The average age of participants at index hospitalization was 27 (OS = 5,9; age range 18–43). All participants gave their informed consent to participation in the study. The group consisted of 57% women and 43% men, 68% single and 32% in marital relationships. The majority of the participants had completed secondary (41%) or higher (29%) education; 62% were working or studying. Social functioning (assessed according to DSM IV-TR) was average for 30% of participants, good for 25%, very good for 20%, poor for 20% and very poor for 5%. As many as 64% of participants were characterized by a short course of illness (up to 6 months) while 36% had a long DUP (longer than 6 months).

Method

The predictors were assessed using the modified Carpenter-Strauss Prognostic Scale, the indicator of expressed emotions by the Camberwell Family Interview (CFI), and symptom severity by the UCLA-modified BPRS-E scale. Data were collected at the index hospitalization as well as at successive follow-up assessments 3, 7 and 12 years after the index hospitalization using an adaptation of the Alanen and Rekkolainen Anamnestic and Catamnestic Interview [8]. The analysis yielded two independent inter-group variables, an intra-group independent variable (repeated measures), and the dependent variables, i.e. the treatment outcome indicators. The two independent inter-group variables are:

- duration of DUP: two levels – up to 6 months and over 6 months,
- indicator of EE: two levels – high and low.

The treatment outcome indicators or (dependent variables) selected were:

- number of relapses (measured at follow-up assessments 3, 7 and 12 years after the index hospitalization),

- number of rehospitalizations (measured at follow-up assessments 3, 7 and 12 years after the index hospitalization),
- duration of rehospitalizations (measured at follow-up assessments 3, 7 and 12 years after the index hospitalization),
- severity of symptoms (assessed on the BPRS scale: overall result, positive syndrome and negative syndrome – measured at the index hospitalization on admission and discharge, and at follow-up assessments 3, 7 and 12 years after the index hospitalization).

The independent variables formed a 2x2x3-type three-factor research plan, and a 2x2x5 plan with two inter-group factors (DUP and EE) and one repeated measurement factor in relation to the BPRS. Analysis of variance (ANOVA) with repeated measurements was used for calculations. For significant interactions, analysis of simple effects was used to measure the significance of the difference between the groups with long and short DUP and high and low EE at the various intervals.

Results

During the initial analysis numerous correlations were found between DUP and a number of predictors, such as social functioning, lack of social contacts outside of the family, or chronic onset of illness (Fig. 1).

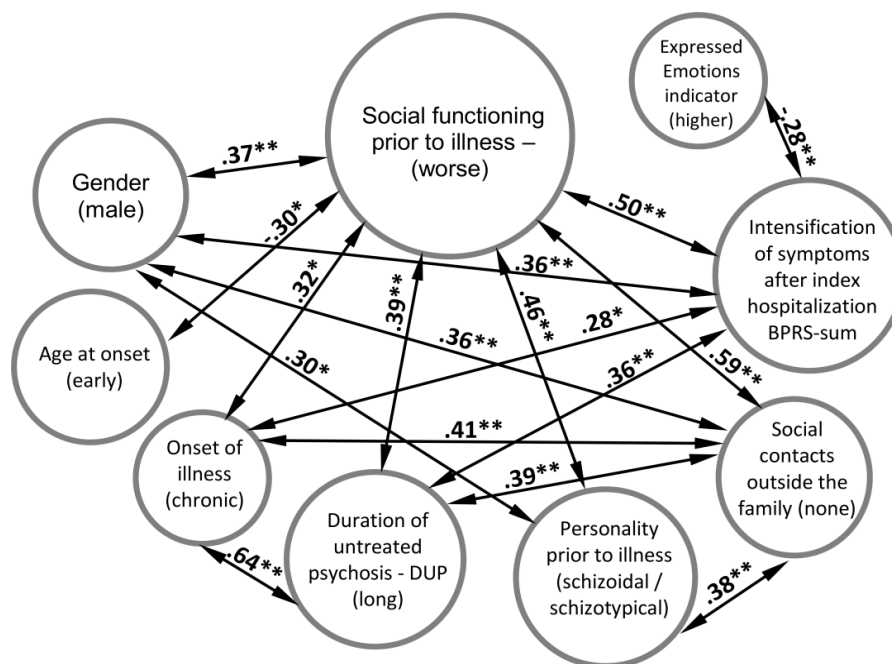


Fig. 1. Correlations between demographic and social factors and clinical factors for the course of schizophrenia at index hospitalization – group n=56. The Spearman rank coefficient was used to calculate the correlations (** signifies $p \leq 0.001$, * signifies $p \leq 0.05$)

While at the onset of the illness a longer DUP was associated with chronic onset of illness, more severe symptoms, lack of social contacts outside of the family and overall poorer social functioning prior to illness, there was no association between EE and any of the predictors under study other than a weak correlation with intensification of symptoms. No correlation was found between DUP and the EE indicator measured at index hospitalization.

Further analysis assessed changes in number of relapses and number and duration of rehospitalizations, and the relationship of these changes with EE and DUP. The results are presented in Tab. 1.

Tab. 1. Analysis of variance assessing change over time in number of relapses, number and duration of rehospitalizations in interaction with EE and DUP

Effect	Number of relapses		Number of rehospitalizations		Duration of rehospitalizations	
	F-ratio	p-level	F-ratio	p-level	F-ratio	p-level
Overall change over time	28.604	<0.001	18.387	<0.001	20.540	<0.001
Interaction between time and DUP	2.119	0.125	2.508	0.086	3.603	0.031
Interaction between time and EE	0.594	0.554	0.236	0.790	0.034	0.967
Interaction between time, DUP and EE	1.845	0.163	3.116	0.048	2.776	0.067

The analysis of variance showed a statistically significant change ($p < 0.001$) for all three dependent variables: number of relapses, number of rehospitalizations and duration of rehospitalizations –the results increase significantly at each successive follow-up point (all simple effects were significant at the level $p \leq 0.001$). Numbers of relapses and rehospitalizations in individuals with short and long DUP did not differ with any statistical significance at any of the follow-up assessments. Duration of rehospitalizations did change differently depending on the length of DUP ($p < 0.031$). In the group with a long DUP accelerated growth was noted at each follow-up assessment (the difference in measurements after 3 and 7 years was significant at the level of $p < 0.001$, and that between 7 and 12 years at $p = 0.003$), while in the group with a short DUP the growth was slower (any significant difference only appeared between the measurements after 7 and 12 years, $p = 0.43$). Analysis of the number of relapses, and number and duration of rehospitalizations in relation to EE revealed no significant effect of interaction for any of these three variables.

The three-way interaction in the change in number of relapses and number and duration of rehospitalizations with DUP and EE levels over a 12-year period was found to be statistically insignificant for number of relapses and duration of rehospitalizations. In number of rehospitalizations, however, interaction between this change and both independent variables was observed, which signifies that changes to this parameter over time depend on both DUP and EE ($p = 0.048$) (Fig. 2 – next page).

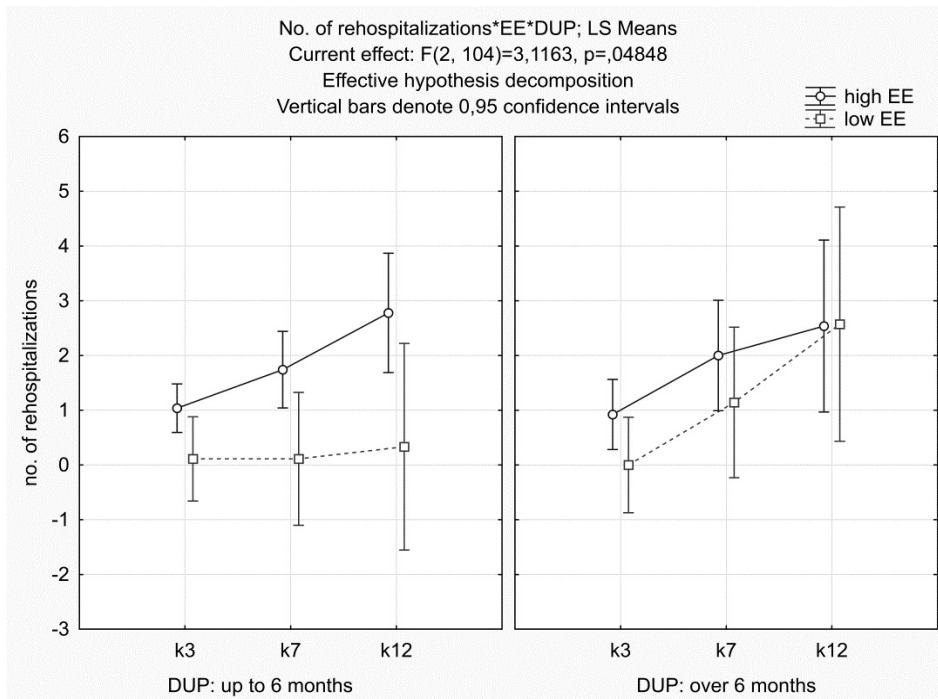


Fig. 2. Change in number of rehospitalizations divided into short and long DUP and high and low EE

In the group of subjects with a short DUP the differences between individuals with high and low EE showed up in the 3-year follow-up assessments as a distinct trend ($p=0.038$), and it was statistically significant at 7 years ($p=0.022$) and 12 ($p=0.038$) years. For individuals with a long DUP the differences between high and low EE were not significant at any of the follow-ups.

The graph illustrates that in instances of a short DUP, individuals with low EE have a favorable subsequent course of rehospitalizations (a “flat” change), as opposed to individuals with high EE, who experience an unfavorable course. For a long DUP, however, in individuals with both low and high EE the illness develops unfavorably in terms of number of rehospitalizations. In summary, low EE may be a protective factor in terms of number of rehospitalizations, but only for individuals with a short DUP.

Subsequent analysis focused on the PBRs-L.A. scale. Five measurement points were used: admission, discharge, and follow-up assessments at 3, 7 and 12 years. The table below presents the analysis of variance of the change in the BPRS and its interactions with DUP and EE (Tab. 2 – next page).

Both overall BPRS and the positive and negative syndrome subscales demonstrated a statistically significant change over time ($p<0.001$). Analysis of the simple effects for overall prognostic value showed a significant difference in values between admission and the other points of measurement (all $p<0.001$), discharge and the other points of

Tab. 2. Analysis of variance of change over time in BPRS scores in interaction with DUP and EE

Effect	Total BPRS score		Positive symptoms		Negative symptoms	
	F-ratio	p-level	F-ratio	p-level	F-ratio	p-level
Overall change over time	89.630	<0.001	95.804	<0.001	16.051	<0.001
Interaction between time and DUP	2.992	0.020	5.169	<0.001	0.180	0.948
Interaction between time and EE	4.845	<0.001	2.646	0.035	1.575	0.182
Interaction between time, DUP and EE	2.110	0.081	2.832	0.026	0.545	0.703

measurement except the 12-year follow-up (for significant differences $p < 0.001$), the measurements after 3 and 12 years ($p = 0.019$), and the measurements after 7 and 12 years ($p = 0.027$). The lowest scores were recorded in the follow-up assessments at 3 and 7 years. For positive symptoms significant differences were recorded between admission and the other points of measurement (all $p < 0.001$). For negative symptoms significant differences were found between values at admission and the other values ($p = 0.019$ at discharge and $p < 0.001$ at later follow-up assessments), as well between the values at discharge and at the successive follow-ups ($p < 0.001$ at 3 and 7 years, $p = 0.008$ at 12 years).

After allowance for the inter-group DUP factor, numerous interesting interactive correlations were found. Decreased results (improvement of symptoms) in the overall BPRS as well as in the positive syndrome were associated with length of DUP ($p = 0.020$ and $p < 0.001$, respectively). In the overall BPRS simple effects showed significantly lower results in individuals with a short DUP at all follow-up points except admission ($p \leq 0.008$) than in individuals with a long DUP. The pattern was similar in the case of positive symptoms ($p \leq 0.023$). In short, individuals with a short DUP displayed better improvement in results over the course of treatment than those with a long DUP.

The interaction of the change in symptoms measured using the BPRS scale (overall assessment and of positive symptoms) with the expressed emotions indicator (EE) pointed to differences between individuals with low and high EE, but only at the point of hospital admission. Individuals with high EE had higher results on the BPRS scale at admission to an in-patient facility, and a clear difference between these individuals and those with low EE was visible only at admission ($p = 0.004$ for the overall assessment and $p = 0.070$ for positive symptoms). After discharge individuals with high and low EE did not differ significantly in terms of their overall range of BPRS scores or their positive symptoms.

Of the interactions of symptoms measured using the BPRS scale with DUP and EE levels, only in the case of the positive syndrome was interaction was found to be significant (Fig. 3 – next page).

Analysis of simple effects revealed the following differences: in the high EE subgroup individuals with a short DUP differed from those with a long DUP at discharge ($p = 0.023$) as well as at the 7-year ($p = 0.009$) and 12-year ($p = 0.050$) follow-up assessments, while in the low EE subgroup differences emerged at discharge ($p = 0.005$) and at the 3-year ($p = 0.038$) and 12-year ($p = 0.001$) follow-up assessments. Nevertheless,

the graph clearly illustrates that it is DUP, not EE, that creates a more significant difference between the groups, because all the results, apart from those at index hospital admission, point to a correlation between a longer duration of untreated psychosis (DUP) and higher positive syndrome results.

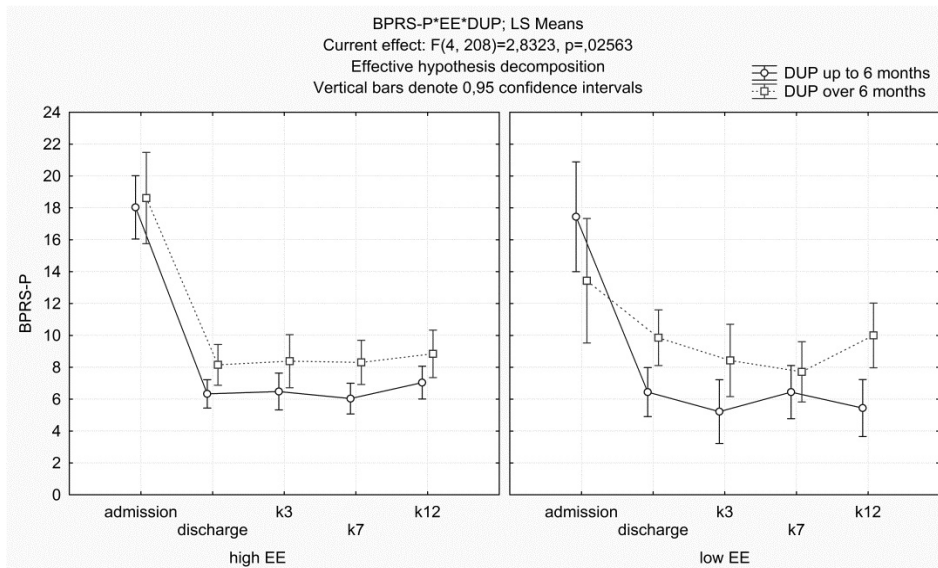


Fig. 3. Change in positive syndrome divided into short and long DUP and high and low EE

Discussion

Although the literature dealing with the effects of DUP and EE on the course of schizophrenia is vast [1-26], the present authors have not come across any studies dealing with the direct interaction between these predictors or their effect on treatment outcomes. In everyday clinical practice, criticism, hostility and emotional overinvolvement observed in the family, affect the severity of psychotic symptoms and the time required for a decision to make appropriate treatment.

Already 20 years ago de Barbaro [30], based on clinical summaries, pointed out an association between delay in deciding to access treatment (known today as DUP) and issues within the family (described nowadays by EE). He indicated that an overinvolved family, just like a critical one, does not recognize the illness as an issue and this lengthens the time from the first clear symptoms of psychosis to the point of obtaining psychiatric treatment [30]. These interactions also proved significant 20 years later, but their relationships form much more complicated patterns. Studies of the effect of the interaction of predictors, here DUP and EE, on long-term treatment outcomes proved valuable because they show an association between fewer rehospitalizations and increased positive symptoms, and short duration of untreated psychosis and a lower level of expressed emotions in the family. In a different study, Cechnicki et al. [5] pointed to an association between DUP and number of rehospitalizations which

was not statistically significant; what is more, the number of rehospitalizations showed no association with family EE levels [7]. In the present study the interaction between the DUP and EE has shown up with significance since fewer rehospitalizations occur only in subjects with a combination of short DUP and low EE.

In previous studies Cechnicki et al. [5, 7] observed that the long duration of untreated psychosis (DUP) was associated with more relapses in the subsequent follow-ups. Similarly, it was also shown that a high rate of expressed emotion (EE) was associated with more relapses. However, in the case of relapses, this study found no significant interaction between both factors and repeated measurements.

Analysis of the mutual interaction between the predictors studied and “acute” psychopathology provides new information. When studied in isolation, the change in the positive syndrome was associated with EE level at index hospitalization only [7]. Currently, it has been established that, beginning with the first episode and throughout 12 years with the illness, individuals with a short DUP have a less severe positive syndrome in both the high and low EE groups, which clearly indicates a significant role of DUP in differentiation between the groups. Similarly, at the 8-year follow-up assessment conducted by Crumlish et al. [31] a shorter DUP was associated with positive symptoms and better social functioning. The Cracow study did not find an association with the negative syndrome but in the Irish study the improvement in the area of negative symptoms observed between years 4 and 8 was associated with the duration of untreated illness (DUI) [30]. In the research by Ross et al. [27], this longer DUI was associated with negative symptoms which were not recognized by the family as symptoms of illness. Compton et al. (2008) point to an relationship between a longer DUP and less family involvement in seeking out help for its sick member [29].

It was previously noted that families with low EE seek help quickly, and this was the explanation given for the positive impact of this indicator on the course of treatment, especially in respect of relapses. The positive association between low EE and fewer relapses found in the previous study disappears in interaction with a long DUP [7]. Observation of the subgroup of patients with a combination of longer DUP and low EE shows that the decisive unfavorable factor in our study is a longer DUP. This means that low EE indicator does not protect from a poor course of illness.

The study of interactions between factors enables us to monitor more complicated relationships between various issues. It strengthens clinicians’ convictions that therapeutic efforts should be undertaken to improve relations within the family, but that simultaneously everything possible should be done to accelerate access to treatment and reduce the duration of an untreated psychosis. The practical implications of this knowledge involve taking preventative and psycho-educational action which could protect schizophrenia patients from a negative course of the illness.

Влияние интеракции двух предикторов на ранние и поздние результаты лечения шизофрении

Содержание

Задание. Прослеживание влияния интеракции двух предикторов на ранние и отдаленные результаты лечения шизофрении.

Методы. Анализу подвергнуты результаты исследований 56 больных шизофренией в 4 временных пунктах. В качестве показателей течения болезни принято число рецидивов и регоспитализации время регоспитализации и утяжеление симптомов при первой госпитализации и катамнезах полс 3,7 и 12 лет.

Результаты. Не отмечено корреляции между продолжительностью и тяжестью психоза (ПТП) и показателем эмоциональной экспрессии (ЭЭ), определенным во время первой госпитализации у лиц с коротким ПТП и низкой ЭЭ. В группе с длительной ПТП число регоспитализации увеличивалась, независимо от ЭЭ. Утяжеление позитивного синдрома было ниже в группе больных с коротким ПТП и высокой ЭЭ. В группе с низкой ЭЭ в сравнении с лицами с длительным ПТП и высокой ЭЭ. В группе с низкой ЭЭ появились аналогичные разницы пр ПТП. В двенадцатилетнем периоде число госпитализаций и регоспитализации у больных с коротким ПТП и низкой ЭЭ не увеличивалась в сравнении с больными с коротким ПТП и высокой ЭЭ.

Выводы. 1. Не отмечено корреляции между ПТП и показателем ЭЭ, определяемых во время первой госпитализации. 2. Число регоспитализации, а также динамика позитивных симптомов были связаны с взаимной интеракцией факторов ДТП и ЭЭ. 3. Длительное наблюдение и многократные исследования позволяют на получение более верных результатов.

Ключевые слова: шизофрения, результат лечения, проявляемые чувства

Interaktion von zwei Prädiktoren auf Früh- und Langzeit – Outcome von Schizophrenie

Zusammenfassung

Ziel. Beobachtung des Einflusses von Interaktion auf Früh- und Langzeitbehandlung der Schizophrenie.

Methoden. Die Befunde von 56 Personen mit der Diagnose Schizophrenie in 4 Zeitpunkten wurden analysiert. Als Indexe des Krankheitsverlaufs wurden die Zahl der Schübe und wiederholten Krankenhausaufenthalte, Zeit der Krankenhausaufenthalte und Intensität der Symptome angenommen, die bei dem ersten Krankenhausaufenthalt und in den Katamnesen nach 3, 7 und 12 Jahren bewertet wurden.

Ergebnisse. Es wurde keine Korrelation zwischen der Dauer der unbehandelten Psychose (DUP) und dem EE – Index nachgewiesen, der im Moment der ersten Krankenhausbehandlung gemessen wurde. In zwölf Jahren ist die Zahl der wiederholten Krankenhausaufenthalte bei den Personen mit der kurzen DUP und niedrigen EE nicht gestiegen, im Gegensatz zu den Personen mit der kurzen DUP und hohen EE. In der Gruppe mit der langen DUP stieg die Zahl der wiederholten Krankenhausaufenthalte unabhängig von dem EE - Level. Die Intensität des positiven Syndroms war in der Gruppe der Personen mit der kurzen DUP und der hohen EE niedriger im Vergleich mit den Personen mit der langen DUP und der hohen EE. In der Gruppe mit der niedrigen EE traten ähnliche Unterschiede im Bezug auf DUP auf.

Schlussfolgerungen. 1. Es wurden keine Korrelationen zwischen der DUP und dem EE – Index nachgewiesen, der im Moment der ersten Krankenhausbehandlung gemessen wurde. 2. Die Zahl der wiederholten Krankenhausaufenthalte und die Dynamik der positiven Symptome schienen mit der gegenseitigen Interaktion der DUP und EE – Faktoren verbunden zu sein. 3. Eine Langzeit – Beobachtung und mehrmalige Messungen erlauben glaubhafte Ergebnisse zu erzielen.

Schlüsselwörter: Schizophrenie, Befund, Expressed Emotion

L'influence de l'interaction de deux prédicteurs sur les effets de court terme et de long terme de la thérapie de la schizophrénie

Résumé

Objectif. Observer l'influence de l'interaction de deux prédicteurs sur les effets de court et de long terme de la thérapie de la schizophrénie.

Méthode. On analyse les résultats de 56 patients diagnostiqués « schizophrénie » dans 4 points de temps. Comme indice du cours de la maladie on accepte : nombre des rechutes, nombre d'hospitalisation et leur durée, sévérité des symptômes après la première hospitalisation et après 3, 7 et 12 ans.

Résultats. On ne note pas de corrélation de DUP (duration of untreated psychosis) et EE (expressed emotion) mesuré durant la première hospitalisation. Durant la période de 12 ans le nombre d'hospitalisation des patients avec le court DUP et le petit EE n'accroît pas, inversement dans le groupe avec court DUP et grand EE. La sévérité des symptômes est moins élevée dans le groupe avec court DUP et grand EE. Dans le groupe avec petit EE on note les différences analogues envers DUP.

Conclusions. 1. On ne note pas de corrélations de DUP et d'EE durant la première hospitalisation. 2. Le nombre d'hospitalisation et l'intensité des symptômes positifs se lient avec l'interaction de DUP et d'EE. 3. L'observation de long terme et plusieurs mesures permettent obtenir les résultats plus fiables.

Mots clés : schizophrénie, effet thérapeutique, émotions exprimées

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