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Controversies about duration of untreated psychosis as independent prognostic variable of the evolutive course of schizophrenic psychoses

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This study reviews recent literature on duration of untreated psychosis (DUP) and its most relevant characteristics and controversial issues, such as: *a)* why DUP has been pointed out as a main variable in first-episode psychosis research, and *b)* the role of DUP in designing intervention programs for the design and different action strategies in early intervention programs in psychoses. The authors also present data from a 2 year follow-up study of 231 patients with a diagnosis of schizophrenia and/or schizophreniform disorder (according to DSM-IV criteria). Results are included, analyzing DUP as prognostic factor for clinical outcome. Our conclusions suggest that DUP is a risk marker but not an independent prognostic factor determining follow-up in schizophrenic psychoses. Therefore, DUP's role in early intervention programs should be redefined.

Key words:
First episode psychosis. Duration of untreated psychosis (DUP). Early intervention. At risk mental states. Schizophreniform disorder.

Actas Esp Psiquiatr 2006;34(6):377-385

Controversias en torno al tiempo de psicosis no tratada (DUP) como variable pronóstica independiente del curso evolutivo de las psicosis esquizofrénicas

El objetivo del presente trabajo es detallar aquellos aspectos, a nuestro entender más relevantes, extraídos de la creciente literatura sobre el tiempo de psicosis no tratada (DUP), incidiendo sobre dos aspectos nucleares y objeto de una creciente controversia, como son: *a)* aquellas razones que a lo largo de la última década han llevado a catapultar el DUP a la primera plana de la investigación en el terreno de los primeros episodios psicóticos, y *b)* el papel último del DUP a la hora de vertebrar el diseño y las diferentes estrategias de actuación en los programas de intervención precoz sobre las psicosis. Se aportan datos correspondientes a la evaluación del DUP, como variable pronóstica independiente, en una muestra de 231 pacientes, con un diagnóstico de trastorno esquizofrénico y/o trastorno esquizofreniforme (criterios DSM-IV) y un seguimiento de 24 meses. La conclusión final es que el DUP funciona más como un marcador de riesgo que como una variable pronóstica independiente, determinante del curso evolutivo de las psicosis esquizofrénicas. En este sentido su papel dentro de los programas de intervención precoz en las psicosis debería revisarse.

Palabras clave:
Primer episodio psicótico. Tiempo de psicosis no tratada (DUP). Intervención precoz. Estados mentales de riesgo. Trastorno esquizofreniforme.

INTRODUCTION

The objective of this article is to detail those aspects which, to our understanding, are most relevant, drawn from the growing literature on DUP (duration of untreated psychosis), emphasizing two core aspects that are the object of a growing controversy. These are.

- Why DUP has been pointed out as a main variable in first-episode psychosis research.
- The role of DUP in designing intervention programs for the design and different action strategies in early intervention programs in psychoses.

THE «SACRALIZATION» OF «DURATION OF UNTREATED PSYCHOSIS» (DUP)

During the past decade and based on the promising results from the pioneer study of Falloon[1], a growing and enthusiastic interest in the development of early intervention programs on psychoses stands out. This is focused, among other aspects, on shortening the duration of untreated psychosis (DUP) as a determining prognostic factor of its final evolutive course.

The apparently solid and contrasted hypothesis that those patients with a longer duration of untreated psychosis (DUP), in general terms, have a worse clinical, evolutive and functional prognosis of their psychotic disorder is used[2].

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In fact, according to this model, late intervention is associated to a greater prevalence of negative psychotic symptoms and worse response of the positive symptoms to antipsychotic treatment, at least in the short term, independently of age and premorbid adjustment of the individual[3].

Many authors support the idea, thorough the results obtained in other studies, of DUP as an independent and determining value of better or worse evolutive course of psychotic disorders[4-8].

And even more, early intervention programs have been developed on psychosis, mainly oriented at shortening DUP. In this sense, the results obtained by the Melbourne group, headed by McGorry stand out. They have no doubt that the short, middle and long-term prognosis is better among those schizophrenic patients in whom there is early and intensive intervention, even in the prodromic phase of the psychotic disease, shortening the time of psychosis without treatment to under three months[9,10].

Everyone knows that the acceptance of these postulates means a theoretical positioning in favor of the neurodegenerative model of schizophrenia. That is, independently of the assumption or not of certain abnormalities in the cerebral neurodevelopment of schizophrenic patients, the «toxic» action on the brain of the psychotic episode, mediated by different biological mechanisms (theory of dopaminergic hyperfunction, theory of glutamatergic hypofunction, theory of stress-cortisol, etc.) is accepted.

Thus, a delay in the initiation of antipsychotic treatment theoretically prolongs the lesion-causing action of the intercurrent morbid condition and generates cerebral biological alterations which, in the long term, go deeper into the dysfunctionality of the individual, and into the worse evolutive course of his/her psychotic condition.

However, there are some criticisms attributable to this neurodegenerative model, among them: absence of gliosis and alterations of the cytoarchitecture in the histopathological analysis of the brains of schizophrenic patients[11,12] and lack of progression of cerebral morphological alterations (ventricular dilation, cortico-subcortical atrophy)[13] and of cognitive deficits present from the first psychotic episode and more probably from the premorbid period until advanced stages of the disease[14].

CONTROVERSIES ABOUT «DURATION OF UNTREATED PSYCHOSIS» (DUP) AND «PROGRAMS OF EARLY INTERVENTION ON FIRST SCHIZOPHRENIC PSYCHOTIC EPISODES» CURRENT STATE OF THE QUESTION

However, in recent years, and in spite of the initial enthusiasm given by many investigators on the concept of DUP and on the convenience of shortening it as principal way to modify and improve the evolutive course of schizophrenic psychoses, there are other authors who, on the basis of their own results, do not find a link between DUP and the clinical and functional course of the psychotic disease, not even in the short term[15-18].

And the same occurs when trying to link DUP with other cognitive and biological evolutive variables[19].

This inconsistency of findings about the DUP concept as independent variable and its predictive and prognostic capacity of the evolutive course of the first schizophrenic episodes, together with the opinion of authors such as:

- McGlashan, for whom the DUP is a «risk marker» on which many other independent variables have an influence and whose pathogenic effect is far from being demonstrated[20].
- O Verdoux and Van Os[21], who within a new approach, at that time, emphasize the role of premorbid psychosocial adjustment or of cognitive function in detriment of the DUP, about which they even say that its final effect on the evolutive course of schizophrenic psychosis may be spurious.

Are the main mainstays on which this present work is based.

Before commenting on the main aspects of our study, we will spend some time on some controversial aspects of DUP.

What do we really understand by «duration of untreated psychosis» (DUP)?

DUP is defined as the time period that passes from the appearance of the first positive psychotic symptoms with relevant seriousness (according to different authors hallucinations, delusions, bizarre behaviors, formal thought alterations) until antipsychotic treatment is initiated[17].

In the concept of DUP, certain limitations occur from the beginning:

- For example, it does not consider what happens before the «first serious positive psychotic symptom» appears.
- Furthermore, the initial point on which the consideration of DUP is based is questionable, since it is at least doubtful that the morbid condition begins at the same time in which a certain positive psychotic symptom can clearly be identified.
- And even more, the concept of DUP does not consider the importance of the time that passes from the onset of the antipsychotic treatment to the resolution of the psychotic symptoms that define the DUP itself.

For all these reasons, there are currently authors who prefer to speak of «duration of untreated illness» or DUI (fig. 1), that considers the prodromic symptoms that precede most

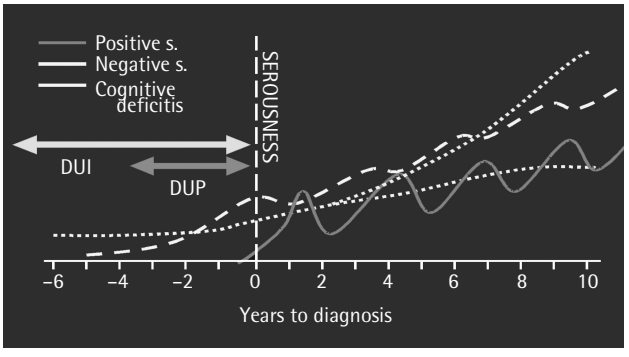

Figure 1 *Long term symptomatic patterns of schizophrenia.*

of the psychotic conditions. However, the concept DUI may also be erroneous when defining the onset of the disease, since it is sometimes difficult to determine what prodromic symptoms, usually non-specific (anxiety, alteration in sleep pattern, irritability, emotional changes, decrease in adaptive capacity of the individual) form a part of the psychotic morbid condition and which do not.

What do we really prevent when we reduce «duration of untreated psychosis» (DUP)?

In a recent review work of the most recent literature about DUP, Verdoux[22] concluded that, with the data we currently have, it is not possible to conclude if the association between DUP and the evolutive course of schizophrenic psychoses is due to its condition of independent variable, is a casual finding, or if it responds to the intrinsic nature of the different variables that make up the DUP (understood as a «risk marker»).

Literally, Verdoux states that[22]: «The claim, initially optimistic, that reduction of DUP has an impact on the natural evolutive course of psychoses is unenthusiastically and cautiously presented in recent literature. Since the neurotoxic effect of untreated psychosis is currently an undemonstrated fact, the arguments that defend early intervention in psychoses are clearly shifting from the (speculative) prevention of neurotoxicity to the well-established prevention of "psychosocial toxicity" of psychoses. Even more, the short term benefits of early intervention in terms of prevention of risk behaviors such as aggressiveness, self-injury, toxic consumption and social, educational and work disruption of the individual» are stressed.

That is, Verdoux shares the opinion of McGlashan[20]: «The DUP in the first episodes of psychosis is clearly pathological. The question is to know if it is also pathogenic».

Or what is the same, no one doubts the convenience of treating a patient who has a psychosis as soon as possible. Another thing is if beyond preventing the risks and sufferings of a subject and others in the short term, if we are also changing the natural course of the psychotic disease when we shorten the DUP. Even more, if the educational campaigns on the general population and/or at risk population are justified based on realistic parameters in order to shorten the DUP and even to treat the «high risk prodromic mental states.»

Are the educational campaigns that seek to shorten «duration of untreated psychosis» (DUP) useful?

The answer seems to be yes, as Larsen et al. demonstrate in a recent study carried out in Norway in which they compare two samples of patients suffering a first psychotic episode. In the sample analyzed after the development of an educational campaign on the general population, DUP is reduced to 4.5 months as a mean, while the mean DUP in the other sample is 26 months[23].

Another thing is, as was commented in the previous section, that we really obtain a shortening of the DUP from the point of view of natural course of psychoses and of the «secondary prevention.» And even more, if the educational campaigns are aimed at seeking an alleged «risk population». And in the prodromic stage. And with intention to treat, nothing more.

Speaking of «early intervention»: when should we begin to act?

There are currently no doubts that when we are considering a first psychotic episode, action must be taken as soon as possible. And there is also no doubt regarding the fact that the treatment of choice is antipsychotics called atypical or second generation. We are speaking, that is, of secondary prevention.

Well, what happens in the prodromic stage? Is primary prevention in the area of psychoses possible? Things are not so clear there, although the most adequate response with the data we have seems to be «not yet».

We are really immersed in a debate that seeks the limits between psychosis and normality. For some authors such as Van Os, there is a «continuum of normality-psychosis», supported by genetic and epidemiological studies, that indicate the presence of a high percentage of psychotic symptoms in the general population without a specific psychiatric diagnosis[24]. And in addition, along this same line, patients affected by a first psychotic episode more frequently have a background of pre-psychotic prodromic symptoms, whether in regarding to their intrinsic nature, or in regards to their intensity and duration[25].

The question is: when should treatment be given? This is clear to the McGorry group: it is necessary to treat the

patients who have an «at risk mental state», or, what is the same, are immersed in a «prodromic stage of psychosis with need or treatment». But let's go slower: this postulate is purely theoretical and not necessarily true. And it also is supported by the primary idea that the DUP is an independent prognostic variable regarding the evolutive course of schizophrenic psychoses, which is at least doubtful.

Furthermore, the different attempts of the different research groups to outline some diagnostic criteria of the «prodromic psychosis» based on symptoms and first-degree family background of psychosis does not always coincide or necessarily adjust to an objective reality. To validate these criteria, it is at least necessary to demonstrate that the subjects included in the risk group will benefit from the primary intervention models proposed.

Thus we share a call to caution with Malla, while waiting for new research works to shed more light on this controversial area[26].

And this is connected with the following question.

Do we have appropriate diagnostic tools to identify the «target population»?

Once again, the answer seems to be negative, since in spite of the fact that different instruments have been developed to evaluate prodromic psychoses (Comprehensive Assessment of At Risk Mental States, Bonn Scale for Assessment of Basic Symptoms, Scale of Prodromal Symptoms [SOPS] and Structured Interview for Prodromal Symptoms [SIPS], designed by the McGlashan group and based on Australian criteria of «high risk mental states», etc.), we still do not have sufficient information on its usefulness in terms of reliability, sensitivity and specificity.

Furthermore, these diagnostic criteria have not been evaluated in non-clinical samples[27], although this objection seems to have been overcome in a recent work of the McGorry Australian group[28], which analyzes the Comprehensive Assessment of At Risk Mental States (CAARMS) from different points of view, including samples of non-clinical population. It concluded that this instrument has a good/excellent discriminative and predictive validity of transition from prodromic symptoms to psychoses and excellent interrater reliability.

There is also the question of what is the target population. The most frequent conclusion in recent literature is that the screening of early psychoses is not applicable to the general population[29] and that the «prevention indicated» must be focused on that population having high symptom risk, with deterioration in its daily functioning and that seeks help.

This presents a bias when there are patients with better prognosis based on their better introspective capacity and another in the sense that many patients who do not fulfill these characteristics but who will suffer a psychosis will not be treated[27].

In fact, from the point of view of detection of patients at risk of transition to psychoses, there are two ways of approach[30]:

1. That of «basic symptoms», that is, subthreshold symptoms, determinants in several psychopathological domains, that only the patient may experience and he/she must be capable of reporting them. This European approach is based on, among others, the results of the Cologne Early Recognition Study, using the Bonn Scale for Assessment of Basic Symptoms (BSABS). The conclusion, besides a predictive capacity of transition towards psychosis of this approach (valued at 78% of the cases), is that 10 symptoms of the BSABS scale may be crucial when establishing the «risk of transition to psychoses». This concept is currently subjected to investigation by the German Research Network on Schizophrenia, directed by Klosterköter.
2. The ultra high-risk-criteria. This approach, defended by the Australian group headed by McGorry, combines the presence in an individual in a «high risk state» of:
   - Attenuated positive psychotic symptoms: unusual contents of thinking-delusions, suspicion-persecutory ideation, ideas of grandeur, unusual-hallucinations perceptions extravagant behavior.
   - Brief intermittent psychotic symptoms: similar to those of DSM IV definition for schizophrenia, that is, hallucination, delusions and formal thought disorders, but with a duration less than 1 week. These two points define the so-called «late-initial-prodromal-state.»
   - And certain risk factors, that include:
     - A decrease of the individual's functionality of at least 30% on the global assessment of function (GAF) scale, for one month or more, in the last year.
     - One or more direct family members with background of psychosis.
     - Occurrence of schizotypal disorder of the baseline personality.
     - Pre/postnatal complications.

Another sensible strategy may be that of choosing possible patients based on supposed genetic risk (for example, presence of first degree family members with schizophrenia). However, making numeric calculations, this strategy is not very effective since, according to Woods, from the McGlashan group, it is necessary to screen 10,000 first-degree family

members to identify 19 new cases of schizophrenia yearly[31]. Furthermore, with this approach, only between 11%-37% of the cases of schizophrenia are potentially detected[31].

A third screening pathway would be that of mixing the selection criteria of the previous groups.

Is there an adequate treatment? What are its risks and benefits?

Supposing that we already have the necessary tools to identify patients who have a «high risk mental state», that is, that shift sooner or later towards an active psychosis and whose clinical and functional prognosis will become worse as the duration of the untreated psychosis is increased, and that is a great deal to suppose, the question is now: do we have adequate treatment for this group of patients?

Well, once again, the response is between doubtful and negative, since although the efficacy of low doses of atypical antipsychotics in this group of patients and even the concomitant psychotherapeutic approaches of psychoeducative and cognitive-behavioral type have been indicated in the literature, both the doses and maintenance time of the therapeutic strategies proposed are uncertain at present. Furthermore, recent studies extend the focus of therapeutic interest in this group towards selective serotonin reuptake inhibitors[32-34].

That is, and to summarize:

- We do not have an exact definition of that which we call «patient in at risk mental state».
- We do not have screening tools that allow us to identify these patients in the borderline between normality and psychosis in an effective, sensitive and specific way.
- We do not have the evidence that the DUP is an independent prognostic variable or that a better DUP conditions worse evolutive and prognostic course of schizophrenic psychoses.
- And if this were not enough, we do not have specific treatments in regards to drug group, time and type of intervention or in regards to dosage applicable to the alleged «high risk mental states.»

Thus, we ask the following question.

Is early intervention (primary prevention) on the first schizophrenic psychotic episodes ethically assumable?

Well, the first question that we should ask is what are the risks and benefits of early treatment of first schizophrenic psychotic episodes in the prodromic stage?

Considering the benefits, and within the clinical population group that they call «high risk mental state», McGorry and his team[35] speak about 10% conversion rates to psychosis at 6 months among those patients who received a therapeutic combination based on low dose second generation antipsychotics (risperidone) and cognitive-behavior therapy and 36% among those patients who only received support psychotherapy.

The results of this work were immediately responded to by Warner[36]. He in turn opened the chapter of disadvantages of this type of interventions, that is, 21 patients are included in the high-risk group for schizophrenia and take risperidone when their evolutive course really demonstrates that they do not need it.

In a subsequent work, again from the McGorry group[37], these values improve and they speak of conversion rates to psychosis of 40.8% in a sample of 49 patients with «high risk mental state» follow-up in a 12 month period. Those with a history of family psychosis, schizotypal disorder of personality, subthreshold prodromic symptoms or brief and transitory psychotic symptoms (less than one week in duration) are included among the patients.

In this study[37], the authors conclude that there are a series of «conversion to psychosis predictor» factors such as long duration of prodromic symptoms, poor premorbid psychosocial functioning, diminished psychotic symptoms and symptoms of the depressive and disorganized sphere. Combining the predictive capacity of some of these variables, the authors speak about an 86% sensitivity and 91% specificity, 80% negative predictive value and 94% negative predictive value of their screening method in regards to a possible conversion to psychosis.

In spite of all that has been said, there is currently more concern from an ethical point of view than from the information contrasted in recent literature on potential risks of early treatment of psychosis, to not mention the false positives of the studies with patients «in high risk mental state», who are subjected to drug treatments at first unnecessary (with their corresponding adverse events), outside of the stigmatization, added stress and consequences in the psychosocial sphere of such an important diagnosis. And the false negatives and consequences of excluding such risk groups should not be forgotten[27].

Furthermore, there are few studies that have analyzed the short and long term consequences of exposing a still developing brain to the effects of antipsychotic drugs. Standing out among these is the monograph that the journal Schizophrenia Research dedicated in August 2001 to the ethical aspects of early intervention in psychosis and the United States NIMH (National Institute for Mental Health) study on informed consent in research studies in early psychoses[38].

The latter briefly analyzes the fact of including adolescents in clinical trials, evaluating the effectiveness of the treatments versus possible adverse events. Logically, both the patient and his/her family members must have detailed and up-dated information not only of these aspects concerning the medication but also on the reliability of the screening tests applied, sensitivity and specificity of the calculation of probabilities of a shift to psychosis and risk of psychosocial stigmatization derived from such a diagnosis and even more, considering the risk of false positives.

On the other hand, the competence of the adolescent in a «high risk mental state for psychosis» when he/she grants his/her consent to participate in these studies is questioned.

And another aspect to consider from the ethical point of view is that of the role developed by the drug industry in the extension of the frontiers of treatment of psychosis, including the prodromic period[39]. There is no doubt that the entry of the new second generation antipsychotics on the market has improved substantially quality of life and the profile of adverse events experienced by psychotic patients. However, there is also not much doubt about the possibility of large drug industries to generate opinion trends within the field of medicine in general and psychiatry in particular. This is thanks to their potential to select certain research lines in detriment of others, and if pressed, win over oneself and others.

As a sample, there are three recent articles published by McGlashan, McGorry and Parnas in the *British Journal of Psychiatry*[40-42].

However, we have already previously commented how the debate about risk/benefit of treatment of patients «in high risk mental state» is far from being resolved, outside of the above-mentioned ethical considerations of treating adolescents whose brain is in the phase of development, with doubtful capacity to give consent and with the possibility of a false positive.

Furthermore, we have also referred to the fact that neurodegenerative theory and the alleged «toxic» capacity of the psychotic episode on the brain are theoretical speculations that are still unconfirmed. And the same can be said on the lengthening of the DUP and its noxious predictive and prognostic capacity on the evolutive course of first schizophrenic psychotic episodes.

What we do not doubt any less is the economic benefits that early treatment would generate in prodromic phase of first psychotic episodes between pharmaceutical laboratories that produce second-generation atypical antipsychotics. In this sense, the recently published ideas of Monjyan, Heath and Henry in the *British Journal of Medicine* are interesting. This was on the capacity of pharmaceutical laboratories of extending the limits of apparently treatable diseases[43].

At present, there are at least three on-going controlled studies of early intervention in the initial phases of psychoses[30]: the PACE (Personal Assessment and Crisis Evaluation) study in Australia, directed by the McGorry group, that uses low doses of risperidone and cognitive-behavior therapy; the PRIME (Prevention through Risk Identification Management and Education) study in the United States, directed by the McGlashan group, that compares olanzapine versus placebo; and the European study of GNRS-LIPS, directed, among others, by the German group of Klosterköter, that compared a psychotherapeutic management with the use of the antipsychotic agent, amisulpride.

Table 1 The DUP as independent prognostic variable

Intra-subject effect
On CGI-Improvement ($p < 0.05$)
On GAF ($p < 0.01$)
Inter-subject effect
On PANSS ($p < 0.001$)
On PANSS gral. ($p < 0.05$)
On PANSS total ($p < 0.01$)
On CGI severity ($p < 0.01$)
On CGI improvement ($p < 0.01$)
On GAF ($p < 0.001$)

Finally, we recommend the careful reading of the Declaration of Consensus on the Early Intervention in Initial Phases of Psychoses, taken from the 3rd International Conference on Early Psychoses held in Copenhagen in September 2002 and recently published in the *British Journal of Psychiatry*[44].

THE DUP AS AN INDEPENDENT PROGNOSTIC VARIABLE IN A SAMPLE OF 231 PATIENTS WITH FIRST SCHIZOPHRENIC AND/OR SCHIZOPHRENIFORM EPISODE (DSM IV CRITERIA) FOLLOWED-UP FOR 24 MONTHS

In a recent work of our research group[45], based on 231 patients with diagnosis of schizophrenic and/or schizophreniform disorder, the prognostic role of 14 independent variables on their evolutive course was analyzed, considering evolution, during a 24 month follow-up period, of the PANSS scales (positive, negative, general psychopathology and total PANSS subscale), CGI (subscale of severity and improvement and effectiveness of the treatment) and global assessment of function (GAF).

Finally, the prognostic variables with effect on the evolutive course of the psychotic disorder are the following: gender, premorbid psychosocial adjustment, duration of untreated psychosis (DUP); type of onset of psychotic disease; psychosocial stress; family background of mental disease;

age of onset of psychotic picture; presence of manic and/or depressive symptoms, toxic consumption; therapeutic compliance; and presence of certain prodromic symptoms of the positive, negative and disorganized psychotic dimensions.

Considering the DUP, our attention is first called to the fact that its prognostic capacity, considered an independent variable is, based on our results, less than that expected from the results of other similar studies. This is, above all, if we consider a 3 month DUP (in accordance with the median) and from an individual longitudinal evolutive point of view (intra-subject effect).

However, the effect of DUP when forecasting a better DUP < 3 months or worse clinical, psychopathological and functional course in the general sample seems to be more relevant.

These data speak more in favor of the hypothesis of DUP as a «risk marker» than as an independent prognostic variable. Thus, the DUP variable seems to be extremely complex and conditioned by the interaction of other concurrent clinical-prognostic variables («primaries»), that change based on duration of untreated psychosis (DUP) considered, according to different etiopathogenic models.

Thus, the clinical-prognostic implications of DUP vary according to this model based on greater or lesser duration of untreated diagnosis (DUP) considered. However, it does not seem to do so due to the direct prognostic capacity of the DUP itself but rather as a reflection of the changing nature of the «primary variables» that make it up.

In our study, for a 3 month DUP (according to the median), the variables having a significant interrelationship with the DUP risk marker and that can be considered as «primaries» are: premorbid psychosocial adjustment; premorbid cognitive functioning; certain prodromic symptoms of the negative dimension (psychosocial isolation, affective flattening, deterioration in personal hygiene, loss of initiative) and disorganized (distinctive behavior, deterioration in daily activity); predominance of negative psychotic symptoms on enrolment; type of onset of psychotic disorder; presence or absence of acute psychosocial stress in the previous 6 months and socio-cultural setting of the individual (fig. 2).

Jointly analyzing the prognostic and predictive capacity on the evolutive course of the first schizophrenic psychotic episodes of the three main independent variables obtained from the literature (duration of untreated psychosis (DUP), cognitive function and premorbid psychosocial adjustment) in a multivariant analysis, it is deduced that: except for some effect of the subscale of CGI-clinical improvement and on the GAF functionality scale (partially shared with the two other variables analyzed), the independent predictive and prognostic capacity of the DUP in the remaining areas is practically symbolic.

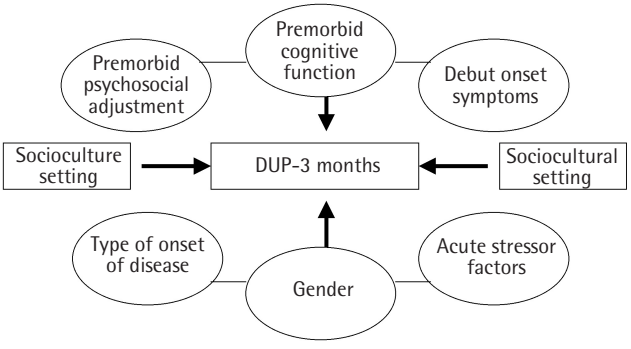

Figure 2 *Multietiological model of the DUP-3 months as risk marker.*

Those effects observed on the CGI and GAF scale and attributed to the DUP as independent variable could even be explained by the intervention of other «primary» prognostic variables included in the etiopathogenic model that we have proposed for the DUP 3-month «risk marker.»

Based on the following results, it can be deduced that the care efforts in the secondary treatment and prevention of the schizophrenic and/or schizophreniform type first psychotic episodes should be focused on the management and treatment of the independent clinical-prognostic variables and those with predictive capacity of the evolutive course of the psychoses more than on the mere shortening of the duration of untreated psychosis (DUP).

Among the care efforts, we include:

- The incisive and early therapeutic management of the negative symptoms.
- Evaluation and cognitive rehabilitation programs.
- Psychotherapeutic management of certain psychopathological symptoms (delusional ideas, hallucinatory symptoms, «neurotiform» psychopathology, depressive syndromes, etc.) based on realistic approaches and those of contrasted clinical efficacy.
- Psychoeducational strategies that promote therapeutic compliance and awareness of disease in which the family members or caregivers are involved.
- Social and work rehabilitation of the chronic psychotic patient.

According to our opinion, the development of specific units of specialized care for first psychotic episodes is urgent. This should be preferentially separated by diagnostic groups in which the access to longitudinal follow-ups of the patients and diagnostic and standardized therapeutic procedures are set up.

Finally, in our study, therapeutic compliance has been shown as predictive independent variable of the course and

prognosis of the most relevant first schizophrenic and/or schizophreniform type psychotic episodes on the individual longitudinal level (effect-intrasubject), with effect on practically all the clinical, psychopathological and evolutive scales considered.

CONCLUSIONS

It is obvious that new studies that support or contradict the results herein presented and that place the DUP and its alleged independent prognostic and predictive capacity of the evolutive course of the schizophrenic and schizophreniform type first psychotic episodes on the real level that corresponds to it are needed.

And finally, if it is shown that we are facing a «risk marker» and not an independent prognostic variable, it would be well to reevaluate the role of shortening the duration of untreated psychosis (DUP) within the early intervention therapeutic programs in psychosis in a possibilistic setting of secondary prevention.

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