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Duration of untreated psychosis: Impact of the definition of treatment onset on its predictive value over three years of treatment

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ABSTRACT

Background: While reduction of DUP (Duration of Untreated Psychosis) is a key goal in early intervention strategies, the predictive value of DUP on outcome has been questioned. We planned this study in order to explore the impact of three different definition of "treatment initiation" on the predictive value of DUP on outcome in an early psychosis sample.

Methods: 221 early psychosis patients aged 18–35 were followed-up prospectively over 36 months. DUP was measured using three definitions for treatment onset: Initiation of antipsychotic medication (DUP1); engagement in a specialized programme (DUP2) and combination of engagement in a specialized programme and adherence to medication (DUP3).

Results: 10% of patients never reached criteria for DUP3 and therefore were never adequately treated over the 36-month period of care. While DUP1 and DUP2 had a limited predictive value on outcome, DUP3, based on a more restrictive definition for treatment onset, was a better predictor of positive and negative symptoms, as well as functional outcome at 12, 24 and 36 months. Globally, DUP3 explained 2 to 5 times more of the variance than DUP1 and DUP2, with effect sizes falling in the medium range according to Cohen.

Conclusions: The limited predictive value of DUP on outcome in previous studies may be linked to problems of definitions that do not take adherence to treatment into account. While they need replication, our results suggest effort to reduce DUP should continue and aim both at early detection and development of engagement strategies.

1. Introduction

Delay between psychosis onset and exposure to appropriate treatment or duration of untreated psychosis (DUP), has been identified as a key target in programs specialized in the treatment of the early phase of psychotic disorders, based on the rationale that it's reduction should have an impact on the course of symptoms and functioning (Melle et al., 2008). While numerous papers have indeed shown DUP to be significantly associated with clinical and social outcomes (Malla et al., 2014; Marshall et al., 2005), this possible correlation was modest and has been a matter of an intense controversy (Craig et al., 2000; Harrigan et al., 2003; Ho and Andreasen, 2001).

Various factors may explain the contradictory nature of results in this domain and the only modest association found between DUP and outcomes in first episode psychosis (FEP) patients. First, in an extensive review, it has been suggested that considerable variability exists in the definition of both onset and endpoint of DUP (Compton et al., 2007). In particular, the literature reveals significant differences between studies regarding the definition of treatment onset, hence "end" of DUP. In a previous paper, we reported that while considerable attention has been paid to the assessment of psychosis onset, resulting in a certain degree of consensus

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regarding its definition, this is not true for criteria applied to define the end of DUP: definitions applied ranged from “start of medication” to “hospitalization” and “entry to a specialized program”, and were therefore based on many different conceptual levels (Polari et al., 2009). Second, when definition of DUP's end is based on medication, various definitions have been considered, ranging from “initiation of medication”, “start of any form of treatment”, or “initiation of adequate treatment”, to “time of first effective treatment” (Norman and Malla, 2001; Polari et al., 2009). Thirdly, when end of DUP is based on exposure to a certain level of medication, the definition of “adequate treatment” can be the matter of important debate, some authors requiring 12 weeks of medication (Loebel et al., 1992) while 3 weeks were sufficient for others (Larsen et al., 1996). Globally, in a review of 16 FEP studies, Norman and Malla (2001) found that definition applied to identify initiation of treatment varied greatly. Fourthly, patients' adherence to the prescribed medication has not been taken into consideration in the majority of studies (Norman and Malla, 2001). Considering the high rate of non adherence to treatment in FEP patients, it is therefore likely that DUP may have been considered finished for many patients while they actually did not receive any adequate medication yet.

In this context, it can be argued that such a lack of consistency in definition could be one of the critical factors that so far limited the conclusiveness of studies exploring consequences of DUP (Polari et al., 2009). Indeed, when applying 3 possible definitions for treatment onset in a FEP sample, we confirmed that estimation of DUP could vary greatly, which in turn could significantly influence the measurement of its impact on outcome variables.

Considering that the existence or not of a correlation between DUP and outcome is critical when choosing strategies that should be applied in specialized programs for the early phase of psychosis, we designed the current study in order to compare different definitions of DUP in their ability to predict outcome in FEP patients. Our hypothesis was that when defining beginning of treatment in a restrictive manner on the basis of both engagement in a specialized program and adherence to adequate medication according to current guidelines, DUP would be significantly correlated to outcome. Considering some patients may never adhere to treatment despite our efforts (Lambert et al., 2010) our secondary aim was to characterize patients who never met these restrictive criteria and could never be engaged into effective treatment within the 3-years of our program and therefore remained in a phase of “untreated psychosis”.

2. Material and methods

2.1. Procedure and participants

TIPP (Treatment and early Intervention in Psychosis Program), a specialized early psychosis program, was launched in 2004 at the Department of Psychiatry CHUV, in Lausanne, Switzerland (Baumann et al., 2013). Entry criteria to the program are: (I) age between 18 and 35; (II) residing in the catchment area (Lausanne and surroundings; population about 300′000); (III) meeting threshold criteria for psychosis, as defined by the ‘Psychosis threshold’ subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS) scale (Yung et al., 2005). Patients are referred to other treatment programs if they have psychosis related to intoxication or organic brain disease, or have an intelligence quotient below 70 or have been taking antipsychotic medication for more than a total of 6 months. This latter criteria, which allows admission of patients who would have been treated unsuccessfully for a limited amount of time explains why we refer to early psychosis rather than to first episode psychosis patients.

The Research and Ethics Committee of the Faculty of Biology and Medicine of Lausanne University granted access to TIPP clinical data for research purposes. Therefore all patients who take part in this program (who fulfil the inclusion criteria mentioned above) are automatically included in this study.

A specially designed questionnaire (the TIPP Initial Assessment Tool: TIAT, available upon request) is completed for all patients enrolled in the program by case managers who have up to one hundred contacts with patients during the three years of treatment. It allows assessment of demographic characteristics, past medical history, exposure to life events as well as symptoms and functioning. It is completed on the basis of information gathered from patients and their family over the first weeks of treatment and can be updated during follow up if new information emerges. Follow-up assessments exploring various aspects of treatment and comorbidities as well as evolution of psychopathology and functional level are conducted by a psychologist and by case managers at baseline, after 2, 6, 12, 18, 24, 30 and 36 months in treatment. Symptoms assessment was conducted by a psychologist who was 100% independent of patients’ treatment and had received standardized training prior to the study. Inter rater reliability standards for the PANSS (Kay et al., 1991) have been verified throughout the training using video-taped interviews and consensus reference ratings.

The current paper is based on the prospective follow-up of the first 229 patients who had been enrolled in TIPP and where 36 months had elapsed since entry to the program by January 2014. This study focused on assessments made 2 and 6, 12, 24 and 36 months after entry to the program. Eight patients were excluded because they were early drop-outs and for whom estimation of DUP was made impossible by the very short time spent in the program.

2.2. Measures

2.2.1. Diagnostic assessment

Diagnosis is the result of an expert consensus and is based on the following elements: (1) Diagnosis reported by a treating psychiatrist in all medical documents and at the end of any hospitalization; (2) Longitudinal assessment by clinical case managers over the 3 years of treatment. The consensus diagnosis procedure is carried out by a senior psychiatrist and the senior psychologist who is in charge of scale based assessment over the treatment period. They both review the entire file once after 18 months and again after 36 months, or at the end of treatment. They then conduct a diagnostic process based on DSM-IV criteria (American Psychiatric Association, 1994) discussing any unclear issue with the clinical case managers. In this paper, only the final diagnosis, defined at the end of TIPP treatment period, was considered

2.2.2. Duration of untreated psychosis (DUP)

DUP was measured using three progressively more stringent criteria to define treatment onset according to Polari et al. (2009): DUP1, DUP2 & DUP3 were obtained on the basis of an expert consensus and were considered as the time between the time of onset of psychotic symptoms and the time where patient met 3 distinct definitions: (1) initiation of antipsychotic medication (DUP1), (2) enrolment into the TIPP programme (DUP2) (3) enrolment into the TIPP programme and adherence to adequate medication as defined by current clinical guidelines (DUP3). This latter definition was chosen in order to take into account international guidelines which suggest that adequate treatment is not limited to adherence to medication and should combine it with psychosocial intervention. Treatment adherence was assessed by the case managers during the follow-up with a Treatment Adherence Scale