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Clinical trajectories in the ultra-high risk for psychosis population

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ABSTRACT

Background: Traditionally, research in the ultra-high risk (UHR) for psychosis population has focused on the treatment of existing symptomatology and prevention of transition to psychosis. Recently, there has been an increase in focus on outcomes in individuals who do not transition to psychosis. However, there is a lack of standardised definitions of remission, recovery, recurrence and relapse in UHR, resulting in the inability to generalise and replicate outcomes.
Method: The aims of the current study were to develop definitions for remission, recovery, recurrence and relapse, and apply them to a UHR cohort allowing the identification of longitudinal clinical trajectories. Further stratification in broader categories of favourable and unfavourable outcomes was applied. The predictive value of various baseline factors on specific clinical trajectories was also assessed.
Results: 17 different trajectories were identified in a cohort of 202 individuals within a 12-month period and classified according to the suggested definitions for recovery (35.7%), remission (7.5%), any recurrence (20%), no remission (17.3%), relapse (4.0%) and transition to psychosis (15.8%). Favourable and unfavourable trajectories represented 43.2% and 57.1% respectively. Long duration of untreated symptoms and high depression scores were associated with unfavourable outcomes.
Discussion: It is possible to apply clear definitions of remission, recovery, recurrence, relapse and transition to psychosis to a UHR cohort to evaluate longitudinal clinical trajectories. Acceptance and use of these definitions will help to facilitate comparisons between trials and to improve clinical clarity across the range of available therapeutic options in UHR individuals.

1. Introduction

For the last two decades, there has been increasing academic and clinical interest in young people presenting with potentially prodromal symptoms of a psychotic disorder. This clinical syndrome has been defined as the at-risk mental state (ARMS, Yung et al. 1996) and operationalised with the ultra-high risk (UHR, Yung et al. 2004a) or clinical high risk (CHR, (CHR, Cornblatt et al. 2003) criteria. The ARMS is acknowledged in Section 3 of the DSM-5 as Attenuated Psychotic Syndrome (APS), a "condition for further study" (APA 2013). The UHR criteria apply to young help-seeking individuals and require one or more of the following three presentations: 1) attenuated psychotic symptoms, 2) full-blown psychotic symptoms that are brief and self-limiting (Brief Limited Intermittent Psychotic Symptoms, BLIPS), and/or 3) genetic risk for psychosis or presence of schizotypal disorder, all of which with significant decrease or chronically low functioning.

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Although some studies suggest different level of transition risk between these groups (Fusar-Poli et al. 2016; Schultze-Lutter et al. 2015), other results indicate no difference in terms of clinical outcomes and risk of transition (Georgopoulos et al. 2017; McHugh et al. 2016).

The UHR concept has been increasingly integrated into clinical practice and multiple clinical services around the world have been providing clinical care to this population (Fusar-Poli et al. 2013). When the UHR concept was established, the initial goal was to identify individuals at incipient risk of transitioning to psychosis. However, because of the observations that a majority of the UHR population does not go on to transition to psychosis (Fusar-Poli et al. 2016; Nelson et al. 2013a), that non-psychotic disorders are common in this group (Salokangas et al., 2012; Velthorst et al. 2009; Woods et al. 2009) and in view of the declining rate of transition to psychotic disorder in recent cohorts (Fusar-Poli et al. 2012; Hartmann et al. 2016; Nelson et al. 2013b; Yung et al. 2007), there has been an increase in focus on outcomes in the group of UHR individuals who do not transition to full-blown psychosis (UHR-NT). Increasing agreement is leading towards the conceptualisation of the UHR state as a syndrome in itself, rather than merely a risk syndrome (Carpenter 2015; Carpenter and Schiffman 2015; Fusar-Poli et al. 2015; Schiffman and Carpenter 2015). As such, several outcomes in the UHR-NT have been investigated, including remission from UHR status, improvement in functioning, and onset/persistence of non-psychotic disorders (Lee et al. 2014; Lin et al. 2015; Schlosser et al. 2012; Simon et al. 2013). The definition of outcomes in the context of UHR is complicated by the fact that individuals do not only present with attenuated psychotic symptoms (Fusar-Poli et al. 2013), as described in the DSM-5 definition of APS (APA 2013), but also present with clinically significant comorbid disorders (Lim et al. 2015; Lin et al. 2015) and increased suicidal risk (Kelleher et al. 2012), which may influence the course of illness in various ways. It can be hypothesised that a person's attenuated psychotic symptoms may abate but the persistent comorbid depression or anxiety may influence negatively on the functional and/or the general recovery process.

Key concepts like remission, recovery, recurrence and relapse are well defined in major psychiatric disorders such as schizophrenia (Andreasen et al. 2005; van Os et al. 2006) (with the caveat of social and functional recovery needing further development (Emsley et al. 2011)), depression (Frank et al. 1991), borderline personality disorder (BPD, Winograd et al. 2008; Zanarini et al. 2010) and non-psychiatric conditions (e.g. diabetes, WHO 2016). Although some studies have investigated clinical outcomes in UHR in terms of transition with or without including the concept of symptomatic/functional remission (Clark et al. 2015; de Wit et al. 2014; Schlosser et al. 2012; Simon et al. 2013), only two have attempted to describe status specifiers. Woods et al. (2014) suggested the possible application of definitions of progression, persistence, partial and full remission, but validity analyses only partially supported those categories, and definitions were based on symptoms alone without considering functioning. Carrion et al. (2017) investigated the course of illness in terms of full recovery, remission, worsening and conversion, based on attenuated positive symptoms and negative symptoms. However, no dynamic evaluation between entry and final evaluation was conducted, resulting in the inability to define clinical trajectories and failing to qualify possible fluctuations within observation points.

The lack of clear definitions to allow identification of clinical trajectories in the UHR-NT population has important diagnostic and therapeutic implications, for example the inability to refine the diagnostic and prognostic estimate for a specific individual allowing the adjustment of the length and content of the clinical episode of care that need to be provided. Moreover, the progressive conceptualisation of mental illness using the staging model, which defines not only the extent of progression of a disorder at a particular point in time but also where a person lies along the continuum of the course of illness (McGorry et al. 2006; McGorry et al. 2010), may be enriched with more nuanced stages reflecting treatment response and needs using clear definitions of remission, recovery, recurrence and relapse.

Definitions of remission, recovery, recurrence and relapse suggested in the present report were the product of a consensus process among clinical and research experts in the field of UHR and modelled on schizophrenia course findings and definitions by Andreasen et al. (2005), with the addition of functioning levels assessed with the Social and Occupational Functioning Assessment Scale (SOFAS, Goldman et al. 1992). They were defined as follows:

Remission: No longer presenting with attenuated psychotic symptoms that meet threshold for UHR status as defined by the Comprehensive Assessment of the At Risk Mental States scale (CAARMS, Yung et al. 2005), along with good functioning (a SOFAS score of 70 or greater) or improved functioning (at least 5-point improvement compared with baseline functioning). This definition was based on a consensus among experienced clinicians and researchers working with UHR populations and is currently used in the STEP intervention trial in Melbourne, Australia (Nelson et al. 2017).

Recurrence: Presence of UHR status after remission and before recovery.

Recovery: Remission maintained for at least six months.

Relapse: Presence of UHR status after recovery.

Transition to psychosis: Meeting the exit criteria on the CAARMS of daily full-threshold positive symptoms for a week or longer.

Favourable outcomes: Recovery and/or remission.

Unfavourable outcomes: Any recurrence, relapse, no-remission and transition to psychosis.

The aims of the current study were to use these suggested definitions to allow identification of longitudinal clinical trajectories of UHR patients with a further stratification according to favourable and unfavourable outcomes. Additionally, factors such as UHR intake groups, duration of untreated symptoms prior to referral, depressive symptoms and functioning were analysed as predictors for specific clinical trajectories. Finally, the possible association between early remission and favourable outcomes was evaluated.

2. Methods

2.1. Design and setting

The data used for the current study was derived from the Neurapro study, an international multi-site double-blind, randomized placebo-controlled trial of omega-3 polyunsaturated fatty acids (PUFA). The trial's methodology and outcomes have been described in detail elsewhere (Markulev et al. 2015; McGorry et al. 2017). During the 6-month treatment period, in addition to omega-3 PUFA/placebo, all participants also received cognitive behavioural case management (CBCM), which consisted of CBT embedded within case management, as implemented in numerous UHR clinics internationally and described in the PACE clinic manuals (Nelson et al., 2014; The-PACE-Manual-Writing-Group 2012).

UHR status, duration of untreated symptoms, functioning and depressive symptoms were assessed at baseline. Attenuated psychotic symptoms, transition status and change in functioning were assessed at months 3, 6, 9, 12, and at medium-term follow up defined as 24 months or longer since baseline assessment.

2.2. Participants

Individuals aged between 13 and 40 years referred to the participating treatment services and meeting standardised UHR criteria were approached to participate in the Neurapro clinical trial. Individuals were identified as being at UHR for psychosis by fulfilling one or more of the following criteria: 1) Vulnerability group — individuals with a

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