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Review

Predictors of functional recovery in first-episode psychosis: A systematic review and meta-analysis of longitudinal studies

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HIGHLIGHTS

- Systematic review and meta-analysis
- All predictors of functional recovery in first-episode psychosis patients
- Shorter duration of untreated psychosis as an important predictor of functioning
- Cognitive variables as predictors of long-term functioning
- Importance of early intervention in first-episode psychosis

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ABSTRACT

Background: Three out of four first-episode psychosis (FEP) patients achieve clinical remission following treatment. Unfortunately, functional recovery lags behind symptomatic remission, and many individuals with FEP remain socially isolated with poor functional outcomes.
Aims: To systematically compile and analyse predictors of functional recovery in FEP.
Method: Systematic review and meta-analysis of peer-reviewed, longitudinal studies reporting predictors of functioning, with a minimum 12-month follow-up and at least 80% of participants diagnosed with FEP.
Results: Out of 2205 citations, 274 articles were retrieved for detailed evaluation resulting in 50 eligible studies (N = 6669). Sociodemographic, clinical, physical and neuroimaging variables had little impact on long-term functioning. Conversely duration of untreated psychosis (DUP), most cognitive variables, and concurrent remission of positive and negative symptoms were independently related to functional recovery.
Conclusions: These findings strongly support the rationale for early intervention in FEP. Novel treatments targeting cognitive deficits may improve functional outcomes in FEP.

1. Introduction

Around 75% of first-episode psychosis (FEP) patients achieve symptomatic remission following antipsychotic treatment (Cassidy, Norman, Manchanda, Schmitz, & Malla, 2010; Lieberman et al., 1993; Tohen et al., 2000). Unfortunately functional recovery lags behind clinical remission and many individuals with FEP remain socially isolated with poor functional recovery (Lieberman et al., 1993). While clinical remission was long considered the critical treatment goal, there is now growing widespread interest in addressing functional recovery from the perspective of researchers, clinicians and consumers (Alvarez-Jimenez et al., 2016). Indeed, the onset of psychosis usually results in a downward spiral of loneliness and detachment from community and peers, discontinuation of hobbies and school, and impairment in work-

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related activities directly impacting long-term wellbeing (Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005). Not surprisingly, functional recovery (i.e., engagement with vocational and educational pathways) is the treatment outcome (Iyer, Mangala, Thara, & Malla, 2010) most valued by FEP patients (Iyer, Mangala, Anitha, Thara, & Malla, 2011).

Identifying risk factors for poor functional recovery may help to identify FEP patients at higher risk of poor long-term functioning. Targeting direct, more intense treatment resources towards such cohorts may assist to offset long-term impairment and improve functional trajectory. Similarly, the identification of modifiable risk factors affecting functional outcomes will inform the development of novel targeted treatments designed to address such mechanisms and thus improve functional recovery.

Identifying robust predictors of functional recovery in FEP is essential to advance the field. It is thought that the first 3–5 years post diagnosis may constitute a critical period in shaping long term outcome (Birchwood, Todd, & Jackson, 1998; Crumlish et al., 2009). Hence, evaluating the impact of potential predictors up to this 5-year window is especially important. Furthermore, maintenance of functional improvements is important to determine whether meaningful recovery is achieved, with studies recommending a follow-up period of at least 15 months (Kane, Leucht, Carpenter, & Docherty, 2003). Thus, analysis of longitudinal studies (with a follow-up of at least 12 months) are needed to effectively assess long-term functional recovery as opposed to shorter-term periods that are typically used to assess remission (Kane et al., 2003). To date there have been no meta-analytic studies undertaken on long-term recovering in FEP patients. Restricting studies to a homogenous cohort of FEP patients (where individuals fall under the same stage of illness), is essential to identifying salient (i.e., modifiable) predictors of long term-functioning for this group. As such, the aim of this study was to conduct a rigorous evaluation of the available evidence for predictors of functional outcome in FEP from longitudinal studies with a minimum 12-month follow-up. This is both overdue and essential to identify patients at high risk of poor functional recovery, and to inform novel approaches to early interventions.

2. Method

2.1. Data sources

Electronic systematic searches employing Cochrane methodology, from inception until March 2016, were performed to find relevant English language reports from the following databases: Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL, EMBASE, ISI Information Social Science & Humanities proceedings, ProQuest Dissertations & Theses (PQDT) and Conference Proceedings Citation Index (CPCI). The abstracts, titles and index terms of studies were searched using combinations of relevant keywords (see Supplementary information). Additional articles were identified by hand-searching the references of retrieved articles and reviews. Authors were contacted for studies without online access.

2.2. Study selection

Considered for inclusion were longitudinal or prospective studies examining sociodemographic, clinical, psychological, biological or treatment predictors of functioning, which comprised at least 80% of participants with a FEP using either DSM (APA, 1994) or ICD (WHO, 1992) criteria (Álvarez-Jiménez, Hetrick, González-Blanch, Gleeson, & McGorry, 2008; Álvarez-Jiménez, Parker, Hetrick, McGorry, & Gleeson, 2011; Alvarez-Jimenez, Priede, et al., 2012). A wide-ranging definition of FEP was considered including both non-affective psychoses (i.e., schizophrenia spectrum and other psychotic disorders) and affective psychoses (i.e., bipolar disorder, or major depressive disorder with psychotic features). FEP was based on baseline status and when the threshold for the diagnosis was first met (i.e., presence of a psychotic symptom for the first time, consisting of hallucinations, delusions, disorganized behaviour or disorder of thinking) reaching adequate severity for at least 7 days, with < 12 weeks of lifelong antipsychotic medication (Larsen, McGlashan, & Moe, 1996; van der Gaag et al., 2013). Non-English language articles, retrospective studies, studies with a follow-up period < 12 months and studies with $n < 30$ were excluded. Three reviewers (M.P., O.S-E. and S.R.) independently assessed all potentially relevant articles for inclusion. Cases of conflict were resolved through discussion with other authors.

Overall functioning was broadly defined including one or more of the following: 1) Global functioning as measured by standardized measures (e.g., GAF, SOFAS); 2) Social functioning or social connectedness as measured by standardized measures (e.g., SFS); 3) Quality of Life as measured by standardized measures (e.g., QoL scale, WHOQoL-Bref); and 4) Individual definitions of functioning covering one or more of the following areas: vocational functioning, educational functioning, degree of independence and social functioning.

2.3. Data extraction

Data were extracted on all the predictors considered for analysis for each study. Two reviewers (O.S-E. and M.P.) independently extracted relevant data, including study and participant characteristics, functioning criteria and measurement, and predictors examined. Standardized data extraction forms were used. Any discrepancies were resolved by consensus.

2.4. Assessment of methodological quality

Two of the reviewers (O.S-E. and S.R.) rated each study on 4 domains of methodological quality (Downs & Black, 1998; Hackett, Hons, & Anderson, 2005), including: reporting and external validity (i.e., representativeness and generalizability of the predictive model); internal validity (i.e., risk of bias of the model), statistical validity (i.e., quality of the models reported), and quality of functioning measurement (assessed against the criteria put forward by Liberman (Liberman, Kopelowicz, Ventura, & Gutkind, 2002) as well as expert consensus guidelines (Kane et al., 2003) (e.g., occupational functioning, peer relationships and independent living)).

2.5. Data analysis

Pooled functioning rates were estimated with Comprehensive Meta-Analysis Software, Version 2.2 (Borenstein, Hedges, Higgins, & Rothstein, 2006). When the same outcome was evaluated with different scales or domains within the same study, we retained one measure corresponding to a pre-established order (Borenstein, Hedges, Higgins, & Rothstein, 2009; Fusar-Poli et al., 2015) (see Supplementary information; Method).

The majority of effect sizes reported in the studies were in the form of correlations (r). Therefore, associations of predictors of functioning were estimated by using Pearson correlations (r). Although only two studies are needed to perform a meta-analysis (Valentine, Pigott, & Rothstein, 2010), effect sizes were pooled for predictors analysed in 4 or more studies reporting data in a usable format in order to provide a more reliable information and not to compromise statistical power (Cooper, 2003). We used Fisher's r-to-z conversion for variance stabilization and normalization (Borenstein et al., 2009) and transformed all the outcomes to r scale. Due to the considerable heterogeneity in adjustment for potential confounders across studies, we used unadjusted data when available, for primary analysis (Alvarez-Jimenez, Priede et al., 2012; Glass, McGaw, & Smith, 1981). When *Betas* from regression analysis were provided, we employed the mathematical transformation proposed by Peterson and Brown (2005) to derive an approximation to r from the corresponding *Beta*. When conversion was