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Predicting clinical response in people at ultra-high risk of psychosis: a systematic and quantitative review

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People at ultra-high risk (UHR) of psychosis have ~30% chance of developing the illness within two years. A range of pharmacological and psychosocial interventions are now available but there is great individual variation in clinical response. Here we examine the evidence for clinically applicable predictors of clinical response in people at UHR of psychosis. We report that currently there are no reliable predictive markers that can be used to optimise treatment. We argue that there is an urgent need for a better understanding of why some people at UHR of psychosis benefit from a certain treatment whereas others do not. This information will help clinicians make more-effective treatment decisions, and improve long-term clinical outcomes in this population.

Introduction

Psychosis is common, severely disabling and has a major socioeconomic impact [1]. The onset of the illness is typically preceded by a prodromal phase that is characterised by the emergence of 'attenuated' psychotic symptoms; because only about one-third of people with these symptoms subsequently develop a psychotic disorder, this phase is described as ultra-high risk (UHR) or at-risk mental state (ARMS) of psychosis [2]. In the past two decades, with the increasing appreciation of the necessity for early intervention in psychosis worldwide [3], a number of treatments have been employed to delay or prevent the onset of psychosis in people at UHR of psychosis. These treatments include antipsychotic medication [4–6], nutritional supplements such as omega-3 fatty acids [7] and psychological treatment [8–13]. A recent meta-analysis suggests that, based on evidence of very low to moderate quality, these interventions appear to be effective in delaying and even preventing the onset of psychosis [14]. However there is great individual variation in clinical response to treatment among people at UHR of psychosis. For example, although some respond well to antipsychotic medication and report minimal side-effects, others do not show any clinical benefits and suffer from life-threatening side-effects such as weight gain, hyperlipidemia, movement disorders and agranulocytosis [15]. Furthermore, persisting with treatment in people who do not benefit from it could lead to a worsening of symptoms [16]. One way of addressing these challenges is to gain a better understanding of why some people at UHR of psychosis benefit from a certain intervention whereas others do not, and then use this information to target delivery of intervention to the subgroup of patients most likely to benefit. In the present systematic and quantitative report, we therefore consider the current literature on predictors of clinical response to available treatments in this population (i.e. predictive markers).

Literature search and article evaluation

We searched the PubMed database for extant literature published online up to 16th February 2015, using the following search syntax: (marker OR biomarker OR outcome OR response OR prognosis OR prediction OR predictor OR predict) AND (at-risk mental state OR ultra-high risk OR ultrahigh risk). This identified articles containing the terms 'marker', 'biomarker', 'outcome', 'response', 'prognosis', 'prediction', 'predictor' or 'predict' in conjunction with 'at-risk mental state',

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TABLE 1

Criteria for quality of evidence and effect size to grade predictive biomarkersAdapted, with permission, from [17].

Quality of evidence		
An observation of a positive result ($P < 0.05$, corrected for multiple comparisons)	**Approximate equivalence to drug effects**	**Score**
In an uncontrolled study	–	0
In a study controlled for relevant extraneous variables (confounding, nuisance or effect modifiers)[a], that is, matched, restricted or adjusted for treatment, age, gender and (for genetic studies) ethnicity	Exploratory	1
In a study as above (grade 1), but with an explicit a priori intent to discover a precisely defined biomarker, that is, with a given measure or modality, cut-off and direction of effect of biomarker and response	~Phase I drug trial	2
In a study as above (grade 2), but designed with adequate power informed by previous positive studies of the same biomarker, that is, replication in a larger cohort	~Phase II drug trial	3
In at least two studies as above (grade 3)	~Phase III drug trial	4
Effect size		
An observation of a statistically significant (positive) result ($P < 0.05$, corrected for multiple comparisons)	**Approximate equivalence to drug effects[a]**	**Score**
With estimate from studies with quality of evidence $\leq$1	–	0
With marginal effect (OR < 1.3, SMD < 0.2 or $r < 0.1$)	–	1
With small effect size (OR = 1.3–1.5, SMD = 0.2–0.5 or r = 0.1–0.3)	Effect of psychiatric drugs on symptom improvement (median SMD = 0.41, mean SMD = 0.49)	2
With medium effect size (possibly rivalling the drug effect; OR = 1.5–2.0, SMD = 0.5–0.8 or r = 0.3–0.5)	Effect of antipsychotic drugs on acute symptom improvement (SMD = 0.51)	3
With large effect size (possibly exceeding the usual drug effect; OR > 2.0, SMD > 0.8 or $r > 0.5$)	Effect of antipsychotic drugs on relapse prevention (SMD = 0.92)	4

Abbreviations: OR, odds ratio; SMD, standard mean difference; *r*, correlation coefficient.

[a] In genetic studies, this only needs to be applied in relation to the outcome variable, provided that genotypes are unknown (and thus naturally randomised) before subject inclusion, with the exception of ethnicity which affects linkage disequilibrium patterns.

'ultra-high risk' or 'ultrahigh risk' or related medical subject heading (MeSH) terms such as 'biological markers' or 'psychotic disorders' in any of the fields searchable in PubMed. We read the abstracts and/or full text of the articles yielded from this search with the aim of identifying those studies that had used a longitudinal design to examine predictors of clinical response to treatment. We then used a recently developed two-dimensional scale [17] to rate the clinical applicability of the predictive markers identified in these studies. This scale, which is reported in Table 1, was adapted from a biomarker rating system proposed by Lassere [18] and is based on quality of evidence (scored 1–4) and effect size (scored 1–4). Quality of evidence is assessed based on whether studies include a control group, test-specific hypotheses, are prospectively designed, appropriately powered and independently replicated; whereas effect size is assessed based on odds ratios. Predictive markers that reach a sum score of 6 (out of 8) are considered clinically applicable (i.e. particularly worthy of clinical consideration).

Systematic and quantitative review observations

Our literature search identified 314 articles published between 1990 and 2015. Careful examination of each article, however, revealed that only two studies had investigated predictors of clinical response to a given treatment and, as such, were relevant to the present article. In the first study, Morrison and colleagues carried out exploratory analyses of the impact of pre-treatment metacognitive and sociotropic scores on clinical response to cognitive therapy [13]; these exploratory analyses were carried out in the treatment group but not the control group and did not detect any statistically significant effects, resulting in a grade of 1 for quality of evidence and for effect size. According to our scoring system (Table 1) this yielded a sum score of 0 that was well below our threshold for clinical applicability. In the second study, Amminger and colleagues examined biological and clinical factors associated with clinical improvement following 12 weeks of treatment with long-chain omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) [19]. An initial analysis using standard univariate statistics revealed that higher levels of erythrocyte membrane α-linolenic acid (ALA; the parent fatty acid of the ω-3 family) predicted subsequent functional improvement in the treatment group but not in the placebo group. A subsequent analysis using multivariate machine learning confirmed that baseline fatty acids allowed prediction of response to treatment in the ω-3 PUFA group with high levels of sensitivity, specificity and accuracy. According to our

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