Treatment Resistance in Early Psychosis

Subjects: Clinical Neurology
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Treatment resistance is prevalent in early intervention in psychosis services, and causes a significant burden for the individual. A wide range of variables are shown to contribute to treatment resistance in first episode psychosis (FEP). Heterogeneity in illness course and the complex, multidimensional nature of the concept of recovery calls for an evidence base to better inform practice at an individual level. Current gold standard treatments, adopting a 'one-size fits all' approach, may not be addressing the needs of many individuals.

Keywords: Treatment Resistance in Early Psychosis

1. Introduction

The lack of consensus over a clear definition of treatment resistance and validated instruments to assess the concept remains problematic for research in this area[1][2]. Treatment resistance is often conceptualized by the persistence of unremitted positive symptoms, despite the sequential use of at least two antipsychotic medications at a therapeutic dose, for a minimum duration of six weeks[3][4].

However, this definition disregards other symptoms which are shown to influence outcomes in psychosis, such as cognitive impairment and negative symptoms, which tend to be unresponsive to standard treatments[5][6][7]. The lack of broadness in the definition of treatment resistance has also meant that other key outcome domains, such as one's social and role functioning and quality of life, are overlooked[8]. Finally, the term itself may be conceived as stigmatizing, as it places onus on the individual for 'not responding adequately' or 'failing' their treatment, which may add to the increased shame and stigma that an individual may already experience as a result of receiving their diagnosis[9].

An alternative definition that has been proposed is the concept of 'incomplete recovery', which considers persisting impairment in psychosocial and functional domains, despite intervention with evidence-based psychosocial and pharmacological treatments; the term also reflects the potential for improved therapeutic outcomes[2][10]. Within this concept, the lack of recovery following adequate treatment is distinguished from non-adherence to treatment; each may contribute to incomplete recovery and should be identified and addressed early to promote recovery in FEP[1][2].

2. Prevalence and Predictors of Treatment Resistance and Incomplete Recovery

The rates of treatment resistance and incomplete recovery vary widely in FEP. This disparity is likely a result of studies adopting different criteria to define treatment resistance. The inclusion of participants with affective and non-affective psychosis is also likely to add to this heterogeneity, given that outcomes tend to be more favorable in those with prominent affective trajectories[11][12]. Recent publications in longitudinal FEP cohorts report rates between 22–34% for individuals who are resistant to antipsychotic medication[13][14][15]. Findings from systematic reviews on relapse and incomplete symptomatic recovery in FEP again show variation in the rates reported (19–89%), but notably, the risk of relapse is significantly reduced by sustained antipsychotic therapy [16][17][18][19]. Finally, incomplete recovery within social and vocational domains are shown to vary between 46% and 86% in FEP[16][20]. These findings highlight that current evidenced-based treatments and services are not adequately addressing the needs of all its service users.

There is also complexity in predicting outcomes in FEP; incomplete recovery appears to be multidimensionally determined and impacts separable domains of recovery[21][10]. Variables shown to contribute to incomplete recovery include: long delay in untreated psychosis (DUP), younger age at onset of psychosis, poorer premorbid adjustment, cognitive impairment, negative symptoms, affective comorbidity, non-adherence and disengagement with treatment, male gender, and initial response to treatment[3][13][7][22][23][24][25][26][27]. It is likely that each individual will have their own unique combination that will determine their outcome, which makes predictions at the individual level challenging, particularly in the early stages of psychosis where illness trajectories are forming and the clinical picture is still emerging[21].

It is also likely that illness trajectories are long-standing, and impairment pre-dates formal illness onset[28]. Supporting this view is the dimensional approach to illness whereby the heterogeneity in early psychosis is characterized by differing illness subtypes, rooted early in development[29][30]. Indeed, early cognitive and neurodevelopmental impairment has been associated with psychosis liability and core schizophrenia[8][31], and it is hypothesised that aberrations in the neurodevelopmental process, linked to cognitive deficits, lie at the heart of early and enduring impairment in psychosis[8]. Such an approach may have utility for subtyping individuals on their early course or premorbid features, potentially aiding in the parsing of clinical heterogeneity.

There are also a number of established social antecedents in the development of psychosis; an accumulation of these risk and protective factors over time may not only increase someone's risk of psychosis, but may continue to operate within the process of recovery[21]. It is established that social gradients are heavily implicated in the development of psychosis, such as: urbanicity, social marginalization and fragmentation, ethnic minority status, and childhood adversity[32][33]. These factors are likely to lead to a vicious cycle of disadvantage, which, if not addressed, will continue to drive enduring impairment[34]. For example, hostile and critical family environments are associated with relapse and depression in psychosis, and changing these environments via family interventions are indeed shown to be effective at reducing relapse rates[35]. More recently, the concept of urban remediation in psychosis has been proposed as a new recovery-oriented strategy to manage urban stress, but at present, this remains a goal for future research[36].

From the evidence presented above, there appears to a gap in the knowledge base for understanding the evolutionary continuity between alterations in neurodevelopmental process and exposure to stressful life events, with later onset of psychosis[30]. Longitudinal prospective studies in children and young people are essential to improve our understanding of neurodevelopmental markers in children and young people with varying levels of psychosis risk, and how these might be linked to long term prognoses.

3. Current Approaches for Managing Emerging Treatment Resistance in Early Psychosis

The first 3–5 years following illness onset, including the period of untreated psychosis, represents a 'critical period' of illness progression[37][38]. It is during this time in which interventions are likely to have their greatest impact[38].

EIS provides specialist assertive outreach-style care during the 'critical period', and are effective at improving a number of clinical and functional outcomes for young people with FEP[39]. However, there appears to be a group of individuals whose psychosis remains 'unresponsive' to standard high quality EIS care, embodying National Institute for Clinical Excellence (NICE) approved psychosocial and pharmacological interventions; strongly suggesting that earlier, targeted interventions are urgently needed to allow such individuals to maximise their life chances[16][17].

A recent publication by Drake and colleagues[23] demonstrated the importance of having such timely interventions. In their longitudinal modelling study, they demonstrated a curvilinear relationship between DUP with symptom severity and treatment response, meaning that symptoms become more refractory with a longer DUP, but this response was more rapid at first and then plateaued[23]. These recent findings place even greater emphasis on providing individuals with prompt access to a range of interventions ideally within the first few weeks of illness onset[23].

However, despite the implementation of EIS leading to a significant reduction DUP, a proportion of individuals continue to have DUPs exceeding 6 months[40][41]. Furthermore, whilst earlier studies provide evidence that intervention programmes can be successful at reducing DUP, for example, the Treatment and Intervention in Psychosis Study (TIPS), where DUP was reduced from 16 to five weeks, a recent systematic and meta-analytic review of 16 studies did not find any conclusive summary evidence for controlled interventions in reducing DUP[42][43].

Reducing DUP, particularly in areas where DUPs are consideringly long, should remain a priority to improve outcomes. Large scale collaborative studies with rigorous study designs and robust assessments of DUP are needed to inform more effective interventions[43].

Another important finding by Drake and colleagues was that DUP was not linked to any symptoms at presentation, except depression[23]. It is established that depression in psychosis is associated with a range of poor outcomes, but yet there is a lack of large-scale controlled trials investigating the effectiveness of adjunctive antidepressants, or cognitive behavioural therapy (CBT), to target depression within psychosis[22][44][45]. This calls for more effective recognition and management of depression to maximise recovery within EIS.

NICE guidelines in the UK advocate for antipsychotic medication and CBT as first line treatments for all individuals with psychosis[4] [11]. Clozapine is the only evidence-based treatment for refractory psychosis, and current guidelines recommend commencement after two unsuccessful trials of standard antipsychotics[4][46]. A recently published study investigating the pathways to prescribing clozapine for treatment resistance within UK EIS centres, showed a marked delay in clozapine prescription for those who were eligible[15]. A clear stasis in treatment was evident for these individuals, where the majority either remained on the same medication despite persisting symptoms, or they continued to be placed on other antipsychotics which were also unsuccessful[15].

Given the evidence of the superior efficacy of clozapine in reducing suicide risk, improving symptomatic and functional recovery, and reducing mortality rates, this may reflect a missed opportunity to influence recovery during the significant 'critical period'[15][47][48].Ongoing education of the benefits of clozapine and emphasis on the national standards for commencement of clozapine in the community is perhaps needed to improve uptake on clozapine for those who are eligible[16]. But despite its superiority in treating refractory symptoms, it must be acknowledged that 30–40% of individuals will still show an insufficient response to clozapine, and others are unable to tolerate the medication; the move toward community commencement of clozapine would also require national standards on clozapine discontinuation for those who are unable to tolerate[49][50].

Conventional CBT for psychosis is also less likely to be effective for subgroups of individuals with particularly complex illness presentations[49][51][52], and there is considerable heterogeneity in response to psychosocial interventions in psychosis[53]. Baseline factors are shown to contribute a large amount of this variance. For example, cognitive impairments are shown to have a rate-limiting impact on treatment progress [54][55].

Encouragingly, a recent randomised controlled trial provides an example of a tailored approach to those who are treatment resistant within early psychosis. A specialised social CBT, namely social recovery therapy (SRT), is shown to be effective at increasing structured activity in a sizeable group of young people whose severe social disability had proved unresponsive to standard EIS[51]. Potentially, individuals who are likely on a pathway to treatment resistance may receive SRT earlier in their illness trajectory to prevent their disability from becoming entrenched.

The benefits of such an intervention may also potentially extend to individuals who are disengaged with their treatment; the basis of SRT is to motivate individuals who are perhaps ambivalent about change, whilst also addressing any underlying blocks to change, or in this instance, interventions such as SRT may be helpful to address any underlying reasons for non-adherence to treatment[51].

Finally, there is further scope for the refinement of the SRT to ensure that the therapy is being delivered appropriately, such as greater precision in the identification of individuals who are less likely to benefit from such interventions, and a greater understanding of the mechanistic markers of change to inform the process of early treatment stratification[56].

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