Clozapine use in Early Intervention Services: missed opportunities in the management of early treatment resistance?

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Abstract 247
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Abstract

Background: Treatment resistance causes significant burden in psychosis. Clozapine is the only evidence-based pharmacological intervention available for people with treatment resistant schizophrenia; current guidelines recommend commencement after two unsuccessful trials of standard antipsychotics.

Aims: This paper aims to explore the prevalence of treatment resistance and pathways to commencement of clozapine in UK Early Intervention in psychosis (EIP) services.

Method: Data were taken from the National EDEN study (N=1027) and included demographics, medication history, and psychosis symptoms measured by PANSS (Positive and Negative Syndrome Scale) at baseline, 6 months and 12 months. Prescribing patterns and pathways to clozapine were examined. We adopted a strict criterion for treatment resistance which was defined by persistent elevated positive symptoms ($\geq$16 on PANSS positive score); equating to at least 2 items of at least moderate severity across three time points.

Results: 143 (18.1%) participants met the definition of treatment resistance of having continuous positive symptoms over 12 months, despite treatment in EIP services. 61 (7.7%) were treatment resistant and eligible for treatment with clozapine, having had two trials of standard antipsychotics. Despite this, only 25 (2.4%) participants were prescribed clozapine over the 12-month study period. Treatment resistant participants were more likely to be prescribed additional antipsychotic medication and polypharmacy, instead of clozapine.

Conclusions: Prevalent treatment resistance was observed in UK EIP services, yet few were prescribed clozapine, with polypharmacy a more common scenario. Significant delays in the commencement of clozapine may reflect a missed opportunity to promote recovery in this critical period.

Key words: Treatment resistance; Schizophrenia; Clozapine; Early psychosis.

Introduction

Psychosis is a common, often disabling disorder that occurs at a critical time in a young person's development. In spite of advances in mental health treatment, the outcomes for psychosis remain poor for many [1]. A recent meta-analytic review of longitudinal outcomes in first episode psychosis (FEP) reported a 38% pooled recovery rate [2]. Other systematic reviews have explored relapse and recovery rates following medication discontinuation in FEP; whilst there's a variation in the rates reported across studies (19-89%), the risk of relapse is significantly reduced by sustained anti-psychotic therapy [3-5] . These findings have important consequences for the selection of interventions in FEP [5].

Birchwood proposed the concept of a 'critical period' in the development and treatment of psychosis [6-8], with sustained and intensive intervention within early intervention in psychosis (EIP) services potentially improving outcomes. Adopting an assertive outreach community framework, EIP services within UK offer a range of treatment modalities in addition to psychopharmacology, including psychosocial, vocational and family interventions to promote recovery. [6, 9].

Such intensive, early treatment includes the identification and active management of early treatment resistant symptoms. In England, EIP services are now highly developed and monitored for the identification of such treatment resistance, which can be defined as the continued presence of symptoms despite the adequate trial of two antipsychotic medications, and the offer of clozapine to individuals who meet these criteria [10, 11].

Management of treatment resistant psychosis

Whilst the response rate to antipsychotic medication in the early phase of psychosis is generally good compared to established cases [12], Clozapine is the only available medication with proven efficacy for patients with treatment-resistant schizophrenia [13, 14]. Clozapine has superior efficacy in reducing symptom burden, reducing completed suicide and in improving functioning in patients with treatment resistant psychosis [15]. It is also shown to substantially reduce mortality rates in individuals with Schizophrenia [10]. Demjaha *et al*. brought to light the large proportion of patients who were treatment resistant from the outset of their FEP; Demjaha *et al*. recommended clozapine treatment as early as possible during the first presentation of psychosis [16]. However, literature suggests that clinicians are more inclined to prescribe a dose higher than recommended of a standard antipsychotic than to prescribe clozapine [10, 15]. Furthermore, patients eligible for treatment with clozapine were found to face delays in commencement of treatment ranging from 19.3 weeks to 5.5 years [15]. Other literature suggests delays in utilising clozapine are even more extensive; Wheeler carried out a retrospective chart review of adult outpatients in New Zealand, finding an average duration of illness of 9.7 years before initiation of clozapine [17]. In 2017, Doyle *et al*. studied a cohort of patients with first episode psychosis and demonstrated that clozapine was significantly underutilised, yet after the initiation of clozapine, the mean number of hospital admissions significantly reduced [18].

The present study

The National EDEN study is the largest cohort study of young people with FEP, who received care under comprehensive early intervention services in the UK [19]. This paper aims to utilise this comprehensive longitudinal study data to present the prescribing patterns of antipsychotic medication and present the pathways to, and prescribing of, clozapine for treatment of early

treatment resistant psychosis [11]. Furthermore, this paper aims to explore the wider prescribing patterns of psychiatrists in UK-based EIP services in the pharmacological management of first episode psychosis.

Methods

Study Overview

Data used were from the longitudinal 7 site UK National Evaluation of the Development and Impact of Early Intervention Services (National EDEN) study. Recruitment concluded in April 2009, with the final 12-month follow-up completed by April 2010 [19]. Data for this paper included patient demographics, full medication history, and Positive and Negative Syndrome Scale (PANSS) score. Pathways for those with treatment resistance both with and without clozapine, and the co-prescribing of other psychotropic mediation (e.g. antidepressants) are presented.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by Suffolk Local Research Ethics Committee, UK. Approval number: 05/Q0102/44. Written or verbal informed consent was obtained from all patients. Verbal consent was witnessed and formally recorded.

Inclusion and Exclusion Criteria

The EDEN studies enrolled patients with FEP (ICD-10 diagnoses F29, F20, F25, F31, F32.0-F32.1, F32.3 and F30.2) from Early Intervention Services across England, including Birmingham, Cornwall, Cambridge, Norwich and Lancashire. As the study progressed, four other Early Intervention Services were added into the study to increase the diversity of demographics; these included Solihull, Cheshire and Wirral, Peterborough and Kings Lynn. The EDEN studies included consented patients aged 14-35, with a first presentation of psychosis symptoms; see Birchwood *et al.* for full study description [19].

Baseline and Follow-up Measures

The EDEN study recorded baseline demographics of the entire cohort (n=1027), in addition to full medication record. Severity of psychosis symptoms was measured using The Positive and Negative Syndrome Scale (PANSS), which is a widely used and validated scale [19, 20]. These measures were collected at baseline, 6 months and 12 months by trained research assistants.

Although there are clear international criteria for remission, the agreed definitions for treatment resistance in established schizophrenia require repeated episodes and functional impairment [13, 21, 22]. There are no internationally agreed criteria for treatment resistance after first episode, where diagnoses are more fluid, but positive symptoms are generally more responsive [23]. Therefore, in line with previous literature, we used strict criteria for persistent positive symptoms ('treatment resistance') of $\geq$16 on PANSS positive score (equating to at least 2 positive items of at least moderate severity) at all three time points, in order to capture those participants most likely to be unresponsive to antipsychotic medication after FEP [16]. Those identified as having treatment resistance, and who had been treated with at least two different antipsychotic medication were identified as eligible for clozapine [24, 25].

Analysis

The prescribing patterns at baseline were explored descriptively to determine the overall percentage of each medication-type prescribed for the full sample (N=1027). A percentage breakdown of medication class (e.g. antipsychotic, antidepressant, mood stabilizers and anxiolytics) was calculated to explore co-morbid prescribing within the cohort. To explore polypharmacy within the treatment resistant patient cohort, the full prescribing history from baseline to 12-month was scrutinised; the prescribing history was examined for co-prescribing of antipsychotics and for co-prescribing of antipsychotics with an antidepressant. The duration of clozapine prescriptions was also examined within the group prescribed clozapine.

Results

Sample

1027 participants consented to participate in the National EDEN study, of which 75% (n = 791) were successfully followed up from study entry to 12-month follow up, with high retention of data across clinical measures [19]. The full baseline sample had a mean age 23 years (SD 5.08), 69% were male and 73% were of a white ethnic group. Based on OPCRIT criteria, the majority of the sample (47%) had a diagnosis of schizophrenia spectrum disorder (ICD-10 diagnoses F29, F20, F25) [19]. The sample characteristic for the 791 individuals followed up to 12 months were as follows: mean age 22.58 (SD 4.96), 68.4% male and 74.2% white ethnic group (See Table 1). OPCRIT diagnoses were only assessed at baseline.

143 were identified as treatment resistant by a continuously raised PANSS positive sub-score total of $\geq$16 at baseline, 6 months and 12-month time points. 61 out of this 143 were eligible for clozapine based on having treatment resistant symptoms and trialled with two different antipsychotic medications. Please see Table 1 for sample characteristics of the treatment resistant groups.

25 participants had been offered a prescription of clozapine by the 12-month time point, including 9 that had been identified as treatment resistant using the defined criteria, and 16 who had been started on clozapine where treatment resistance had not been captured at the follow up time points.

56 participants were identified as treatment resistant and eligible for clozapine (meeting our criteria for treatment resistance and trialled with 2 or more antipsychotic medications), but were not prescribed clozapine over the 12-month period.

*********Table 1 about here**********

Prescribing Patterns

A total 1746 individual (psychotropic) medications were prescribed across the full EDEN sample (n = 1027) at baseline. There were 1157 prescriptions for antipsychotics (66.3% of all prescriptions), 334 prescriptions for antidepressants (19.1% of all prescriptions), 334 prescriptions for anxiolytics (11.9% of all prescriptions), and 47 prescriptions for mood stabilisers (2.7% of all prescriptions); 6 of which of were lithium carbonate (0.3% of all prescriptions; 12.8% of mood stabilizer prescriptions).

Analysis of all antipsychotic prescriptions (n=1157) showed that the five most commonly prescribed antipsychotics were olanzapine (19.4%), risperidone (7.2%), aripiprazole (6.9%), quetiapine (2.6%) and haloperidol (1.7%). In comparison, clozapine only made up 0.3% of antipsychotic prescriptions.

Analysis of all antidepressant prescriptions (n=334) showed the five most commonly prescribed antidepressants were citalopram (45.2%), fluoxetine (26.9%), mirtazapine (11.1%), sertraline (6.9%) and escitalopram (3.3%).

******** Table 2 and Fig. 1 about here***********

Prescribing in treatment resistant participants

Analysis of polypharmacy in the treatment resistant group showed that, within the 12-month follow up window, 54 (37.8%) participants were co-prescribed 2 antipsychotics; 9 (6.3%) were co-prescribed 3 antipsychotics, and 4 (2.3%) were co-prescribed 4 antipsychotics. Moreover, the analysis found that many participants were co-prescribed antidepressants with an antipsychotic: 57 (39.9%) participants were co-prescribed an antidepressant with a single antipsychotic; 15 (10.4%) were co-prescribed alongside 2 antipsychotics; 3 (2.1%)w ere co-prescribed alongside 3 antipsychotics and finally, 3 (2.1%) participants were co-prescribed an anti-depressant alongside 4 antipsychotics**.**

With regards to medication compliance, there was a significant difference between compliance ratings of the treatment resistant group compared with the remaining EDEN participants (not identified as treatment resistant). Less than quarter of the treatment resistant group (18.8%) were actively engaged with their treatment, and 9.7% refused (or partially refused) their treatment (Table 3). This is compared with 35% and 5.5% respectively in the remaining sample (Table 3).

******** Table 3 about here***********

Pathways to Clozapine

Participants were trialled on up to 5 different antipsychotics before being prescribed clozapine; the breakdown is as follows: 4.0% of patients were not trialled on an antipsychotic before being prescribed clozapine; 24.0% were prescribed 1 antipsychotic, 44.0% were prescribed 2; 16.0% were prescribed the 3; 8.0% were prescribed after 4 different antipsychotics; finally, 4.0% of patients were prescribed clozapine after 5 different antipsychotics. The mean duration of time spent on clozapine was 5.44 months, and the median duration of clozapine was 5.50 months. See Fig. 1.

Furthermore, 4.0% of patients were not trialled on a second-generation antipsychotic before clozapine. 32.0% of patients were prescribed 1 non-clozapine second-generation antipsychotic before being prescribed clozapine. 52.0% of patients were prescribed 2 different non-clozapine second-generation antipsychotics before being prescribed clozapine. 0.0% of patients were prescribed 3 different non-clozapine second-generation antipsychotics before being prescribed clozapine. 12.0% of patients were prescribed 4 different non-clozapine second-generation antipsychotics before being prescribed clozapine. See Fig. 1.

Discussion

This data examination has described the prescribing practice and patterns to clozapine use in a large national sample of individuals with FEP with several findings of note. Firstly, treatment resistance

(here defined as a persistently raised PANSS positive score), is common in early intervention services, with nearly 20% of individuals having persistent high levels of symptoms despite intensive EIP care. Secondly, despite continuing positive symptoms, a large number of individuals remain on the same initial medication, and hence did not meet eligibility criteria for clozapine. Of those who were eligible, low numbers were prescribed clozapine. Second generation antipsychotics were prescribed for the majority of FEP individuals, with nearly 20% of antipsychotic prescriptions at baseline being Olanzapine. 39.9% of participants were co-prescribed an antidepressant with an antipsychotic, and 37.8% of participants were co-prescribed at least two antipsychotics.

The rates of treatment resistance in our large sample are comparable to those found by Demjaha *et al*., who reported that 23% of FEP patients were treatment resistant, as defined by NICE guidelines from a sample of 323 FEP participants studied from first contact to 10-year follow-up from services across Southeast London and Nottingham [16].

All participants in the EDEN study were recruited from highly concordant specialist early interventions services and this highlights the fact that despite intensive psychosocial interventions offered as standard in EIP services, treatment resistance does emerge [19], and may need specialist attention. Notably, some participants were trialled on up to 5 antipsychotics before being prescribed clozapine. These findings indicate a clear stasis in treatment progression, despite patients demonstrating persistent symptoms on their current regime. Two longitudinal studies have shown that of those who were identified as treatment resistant, 70% with first episode schizophrenia, and 84% with first episode psychosis, were treatment resistant from illness onset; highlighting that prompt consideration of clozapine may be beneficial in this group [26, 16].

National guidelines and Early Intervention Quality standards advocate use of clozapine for schizophrenia for illness “that has not improved despite the sequential use of adequate doses of at least 2 different antipsychotic drugs [24]. At least 1 of the drugs should be a non-clozapine second generation antipsychotic” [25]. However, there appears to be a hesitancy to prescribe clozapine for eligible patients with only a minority of patients in this sample prescribed clozapine after being trialled on 2 different antipsychotics.

It is apparent from our analysis that clinicians are continuing ineffective antipsychotics and/or trying augmentation with additional antipsychotics and antidepressants. Thompson *et al*. found a similar rate (32.6%) of participants received adjunct psychotropic medications prior to their prescription of clozapine, despite the lack of robust evidence for antipsychotic polypharmacy [27]. Although data from Thompson et al and our study is relatively old, since EDEN data collection concluded in 2012, it appears that there have not been any significant advances in antipsychotic treatments for FEP in this time frame. Recent National Audit data also does not suggest clozapine prescriptions are dramatically improving; with rates of clozapine prescription increasing by 5% since 2017 of those eligible [28]. It is also interesting to note the common prescription of Olanzapine, given both the considerable side effect burden, risk of metabolic syndrome, and explicit NICE guidance on the use of Olanzapine in young people under the age of 18, which advises that weight, and BMI monitoring is needed, but not often completed, with Olanzapine [29, 30]. There is a concern that young people are being exposed to metabolic risk and being set on the path to metabolic dysfunction early in the course of psychosis, without sufficient consideration for the longer-term risks [29]. Further, given the lack of evidence of a significantly enhanced therapeutic benefit of Olanzapine in FEP [31], the Schizophrenia Patient Outcome Research Team (PORT) do not recommend the use of Olanzapine as first-line treatment in first episode [32].

It would be speculative to comment on the reasons for such a low clozapine prescribing rate in EIP, however, despite their specialist psychosocial interventions, it is possible that medical management, and clozapine, has not featured as prominently as needed in the development of EIP services. Another potential barrier to clozapine prescribing in the UK is lack of experience or knowledge in the initiation of clozapine in the community, which maybe an increased issue in areas of limited inpatient beds. In 2015, Tungaraza and Farooq conducted a survey of 243 consultant psychiatrists and identified notable knowledge deficits with regard to the efficacy, risks and benefits of clozapine; results showed that 42.7% of psychiatrists were not aware that clozapine can reduce substance use; a third were not aware that the risk of agranulocytosis changes with time, and 20% were not aware of the benefits of clozapine reducing suicidal risk [33]. Furthermore, there are concerns regarding the known side effects of clozapine, such as neutropenia and potentially fatal agranulocytosis that are recognised to deter psychiatrists from prescribing clozapine, especially in community settings [33, 34]. Despite these reluctancies, a recent longitudinal study demonstrated that clozapine use was not associated with higher risk of severe physical morbidity, in fact, Clozapine was associated with a substantially decreased mortality rate [35].

In another survey of clinical staff conducted by Gee *et al.,* the most commonly stated boundary to clozapine prescribing was perceived concerns regarding patient adherence to blood monitoring [36]. Furthermore, the same authors carried out semi structured interviews of patients eligible for treatment with clozapine; 43.4% of participants said concerns over adverse effects of clozapine were considered sufficient grounds to refuse clozapine treatment, however blood testing was not a significant barrier [37]. In addition, 49% of participants said they would refuse clozapine if it necessitated a hospital admission [37]. Despite these findings, it is encouraging to note the efforts in the UK within a newly established, treatment refractory service for those with schizophrenia. The Treatment Review and Assessment team (TREAT), described by Beck et al., have provided an optimistic framework for prompt clozapine initiation and management in the community, with preliminary data showing 20 patients per year are initiated on clozapine, compared with 4 community initiations prior to the introduction of the TREAT service [38].

The very limited use of clozapine in the EDEN sample shows that barriers to clozapine prescription exist even in specialist early psychosis services, and this would be in keeping with an audit of early intervention services by the Royal College of Psychiatrists, which found that less than half of patients who were eligible for clozapine had received the drug [39]. Yet there is evidence to suggest that earlier clozapine prescribing may have benefit in FEP patients. Lieberman *et al.* performed a 52-week randomised control trial of clozapine versus chlorpromazine in treatment-naive first-episode schizophrenia patients and found that participants prescribed clozapine showed greater symptom improvement and earlier remission compared to participants prescribed chlorpromazine [40]. A follow up study by Girgis *et al.* looked at the 9-year outcomes; they found that 26.3% of participants prescribed clozapine remained on the same treatment, in contrast to 10% of those prescribed chlorpromazine [41]. Sanz-Fuentenbro *et al.* conducted a randomised trial of clozapine versus risperidone in treatment naïve first episode schizophrenia, with a significant improvement in negative symptom scores in the clozapine group [42]. Agid *et al.* investigated response to clozapine when utilised in a standardised treatment programme in FEP; patients received 2 trials with 2 different second-generation antipsychotics, followed by a trial of clozapine as early as 25 weeks into the start of their treatment; the results were highly significant as the group prescribed clozapine demonstrated significant decreases in symptom scores compared to those who refused clozapine [43]. Finally, a recent retrospective study of 105 treatment resistant patients prescribed clozapine showed the length of clozapine delay (time from diagnosis of treatment resistance to initiation of

clozapine) was associated with outcome, with a delay of more than 2.8 years having the largest effect [44]. This is interesting as it reflects the timescales observed in the critical period for psychosis literature [6].

One finding from our study was that several patients were chronically unwell as demonstrated by persistently high PANSS scores, and yet were not eligible for clozapine by virtue of having only been prescribed one antipsychotic medication. This may reflect a lack of focus on the medication management of FEP or a lack of early recognition of poor prognosis. Whilst guidelines currently state that clozapine should be used as a third line treatment, some authors have made compelling argument to consider its use second line, in view of the falloff in response to second line antipsychotic therapy [11, 45]. Indeed, in a recent large-scale, three-phase trial of non-response to Amisulpride in individuals with first episode schizophrenia, Kahn and colleagues demonstrated no added benefit to outcomes when switching to Olanzapine, but concluded that greater symptomatic remission can be achieved by sequential administration of Amisulpride and Clozapine; hence providing rationale for the use of Clozapine as second-line treatment [31].

Taking into consideration the above literature, it is clear there is a strong emerging evidence base for the use of clozapine in FEP, and moving forward, it becomes a question of how to implement an effective action plan to break down the barriers to prescribing clozapine and ensure eligible patients receive this efficacious treatment. Improved patient education regarding clozapine, alongside offering clozapine in the community where appropriate, may improve patient uptake in the future [37].

Study Strengths and Limitations

There are strengths to this study including the large sample of 1027 participants enrolled in a national cohort. The National EDEN study enrolled patients from Early Intervention Services across England over a 12-month period, making the sample highly representative [19]. There were robust data collection techniques at baseline, 6-months and 12-months. There are however recognised limitations, which include the relatively small number prescribed clozapine and our working definition of 'treatment resistance' in FEP. Compliance was not controlled for during the determination of treatment resistance, as to not exclude participants who were potentially most unwell and further reduce our sample size. As there was a significant difference in the compliance ratings between our treatment resistant group compared with the remaining EDEN sample, it is possible that some individuals who were 'deemed' treatment resistant may not meet this criterion had they been compliant with their medication regime [3-5]. There was a relatively short follow-up period of 12 months; given the literature states that the average duration of illness prior to initiation of clozapine is years, rather than months, this may explain the relatively small number prescribed clozapine in the large sample. Recruitment for this study concluded in 2009, with the final 12-month follow up completed by April 2010; hence it is possible that there has been a shift in prescribing practices in first episode psychosis services since this time, and replication of our findings would be warranted. ICD-10 diagnoses were only available at baseline; had this data been available at follow-up, it would have given an insight into change of diagnoses over the 12-month follow up period. Finally, this data exploration did not investigate further contextual information such as the rates of hospital admission and relapses, or qualitative data on the barriers to prescribing clozapine in early interventions services; this would be an area for future exploration.

In conclusion, our data shows that in comprehensive national FEP services there were significant

delays in commencement of clozapine treatment for potentially eligible patients. Antipsychotic medication was often not changed despite symptom persistence, and polypharmacy was more common than use of clozapine. This may reflect missed opportunity to influence recovery during the significant 'critical period'. Strategies to rectify this issue may include the increased recognition of early treatment resistance as a target of therapy, including the development of definitions suitable for use in FEP services, clinical focus on the initiation of clozapine in the community, and on-going education of the benefits, including functional recovery and suicide prevention of clozapine, and further emphasis on national standards for commencing clozapine in the community [22].

Conflicts of interests

Professor Upthegrove reports grants from Medical Research Council, grants from National Institute for Health Research: Health Technology Assessment, grants from European Commission - Research: The Seventh Framework Programme, personal fees from Sunovion, outside the submitted work.

Funding

The National EDEN study was funded by the National Institute of Health Research (NIHR) under the Programme Grants for Applied Research Programme (RP-PG-0109-10074). Birmingham and Solihull NHS Foundation Trust acted as study sponsor.

Acknowledgment

M.B. and S.P.S are part funded by the National Institute for Health Research through the Applied Research Collaboration West Midlands (ARC-WM). P.B.J. is part funded by the NIHR ARC East of England. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. We would like to thank the participants of the National EDEN study and the UK Clinical Research Network for study support.

Author Contribution

M.B. was the CI and grant holder, L.E., P.B.J., D.F., T.A., N.F., J.H., V.S., S.P.S. and M.M. contributed to the EDEN study design and execution. The data were analysed by I.S., S.L.G. and R.U.; I.S., S.L.G., R.U, and R.J. drafted the manuscript with further input from M.B. I.S. and S.L.G. contributed jointly to the manuscript. All authors provided comments on the manuscripts and approved the final version.

Data Availability

The corresponding and senior authors had full access to study data and had final responsibility for the decision to submit for publication. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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