Early access to clozapine in early intervention in psychosis: hope versus reality. A mixed method service analysis

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Title
Early access to clozapine in Early Intervention in Psychosis: hope versus reality. A mixed method service analysis.

Running Title:
Clozapine Eligibility in First Episode Psychosis

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Title

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Abstract

Aim: Improving access to clozapine is a recognised priority nationally across Early Intervention in Psychosis Services (EIPS) in the UK. Treatment resistance (TR) may be identifiable from early episode psychosis and appears to be characterized by negative symptoms and younger age of onset. This mixed method cross sectional snapshot analysis of antipsychotic prescribing in an EIPS, explored clozapine eligibility (CE), and prioritisation of antipsychotic prescribing based on choice, selectivity and appropriateness.

Method: We screened 150 service users and 79% (n=119) were retained after inclusion criteria were applied. We explored CE in all service users who were indicated clozapine based on the product licence (n=78), and whether there was association between CE and number of hospital admissions, antipsychotic trials, age at first episode and duration of untreated psychosis.

Results: Following multidisciplinary clinical discussions, we found that 23 service users were CE; 8 were offered and declined clozapine. When compared to non-CE service users, significant factors associated with CE were history of 2 or more hospital admissions (Mann-Whitney U=269, p=0.008), more than 2 trials of 2 different antipsychotics (Mann-Whitney U=517, p=<0.01), and younger age first episode (independent-samples t-test, *p*=0.047). 47.5% of all service users had been started on olanzapine as their first antipsychotic, despite high risk of cardiometabolic syndrome.

Conclusion: We propose that EIP services adopt a proactive approach in screening for TR, taking into account negative symptoms and young age at onset, prioritising service users with 2 or more hospital admissions and antipsychotic trials.

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Introduction

Evidence of antipsychotic (AP) efficacy in the early stages of psychotic illness, suggests high rates of response. (Jäger et al., 2007; Robinson et al., 1999; Whale et al., 2016) However as many as 23% of service users have been reported to not respond to first line AP treatment. (Demjaha et al., 2017) This is not too dissimilar to an estimated 30% of service users living with schizophrenia who have poor response to non-clozapine APs. (Lally and MacCabe, 2015) Dopamine dysfunction may not be solely responsible for insufficient response in this

subgroup of service users, and APs which are primarily dopamine antagonists may not be the most appropriate choice of treatment e.g. haloperidol, zuclopenthixol. (Demjaha et al., 2014, 2012). It may be possible to identify service users who are later identified as treatment resistant (TR), defined by the lack of response to two or more APsby Kane et al (1988), from a multicentre double-blind comparison with chlorpromazine. It has been proposed that in first episode psychosis (FEP), TR is often characterized by negative symptoms and younger age onset. (Demjaha et al., 2017). In the UK, the importance of early access to clozapine in FEP has been recognised nationally.(NICE, 2016)

Despite this, clozapine remains under prescribed. Most likely reasons for this appear to be clinician knowledge, perception of clozapine side effects and their overestimation, poor management of side effects, complexity of initiation and monitoring required, as well as reluctance to have a regular blood test.(Tungaraza and Farooq, 2015) Yet, 64% of service users receiving clozapine are reported to view blood taking positively, and nearly 90% feel that the benefits of clozapine outweigh the disadvantages and would not change back to a non-clozapine AP.(Taylor et al., 2000)

This mixed method analysis of AP prescribing in an Early Intervention in Psychosis Service (EIPS) aims to explore clozapine eligibility (CE) in FEP, and prioritisation of AP prescribing based on choice, selectivity and appropriateness.

Methodology

The study primarily used a cross sectional design. A snapshot of the caseload (n=150) for EIPS in East Sussex, UK, was obtained for analysis in February 2018, using Sussex Partnership NHS Foundation Trust's Electronic Care Record (ECR) system. This service adopts a classic model of EIP service, focusing on active engagement, providing the full range of psychological, psychosocial, pharmacological and other interventions e.g. early offer of medication, cognitive behavioural therapy, vocational support and support for families and carers, as per the National Institute for Health and Care Excellence guidance and quality standards. (NICE, 2016) Service users with the diagnosis of 'At Risk Mental State', those already on clozapine and those in the assessment phase with the service were excluded.

- Each service user's record was analysed and the following data was collected and validated by a pharmacist and a research analyst: Service User demographics including ICD10 diagnosis
- Duration of untreated psychosis (DUP) and age at onset of FEP
- Substance misuse status
- Review of all historically prescribed APs: perceived efficacy, adherence, and assessment of side effects for each service user
- Any recorded discussion of clozapine treatment with the service users
- Length and duration of hospital admissions including treatment changes

The above chosen variables were robustly recorded in each service user's ECR including medical letters. The standard of detail included was high, enabling inclusion of reliable data. Out of the whole dataset, the only missing data was within the following variables: 37% for DUP (n=119), 1% for age at FEP (n=119), 1% for length of treatment on a specific AP and maximum dose of specified AP (n=119). We intended to include assessments of adherence to treatment, but we were unable to reliably rate this variable retrospectively in absence of objective reporting at the time.

Following the initial data collection, a multidisciplinary team, consisting of EIPS psychiatrists (KH, VW) and lead EIPS pharmacist (NN), reviewed all service users who have trialled two different APs including those currently on second AP, to define CE. We focused on the

following minimum criteria as per the Treatment Response and Resistance in Psychosis Working Group Consensus Guidelines (Howes et al., 2017): current symptomology (assessment interviews rather than prospective evaluation of treatment using standardised rating scale e.g. Positive and Negative Syndrome Scale (PANSS)), functioning, prior treatment efficacy, and adherence to prescribed APs. Each case record was scrutinised by the MDT to clearly identify TR service users; categorisation of CE outcome was based on the common emerging themes of the reviews.

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS; version 23). Descriptive data was obtained and independent-sample t-tests were used to examine the relationship between means for normally distributed data. Chi-square statistics were used to test the relationship between categorical variables.

Audit governance approval to conduct the study was granted by Sussex Partnership NHS Foundation Trust. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Demographic data

Basic demographic data of the sample (total N=150) is shown in table 1 .

The greater majority in this sample of patients (n=119; 80%) had a primary ICD10 F20-29 diagnosis with the most common in the 'other' category being F12 (mental and behavioural disorders due to the use of cannabinoids). The most commonly reported substance misused (excluding alcohol) was cannabis (39.9%), followed by cocaine (14.9%). The mean number of DUP days in the sample was 65 (range 1 to 859).

Review of AP prescribing

Prescribing decisions within this sample had been undertaken by the EIPS and inpatient services. 88 service users in the sample experienced side-effects at cross sectional review (74%) with 66 of those reporting 2 or more. 54 service users (62%) had a change in AP due to side-effects and 12 (10.4%) had a dose change only. 23 service users had been offered side-effect medication and 2 had been offered lifestyle advice. The Glasgow Antipsychotic Side-effect Scale (GASS)(Taylor et al., 2016) had been completed with 8 service users reporting side-effects.

In terms of inpatient admissions, the average was 2 (range 1-7) up to the date of review. Of those admitted to hospital, on discharge 55 (74%) had had a medication change and 16 (22%) were taking the same medication as on admission.

Table 2 displays AP choice by successive medication trial, types of antipsychotic prescribed, rates of depots/ long acting injections (LAI) use and clozapine use. Trial number is the cumulative number of different AP exposures the service users received. The first AP exposed to, was most commonly olanzapine. Oral medications were used more often than depots/ LAIs until attempt 7. Aripiprazole was a very frequently used 2nd line medication after trial 1. Clozapine was not used in the first 9 medication trials, although 8 service users were offered and had declined. Combination of APs, both oral and oral or oral and depot/ LAI, was not commonly used.

Figure 2 displays mean (dot) and range (bars) doses prescribed for each medication for the duration of the caseload's time in EIPS. Wide dose ranges were used for most APs.

Clozapine Eligibility

Based on the frequent outcome themes in the process of the MDT peer review, service users were categorised into:

1. Service user is treatment resistant and therefore clozapine eligible
2. Current AP effective
3. Clozapine not indicated diagnostically i.e. extended assessment required
4. Previous AP trial needs to be rechallenged
5. Current AP ineffective due to likely poor adherence

Figure 1 demonstrates the categorisation of the sample into these groups. 23 service users on the caseload were CE due to likely TR. In comparison, the number of service users already on clozapine treatment at the time of the study was 4; a further 8 had been offered but had declined.

Adherence to prescribed treatment, based on the service users' subjective accounts was categorised into good (more than 75% of the time), partial/ variable and poor from the themes that came out of the conversations between service users and the EIPS practitioners. The categorisation of the sample into the groups was 71:19:25 respectively, (table 1).

The Shapiro-Wilk test of normality was used to investigate the assumption of normality. Age at FEP was found to be normally distributed (W=.96, *p*=.38). However, number of admissions (W=.81, *p*=<0.05), number of antipsychotic trials (W=.91, *p*=<0.05) and DUP days (W=.451, *p*=<0.05) were found to violate the assumptions of normality. A normal Q-Q plot also indicated that, for these variables, data points stray from the line in a non-linear way (figure 3).The variables associated with CE were explored descriptively using differences in observed means (figure 3). An independent-samples t-test was conducted to compare age at FEP in CE and non-CE groups and showed a significant difference (M=21, SD=3.9 for CE, M=24, SD=9.6 for non-CE, t (87) =-2.017, *p*=0.047).The number of inpatient admissions was significantly higher in the CE group (Mann-Whitney U=269, p=0.008). The relation between these variables was not significant (X^2 (1, n=74) =0.987, P=0.32). The number of antipsychotic trials was significantly higher in the Clozapine eligible group (Mann-Whitney U=517, p=<0.01). No significant difference in the number of DUP days between the CE and the non-CE group was observed (Mann-Whitney U=405, p=0.407).

Discussion

Early access to clozapine in the sample studied is a challenge that needs addressing. Our results show that consideration of clozapine use is clinically inadequate in this case. Nearly a fifth of this cohort was not perceived to be on optimally effective pharmacological treatment, and are therefore at a potentially increased risk of rehospitalisation and deterioration in mental health. These findings reflect the National Clinical Audit of Psychosis (NCAP), the EIPS spotlight audit report for 2018/19 in East sussex, in which 60 service users had 2 unsuccessful trials of APs, and 8 had been offered clozapine.(NCAP, 2019) NCAP attempted to assess CE based on clinician self-reporting; their findings could be enhanced by considering each service user's current clinical presentation, detailed MDT review of each service user's recovery whilst on EIPS caseload, and the possibility of rechallenging previous AP trials, including alternative management strategies of side-effects.

We identified that the main reason for non CE was service users being treated effectively by the second AP. This emphasises the importance of appropriate selection and dosing of AP.

This process also determined that side effects were not always being adequately explored. We reflect that the percentage of switching of APs in comparison to dose adjustments (45% v 10%; n=119), insufficient use of other treatment modifying strategies e.g. use of medications and lifestyle changes indicated for the specific side effect, and lack of use of assessment tools such as GASS, may all contribute to potential CE. This coincides with findings of a naturalistic cohort study of effectiveness of APs in FEP, suggesting that greater importance should be given to adherence strategies and optimising treatment through exploring side effects.(Whale et al., 2016)

The results point to a significant difference in the number of hospital admissions between CE and non CE service users, but no significant difference in the length of DUP between the CE and non CE service users. Long DUP has been associated with poor outcomes following FEP including social functioning, global outcomes and lesser likelihood of remission; and more severe positive symptoms with possible effect on dynamic brain changes that could result in enduring negative symptoms. (Hill et al., 2012; Marshall et al., 2005; Penttilä et al., 2014; Ran et al., 2018) We also observed a significant difference in the age of service users between the CE and non CE. Our findings would suggest that reviewing younger people for CE would be an additional appropriate indicator.

Nearly half of all service users with FEP in this service were initially prescribed olanzapine. Olanzapine is popular in the treatment of acute positive symptoms of psychosis, especially due to its antimanic, sedative and violence reducing effects. Balanced analysis of naturalistic and randomised evidence does not suggest one AP has greater effectiveness in FEP than another. (Crossley et al., 2010; Whale et al., 2016; Zhang et al., 2013) The risk of cardiometabolic syndrome combined with hypersomnolence outweighs the benefits of olanzapine and APs with a similar side effect profile in FEP. Rapid AP induced weight gain and glucose intolerance, important risk factors leading to cardiometabolic syndrome, have previously been demonstrated in service users with FEP treated with olanzapine and risperidone.(Alvarez-Jiménez et al., 2008) This can also be seen through subjective reporting of side effects such as weight gain, excessive sleep and increase in appetite, which in turn may have an effect on service users' adherence to prescribed treatment. An effort to minimise these, was likely observed from all further AP attempts in which aripiprazole seems to be the clinicians' preferred choice. This is a reflection of previous work into overall efficacy and tolerability of APs in schizophrenia that challenged conventional categorization of APs into first and second generation, focusing on individualising treatment based on service users' needs. (Leucht et al., 2013).

Doses of APs used in this sample were notably below maximum doses advised and should be optimisedfor appropriate lengths of time if not fully effective. An appropriate length of treatment exposure before inefficacy is decided, is often difficult to determine, particularly in view of rejected "delayed onset" idea..(Agid et al., 2006) At least one month of treatment is an accepted minimum period,(Taylor et al., 2016) Such discussions, including any other decisions around the overall AP efficacy, should integrally involve the MDT and the service user in recovery. The study observed uncommon use of combination of APs, which itself may be an indicator of CE. This was not explored further, but is an important consideration for future work, Effectiveness of such strategies is yet to be demonstrated. (Chakos et al., 2006; Thompson et al., 2016)

It is possible that use of depots/ LAIs may reduce the number of patients defined as CE. This is of particular significance as depot injections and LAIs are likely associated with lesser risk of relapse and hospital admission (Tiihonen et al., 2011). It has been argued, that in order to achieve the highest adherence rates with the prescribed treatment, and true clinical effectiveness in relation to possible TR, an ideal algorithm of treatment leading to clozapine would be two prior consecutive trials of LAIs.(Taylor, 2018)

We propose that EIP services adopt a proactive approach in screening for TR in a phasic approach taking into account negative symptoms and young age at onset, at the point of assessment. In the months following assessment, we suggest regular screening of rehospitalisation, switching of APs and MDT reviews of clinical effectiveness of all previous prescribed AP treatment, prioritising service users with 2 or more hospital admissions and AP trials. This would enable clozapine treatment to be considered as early as possible, empowering the whole MDT, and not just the prescribing doctor, to be accountable for each service users treatment options, as well as both positive and negative outcomes. These findings also indicate that identification of CE is possible within the first 3 years after FEP and is the responsibility of EIP services.

Limitations

The main shortfalls of this study are the focus on a single service, the relatively small size of potentially CE service users, the primary cross sectional nature of our study with varied duration of service exposure, and lack of investigation of associated symptomology. We recognise that we have not explored any barriers to prescribing of clozapine due to local service provision at the time, reasons for frequent changes and the role of service users' choice within the use of APs. Exploring service support to facilitate clozapine treatment, especially when service users are refusing treatment, would have been valuable. This study has pointed out the need to increase the assessment of adverse effects and adherence to prescribed treatment using validated questionnaires. Whilst there is some evidence to suggest that prescribing of antidepressants, anxiolytics and mood stabilisers is a common strategy prior to clozapine initiation ((Chakos et al., 2006; Thompson et al., 2016), we did not explore this in our cohort due to the complexity of additional potential variables.

Conclusion

Treatment resistance in psychotic illness may be identifiable from as early as first episode of psychosis. Conventional primary dopamine antagonist antipsychotics may not be effective in this subgroup of service users. Clozapine may be the most suitable alternative. Early intervention in psychosis services need to develop awareness to identify clozapine eligibility early on in the treatment, by narrowing focus on negative symptoms, young age of onset as well as negative outcome measures such as rehospitalisation and frequent switching of antipsychotics. Appropriate selection of treatment and increased use of long acting injections may reduce the risk of relapse due to non-adherence, and poor tolerability of treatment.

Statement of Author Contribution

NN is the main author of the manuscript including project design and methodology. NN, KH and VW were jointly involved in the qualitative part of the method and analysis. EC was the main research analyst for both quantitative and some qualitative data. RW is NN's clinical supervisor. RW, KH and VW made significant contributions towards the manuscript write up.

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