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Reasons for discontinuing clozapine: A cohort study of patients commencing treatment

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ABSTRACT

Background: Clozapine is uniquely effective in the management of treatment-resistant schizophrenia (TRS). However, a substantial proportion of patients discontinue treatment and this carries a poor prognosis.
Methods: We investigated the risk factors, reasons and timing of clozapine discontinuation in a two-year retrospective cohort study of 316 patients with TRS receiving their first course of clozapine. Reasons for discontinuation of clozapine and duration of treatment were obtained from case notes and Cox regression was employed to test the association of baseline clinical factors with clozapine discontinuation.
Results: A total of 142 (45%) patients discontinued clozapine within two years. By studying the reasons for discontinuations due to a patient decision, we found that adverse drug reactions (ADRs) accounted for over half of clozapine discontinuations. Sedation was the most common ADR cited as a reason for discontinuation and the risk of discontinuation due to ADRs was highest in the first few months of clozapine treatment. High levels of deprivation in the neighbourhood where the patient lived were associated with increased risk of clozapine discontinuation (HR = 2.12, 95% CI 1.30–3.47).
Conclusions: Living in a deprived neighbourhood was strongly associated with clozapine discontinuation. Clinical management to reduce the burden of ADRs in the first few months of treatment may have a significant impact and help more patients experience the benefits of clozapine treatment.

1. Background

The superior efficacy of clozapine has been consistently demonstrated for those with treatment-resistant schizophrenia (TRS) (Kane et al., 1988; Leucht et al., 2009). Clozapine therapy has also been associated with decreased rates of mortality (Hayes et al., 2015), suicide (Meltzer et al., 2003; Tiihonen et al., 2009) and aggression (Chengappa et al., 2002). However, approximately 40% of patients will discontinue clozapine treatment within 24 months of initiation (Ciapparelli et al., 2000; Davis et al., 2014; Whiskey et al., 2003), and this is often followed by a rapid deterioration (Seppala et al., 2005), increased rates of compulsory treatment, re-hospitalisation, and poorer functioning (Atkinson et al., 2007; Wheeler et al., 2009).

Given the benefits of clozapine treatment and the poor prognosis for those who discontinue, efforts have been made to identify patients that may be at increased risk of discontinuation and to understand the causes. An older age at clozapine initiation, Black African/Caribbean ethnicity and substance abuse have been found to be associated with clozapine discontinuation (Davis et al., 2014; Krivoy et al., 2011; Moeller et al., 1995). The most common reasons for discontinuation identified in previous studies were patient decision, non-adherence and adverse drug reactions (Atkinson et al., 2007; Davis et al., 2014; Mustafa et al., 2015; Pai and Vella, 2012; Taylor et al., 2009). Although patient decision and non-adherence have been identified as major reasons for discontinuation of clozapine, there has been no exploration of reasons behind this choice.

The majority of previous studies have not been conducted in patients receiving their first trial of clozapine and thus the identified reasons for discontinuing may have been biased by previous clozapine trials. In the current study, we investigated the risk factors, reasons and timing of clozapine discontinuation in a two-year retrospective cohort study of all patients starting their first clozapine trial over a five-

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year period (2007–2011, inclusive) in South London and Maudsley (SLaM) NHS Foundation Trust.

2. Method

2.1. Setting

The study used data from the Clinical Records Interactive Search (CRIS) system; a large, anonymised case register derived from South London and Maudsley (SLaM) NHS Foundation Trust electronic case records and fully described elsewhere (Fernandes et al., 2013; Stewart et al., 2009). The CRIS system allows researchers to search structured and free text fields. SLaM is the largest secondary mental health care provider in Europe serving approximately 1.2 million people from four London boroughs; Lambeth, Croydon, Lewisham and Southwark.

2.2. Sample inclusion criteria

The cohort consisted of patients who had a lifetime ever ICD-10 primary diagnosis of a psychotic disorder (F20–F29, inclusive) and who began their first trial of clozapine between 1 January 2007 and 31 December 2011. This study period was selected because electronic records were fully implemented during 2006 in SLaM and clozapine initiations on or before 31 December 2011 permitted a two-year follow-up to the time of data extraction (January 2014). Patients were aged 18–65 years at the start of clozapine treatment and initiated clozapine under standard secondary mental health care services, either as an inpatient or outpatient. Patients who received tertiary care from SLAM national services were excluded because complete follow-up data were not always available and they were not a representative sample.

The process of cohort identification is detailed in Fig. 1. A natural language processing application built using general architecture for text engineering (GATE) identified 3242 patients, from approximately 230,000 plus represented in CRIS, who had any evidence of current or previous clozapine use. The application used multiple data sources to identify medication use including pharmacy dispensing events, structured medication field, clinical correspondence and free text entries, resulting in a high degree of sensitivity (Hayes et al., 2015). We then selected patients who had (i) first clozapine prescription between 1 November 2006 (extended due to discussion that precedes clozapine initiation) and 31 December 2011, (ii) ICD-10 F20–F29 diagnosis, and (iii) aged 18 years or over on 31 December 2011 and 65 years or less on 1 January 2007. The data for the 799 patients who met these criteria were manually screened and study eligibility verified from their electronic clinical records.

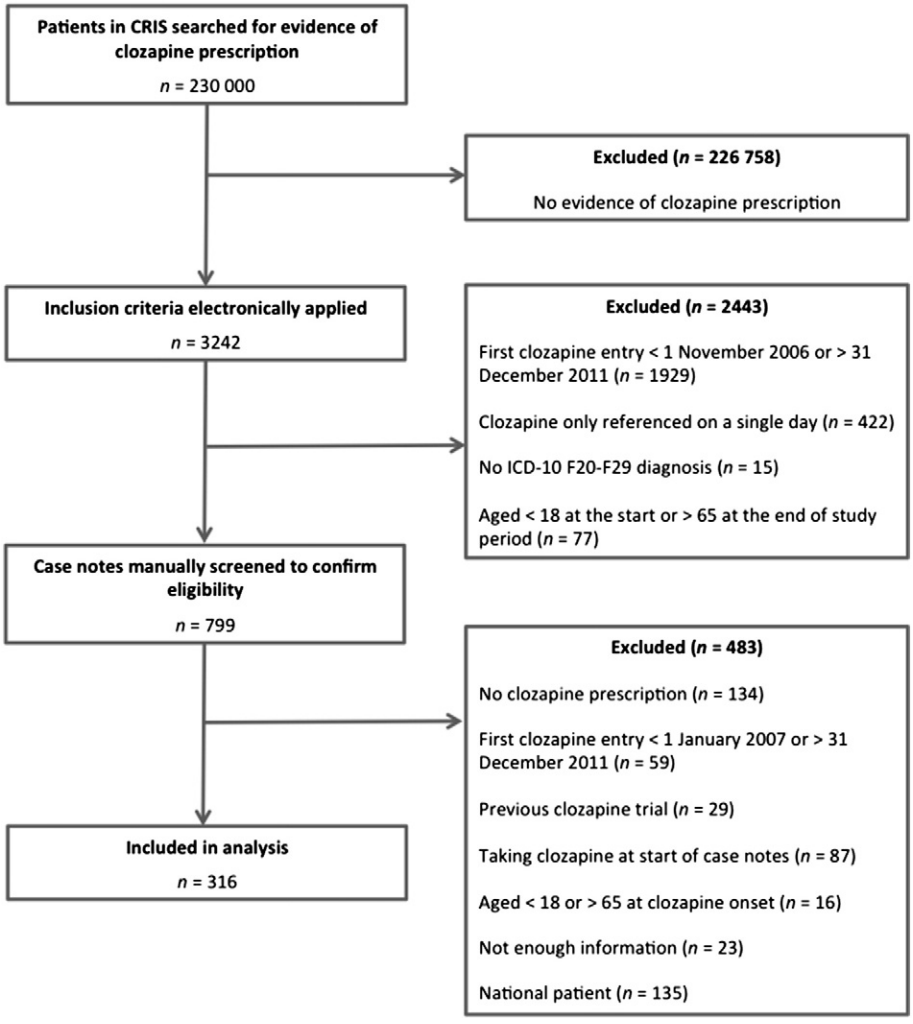

Fig. 1. Process of sample identification. The sample was initially extracted using a general architecture for text engineering (GATE) application, which detected a total of 3242 patients where a prescription of clozapine was indicated. Patients were then selected whose first clozapine entry was between 1 November 2006 and 31 December 2011, had entries that spanned more than a single day, had a lifetime ever ICD-10 F20–F29 diagnosis, and aged 18 years or greater on 31 December 2011 and 65 years or less on 1 January 2007. The data for the 799 patients that met these criteria were manually screened and study eligibility verified from case notes.