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Sodium valproate and clozapine induced neutropenia: A case control study using register data

Steffi Malik [a,b,1], John Lally [c,d,e,*,1], Olesya Ajnakina [c], Megan Pritchard [f], Amir Krivoy [c,g], Fiona Gaughran [c,g], Hitesh Shetty [f], Robert J. Flanagan [c], James H. MacCabe [c,g]

[a] Department of Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
[b] Medical School, University of Bristol, Senate House, Tyndall Ave, Bristol, UK
[c] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[d] Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland
[e] Department of Psychiatry, School of Medicine and Medical Sciences, University College Dublin, St Vincent's University Hospital, Dublin, Ireland
[f] BRC Case Register, South London and Maudsley NHS Foundation Trust, London, UK
[g] National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, UK

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ABSTRACT

Background: The use of clozapine is limited due to the occurrence of neutropenia, and the rare but life threatening adverse event of agranulocytosis. There is little epidemiological research into clinical factors that may impact on this risk. We conducted a case control study examining the clinical risk factors for neutropenia patients treated with clozapine.

Method: A case-control study was conducted within a database of anonymised electronic clinical records. All patients who discontinued clozapine due to a neutropenic event were included as cases. Matched controls were selected from patients with a documented clozapine exposure at the time of the clozapine neutropenic event of the case patient, matched by duration of clozapine treatment.

Results: 136 cases and 136 controls were included. In multivariable analysis, the concurrent use of sodium valproate was associated with neutropenia (Odds Raito (OR) 2.28, 95%CI: 1.27–4.11, $p = 0.006$). There was a dose-response effect, with greater associations for higher doses. Patients who discontinued clozapine due to neutropenia were more likely to be of black ethnicity (OR 2.99, $p < 0.001$), were younger ($t = 5.86$, df = 267, $p < 0.001$), and received lower doses of clozapine ($t = -2.587$, $p = 0.01$) than those who did not develop neutropenia.

Conclusion: We identified an association between the concurrent use of sodium valproate and an increased risk of clozapine associated neutropenia. These results, taken in combination with the results from previous case series, suggest that the risk of clozapine associated neutropenia could be reduced by avoiding concurrent valproate treatment.

1. Introduction

Treatment resistant schizophrenia (TRS) affects approximately 1/3 of patients with schizophrenia, with 70% of TR cases not responding to antipsychotics from illness onset (Lally et al. 2016a). Clozapine is the only evidence based medication in treatment resistant schizophrenia (TRS) (Essali et al. 2009) with 60–70% of those treated with clozapine showing a response (Chakos et al. 2001; McEvoy et al. 2006; Meltzer 1992). Clozapine is not only an effective treatment in TRS (Siskind et al. 2016) but is associated with long term reductions in mortality (Hayes et al. 2015; Tiihonen et al. 2009).

However, despite this, clozapine is underutilised (Manuel et al. 2012; Nielsen et al. 2016; Stroup et al. 2014), with delays of up to four years in its use in clinical practice (Howes et al. 2012; Nielsen et al. 2016; Taylor et al. 2003). Despite its beneficial effects, approximately 25% of clozapine users discontinue treatment due to adverse effects (Legge et al. 2016). Although the more common clozapine adverse events can generally be symptomatically managed, one of the primary reasons for clozapine underprescribing and delays in its use, is patient and clinician fears about the emergence of life threatening adverse events, and in particular agranulocytosis (Nielsen et al. 2010).

Clozapine induced agranulocytosis (CIA) occurs with a period prevalence of 0.8% in the first year of clozapine treatment (Alvir et al. 1993),

* Corresponding author at: Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, SE5 8AF, UK.
E-mail addresses: sm15121@my.bristol.ac.uk, Steffi.malik@kcl.ac.uk (S. Malik).
[1] Both are first named authors and should be acknowledged as such.

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with peak incidence at 6–18 weeks after commencing clozapine (Atkin et al. 1996). The one year prevalence of clozapine-induced neutropenia is 2.7% in the first year, with the peak incidence occurring at 6–18 weeks (Munro et al. 1999). In the UK, stringent and mandatory full blood count (FBC) monitoring is a requirement for continuing clozapine therapy so that the emergence of neutropenia can be detected early and clozapine treatment can be promptly discontinued if indicated (Atkin et al. 1996; Patel et al. 2005).

The occurrence of clozapine associated neutropenia and agranulocytosis necessitates discontinuation of clozapine. However, if the risk neutropenia could be reduced, this would have the additional effect of denying fewer patients the potential long term benefits of clozapine treatment. Recent evidence suggests that psychotropic medications and other drugs when, administered with clozapine may contribute to the development of neutropenia. Olanzapine, chlorpromazine, benzodiazepines, and anticonvulsants have been shown to be independently associated with increased incidence of neutropenia (Andres et al. 2008; Andres and Maloisel 2008; Garbe 2007; Meyer et al. 2015).

There is little research into clinical factors that may impact on the risk of clozapine associated neutropenia. The aim of the study was to identify concurrent medication use that increases the risk of clozapine associated neutropenia. We analysed factors related to clinical management (i.e. concomitant medication) and demographic characteristics (gender, age, ethnicity) which may predispose to the development of neutropenia in individuals treated with clozapine.

2. Methods

2.1. Data source and ethical approval

A case control study was performed using de-identified clinical records at South London and Maudsley NHS Foundation Trust (SLaM). This anonymised data was accessed using the Clinical Record Interactive Search (CRIS) facility. This was developed by the National Institute for Health Research, Biomedical Research Centre at SLaM and full details of this data resource have been provided elsewhere (Stewart et al. 2009). Governance for all CRIS projects is provided by a patient-led oversight committee reporting to the SLaM Caldicott Guardian. CRIS received ethical approval as an anonymised data resource for secondary analysis by Oxfordshire Research Ethics Committee C in 2008. The CRIS oversight committee application number corresponding to this particular study is 15–027 and was approved on 20th March 2015.

2.2. Documentation of cases and controls

Two thousand four hundred and seventy-three patients treated in SLaM with a clozapine prescription start date between January 2007 and May 2015 (inclusive) were screened for inclusion in the study using CRIS.

An exhaustive automated free text search of clinical records using the search terms “neutropenia”, “neutropenia + red”, “neutropenia + amber” and “agranulocytosis” in CRIS was completed. The selection of these terms was based on commonly used terminology referring to a neutropenic event by SLaM clinicians and was therefore best suited in identifying a neutropenic event. In the UK, clozapine monitoring uses a ‘traffic light system’. When neutrophil counts are $>2.0 \times 10^9$/L (and white cell count (WCC) $>3.5 \times 10^9$/L), a “green” result is recorded and clozapine is prescribed. If a neutrophil count $1.5–2.0 \times 10^9$/L is recorded, denoted “amber”, clozapine can be prescribed but with twice weekly FBC monitoring. A “red” result refers to a neutropenia with a neutrophil cell count below 1.5×10^9/L and/or a leucopenia with a WCC below 3.0×10^9/L. Similarly, a neutrophil count below 0.5×10^9/L is also referred to as a “red result” or “agranulocytosis”. Under the UK monitoring rules, clozapine must be stopped in the event of a red result.

This search identified 544 cases with suspected neutropenia.

2.3. Ascertainment of clozapine associated neutropenia cases

For inclusion as a case, patients were required to have at least one discontinuation of clozapine due to a neutropenic event i.e. a reduction in neutrophil and/or white cell count below 1.5×10^9/L, and 3.0×10^9/L respectively.

All 544 patients identified as potential cases had their clinical records manually reviewed. 136 patients had a confirmed clozapine related neutropenic event necessitating cessation of clozapine treatment between January 2007 and May 2015 (inclusive). For patients with more than one clozapine discontinuation due to an neutropenic event, only the first event was included, thus all clozapine rechallenges were excluded.

2.4. Matching to controls

For each case, an index date was defined as the date on which the neutropenic event occurred. Each case was matched 1:1 to a control drawn from the 1929 patients with no mention of neutropenia in their records using risk set sampling (Goldstein and Langholz 1996), matched by duration of clozapine therapy at the index date (<6 months; 6–12 months; or >12 months of clozapine treatment). This sampling strategy was designed to randomly match each case with a control with a similar duration of exposure to clozapine as the case. We selected controls from the cohort of 1929 patients that had a continuous repeat clozapine prescription ± 3 months from the index date when matching to cases. This was done to ensure the ongoing use of clozapine in controls at the time of the index neutropenic event.

2.5. Data collection

Data collected for cases and controls included gender, age at time of neutropenic event and ethnicity as documented in clinical records [categorised as: White (British, Irish, White and Asian and any other White background), Black (African, Caribbean, White and Black African, White and Black Caribbean and any other Black background) and other (Bangladeshi, Chinese, Indian, Pakistani, any other Asian background, any other ethnic group and any other mixed background)]. We also documented clozapine start date, daily dose of clozapine administered at the index date of neutropenic event, and concurrent medication used at the index date. The 136 cases were categorised by duration of clozapine treatment at the time of the neutropenic event (<6 months; 6 to 12 months; and >12 months).

Concurrent medication use represents a time-varying element of treatment. We collected in both cases and controls concurrent medication use on the index date. These included concomitant psychotropic medications (e.g. first generation antipsychotics, second-generation antipsychotics, mood stabilisers, antidepressants and anxiolytics).

In addition, to ensure reliability, a second author (JL) reviewed the extracted data. Any disagreement was discussed, decisions documented and, if necessary, we planned that a third author (JM) would help clarify issues and these final decisions would be documented. However, this did not happen.

2.6. Statistical analysis

Analyses were conducted using STATA (StataCorp, Stata Statistical Software, Version 12). Crude Odds Ratios (ORs) for neutropenia associated with concurrent medication exposure were estimated using conditional logistic regression. Multivariable analysis was conducted for each variable adjusted for age, ethnicity and concurrent sodium valproate use.

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