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SHORT REPORT

The impact of switching to clozapine on psychiatric hospital admissions: a mirror-image study

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Background. Clozapine is an atypical antipsychotic agent used primarily in the management of treatment-resistant schizophrenia. Previous studies have demonstrated clozapine's superior efficacy over other antipsychotic medications in treating this population of patients. The aim of this study was to assess if the number of hospital admissions and days spent in hospital reduced with the initiation of clozapine, compared with when the same sample of patients were prescribed other antipsychotics prior to clozapine initiation.

Method. A mirror-image study design was adopted. In this case the intervention under study was the initiation of clozapine. Information was collected retrospectively from the charts of patients attending the University Hospital Galway clozapine clinic. The number of admissions and number of hospital days were collected for each patient over the 3 years before and after clozapine initiation. Wilcoxon's signed-rank test was used to test for statistical significance.

Results. The total sample size comprised of 62 patients, of which the majority were male (74.2%) and had a diagnosis of schizophrenia (82.3%). The mean dose of clozapine was 417 mg, and mean age of the sample was 38 years. Mean number of hospital admissions reduced from 2.8 to 0.8 ($p < 0.0001$) following initiation of clozapine. Mean number of days spent in hospital reduced from 116.4 to 17.1 ($p < 0.0001$).

Conclusion. After initiation of clozapine treatment, patients experience a substantial reduction in number of hospital admissions and number of days spent in hospital when compared with a similar period prior to clozapine initiation.

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Key words: Antipsychotic, clozapine, schizophrenia, treatment-resistant.

Background

Clozapine is an atypical antipsychotic medication which is recommended for patients who fall into the category of treatment-resistant schizophrenia (Essali *et al*. 2009). The most common accepted definition of treatment-resistant schizophrenia refers to patients who, despite at least two adequate trials of antipsychotic medication, have severe positive symptoms, negative symptoms or disorganisation of thoughts and/or speech, together with poor social and work function over a prolonged period of time (Meltzer, 1997).

A number of studies have shown clozapine to be more clinically effective than other antipsychotic medications (Kane *et al*. 1988; McEvoy *et al*. 2006; Essali *et al*. 2009; Asenjo Lobos *et al*. 2010; Glick *et al*. 2011; Meltzer, 2012). Previous research has also shown that, in addition to improving psychiatric well-being, people who are prescribed clozapine tend to have a lower number of hospital admissions than persons prescribed other antipsychotic medications, thus indicating more favourable outcomes for patients who are prescribed clozapine (Zvolsky & Hulinsky, 1994; Conley, 1998; Dickson *et al*. 1998; Conley *et al*. 2003; Nyakyoma & Morriss, 2010; Ringback *et al*. 2014; Stroup *et al*. 2016). Other studies, however, have provided conflicting results (Drew *et al*. 1999; Herceg *et al*. 2008; Valevski *et al*. 2012).

In addition to indicating more stable clinical recovery for patients, a reduction in bed days has important economic implications. Several studies have been conducted which demonstrate a reduction in hospital expenditure, attributable to psychiatric admissions, following the initiation of clozapine (Meltzer *et al*. 1993; Aitchison & Kerwin, 1997; Oh *et al*. 2001). There do not appear to be any published studies of this nature examining the association between clozapine and psychiatric admissions in patients attending an Irish service.

We sought to investigate if there was an association between commencement of clozapine and a reduction in psychiatric inpatient admissions, using a mirror-image study design.

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Materials and methods

Mirror-image is a retrospective study design, which involves collecting data with regard to a particular outcome over a specified time period before and after an event (e.g. a change in medication) (Faries *et al*. 2009). Outcomes before and after the event are then compared. We chose this study design as it is inexpensive, can be conducted within a reasonably short period of time, and allows for a 'real-world' analysis of the variables under scrutiny, as it does not follow the more strict rigours of a randomised controlled trial. The intervention under scrutiny in this study was the commencement of clozapine in the management of treatment-resistant schizophrenia. The outcomes under scrutiny were the number of admissions to a psychiatric ward and number of bed days prior to and after commencing clozapine. In each case, it was decided to exclude the index hospital admission, where clozapine was commenced, from the final analysis, since many of these admissions were not indicative of symptomatic deterioration, but were elective admissions for the purposes of carrying out the necessary investigations prior to clozapine commencement, and to allow for titration and optimisation of clozapine dose. This approach was also taken by Hayhurst *et al*. (2002) in a similar study.

The Department of Psychiatry in University Hospital Galway (UHG) operates a clozapine clinic which is managed by a team of specialist nurses, with input from doctors, pharmacists and other members of the multidisciplinary teams as appropriate. Patients considered for inclusion were all patients attending the UHG clozapine clinic. In order to avoid limiting the sample to those patients who were most compliant with medication, an intent-to treat approach was taken, in that the number of hospital admissions and bed days would be carried forward from the time of exit if a patient discontinued clozapine. Therefore, an additional list of patients who had previously been registered with the clozapine clinic but who had not continued clozapine was also obtained.

Patients were then excluded subject to the following criteria:

1. Treatment period with other antipsychotics prior to clozapine initiation of less than 3 years, or patient prescribed clozapine for less than 3 years at time of data collection, without clozapine having been discontinued.
2. Any significant previous clozapine treatment within the 3 years prior to the period of clozapine treatment, defined as greater than 10 weeks duration.
3. Key salient data missing from files, for example, admission duration.
4. Files not found despite best efforts being made to locate them.

If information was missing from the files, all efforts were made to remedy this before making a decision to exclude that particular case.

A 3-year period prior to and following clozapine initiation was chosen for all cases. This time period was chosen to maximise the amount of data eligible for collection, while minimising the number of cases likely to be excluded due to an insufficient time period over which a relapse might occur. This time period was similar to other published studies addressing the topic (Aitchison & Kerwin, 1997; Drew *et al*. 1999; Hayhurst *et al*. 2002).

Each individual patient's paper chart was sought and examined regarding their suitability for inclusion. Data regarding the variables under scrutiny were recorded on a proforma designed by the primary researcher. The month and year of clozapine initiation for each patient were initially recorded, and information regarding admissions over the 3 years prior to and following this month and year was sought (6 years in total). Therefore, despite excluding the index admission, part of the mirror-image period would have comprised of some of the time spent in hospital when clozapine was commenced. If the mirror-image period began or ended at a time point that was in the midst of an admission, then this admission was included in the final analysis.

Data were analysed using SPSS Version 21. Data were not normally distributed, therefore a Wilcoxon signed-rank test was used to compare paired sets of data and assess for statistical significance. Ethical approval was obtained from the UHG ethics committee.

Results

The study was commenced with a total of 219 potential patients for inclusion in the final analysis ($n = 167$ patients attending the clozapine clinic at time of study commencement, $n = 52$ patients who had been registered with the clozapine clinic but who had since discontinued clozapine). The final number of cases included was 61 from the former group and one from the latter group (62 cases in total). Therefore, 157 cases were excluded overall. The specific number of cases that were excluded for each criterion was not recorded.

In terms of demographics, the majority of cases included were male (74.2%, $n = 46$), with 82.3% ($n = 51$) having a clinical diagnosis of schizophrenia, 12.9% ($n = 8$) diagnosed with schizoaffective disorder and 4.8% ($n = 3$) with another diagnosis. Mean dose of clozapine at end of year 3 was 417.21 mg

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Table 1. *Main results of study*

	Pre-clozapine	Post-clozapine	*p* value
Mean number of admissions (S.D.) {range}	2.82 (3.20) {0–17}	0.76 (1.48) {0–7}	<0.0001
Mean number of days spent in hospital (S.D.) {range}	116.39 (151.98) {0–635}	17.1 (39.99) {0–223}	<0.0001

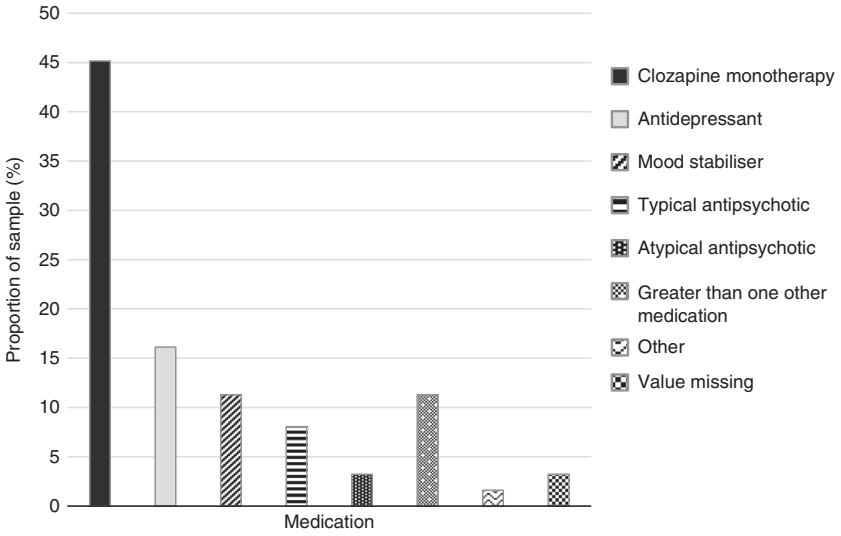

Fig. 1. Proportion of patients prescribed clozapine as monotherapy or prescribed it in combination with other psychotropic medications.

(S.D. = 161.16 mg), while mean age was 38.36 years (S.D. = 10.07).

The main findings of this study are displayed in Table 1. After the commencement of clozapine there was a 73.05% reduction in the number of hospital admissions, and an 83% reduction in the number of days spent in hospital. A secondary statistical analysis was undertaken which excluded 7 cases with extreme variables in terms of number of admissions, and 16 cases with extreme variables in terms of duration of admissions. The Wilcoxon signed-ranks test was then repeated, which showed that the study results remained statistically significant following removal of said outliers ($p < 0.0001$).

The minority of patients in this study were treated with clozapine as monotherapy (45.2%), with most patients prescribed a combination of clozapine with other neuroleptics, mood stabilisers and/or antidepressant medication (Fig. 1). This may have been due to the initiation of augmentation strategies, or due to comorbid mental illness, such as depression or anxiety disorders. It may also have been due to the fact that some patients' pre-clozapine medications may not have been stopped with the introduction of clozapine, for reasons unknown.

Discussion

The results of this study indicate a substantial and statistically significant association between commencement of clozapine and a reduction in the number of both hospital admissions and days spent in hospital, when compared with the time period prior to commencement of clozapine, where patients were prescribed other antipsychotic medications.

Of note, a study by Dickson *et al*. (1998) employed a similar methodology to our study, and obtained similar results. Our study has built upon this, however, by improving upon the modest sample size employed by said study (26 cases analysed, in comparison with 62 cases analysed in this study). Basic demographic information was similar to other published studies, however, the number of patients included in the final analysis were equal to or greater than previously published mirror-image studies.

It is important to note that the patients who were treated with clozapine also had access to a clozapine clinic which offers increased support in addition to monitoring their full blood count. It could, therefore, be argued that clozapine clinic attendance also plays a role in preventing admission to hospital. In addition to this, treatment may

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vary across sector teams in terms of resource allocation, treatment planning, etc. However, in the case of the catchment area studied, teams are similarly resourced and all patients had access to the clozapine clinic.

The main strengths with regard to this study are that each patient effectively acts as their own control (essentially comparing each patient to themselves, rather than to another person), that it is more time efficient and less costly than other studies, and that it allows for effectiveness of treatments to be assessed in a 'real-world' setting, outside of the constraints of a randomised controlled trial.

However, the study also has a number of limitations. This was a retrospective study, involving collection of pre-existing data from patient files. Therefore, the researcher has no control over the accuracy of information entered into patients' charts by treating teams over the years.

Another potential limitation is that this study's sample may not be entirely representative of the entire group of patients who are prescribed clozapine. This is due to the fact that a treatment period of greater than or equal to 3 years prior to the prescription of clozapine may suggest more chronic or enduring cases of mental illness. Guidelines state that clozapine should be commenced after two 4–6-week trials of non-clozapine antipsychotic medications (Conley & Buchanan, 1997; National Institute for Health and Care Excellence Guidelines, 2015). This study may not, therefore, look at outcomes for patients who may have had a more rapid pathway to the diagnosis of treatment-resistant illness and the initiation of clozapine.

Another potential limitation is that no data regarding duration of illness was collected, nor was data collected with regard to the exact numbers excluded for each exclusion criterion.

There may have been periods of unreported and, therefore, undocumented prolonged periods of non-compliance, which may have influenced the results of the study. There are certain assumptions associated with a mirror-image study design, chief among these being the assumption that the course of the illness would remain static if not for the intervention. Additional limitations include tendency for data to regress towards the mean (or natural subsidence of symptoms) and that mirror-image studies tend to display asymmetry of data, therefore placing the new treatment at a disadvantage (Gianfrancesco *et al*. 2002). The fact that the index admission was excluded in this study may have resulted in the pre-clozapine admission duration being eroded, particularly if the admissions were prolonged. However, despite this potential limitation, the results substantially favoured the post-clozapine period.

The results of this study have significant economic implications with regard to hospital expenditure. By reducing the amount of days spent as an inpatient, associated hospital expenditure is reduced, arguing for an economic benefit to prescribing clozapine. This benefit has been demonstrated by several published studies (Meltzer *et al*. 1993; Aitchison & Kerwin, 1997; Oh *et al*. 2001).

As mentioned, there do not appear to be any other published studies which have investigated the association between clozapine and hospital admissions in patients attending an Irish service. There is also a lack of published information with regard to clozapine prescribing patterns in Ireland. However, several international studies have shown that a minority of patients with treatment-resistant schizophrenia are actually prescribed clozapine, contrary to prescribing guidelines (Downs & Zinkler, 2007; Warnez *et al.* 2014). There are several factors which influence the decision to prescribe clozapine including patient choice, tolerability of side effects and complications, capacity of patient to adhere to twice daily oral medication and clinician choice. It is therefore likely that not all patients who are 'treatment resistant' can successfully switch to clozapine. More research into prescribing patterns and into clinician and service user decision making may help to elucidate variable prescribing patterns and ensure that this medication is being prescribed optimally. The current study does indicate that those patients with chronic illness who manage a sustained switch to clozapine derive substantial benefits from it.

Conclusion

The main finding from this study was that there was a significant association between switching to clozapine and reduced psychiatric admissions and bed days. This has a number of implications with respect to psychiatric wellness, as well as reducing costs associated with frequent admissions and prolonged hospital stays.

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Conflicts of Interest

None.

Ethical Standards

There were no human participants involved in this study. There were no animals involved in this study. Data collection was by means of a retrospective chart review. Informed consent was not required for this reason. All data collected were anonymised. Ethical approval was

obtained from the UHG Ethics Committee. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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