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ANTIPSYCHOTIC PRESCRIBING BEFORE CLOZAPINE IN A COMMUNITY PSYCHIATRIC HOSPITAL: A CASE NOTE REVIEW

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SUMMARY

Objectives: *To examine whether prescribing Clozapine was delayed in Treatment Resistant Schizophrenia (TRS), and elucidate possible reasons for this.*

Methods: *A retrospective Case note review was done. The main outcome measured was the mean maximum theoretical delay in starting Clozapine. In analyses, mean values were compared using an unpaired, 2-sided Student t-test. The association between duration of illness and theoretical delay was analysed by scatterplot and Pearson correlation coefficient.*

Results: *42 case notes were reviewed. Mean age of subjects was 40.1 years. The mean maximum theoretical delay in all patients was 5 years. A statistically significant longer delay was found in patients over 30 years, patients diagnosed with TRS before 1991,and for patients before the introduction of Risperidone. Delay was significantly shorter for patients admitted to a psychiatric hospital more than once a year.*

Conclusion: *There is a strong indication that Clozapine was not introduced at the earliest opportunity. Factors contributing to the delay include the patient's age, using sequential antipsychotic trials, and the failure to identify TRS. The use of Clozapine appears to have been adopted more in recent years, with a delay of five years to Clozapine for those diagnosed pre-1991, reducing to two years for those diagnosed pre-2003.*

Significant outcomes: *Mean average delay of prescribing clozapine was 5 years. Statistically significant delays in patients over 30 years of age.*

Limitations: *There was no evaluation of: Reasons for co-prescribing of antipsychotics. Reasons for delay in prescribing Clozapine, e.g. prescriber inexperience, patient choice, risk of non-compliance etc. Evidence of treatment resistance, and whether primary or secondary in onset.*

Key words: *Clozapine - schizophrenia*

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INTRODUCTION

Clozapine remains the gold standard for the pharmacological management of patients with treatment-resistant schizophrenia (TRS), currently being the only atypical to have a product licence in this patient group. Clozapine has demonstrably better efficacy and effectiveness than other antipsychotics, and is useful when concerns exist over suicidality, aggression and comorbid substance misuse (Leucht 2009, Farooq 2011). TRS is suggested by a lack of satisfactory clinical improvement despite the sequential use of the recommended doses, for 6 to 8 weeks, of at least two antipsychotics, at least one of which should be an atypical. The National Institute for Clinical Excellence recommends that in individuals with evidence of TRS, Clozapine should be introduced "at the earliest opportunity" (NICE 2009).

Taylor et al. (2003) investigated the prior prescribing of antipsychotics in patients currently receiving Clozapine. They sought to discover patterns of antipsychotic prescribing before Clozapine. They concluded that a mean delay of using Clozapine was five years. Sheachnasaigh et al. (2005) observed a mean delay to Clozapine of 3.3 years; Wheeler et al. (2008) reported 9.7 years duration of illness before starting Clozapine without identifying the time at which patients were considered as TRS. Weissman et al. (2007) reported a decrease in the use of Clozapine after the advent of second generation antipsychotics (SGA), which indicates that clinicians have the wrong impression that (SGA) are effective in TRS. Data from 41 Mental Health Trusts in England found that only 30% of those eligible were receiving Clozapine (Downs 2007). The danger in delaying prescribing Clozapine results in a more chronic course of the illness. It elongates patient and family suffering, in addition, to waste of resources.

AIMS

- To investigate Clozapine prescribing in a community psychiatric hospital in a semi-rural area (Basildon, South Essex, United Kingdom).
- To examine whether Clozapine was introduced at the earliest opportunity in individuals with evidence of TRS.
- To evaluate and elucidate reasons for delaying Clozapine treatment.

METHOD

Outpatients taking Clozapine, with a diagnosis of schizophrenia or schizoaffective disorder, resident in the communities of Thurrock, Grays, Basildon and Billericay, were included. Appropriate ethical approval was obtained. Clozapine is supplied to patients by the

Pharmacy at Basildon Hospital and is supervised by a designated Pharmacist (DH). Patients receiving Clozapine on an outpatient basis were identified from the pharmacy computer system; a random selection of every fifth patient on the register was made. A form was devised specifically for this study, available on request from the authors. The following information was collected. A full history of antipsychotic treatment from prescriptions and case notes was obtained. A summary of the number of antipsychotics used, their duration, and the number of episodes of antipsychotic-use before Clozapine was obtained for each patient. The most recent diagnosis was recorded. Duration of illness was calculated as the time from first diagnosis of psychotic illness. The main outcome measured was the maximum theoretical delay in starting Clozapine, defined as the time from the end of the sixth week of continuous treatment with a second antipsychotic given at a recognised therapeutic dose, to the first use of Clozapine, but excluding the period before January 1990

In analyses of factors associated with theoretical delay, mean values were compared using an unpaired, 2-sided Student t-test, after assuming normal distribution of data. The association between duration of illness and theoretical delay was analysed by scatterplot and Pearson correlation coefficient.

For those patients diagnosed with schizophrenia / schizoaffective disorder after January 1990, the duration of pre-clozapine illness was calculated, defined as the time from being diagnosed to the time of starting Clozapine. Patients diagnosed before 1990 were excluded.

The association between duration of pre-clozapine illness and theoretical delay was analysed by Pearson correlation coefficient and was calculated in addition to the percentage of pre-clozapine illness and the delay to start Clozapine.

The nature of prescribing between the end of the second antipsychotic trial and the date of starting Clozapine was documented and tabulated.

The duration of the first two antipsychotic trials was calculated and compared by scatterplot, with the date of diagnosis of schizophrenia/ schizoaffective disorder.

The number of admissions to a psychiatric hospital before taking Clozapine was recorded, and the admission rate calculated as admissions per year, to allow differential analysis of patients experiencing high and low admission rates.

RESULTS

Table 1 shows demographic characteristic of patients. 83% were Anglo-Saxons and no Afro-Caribbean's. Mean duration of illness 11.5 years, mean duration of Clozapine use 4.4 years. Co-prescribing was 36%. 64% had an atypical before Clozapine, 60% had a depot and 36% were switched from atypical. All patients had two adequate trials of different antipsychotics.

Table 1. Patient demographics and previous prescribing

Date of study	August 2004 - October 2006
Patients excluded (diagnoses other than schizophrenia or schizoaffective disorder	0
Patients included (diagnoses of schizophrenia or schizoaffective disorder)	42
Mean age of patients (years)	40.1; Range 23-74
Race: white	35 (83%)
Race: black African or Afro-Caribbean	0
Race: mixed	0
Race: Asian	7 (17%)
Mean duration of illness (years)	12.4; Median 11.5, range 3.2-39.9
Mean duration of Clozapine use (years)	4.9; Median 4.4, range 0.3 - 15.7
Mean duration of pre-clozapine illness (years) for those diagnosed with schizophrenia or schizoaffective disorder after the introduction of Clozapine	5.5; Median 4.9, range 0.6-14.7 (n=32)
Mean duration of first two therapeutic antipsychotic trials (years), all patients	2.5; Median 1.1, range 0.23-14.7
Mean duration of first two therapeutic antipsychotic trials (years), for those diagnosed with schizophrenia or schizoaffective disorder after the introduction of Clozapine	1.6; Median 0.9, range 0.23-10.2 (n=32)
Received an atypical before Clozapine	27 (64%)
Received a depot before Clozapine	25 (60%)
Previously co-prescribed 2+ regular antipsychotics for >6 weeks	15 (36%)
Switched directly from depot to Clozapine	5 (12%)
Switched directly from oral typical to Clozapine	13 (31%)
Switched directly from oral atypical to Clozapine	19 (45%)
Switched directly from depot and oral typical to Clozapine	5 (12%)
Switched directly from depot and oral atypical to Clozapine	0
Received no treatment in the month (oral) or 3-months (depot) before Clozapine	0
Received 2 adequate trials of different antipsychotics	42 (100%)

Table 2 summarises mean maximum theoretical delay (MMTD) in patients receiving adequate trials of antipsychotics. A statistically significant difference in MMTD was observed between patients younger / older than 30 years at the time of the study, patients diagnosed with schizophrenia / schizoaffective disorder before / after the introduction of Clozapine in 1990 and patients diagnosed before / after the introduction of Risperidone in 1992.

Table 3 illustrates prescribing histories of patients, showing number of episodes of antipsychotic use and similar numbers of antipsychotics used and adequately tried.

Table 4 Illustrates the number and duration of antipsychotics used after reaching potentially treatment-resistant status. Six of the 42 patients finished their second trial before 1990.

Table 2. Mean maximum theoretical delay to Clozapine (MMTD), (in years) in those patients receiving two adequate trials of different antipsychotics, P values shown are comparisons made using the Student t-test

Date of study	August 2004 - October 2006	
Patients included	42	
MMTD for all patients	5.0; Range 0.2 - 16.1	
MMTD for patients aged over 30 years at the time of analysis	6.0	p=0.006
MMTD for patients aged 30 years or younger at the time of analysis	2.3	
MMTD for patients diagnosed with schizophrenia / schizoaffective disorder before the introduction of Clozapine	8.4 (n=10)	
MMTD for patients diagnosed with schizophrenia / schizoaffective disorder after the introduction of Clozapine	3.9; Median 3.3, range, 0.2 -13.7 (n=32).	p=0.001
MMTD for patients completing adequate trial of 2nd antipsychotic before the introduction of Clozapine	7.5	p=0.106
MMTD for patients completing adequate trial of 2nd antipsychotic after the introduction of Clozapine	4.5	
MMTD for patients completing adequate trial of 2nd antipsychotic before the introduction of Risperidone in December 1992	7.6	p=0.002
MMTD for patients completing adequate trial of 2nd antipsychotic after the introduction of Risperidone in December 1992	3.6	
MMTD for men	6.3 (n=32)	p=0.232
MMTD for women	4.5 (n=10)	
MMTD for white patients	5.4	p=0.141
MMTD for non-white patients	2.9	
Percentage of pre-clozapine illness that the MMTD represents (for patients diagnosed with schizophrenia or schizoaffective disorder after the introduction of Clozapine)	67% Median 82%, range, 2% - 97% (n=32)	
MMTD for patients admitted to a psychiatric hospital as an inpatient on average more than once per year before starting Clozapine	5.7	p=0.018
MMTD for patients admitted to a psychiatric hospital as an inpatient on average less than once per year before starting Clozapine	1.9	
Correlation between MMTD (all patients) and duration of illness	Pearson correlation coefficient=0.23	p=0.001 (Figure 1)
Correlation between MMTD for patients diagnosed with schizophrenia or schizoaffective disorder after the introduction of Clozapine, and duration of pre-clozapine-illness	Pearson correlation coefficient=0.66 (n=32)	p<0.01

Table 3. Prescribing histories of patients receiving Clozapine

Study location	South Essex			
Variable	Mean	Median	Range	
			Min	Max
No. of episodes of antipsychotic use	5.8	5	1	18
No. of antipsychotics used	4.0	4	2	7
No. of episodes of adequate trial	5.0	4	1	18
No. of antipsychotics given adequate trial	4.0	4	2	7
No. of atypical antipsychotics used	1.2	1	0	3

Table 4. Antipsychotics tried after the patient reached potentially treatment-resistant status, (South Essex, 42 patients)

Regarding the 6 patients who finished their second trial before 1990:						
None stayed on the second drug.						
1	went on to try	4 drugs	over an average duration of:	3.2	years	before Clozapine
1	went on to try	5 drugs	over an average duration of:	16.1	years	before Clozapine
2	went on to try	6 drugs	over an average duration of:	8.4	years	before Clozapine
2	went on to try	7 drugs	over an average duration of:	4.5	years	before Clozapine
Of the 36 who finished their second trial after 1990:						
7	stayed on the second drug		over an average duration of:	2.9	years	before Clozapine
11	went on to try	3 drugs	over an average duration of:	3.3	years	before Clozapine
8	went on to try	4 drugs	over an average duration of:	6.4	years	before Clozapine
5	went on to try	5 drugs	over an average duration of:	5.8	years	before Clozapine
4	went on to try	6 drugs	over an average duration of:	3.0	years	before Clozapine
1	went on to try	7 drugs	over an average duration of:	13.7	years	before Clozapine

The association between duration of illness and theoretical delay was analysed by scatterplot (Figure 1), and Pearson correlation coefficient (0.23, p=0.001). It is evident that a longer illness is associated with a delay in the use of Clozapine in established TRS.

Figure 2 demonstrates the association between year of diagnosis and theoretical delay. Patients diagnosed before 1990 are included in the category "1990-1", as Clozapine was introduced that year. It suggests a general trend to shortening of the delay over time, although the overlap of confidence intervals demonstrates that this evidence is not definitive.

Figure 3 shows the association between date of diagnosis and duration of the first two antipsychotic trials as scatterplot. The Pearson correlation coefficient for the association is 0.5, p<0.01, it indicates a shortening of this duration over recent decades.

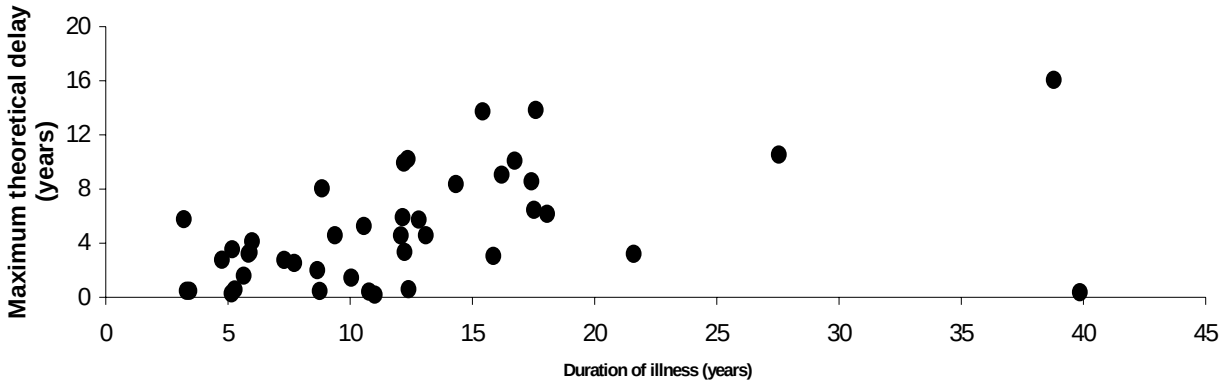

Figure 1. Duration of illness versus theoretical delay, South Essex (n=42)

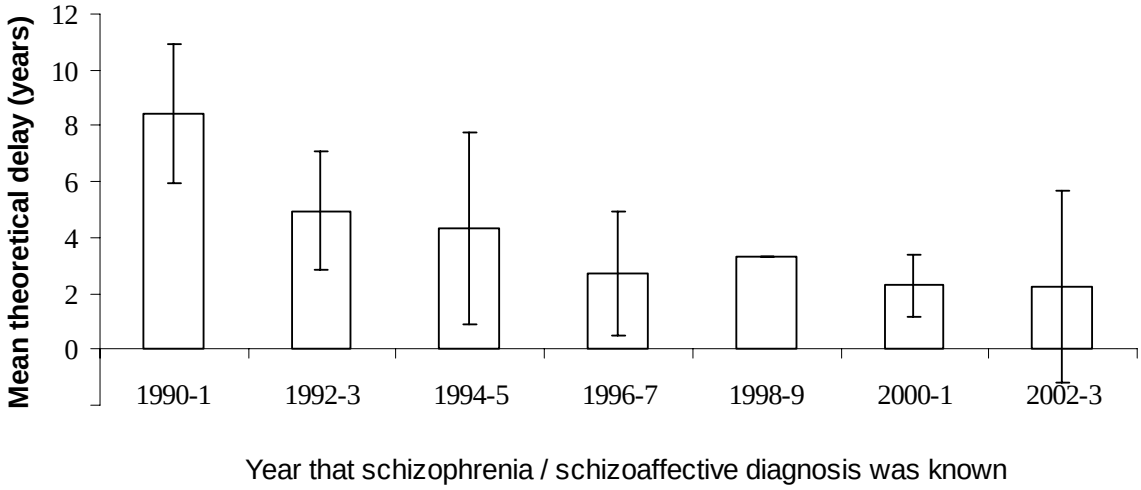

Figure 2. Theoretical delay versus year that schizophrenia / schizoaffective diagnosis was known after January 1990, South Essex (n=42). Bars indicate 95% confidence intervals (1.96 x standard error)

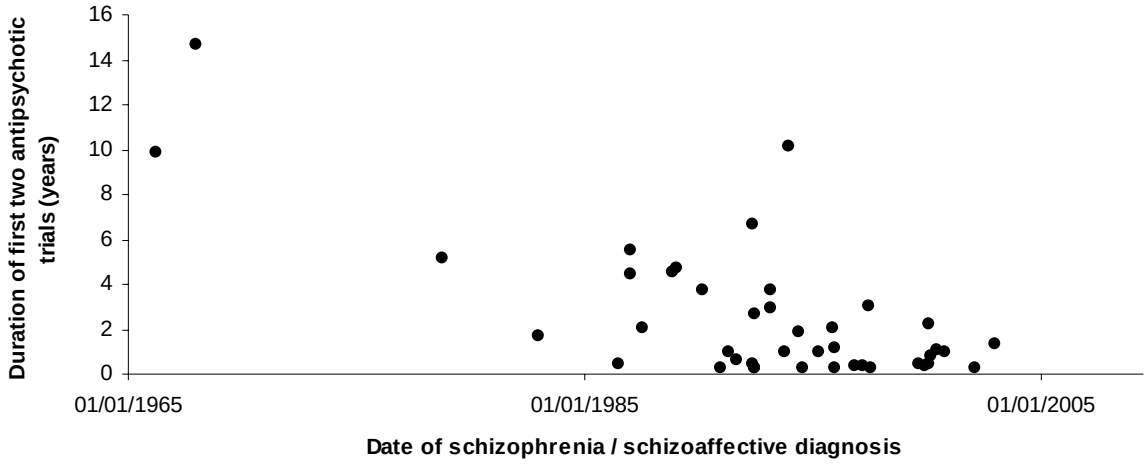

Figure 3. Association between date of diagnosis and duration of the first two antipsychotic trials

DISCUSSION

The most similar study to the present study was Taylor et al (Taylor 2003), for that reason our results are mainly compared with that study. Both studies observed the same mean theoretical delay i.e. five years although there were differences between demographics and psychiatric services setup in the two studies. As both studies did not evaluate true time to onset of treatment-resistance, it is difficult to comment as to whether the theoretical delay represents a true delay, or the illness was well-controlled until the onset of treatment resistance.

Patients in the Taylor study experienced a higher level of co-prescribing of antipsychotics, representing the difficult cases that these hospitals treat as tertiary referral centres.

Taylor et al showed significantly longer delays to Clozapine across all subgroups in the analysis, whilst our study showed that patients who completed two trials before the introduction of Clozapine did not experience significantly longer delays. Although the evidence is not particularly strong, this may be an indication that Clozapine was used "at the earliest opportunity".

Our study found that the correlation between theoretical delay and duration of illness is notably high, and when the analysis is extended to just those patients diagnosed after 1990, the correlation was even stronger. This suggests that our patients did experience a longer theoretical delay as a result of the longevity of their illness, possibly age-related.

There were some notable consistencies across both studies with regards to patient histories, in particular the mean number, per patient, of antipsychotics given (adequate trial was four). Given the mean duration of illness (12–15 years), a trial of four antipsychotics can be considered reasonable.

All the patients in the cohort had TRS at the time of starting Clozapine, but when did this TRS first become apparent?

There was no significant difference in MMTD between patients completing adequate trials of two antipsychotics before and after 1990. This indicates that patients were given Clozapine irrespective of its availability and it was eventually used as soon as possible, once TRS had been established.

It has been argued that high number of antipsychotics used (up to thirteen) was evidence of a delay in the use of Clozapine in patients with unidentified TRS (Taylor 2003). Having said that, it has been shown that switching between typical antipsychotics is unlikely to be effective in acute relapse (Kinon 1993). The present study showed that the progression of patient's treatment (Table 4) after the first two trials, presents a strong evidence of probable TRS.

It is difficult to explain the high numbers of episodes, as it can be explained by incompliance, disengagement, relapse, drug and alcohol misuse or lack of response and unidentified TRS.

An "extensive difference" between mean duration of illness (15.1 years, 12.4 years) and mean duration of use of Clozapine (2.4 years, 4.9 years) was highlighted in Taylor et al. (2003) and our study respectively. This argument can be extended further if it is realised that on average 68% of pre-clozapine duration was spent for patients who were diagnosed as TRS after 1990. This "wait and see" approach is cause for concern as evidence is emerging (Szymanski 1996, Schooler 1997) that schizophrenia is a neurotoxic illness and the longer it stays untreated or partially treated the more severe it will be. This is the crucial issue every clinician needs to consider carefully.

The question whether TRS is primary or developing is a considerable challenge. If TRS is a developing phenomenon, perhaps as a result of pathology caused by progressive neurotoxicity and inadequate treatment, then rigorous assessment and regular review will be required to spot the developing signs of failure. If TRS is primary then it will still be the prescriber's duty to constantly question whether the patient is failing to achieve or sustain a satisfactory clinical improvement.

It has been argued that, early co-prescribing of antipsychotics can be a sign of primary TRS. Eight patients

in our study received two concomitant antipsychotics as soon as they were diagnosed with schizophrenia, and as such provided early evidence of TRS.

The fact that there was a longer MMTD in patients over 30 years old and in those diagnosed before 1990 indicates that age is a statistically significant factor in delay to prescribe Clozapine. The possibility that the older the patient the higher the risk from the adverse effects of Clozapine may apply.

The duration of the first two trials were, on occasions, remarkably long, and is perhaps evidence of developing rather than a primary TRS. The fact that this duration is becoming shorter (Figure 3) suggests that practice is changing towards faster progression through the next two antipsychotics, before Clozapine, and this may well have contributed to the trend of MMTD gradually shortening as seen in Figure 2.

Patients who were admitted more than once a year to a psychiatric hospital experienced a shorter delay in initiating Clozapine. Admission to a psychiatric ward indicates lack of response to treatment and TRS.

There is increasing evidence supporting the notion that treating schizophrenia with ineffective drugs elongates the suffering of patients and make the illness more chronic and resistant to treatment. In addition Clozapine appears to be more cost-effective than typical antipsychotics (Rosenheck 1997). A recent review found Clozapine is associated with a substantially lower mortality than any other antipsychotic (Tiihonen 2009). However 66% of psychiatrists still think that patients treated with Clozapine were less satisfied with their treatment when compared with those treated with other atypical antipsychotics (Nielson 2010).This contrasted with a survey of individuals on Clozapine which reported that 87% felt that advantages of Clozapine outweighed any disadvantages (Taylor 2000).

The observed trend of an earlier use of Clozapine is therefore very welcome, but this needs to be sustained and improved in order to make the fullest use of the only drug available in TRS.

Implications and future research

Our results replicate previous studies in that clozapine prescribing has been delayed on average of five years since patients qualifies for clozapine. Twenty years has lapsed since the reintroduction of clozapine in the United States and the United Kingdom. Experience of clinicians and patients has increased a lot during those years. Prospective studies are invited to improve our practice with clozapine to help patients who are in desperate need of medication to help them overcome their disability when they cross to over to TRS.

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