Routine data linkage to identify and monitor diabetes in clozapine-treated patients with schizophrenia.

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The physical health of people with serious mental illness is an issue of major concern to individuals, their families, clinicians and healthcare policy-makers (The Schizophrenia Commission, 2012). Mortality rates remain around twice those found in the general population (Saha et al., 2007) with high levels of cardiovascular disease (Goff et al., 2005), metabolic disease (De Hert et al., 2006), diabetes (Newcomer et al., 2002), and respiratory illness (Chafetz et al., 2008). Clozapine has been shown to be the most effective medication for treatment-resistant schizophrenia (Essali et al., 2009) but has important side-effects, with higher rates of agranulocytosis, weight gain, metabolic syndrome, hyperglycaemia, and hypertension (Drew, 2013). We aimed to use a health informatics approach with routinely-collected data to determine the prevalence of glucose dysregulation, diabetes mellitus, and treatment levels for diabetes in clozapine-treated patients with schizophrenia.

We used electronically-linked data from the Glasgow Psychosis Clinical Information System (PsyCIS) of around 8,910 patients with serious mental illness (predominantly psychotic disorders) that have been systematically registered over the last 10 years. From this group we identified 1,157 individuals receiving clozapine medication (836 (72.7%) male and 314 (27.2%) female) (Table 1). We then estimated the prevalence of diabetes by firstly identifying patients with a raised plasma glucose (>11.1 mmol/l) or HbA1c (>48 mmol/l), and then finding a second confirmatory test to meet the diagnostic criteria (WHO, 2011). We found that in total 1,086 patients (94%) had a record of screening with at least one routine glucose test, 635 (55%) had a recorded glycosylated haemoglobin test, and 1,063 (92%) had plasma cholesterol levels recorded (Table 1). One hundred and seventy-

five clozapine-treated patients (15.1%) met criteria for diabetes mellitus using plasma glucose measurement, compared to a proportion of 5.8% in the general population (z=11.9, p=0.001). A diagnosis of diabetes mellitus using HbA1c was found in 168 patients (14.4%) but screening for HbA1c was only conducted in 635 individuals. The prevalence of diabetes was higher in men (67.4% 118/175) than in women but this difference was not significant (χ^2=2.6, p=0.11). The prevalence of diabetes increased with age to a peak at age group 40-49 (χ^2=38.9, p=0.001).

Twenty percent of clozapine-treated patients were prescribed a second antipsychotic medication, predominantly amisulpiride and a higher risk of diabetes was associated with the prescription of a second antipsychotic medication (χ^2=190.2, p=0.001). There was a small association between the risk of diabetes and duration of clozapine treatment (OR 1.08, 95% CI 1.02-1.13, z=2.66, p=0.008) but the prevalence of diabetes was not associated with clozapine dose (OR 1.00, 95% CI 0.998-1.000, z=-0.83, p=0.404), or levels of socioeconomic deprivation (χ^2=6.97, p=0.14).

Seventy percent of clozapine-treated patients with diabetes received at least one antidiabetic medication, which was usually metformin (62.9%). In those for whom HbA1c data were available, the control of diabetes appeared to be poor, with a mean (initial) HbA1c of 66.98 mmol/l (SD $\pm$20.84, 95% CI 63.80-70.16), well above the recommended level of $\geq$48mmol/l.

We have identified levels of diabetes of 15% in what is the largest single sample of clozapine-treated patients reported to date. Earlier studies have found different estimates of diabetes, from 6% in patients attending a psychiatric outpatient clinic (Sernyak et al., 2003) to 22% within an inpatient psychiatric hospital setting (Zhang et al., 2011). Electronic linkage of routine data may have identified individuals with diabetes who would have previously remained undiagnosed. This approach may also have helped to avoid the recognised problems of health screening in people with serious mental illness, such as poor access to medical care and low engagement with preventative interventions.

We recognise that a small proportion of patients may have received blood sampling or treatment elsewhere and that we may have potentially missed some individuals who had been diagnosed with diabetes and successfully treated. We were not able to identify other

risk factors which may have contributed to diabetes risk, such as weight problems, poor diet, or lack of physical activity.

Explanations for the high levels of diabetes in people with serious mental illness remain unclear, but are likely to be multi-factorial. These include hereditary factors and environmental influences, such as unhealthy lifestyles with weight gain, poor daily dietary intake, and a sedentary lifestyle. We propose that the electronic linkage of routinely collected clinical data has considerable potential to improve the detection and treatement of medical comorbidities in individuals with severe mental illness.

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Contributors

RP and DJS designed the study. RP and DJS managed the analyses. RP wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declared no competing interests.

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Table 1. Summary Characteristics of Patients Treated with Clozapine

Characteristics	N	%	Mean	SD	Min	Max
Total No of Patients	1157					
Mean Age (yrs)	1157		45.86	11.3	18	84
Age Group (yrs)						
Years						
16- 20	3	0.3				
21- 30	87	7.6				
31- 39	249	21.6				
40- 49	371	32.3				
50- 59	319	27.7				
60- 69	100	8.7				
70- 79	20	1.7				
80+	1	0.1				
Sex						
Female	314	27.2				
Male	841	72.8				
Total Baseline Blood Measurements						
HbA1C	635	55.0	43.10	14.0	25.0	140.0
Glucose	1086	94.0	6.56	2.92	2.6	33.2
Cholesterol	1063	92.0	5.22	1.31	1.8	14.0
HDL		1026	88.7	1.08	0.32	0.2
3.6						
LDL	825	71.3	3.07	1.07	0.4	7.0
Chol/HDL Ratio	999	86.3	5.08	1.79	1.8	20.5
Triglycerides	1058	91.4	2.44	1.69	0.4	16.6
Cholesterol $\geq$5.0	610	52.7	6.09	0.96	5.0	14.0
HDL ($\leq$ 1 mmol/l)	513	44.3	0.84	0.13	0.2	1.0
LDL ($\geq$ 3.0 mmol/l)	427	36.9	3.89	0.75	3.0	7.0
Clozapine						
Clozapine Dose (mg/d)			385.2	163.4	6.25	900
Clozapine Duration (yrs)			7.1	3.16	0.3	18.9