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Clozapine users in Australia: their characteristics and experiences of care based on data from the 2010 National Survey of High Impact Psychosis

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Aims. Clozapine is the most effective medication for treatment refractory schizophrenia. However, descriptions of the mental health and comorbidity profile and care experiences of people on clozapine in routine clinical settings are scarce. Using data from the 2010 Australian Survey of High Impact Psychosis, we aimed to examine the proportion of people using clozapine, and to compare clozapine users with other antipsychotic users on demographic, mental health, adverse drug reaction, polypharmacy and treatment satisfaction variables.

Methods. Data describing 1049 people with a diagnosis of schizophrenia or schizoaffective disorder, who reported taking any antipsychotic medication in the previous 4 weeks, were drawn from a representative Australian survey of people with psychotic disorders in contact with mental health services in the previous 12 months. We compared participants taking clozapine ($n = 257$, 22.4%) with those taking other antipsychotic medications, on a range of demographic, clinical and treatment-related indicators.

Results. One quarter of participants were on clozapine. Of participants with a chronic course of illness, only one third were on clozapine. After adjusting for diagnosis and illness chronicity, participants taking clozapine had significantly lower odds of current alcohol, cannabis and other drug use despite similar lifetime odds. Metabolic syndrome and diabetes were more common among people taking clozapine; chronic pain was less common. Psychotropic polypharmacy did not differ between groups.

Conclusions. Consistent with international evidence of clozapine underutilisation, a large number of participants with chronic illness and high symptom burden were not taking clozapine. The lower probabilities of current substance use and chronic pain among clozapine users warrant further study.

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Key words: Clozapine, metabolic syndrome, schizophrenia, substance use, treatment refractory schizophrenia.

Introduction

Clozapine remains the preferred medication for the pharmacological management of treatment refractory schizophrenia (TRS) (Siskind *et al*. 2016), and is significantly more effective than all other antipsychotic drugs in reducing psychotic symptoms (Leucht *et al*. 2013). However, clozapine use among people with schizophrenia varies internationally from 2 to 3% in the USA (Sernyak & Rosenheck, 2008) to up to 60% in China (Tang *et al*. 2008). This variation reflects global differences in prescribing practices and adverse drug reactions (ADRs) monitoring protocols and focus.

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Clozapine is associated with significant ADRs, notably neutropenia, myocarditis and sedation (Nielsen *et al*. 2011). While it is also associated with increased risk of diabetes and metabolic syndrome (Mitchell *et al*. 2013), one study has reported substantially lower mortality associated with clozapine use compared with other antipsychotics (Tiihonen *et al*. 2009). Concerns about ADRs can lead to clinicians delaying initiation of clozapine (Gee *et al*. 2014). Reported delays of 4–15 years before clozapine commencement may lead to a negative impact on quality of life (Taylor *et al*. 2003; Howes *et al*. 2012).

Much of the clozapine research conducted to date has focused on evaluating its clinical efficacy or on describing national or regional prescribing or dispensing patterns (Nielsen *et al*. 2012; Forrester *et al*. 2015). Relatively few studies have documented the characteristics and experiences of people on clozapine in routine clinical settings. Understanding these factors may provide guidance regarding whether or not clozapine use is being targeted to the most appropriate population, how to better identify the needs of consumers taking clozapine and how to improve the quality and safety of clozapine prescribing.

Developed in the 1950s, access to clozapine was reduced after deaths from neutropenia in the 1970s (Kane *et al*. 1988). Since clozapine's re-introduction in Australia in 1993, there has been a steady increase in dispensing rates, with an estimated 8.3% of people with schizophrenia dispensed clozapine in 2013 (Forrester *et al*. 2015). This is still well below the estimated 20% of people with schizophrenia whose illness is treatment refractory (Agid *et al*. 2011), the target population for clozapine. Antipsychotic polypharmacy for TRS remains common (Waterreus *et al*. 2012), but its efficacy is equivocal at best, with evidence of increased ADRs (Gallego *et al*. 2012). There is a suggestion that clozapine use can reduce the practice of antipsychotic polypharmacy (Chong *et al*. 2000), however this data dates back to the start of the era of second-generation antipsychotic use, and warrants re-examination. Previous studies have also shown that clozapine can be associated with a reduction in alcohol and illicit substance usage (Drake *et al*. 2000).

Surprisingly, few studies have examined the demographic or mental health profiles of people taking clozapine, and even fewer have examined co-morbid substance abuse. Such information can assist in the development of policies to ensure that people with TRS have timely access to clozapine, and the exploration of clozapine's potential in comorbid substance abuse.

Patients appear to have a high level of satisfaction with clozapine, with people remaining on clozapine longer than other antipsychotics and being more adherent (Gilmer *et al*. 2004; McEvoy *et al*. 2006; Forrester *et al*. 2015). A study from Australia's first national survey of people living with psychotic disorders in 1997 (Castle *et al*. 2002) reported high rates of satisfaction and perceived efficacy among people on clozapine. At that time second-generation antipsychotic medications were relatively new to psychiatry. Given the rise in clozapine and second-generation antipsychotic use since the 1997–1998 survey, it would be of value to determine whether these patterns remain current.

In 2010, Australia's second national survey of people living with psychotic disorders, the survey of high impact psychosis (SHIP), was conducted. This provides an opportunity to update available knowledge regarding real world clozapine use patterns in Australia, and to examine the characteristics and personal experiences of care of people taking clozapine. Using data on the subsample of SHIP respondents with schizophrenia or schizoaffective disorder currently taking antipsychotic medication we aimed to answer the following research questions:

(1) What proportions of people with schizophrenia or schizoaffective disorder are using clozapine?
(2) Do the demographic, mental health and comorbidity profiles of people taking clozapine differ from those on other antipsychotic medications?
(3) Do the frequencies of ADRs among people taking clozapine differ from those taking other antipsychotic medications?
(4) Do patterns of psychotropic polypharmacy among people taking clozapine differ from those on other antipsychotic medications?
(5) What proportion of people taking clozapine report adherence with their clozapine regime and satisfaction with clozapine?

Method

Design and sample

The second Australian national survey of psychosis was conducted in 2010. The sample was drawn from seven catchment areas across Australia, covering a population of 1.5 million people aged between 18 and 64 years within a total area of 62 000 km^2. A two-phase sampling design was used. During Phase I, screening for psychosis took place in public mental health services and in non-government services supporting people with mental illness, in March 2010. A psychosis screener was used to identify people likely to meet criteria for formal diagnosis (Jablensky *et al*. 2000). Administrative records were scanned to identify people with a recorded diagnosis of psychosis and in contact with public mental health services in the 11 months prior to census but not in the census month. During Phase 2, 1825 screen-positive

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individuals were randomly selected for interview stratified by catchment site and age. Institutional human research ethics committee approvals were obtained at each of the seven study sites and all participants provided written, informed consent. A detailed description of the sample, methods and aims of the SHIP survey can be found elsewhere (Morgan *et al*. 2012, 2013).

The analyses reported here focus on the 1049 (57.5%) participants who met criteria for an International classification of diseases version 10 (ICD-10) diagnosis of schizophrenia ($n = 789$; 75.2%) or schizoaffective disorder ($n = 260$; 24.8%), and who reported taking any antipsychotic medication in the 4 weeks prior to the survey.

Measures

Medication use

Medication use was based on self-report with participants asked to bring their medications or medications list to the interview (Waterreus *et al*. 2012). Only medications taken for at least 4 weeks were recorded. Data on duration of use extended to the previous 12 months only. Adherence was based on self-report: 'In the last four weeks have you taken your prescribed medication as recommended on the bottle or box?' Participants were asked about ADRs and their perceptions of the helpfulness of each medication they were using. Data on psychotropic medication numbers and class was collected.

Diagnostic interview for psychosis (DIP)

The DIP (Diagnostic Module) (Castle *et al*. 2006), a semi-structured clinical research interview with an associated computer algorithm based on operational criteria checklist (OPCRIT), generates a diagnostic classification in accordance with ICD-10 and diagnostic and statistical manual (DSM-IV) criteria. Questions and probes derived and adapted from the WHO Schedules for Clinical Assessments in Neuropsychiatry assess present state (last 4–6 weeks), past year (excludes present state) and lifetime occurrence of symptoms including depression, mania, hallucinations, subjective thought disorder and delusions.

The survey interview schedule also assessed socio-demographic characteristics, social participation and functioning, physical health, quality of life, cognitive profile, service use, perceived need for services and other psychopathology not fully covered in the DIP (i.e., worry, panic, anxiety and obsessions).

Positive and affective symptoms

In the present study, we looked at binary responses (present/not present) regarding symptoms of depression, mania, hallucinations, delusions and subjective thought disorder.

Negative symptoms

We identified six symptoms/signs over the past 12 months based on the items identified by Carpenter (Kirkpatrick *et al*. 1989) as operationalised in the Schedules for Clinical Assessment in Neuropsychiatry (Wing *et al*. 1990). As we were not able to score attribution, binary responses were summed to produce a score ranging between 0 and 6, with a higher score reflecting increased symptom severity.

Course of disorder

Participants were asked if their symptoms had resolved between acute episodes, or whether they had constant symptoms. These responses were dichotomised into chronic illness (characterised by continuous illness) or non-chronic (characterised by full or partial recovery between episodes).

National adult reading test-revised (NART-R)

The NART-R (Blair & Spreen, 1989) is a word-reading test widely used as an estimate of premorbid IQ (Schretlen *et al*. 2005). It has high construct validity as a measure of general intelligence and high levels of inter-rater and test-retest reliability (Crawford *et al*. 2001). Based on summary NART-R scores ($M = 98.0$, S.D. = 11.3), premorbid IQ was categorised into the three following levels: Below Average (>1 S.D. below sample mean), Average (within 1 S.D. of sample mean), and Above Average (>1 S.D. above sample mean).

Digit-symbol coding

The Digit-Symbol Coding task (DSCT) from the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998), a test of speed of processing, was used to assess current cognitive ability. The lower the test score, the poorer a person's speed-based performance. Based on summary DSCT scores ($M = 38.3$, S.D. = 10.6), current cognitive ability was categorised into three levels: Below Average (>1 S.D. below sample mean), Average (within 1 S.D. of sample mean), and Above Average (>1 S.D. above sample mean).

Personal and social performance (PSP) scale

The PSP Scale is a 100-point rating scale subdivided into 10 categories measuring personal and social functioning over the last 12 months. The interviewer makes a rating based on the degree of disability in four

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domains of socially useful activities (e.g., work and study), personal and social relationships, self-care and disturbing and aggressive behaviours (Morosini *et al*. 2000). Higher scores denote better psychosocial functioning. The PSP has good internal consistency and construct validity (Nasrallah *et al*. 2008; Patrick *et al*. 2009).

Physical health

Participants were asked to self-report physical health co-morbidities, and interviewers measured participants' blood pressure, waist circumference and weight and height to calculate body mass index (BMI) as weight/height^2 (Galletly *et al*. 2012). Participants were categorised as underweight (BMI < 18.5), normal (BMI 18.5–24.99), overweight (BMI 25–29.99) or obese (BMI ≥ 30). Fasting blood was collected at accredited pathology centres for the testing of blood glucose, triglycerides and high-density lipoprotein (HDL).

Metabolic syndrome was classified using the International Diabetes Federation harmonized criteria (Alberti *et al*. 2009). These criteria for metabolic syndrome require three of the following five risk factors to make the diagnosis: at-risk waist circumference; at-risk diastolic and/or systolic blood pressure; at-risk levels of fasting blood glucose, triglycerides, or HDL. People receiving medications for hypertension, hyperlipidaemia or hyperglycaemia were considered to meet the relevant criterion.

Physical activity

Physical activity was measured using the interviewer administered International Physical Activity Questionnaire short form (IPAQ) (Craig *et al*. 2003) and physical activity in the previous 7 days was categorised into three levels (low, moderate or high) using scoring guidelines. Participants were also asked whether they felt they were doing enough physical activity.

Substance abuse

Participants were asked to self-report lifetime and previous 12-month use of alcohol, cannabis, amphetamine and other drugs (tranquillisers, heroin, cocaine, LSD/hallucinogens, ecstasy, inhalants/solvents). Use was dichotomised into any or no use. The Fagerström test for nicotine dependence was administered (Heatherton *et al*. 1991).

Data analyses

Analyses were conducted using SPSS (IBM, Windows Version-22, Armonk, NY, 2011). Means and standard deviations were calculated for continuous variables. Counts were calculated for categorical variables.

A series of logistic regression models were developed to examine factors associated with clozapine use. The binary outcome variable was any clozapine use (with or without other antipsychotic medications use) *v*. other antipsychotic use only in the previous 4 weeks. Factors potentially associated with clozapine use included demographic characteristics, mental health status, physical health and substance use comorbidities, ADRs and other experiences of care. Because some factors were likely to be correlated, we developed separate models for each. Analyses controlled for diagnosis and chronicity of illness, as these were shown in preliminary analyses to be predictive of outcome – people taking clozapine were significantly more likely to have a chronic course of illness (odds ratio (OR) 2.07, 95% confidence interval (CI) 1.35–2.78, $p < 0.001$) and to have a diagnosis of schizophrenia (OR 1.96, 95% CI 1.35–2.78, $p < 0.001$).

Results

(1) *What proportions of people with schizophrenia or schizoaffective disorder are using clozapine?*

Of the 1049 SHIP participants who met ICD-10 criteria for a current diagnosis of schizophrenia or schizoaffective disorder and reported taking any antipsychotic medication in the past 4 weeks, almost one-quarter ($n = 257$; 24.5%) reported taking clozapine with or without other antipsychotics, with 65.5% taking a second-generation antipsychotic without clozapine, and 18.9% taking a first-generation antipsychotic without clozapine. A first and second-generation antipsychotic were taken without clozapine by 8.9%, thus these numbers add to more than 100%. The proportion taking clozapine was higher for those diagnosed with schizophrenia ($n = 215$; 27.2%), than schizoaffective disorder ($n = 42$; 16.2%) (Table 1).

(2) *Do the demographic, mental health and comorbidity profiles of people taking clozapine differ from those on other antipsychotic medications?*

Table 1 shows demographic characteristics of participants by use of clozapine. After adjusting for illness chronicity and diagnosis, the odds of being single and never married were more than two times greater among those taking clozapine compared with those taking other antipsychotic medications. The odds of recent homelessness were more than two times lower among people taking clozapine.

With respect to mental health status, Table 2 shows the odds of having a family history of schizophrenia, were significantly higher among those taking clozapine, as were the odds of having current hallucinations

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Table 1. *Demographic characteristics of 1049SHIP participants with schizophrenia or schizo-affective disorder who reported using any antipsychotic medication in the past 4 weeks, by use of clozapine*

	Clozapine					
	No		Yes			
	n	%	*n*	%	Adjusted OR†	95% CI
Gender						
Male	516	65.2	189	73.5	1.312	0.951–1.809
Female	276	34.8	68	26.5	1.0	
Country of birth						
Australia	640	80.8	227	88.3	1.077	0.737–1.574
Other	152	19.2	30	11.7	1.0	
Marital status						
Single, never married	518	65.4	203	79.0	2.197***	1.397–3.455
Partnered	117	14.8	28	10.9	1.592	0.879–2.833
Separated, divorced, or widowed	157	19.8	26	10.1	1.0	
Post school qualification	352	44.4	107	41.6	0.977	0.706–1.262
Paid employment (last 12 months)	233	29.4	67	26.1	0.929	0.699–1.289
Any homelessness (last 12 months)	108	13.6	17	6.6	0.408***	0.238–0.701
Satisfaction with life (last 12 months)						
Mostly satisfied or better	390	49.7	154	60.4	0.980	0.652–1.474
Mixed	274	34.9	82	32.2	1.185	0.778–1.804
Mostly dissatisfied or worse	121	15.4	19	7.5	1.0	
Age	792	37.69 (11.23)‡	257	37.40 (9.51)‡	0.998	0.985–1.011
Age at Onset	792	23.98 (8.27)‡	257	22.26 (6.49)‡	0.950***	0.989–0.970

SHIP, survey of high impact psychosis; OR, odds ratio; CI, confidence interval.
Satisfaction with life = 9 missing cases.
†All variables are adjusted for chronicity and diagnosis.
‡Mean and (S.D.).
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

and a higher number of negative symptoms (adjusted analysis). Conversely, the odds of lifetime manic symptoms were significantly lower. There was no difference between the two groups in terms of current obsessive-compulsive symptoms or on current or lifetime suicidal ideation. Personal and social functioning, as rated by the PSP, was significantly worse for people on clozapine, although the absolute difference was small. Only one third of people with a chronic course of illness were on clozapine. Similarly low proportions of those with current hallucinations or delusions were on clozapine.

There was no statistically significant difference in the adjusted analysis between those taking or not taking clozapine in terms of NART Full Scale IQ or Digit-Symbol Coding.

Table 3 shows that people taking clozapine differed from those taking other antipsychotics on a number of indicators of physical health (adjusted analysis) with significantly higher odds of a lifetime self-reported diagnosis of diabetes and epilepsy, but lower odds of current chronic pain. They also had higher odds of metabolic syndrome, specifically meeting threshold criteria for elevated triglycerides, glucose, blood pressure and waist circumference. A higher proportion had obese-range BMI. There were no differences in their level of physical activity or self-rated exercise.

People taking clozapine had similar probabilities of lifetime use of alcohol, cannabis and 'other' substances, but lower probabilities of use of these drugs in the previous year *v.* those not on clozapine (adjusted analysis, Table 4). The probabilities of amphetamine use were lower for people on clozapine in both the previous year and lifetime. There was no difference in nicotine dependence as rated on the Fagerstrom test.

(3) *Do the frequencies of* ADRs *among people taking clozapine differ from those taking other antipsychotic medications?*

People taking clozapine had significantly higher odds of reported medication attributed experiences of daytime drowsiness, dry or watery mouth, difficulty swallowing, constipation, dizziness/vertigo or palpitations

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Table 2. *Mental health characteristics of 1049 SHIP participants with schizophrenia or schizo-affective disorder who reported using any antipsychotic medication in the past 4weeks, by use of clozapine*

	Clozapine					
	No		Yes			
	n	%	*n*	%	Adjusted OR†	95% CI
ICD-10 diagnosis (DIP)						
Schizoaffective	218	27.5	42	16.3	1.0	
Schizophrenia	574	72.5	215	83.7	1.475*	1.092–1.992
Course of disorder						
Non-chronic	533	67.3	128	49.8	1.0	
Chronic	259	32.7	129	50.2	1.475*	1.092–1.992
Family history of schizophrenia	223	29.4	93	36.2	1.415*	1.045–1.916
At least one symptom associated with obsessive compulsive disorder in the past 12 months	210	26.5	75	29.2	1.151	0.837–1.583
Suicidal ideation						
Present state	75	9.5	20	7.8	0.835	0.490–1.422
Lifetime	512	64.6	154	59.9	0.868	0.645–1.168
Any hallucinations						
Present state	353	44.6	148	57.6	1.443*	1.072–1.943
Lifetime	693	87.5	234	91.1	1.356	0.836–2.202
Any delusions						
Present state	381	48.1	143	55.6	1.162	0.865–1.559
Lifetime	758	95.7	251	97.7	1.865	0.766–4.539
Any subjective thought disorder						
Present state	211	26.6	86	33.5	1.315	0.961–1.800
Lifetime	449	56.7	152	59.1	1.165	0.870–1.560
Negative symptoms	792	2.88 (1.89)‡	257	3.24 (1.97)‡	1.038*	1.006–1.070
Any depressive symptoms						
Present state	188	23.7	49	19.1	0.795	0.553–1.142
Lifetime	590	74.5	175	68.1	0.886	0.643–1.221
Mania						
Present state	57	7.2	8	3.1	0.472	0.218–1.019
Lifetime	307	38.8	59	23.0	0.570***	0.404–0.804
PSPS	792	55.65 (14.35)‡	257	52.77 (14.36)‡	0.986**	0.977–0.996

SHIP, survey of high impact psychosis; OR, odds ratio; CI, confidence interval; ICD-10, International classification of diseases version 10; DIP, diagnostic interview for psychosis; IPAQ, International physical activity questionnaire; PSPS, personal and social performance scale.

†All variables are adjusted for chronicity and diagnosis; chronicity is adjusted for diagnosis only and diagnosis is adjusted for chronicity only.

‡Mean and (S.D.).

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

in the previous 4weeks, and significantly lower odds of trembling/shaking or increased dreaming (adjusted analysis, Table 5).

(4) *Do patterns of psychotropic polypharmacy among people taking clozapine differ from those on other antipsychotic medications?*

People taking clozapine and those who did not had similar rates of antipsychotic polypharmacy (adjusted analysis, Table 6). Of those in the clozapine group who were taking more than one antipsychotic medication ($n = 79$, 30.7%), the most commonly used second-generation antipsychotics were risperidone ($n = 14$ oral, $n = 9$ parenteral long-acting), and oral amisulpride ($n = 16$), quetiapine ($n = 14$), aripirazole ($n = 13$), olanzapine ($n = 7$) and ziprasidone ($n = 1$). Twelve people were on a first-generation antipsychotic ($n = 3$ oral, $n = 9$ parenteral long-acting).

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Table 3. *Physical health characteristics of 1049 SHIP participants with schizophrenia or schizo-affective disorder who reported using any antipsychotic medication in the past 4weeks, by use of clozapine*

	Clozapine					
	No		Yes			
	n	%	*n*	%	Adjusted OR†	CI
Diabetes	145	18.6	73	28.9	1.744***	1.249–2.435
Epilepsy	50	6.3	28	11.0	1.656*	1.006–2.725
Heart attack	18	2.3	5	2.0	0.795	0.284–2.229
Respiratory problems	134	17.0	56	22.0	1.312	0.916–1.881
Head injury	166	21.0	51	20.0	0.898	0.627–1.288
Chronic pain	230	29.1	57	22.4	0.685*	0.488–0.963
Sleep apnoea	319	42.9	103	43.5	1.080	0.800–1.460
Metabolic syndrome	318	55.5	153	73.6	2.300***	1.610–3.284
HDL§	330	57.9	136	67.0	1.397	0.985–1.981
Triglycerides§	304	53.1	137	66.5	1.575**	1.115–2.226
Glucose§	175	30.9	90	46.2	1.9323***	1.358–2.723
Blood pressure§	368	48.0	143	56.7	1.469**	1.096–1.967
Waist circumference§	619	81.0	225	89.3	2.004**	1.285–3.126
BMI						
Underweight/normal	187	24.3	41	16.3	1.0	
Overweight	228	29.6	65	25.9	1.354	0.870–2.108
Obese	356	46.2	145	57.8	1.899***	1.279–2.725
IPAQ						
Low	379	48.5	129	51.0	1.089	0.682–1.739
Moderate	302	38.6	95	37.5	1.052	0.650–1.703
High	101	12.9	29	11.5	1.0	
Self assessment of doing enough physical activity	275	35.0	96	37.8	1.066	0.790–1.437

SHIP, survey of high impact psychosis; OR, odds ratio; CI, confidence interval; IPAQ, International physical activity questionnaire, divided into low, moderate and high amounts of physical activity.
Missing cases: diabetes = 16; epilepsy, heart attack, respiratory problems, head injury, chronic pain = 4; sleep apnoea = 69; metabolic syndrome = 268; HDL = 6; triglycerides = 1; glucose = 1; blood pressure = 30; waist circumference = 3; BMI = 27; IPAQ = 14.
†All variables are adjusted for chronicity and diagnosis.
§Elevated based on International Diabetes Federation criteria.
* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

The rates of antidepressant and anxiolytic/hypnotic use were similar between those using and not using clozapine (adjusted analysis). People on clozapine had significantly higher odds of taking a mood stabiliser (Table 6). The most commonly used mood stabilisers among those on clozapine ($n = 65$, 25.3%) were sodium valproate ($n = 43$), lithium ($n = 18$) lamotrigine ($n = 3$) and carbamazepine ($n = 1$). Three people on clozapine were on antiseizure medication without mood stabilising properties.

(5) *What proportion of people taking clozapine report adherence with their clozapine regime and satisfaction with clozapine?*

The proportion of people on clozapine reporting that it was 'somewhat' or 'very' helpful was 88.3%, which is higher than the corresponding results for Zuclopenthixol decanoate (71.7%, parenteral long-acting first-generation antipsychotic) and Olanzapine (76.6%), but not Quetiapine (87.3%) (both oral second-generation antipsychotics). Only 5.2% reported clozapine to be 'not helpful' (Olanzapine 8.9%, Quetiapine 3.5% and Zuclopenthixol decanoate 13.6%). Self-reported adherence was high at 91.8% (Olanzapine 85.5%, Quetiapine 82.8% and Zuclopenthixol decanoate 92.6%).

Discussion

Clozapine was used by almost a quarter of all people with schizophrenia or schizoaffective disorder on antipsychotics in recent (12-month) contact with mental

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Table 4. *Substance Abuse (None v. Any) among 1049 SHIP participants with schizophrenia or schizoaffective disorder who reported using any antipsychotic medication in the past 4 weeks, by use of clozapine*

	Clozapine					
	No		Yes			
	n	%	*n*	%	Adjusted odds ratio†	95% CI
Alcohol						
Lifetime	727	91.9	240	93.4	1.184	0.674–2.080
Past year	598	82.4	168	70.3	0.516***	0.366–0.727
Cannabis						
Lifetime	544	69.2	180	70.6	1.046	0.764–1.433
Past year	298	37.8	50	19.7	0.398***	0.282–0.563
'Other' substances						
Lifetime	375	47.8	92	36.1	1.014	0.757–1.360
Past year	132	16.9	18	7.1	0.452*	0.245–0.835
Amphetamine						
Lifetime	311	39.7	103	40.2	0.653**	0.486–0.878
Past year	80	10.2	13	5.1	0.368***	0.219–0.620
Nicotine dependence§						
Very low	268	33.8	102	39.7	0.811	0.4901.341
Low	80	10.1	27	10.5	0.909	0.542–1.522
Moderate	76	9.6	25	9.7	0.715	0.488–1.047
High	197	24.9	56	21.8	0.692	0.462–1.036
Very high	171	21.6	47	18.3	1.0	

SHIP, survey of high impact psychosis; OR, odds ratio; CI, confidence interval.
Missing cases: alcohol lifetime = 1, past year = 84; cannabis lifetime = 9, past year = 7; amphetamines lifetime = 9, past year = 11; other substances lifetime = 10, past year = 9.
†All variables are adjusted for chronicity and diagnosis.
§As rated on the Fagerstrom test for nicotine dependence.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

health services in Australia. After adjusting for diagnosis and illness chronicity, participants taking clozapine had significantly lower odds of current alcohol, cannabis and other drug use despite similar lifetime odds. Metabolic syndrome, diabetes and epilepsy were more common among people taking clozapine; chronic pain was less common. The probability of psychotropic polypharmacy did not differ between the groups.

Although the survey population in this study differs slightly from the first Australian national psychosis survey from 1997 to 1998, some comparisons can be made. In the first survey, 12.1% of people with schizophrenia on any medication were on clozapine (Castle *et al*. 2002). This had more than doubled to 27.2% of people with schizophrenia on clozapine in this 2010 survey. Perceptions of the helpfulness of clozapine remained unchanged between the two surveys, with approximately 5.3% reporting clozapine as being 'not helpful' in the first survey compared with 5.2% in this survey.

Strengths and limitations of the study

This study draws from a large epidemiological sample of people with schizophrenia and schizoaffective disorder. It includes diagnostic survey data, biometric measurements and fasting blood results, as well as information on participants' satisfaction with their medications. However a number of limitations should be taken into account when interpreting our findings.

This survey includes only people in recent contact with mental health services and non-government agencies supporting people with mental illness, and so is missing those people seeing only a private psychiatrist or a general practitioner, which will affect the estimated population with schizophrenia. Given that people on clozapine maintenance were, at the time of the SHIP survey required to attend a hospital affiliated mental health clinic and/or GP appointments every 4weeks, the potential for overestimation is constrained. The 22.4% reported here is considerably higher than the 8.3%

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Table 5. *Adverse drug reactions in past 4 weeks of 1049 SHIP participants with schizophrenia or schizo-affective disorder who reported using any antipsychotic medication in the past 4 weeks, by use of clozapine*

	Clozapine					
	No		Yes			
	n	%	*n*	%	Adjusted OR†	CI
Trembling/shaking	222	28.5	47	18.7	0.581**	0.405–0.832
Daytime drowsiness	393	50.4	143	56.7	1.379*	1.030–1.847
Dry or watery mouth	300	38.5	160	63.5	2.721***	2.016–3.674
Difficulty swallowing	91	11.7	46	18.3	1.754**	1.180–2.607
Skin rashes	61	7.9	18	7.2	0.930	0.533–1.623
Increased dreaming	177	22.9	39	15.5	0.675*	0.458–0.994
Swollen tender chest	35	4.6	6	2.4	0.519	0.213–1.266
Nauseous/feeling sick	122	15.7	51	20.2	1.396	0.964–2.021
Constipation	119	15.3	66	26.4	1.996***	1.404–2.836
Increased sweating	123	15.8	47	18.7	1.269	0.869–1.853
Dizziness/vertigo	156	20.0	71	28.2	1.571**	1.125–2.193
Palpitations	95	12.2	44	17.6	1.543*	1.034–2.303
Change in interest in sex	127	16.4	45	18.1	1.181	0.806–1.730
Sexual dysfunction	86	11.3	29	11.8	1.055	0.668–1.667
Period pain/change in frequency of periods	50	17.5	7	8.8	0.482	2.07–1.125

SHIP, survey of high impact psychosis; OR, odds ratio; CI, confidence interval.
Missing cases: trembling/shaking, daytime drowsiness, dry or watery mouth, increased sweating, dizziness/vertigo = 18; difficulty swallowing, nauseous/feeling sick = 19; skin rashes = 23; increased dreaming = 25; swollen, tender chest = 39; constipation, palpitations = 21; change in interest in sex = 26; sexual dysfunction = 40; period pain/change in frequency of periods = 684.
†All variables are adjusted for chronicity and diagnosis.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

estimated in a dispensing sample from Queensland during the same timeframe (Forrester *et al*. 2015).

As noted by Morgan and colleagues (2012), some people did not participate in the survey due to participant refusal or being too unwell to interview. It is possible that these people would have been more likely to have TRS, with or without treatment on clozapine. However, comparison of available participant screening data, including lifetime symptom profiles, for those included and those selected for interview but not participating for any reason suggested that there was no overt selection bias.

Medication usage was based on self-report, as were ADRs. There is risk that self-report may be inaccurate in some cases. However, as per previous studies of self-report medication use and ADRs, there is no reason to suspect systematic bias with self-report (Castle *et al*. 2002). For participants on more than one psychotropic agent there can be difficulties in attributing particular ADRs to a particular medication. It is possible that the reported ADRs of people on clozapine and another psychotropic may not have been attributable to clozapine, and as such the comparison of ADRs between the clozapine and non-clozapine groups may underestimate the difference between the groups.

Self-reported adherence to clozapine was high despite high rates of some ADRs (e.g., obesity, drowsiness, dry/watery mouth). This may suggest that these symptoms are considered tolerable by people on clozapine when compared with the benefits they perceive to be associated with this medication. However, we do not know whether survey participants not on clozapine had previously ceased clozapine because of tolerability issues. It is also likely that adherence will have been overestimated because of the 4-week reporting window. The SHIP survey did not gather information about whether people who were not taking clozapine had previous unsuccessful clozapine trials, or trials of other antipsychotic medications, nor did it ascertain how long people had been on clozapine beyond 12 months. This limited our ability to determine what proportion of the SHIP sample with schizophrenia or schizoaffective disorder in our sample would have met criteria for TRS. It also limited our ability to examine factors associated with discontinuation. A separate review of dispensing trends in Queensland, Australia

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Table 6. *Rates of Polypharmacy among 1049 SHIP participants with schizophrenia or schizo-affective disorder who reported using any antipsychotic medication in the past 4 weeks, by use of clozapine*

	Clozapine					
	No		Yes			
	n	%	*n*	%	Adjusted OR†	95% CI
Antipsychotics						
One	557	70.3	178	69.3	1.0	
More than one	235	29.6	79	30.7	0.934	0.713–1.332
Antidepressants						
None	540	68.2	168	65.4	1.0	
Any	252	31.8	89	34.6	1.166	0.860–1.580
Mood stabilisers						
None	631	79.7	192	74.7	1.0	
Any	161	20.3	65	25.3	1.433*	1.010–2.033
Anxiolytics/hypnotics						
None	655	82.7	217	84.4	1.0	
Any	137	17.2	40	15.6	0.880	0.595–1.303

SHIP, survey of high impact psychosis; OR, odds ratio; CI, confidence interval.
†All variables are adjusted for chronicity and diagnosis.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

from 2004 to 2013 noted that a quarter of people initiated on clozapine had ceased by 18 weeks (Forrester *et al*. 2015). We were unable to assess the duration between onset of illness and commencement of clozapine.

As this study is a cross-sectional survey, we can only comment on correlations, not causation.

Key findings and implications

People with schizophrenia or schizoaffective disorder on clozapine were more likely to have a chronic course of illness, and after adjusting for chronicity and diagnosis had higher rates of current hallucinations, more negative symptoms, poorer personal and social functioning and were more likely to be single and never married. This would be anticipated given clozapine's indication for TRS, and the associated damaging psychosocial impact.

Although one-quarter of the sample participants were taking clozapine, there were still a large number of people with ongoing chronic illness and high symptom burden who were not on clozapine. Pharmacoepidemiological studies suggest that only a quarter of people with TRS in Australia are currently on clozapine (Forrester *et al*. 2015). Although we could not derive a sample of people with TRS from SHIP, only one third of people with a chronic course of illness were on clozapine. This data provides further evidence that clozapine is underused in Australia and/or its use has not been tolerated by a substantial proportion of people with TRS. Almost half the people on clozapine did not report a chronic course of illness, but we are unable to ascertain whether any alteration of illness course was related to clozapine use.

Although there are suggestions in the literature that clozapine is associated with higher rates of obsessive-compulsive symptoms (Nielsen *et al*. 2011), and lower rates of suicidal ideation (Meltzer *et al*. 2003), we did not find any differences between the groups on these variables.

Of note, people on clozapine were less likely to be homeless. It is unclear as to whether this relates to improved stability associated with clozapine and associated intensive monitoring, or whether homelessness renders use of clozapine too challenging.

Despite higher rates of epilepsy, people on clozapine had lower rates of chronic pain. Clozapine is known to lower the seizure threshold (Pisani *et al*. 2002), but our finding of lower rates of chronic pain among people on clozapine warrants further investigation. A recent Cochrane review suggested that antipsychotics may have a role in reducing acute and chronic pain (Seidel *et al*. 2013), but there has been limited investigation of clozapine in particular.

Clozapine was associated with significant cardiometabolic co-morbidity. The rates of diabetes and

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metabolic syndrome associated with clozapine in this study are consistent with previous reports (Henderson *et al*. 2005; Mitchell *et al*. 2013). These higher rates of metabolic syndrome and obesity do not necessary mean higher rates of mortality, and this was noted by a Finnish population based cohort study of mortality in people with schizophrenia, which found that clozapine was associated with lower rates of all-cause mortality (Tiihonen *et al*. 2009). The lower rate of extrapyramidal side effects and higher rates of cholinergic and sedating ADRs found with clozapine are in keeping with the literature (Nielsen *et al*. 2011).

The rate of satisfaction with clozapine was higher than those reported for other representative antipsychotics, while the reported adherence rate was similar to that of a parenterally-administered long-acting antipsychotic. Rates of antipsychotic polypharmacy were similar between those using and not using clozapine. This may in part be due to augmentation strategies for people with clozapine refractory schizophrenia (Taylor *et al*. 2012), albeit antipsychotic polypharmacy does carry risks and psychiatrist's polypharmacy prescribing practices need critical self-appraisal. People on clozapine were more likely to be on mood-stabilisers. This is likely to be related to the mood-stabiliser's dual role as anti-seizure medication, in response to the impact of clozapine on lowering the seizure threshold, although there is some suggestion that mood-stabilisers may augment the effects of clozapine (Varma *et al*. 2011). It was of concern that one person was on both clozapine and carbamazepine given the contraindication to combining these medications (Varma *et al*. 2011).

One of our most interesting findings is the association between clozapine use and lower current probabilities of alcohol, cannabis and other drug use, despite similar probabilities of lifetime use of these substances. It is possible that this is a selection bias, in that people are less likely to be trialled or remain on clozapine if they have current substance abuse problems. However, previous studies have shown a reduction in alcohol and illicit substance usage among people on clozapine (Drake *et al*. 2000). It has been postulated that clozapine's neurobiological effects on reducing substance abuse may be mediated by its blockade of alpha-2 noradrenergic and dopamine-D2 receptors and its increase in norepinephrine levels, leading to a normalizing effect on the signal-detection capability of the dysfunctional mesocorticolimbic brain reward circuit (Green *et al*. 1999).

Conclusions

Clozapine remains the preferred medication for TRS. This study suggests that clozapine is being used for those with more severe illness and that rates of clozapine use are increasing. However there are many other people with severe illness who are not on clozapine. Given the higher rates of obesity, diabetes and metabolic syndrome among people on clozapine, the choice of a trial on clozapine must be weighed against these ADRs. Our finding of lower probability of current substance use and chronic pain among clozapine users warrants further study.

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Conflict of Interest

None

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