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Pharmacists in clozapine clinics improving physical health monitoring

Greg Spann, BPharm, GCert Psychiatric Therapeutics[1]
Lewis Austin, BBiomedSc, MPharm[2]
Edward King, BPharm[3]

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Abstract

Introduction: People living with schizophrenia have a higher rate of comorbid physical health diseases and compared with the general population die earlier due to these diseases. A pharmacist working in an outpatient mental health clinic setting could assist with the management of physical health disease for this population. The aim of this study was to investigate whether having a pharmacist in a community clozapine clinic would improve adherence to physical health monitoring and whether this would have a positive effect on these physical health outcomes.

Methods: This retrospective observational study compared patient data from 2 clozapine clinics; one where a pharmacist engaged in medication reviews and management of medication side effects, and another that did not have a pharmacist. The rates of physical health monitoring and the changes from baseline of physical health outcomes (weight, BMI, BP, HbA1c, and lipids) were compared after the first pharmacist intervention (medication review).

Results: The pharmacist clinic had statistically higher rates of metabolic and ECG monitoring (glucose 48% vs 11%, $P < .001$; lipids 61% vs 7.1%, $P < .001$; ECG 15% vs 0%, $P = .001$). Positive trends in weight were identified in the pharmacist-group, although this failed to reach statistical significance.

Discussion: This study shows that pharmacists providing regular medication reviews improves physical health monitoring for patients receiving clozapine.

Keywords: pharmacists, clozapine, schizophrenia, metabolic monitoring, physical health

[1] (Corresponding author) Mental Health & Ambulatory Care Pharmacist Team Leader, Logan Hospital, Metro South Hospital and Health Service, QLD, Australia, greg.spann@health.qld.gov.au, ORCID: https://orcid.org/0000-0003-4627-3875; [2] Intern Pharmacist, Princess Alexandra Hospital, Metro South Hospital and Health Service, QLD, Australia, ORCID: https://orcid.org/0000-0003-4938-9486; [3] Pharmacist, Caboolture Hospital, Metro North Hospital and Health Service, QLD, Australia, ORCID: https://orcid.org/0000-0001-5346-3832

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Introduction

Schizophrenia is characterized by continuous and/or relapsing episodes of psychosis, which involve auditory hallucinations, delusions, and disorganized thinking along with negative symptoms.[1,2] In addition to these symptoms, patients also experience high rates of premature death.[3] While suicide and high-risk behaviors are common and contribute to mortality, patients with schizophrenia also experience a 1.32-fold increase of cardiometabolic disease; the leading cause of death among this popula-

tion.[3] Lifestyle factors such as poor physical activity, dietary habits, tobacco smoking, and adverse effects from pharmacologic treatment, such as antipsychotics, lead to earlier progression to cardiometabolic disease.[3,4]

The risk of cardiometabolic disease has led to the development of monitoring guidelines, which include the Royal Australian and New Zealand College of Psychiatrists schizophrenia guidelines[5] along with other local guidelines. This guideline includes monitoring physical observations (eg, BP and weight), pathology testing (eg, lipids and glucose), and cardiac monitoring (eg, ECG monitoring) for patients taking antipsychotics. In clinical practice, however, routine physical health monitoring is not performed as frequently as recommended.[6-8]

The role of pharmacists working in mental health clinics is well documented.[9,10] However, the evidence for their role in supporting physical health in mental health clinics is not well established.[11]

One small US study[12] investigated the role of a pharmacist in a clozapine clinic, including the impact on patient physical health outcomes. Compared with patients seen in the psychiatrist-only arm, there was a trend toward a reduction in antipsychotic and psychotropic polypharmacy, HbA1c, clozapine dose, and total cholesterol, and an increase in the total number of interventions made. However, the small sample size (n = 22 patients) and short time frame (8 months) prevented any firm conclusions being derived, with further research required.

The aim of this retrospective, observational study was to determine whether a pharmacist practicing in a clozapine clinic improves the rates of physical health monitoring and associated physical health outcome measures.

Methods

In 2017, a pharmacist commenced doing medication reviews every 6 months for clozapine patients at one mental health clinic in South East Queensland, Australia. The medication reviews included reviewing physical health monitoring, making recommendations to the provider based on these results (eg, alerting when monitoring had not occurred), and providing lifestyle advice. The pharmacist's scope did not include prescribing or ordering pathology. We compared results to a similar clozapine clinic that did not have a pharmacist but was staffed by the same continuing care community team. Both sites were in the same suburban city council area. Most patients did not switch between clinics during the study period, and the same treating team operated both clinics (ie, the same nurse clozapine coordinator and providers).

TABLE 1: Recommended clozapine monitoring for maintenance therapy[a]

Test/Observation	Frequency
Weight/BMI	Monthly
BP	Monthly
FG or HbA1c[b]	Every 6 mo
Fasting lipids	Every 6 mo
ECG	Every 6 mo
CRP	Every 6 mo
Troponin	Every 6 mo
LFT	Every 6 mo

FG = fasting glucose; LFT = liver function test.

[a]Based on National[5] and State[13] guidelines at the time of the study.

[b]HbA1c if diagnosed with diabetes mellitus.

Data on physical health were sourced from electronic patient progress notes, medical reviews, metabolic monitoring entries, private pathology, and pharmacist review (pharmacist-group only). The physical health outcome measures included weight and BMI, BP, blood glucose (HbA1c or fasting blood glucose [FG]), lipids (total cholesterol, HDL, LDL, and triglycerides), ECG, and other cardiac pathology (troponin and CRP). Identification of underlying diabetes was obtained from the electronic patient progress notes. The study design had IRB approval from Metro South Hospital and Health Service before data were collected.

To measure the rates of physical health monitoring, an audit tool was developed by the researchers to assess appropriate clozapine monitoring using state and national guidelines (see Table 1).[5,13] Physical observations (weight and BP) were to be taken at an appointment every 4 weeks when the patient was seeing the provider as per clozapine protocol. Pathology (glucose, lipids, troponin, and CRP) and ECG monitoring were expected to occur twice a year. The collected data were applied against this audit tool to measure adherence rates to physical health monitoring between the 2 sites. Adherence to monitoring occurred if the frequency of test or observation occurred within the study period. For example, if only 1 lipid result was documented in the study period (ie, 2017), the lipid monitoring for this patient was deemed not adherent. If 2 lipid results were documented in the study period, the monitoring was adherent.

Data were also collected to identify if there was improvement in the physical health outcomes being monitored. For the pharmacist-group, baseline data were collected from the closest data point possible before the patient's first medication review with the pharmacist (early 2017); postintervention data were collected from the closest data point possible 6 months after the first

TABLE 2: Baseline patient characteristics for each clinic[a]

Demographic	Non-Pharmacist Clinic (N = 28)	Pharmacist Clinic (N = 33)	*P* Value
Age, y	45.7 ± 9.8	42.2 ± 10.2	.175[b]
Weight, kg	95.5 ± 19.3	98.3 ± 29	.453[b]
BMI	31.5 ± 6.1	32.3 ± 8.8	.699[b]
SBP, mm Hg	127 ± 13	126 ± 13	.785[b]
DBP, mm Hg	84 ± 11	81 ± 7	.229[b]
TC, mg/dL	197.2 ± 46.4	208.8 ± 42.5	.46[b]
LDL, mg/dL	108.3 ± 38.7	119.9 ± 34.8	.361[b]
HDL, mg/dL	46.4 ± 15.5	54.1 ± 27.1	.407[b]
TG, mg/dL	203.7 ± 177.2	212.6 ± 115.2	.924[b]
Male, n (%)	19 (67.9)	23 (69.7)	.877[c]
Type 2 diabetes mellitus, n (%)	2 (7.1)	11 (33.3)	.013[c]

DBP = diastolic BP; SBP = systolic BP; TC = total cholesterol; TG = triglycerides.

[a]Values presented as median ± SD unless otherwise noted.

[b]Independent sample *t* test.

[c]Pearson χ^2 test.

medication review. For the non-pharmacist clinic, in the absence of intervention dates, 2 separate data points were collected from 2017, ideally 1 in the first half of the year and 1 in the second half of the year. If data were not available in these determined data-collection windows (thus indicating poor adherence to monitoring), they were expanded for up to a maximum of 1 year before or after the study period (ie, 2016 to 2018). In 2019, a pharmacist was added to the multi-disciplinary team of the non-pharmacist clinic, so data collection was not pursued beyond 2018.

The results of cardiac monitoring (ECG, troponin, and CRP) were not analyzed to determine if there was an improvement in this physical health outcome. Clozapine-induced myocarditis is a well-characterized side effect usually occurring in the first month of treatment.[14] Furthermore, if such an event were observed in clinic (eg, troponin leak), this would require urgent referral to hospital.

Adult patients (>18 years old) on maintenance clozapine therapy were included in the study. Patients were excluded if they changed clinics (owing to relocation) during the study period. Patients were also excluded if they were on initiation therapy (first 18 weeks of starting clozapine) or reinitiating clozapine owing to different monitoring requirements and their monitoring also commencing in hospital.

To test for significant differences in means between baseline data (excluding gender and diabetes status), an independent sample *t* test was used. To test for significant differences between remaining baseline data (gender and diabetes status) across clinics, a Pearson χ^2 test was used (no cells had an expected count <5).

To compare monitoring adherence rates between the 2 clinics, the Mann-Whitney *U* test was used to determine differences in the weight and BP (physical observations). The pathology and cardiac monitoring between the 2 clinics were examined using Pearson χ^2 test or Fisher exact test.

To test for significant differences in physical health outcomes between the 2 clinics, the differences between pre- and postintervention data were calculated, and then that data were tested using an independent sample *t* test. Where data were tested using the *t* test, a Levene test for equality of variance was also used to confirm whether the data's variance was homogenous. HbA1c (as opposed to FG) was the preferred physical health outcome to compare glucose control between the 2 clinics. Having a capped population (ie, the clinic patients), the study was not powered to determine sample required for significance.

Results

A total of 61 (out of 85) patients were included in the study. Seven were excluded because they were initiated on clozapine (not maintenance), and 5 were excluded as they changed clinics during the year. The other 12 patients were excluded as there was insufficient data to confirm that they reached the inclusion criteria.

Baseline demographics (Table 2) were similar between the 2 groups, where the only significant difference between groups was their diabetes status ($P = .013$).

TABLE 3: Adherence to physical health monitoring (BP and weight) and adherence to pathology and cardiac monitoring, for each clinic

Measure for Adherence	N	Non-Pharmacist Clinic (N = 28)	Pharmacist Clinic (N = 33)	*P* Value
BP, stat median (CI)	61	1.00 (0.89, 1.00)	1.00 (0.89, 1.00)	.529[a]
Weight, stat median (CI)	61	1.00 (0.89, 1.00)	1.00 (0.90, 1.00)	.871[a]
FG or HbA1c, n (%)	61	3 (11)	16 (48)	<.001[b]
Lipid, n (%)	61	2 (7.1)	20 (61)	<.001[b]
LFT, n (%)	60	2 (7.1)	8 (25)	.209[b]
ECG, n (%)	61	0 (0)	5 (15)	.001[b]
Troponin, n (%)	60	1 (3.6)	2 (6.2)	>.99[b]
CRP, n (%)	61	0 (0)	1 (3.0)	.618[b]

FG = fasting glucose; LFT = liver function test.

[a]Mann-Whitney *U* test.

[b]Pearson χ^2 test or Fisher exact test.

The rate of appropriate physical health monitoring was measured against the developed audit tool (Table 3). No significant differences were detected in the physical observation. A significant difference was observed between the clinics in the level of monitoring adherence for blood glucose (FG or HbA1c; $P < .001$), fasting lipids ($P < .001$), and ECGs ($P = .001$), where a higher proportion of patients had complied with appropriate monitoring in the pharmacist clinic.

An independent sample *t* test was also used to compare the differences between baseline and postintervention data across the pharmacist and non-pharmacist clinic (Table 4). Of all the patient health outcomes (weight, BMI, BP, HbA1c, total cholesterol, LDL, HDL, and triglycerides), the only statistically significant difference between groups was for mean diastolic BP ($t = 2.776$, $df = 59$, $P = .007$).

Regarding metabolic pathology (HbA1c, lipids), there was poor adherence with the recommended routine monitoring (Table 3), making it difficult to obtain data for comparison. There was only 1 patient from the non-pharmacist cohort that had both baseline and post-intervention data available for HbA1c. Many other patients only had either baseline or postintervention data available and were thus excluded from comparison.

Discussion

Baseline data were similar across both groups, which is expected from a cohort of patients taking clozapine for treatment-resistant schizophrenia. A baseline difference was observed with diabetes rates; only 2 patients in the control group had a diagnosis of diabetes (compared with 11 in the pharmacist-group). As this was a retrospective study, lack of documentation may be the cause of this underrepresentation. Lack of formal diagnosis of diabetes may also be a factor, as evidence suggests that 22% of diabetes in Australia has not yet been formally diagnosed.[15] This problem is compounded in the mental health clinic as the diagnosis of diabetes would occur elsewhere, so the team is reliant on correspondence from the general practitioner to document this condition. In Australia, public funding of HbA1c is restricted based on indication. Therefore, patients without a diagnosis of diabetes were more likely to receive a fasting glucose instead. Hence, this difference in documented diabetes may have contributed to the lack of a significant difference between groups in HbA1c.

Physical observations were performed very well across both clinics, which was to be expected as it was the same nursing team making these observations. The significant difference, however, was observed in pathology testing. With medication reviews every 6 months in the intervention group, the pharmacist was identifying when monitoring was not occurring and communicating this to the provider.

Monitoring of troponin, CRP, and liver function test was non-statistically different. This may be a result of the changes to the national guidelines[5] that had taken place at the time of the study, removing the requirement for annual echocardiogram monitoring for clozapine clients and replacing this with troponin and CRP monitoring every 6 months. This change of practice had clearly not been adopted in either clinic at the time of this study.

Improved physical health monitoring did not translate to significant difference when looking at the actual physical health outcomes. Physical health monitoring has become an important task in psychotropic prescribing over the last decade. However, in our review of the literature, we have not found evidence that best practice physical health monitoring, on its own, leads to improvement in physical health parameters. This study, acknowledging the sample

TABLE 4: Physical and pathology (metabolic) observations change from baseline

	Non-Pharmacist Clinic (N = 28)[a]			Pharmacist Clinic (N = 33)[a]			
Measure	Baseline	Postintervention	Change	Baseline	Postintervention	Change	*P* Value[b]
Weight, kg	93.5 ± 18.1	95.5 ± 19.3	2 ± 7.9	98.3 ± 29	97.2 ± 22.1	−1 ± 2.4	.311
BMI	31.5 ± 6.1	32.2 ± 6.5	0.7 ± 2.6	32.3 ± 8.8	32 ± 6.5	−0.3 ± 4.5	.303
SBP, mm Hg	127 ± 13	125 ± 15	−0.7 ± 16	126 ± 13	127 ± 7	1.3 ± 12	.563
DBP, mm Hg	84 ± 11	79 ± 19	−5 ± 8	81 ± 7	82 ± 7	1 ± 8	.007
HbA1c, %[c]	5.5 (n = 1)	5.7 (n = 1)	0.2 (n = 1)	6.4 ± 1.2 (n = 9)	6.8 ± 1.8 (n = 9)	0.4 ± 1 (n = 9)	...
TC, mg/dL	201.14 ± 6.4 (n = 24)	193.4 ± 65.7 (n = 24)	−7.7 ± 34.8 (n = 24)	207.3 ± 42.5 (n = 30)	191 ± 42.5 (n = 30)	−16.2 ± 38.7 (n = 30)	.357
HDL, mg/dL	50.3 ± 15.5 (n = 21)	46.4 ± 11.6 (n = 21)	−3.8 ± 11.6 (n = 21)	55.7 ± 27.1 (n = 18)	49.1 ± 19.3 (n = 18)	−7 ± 19.3	.58
LDL, mg/dL	113.3 ± 38.7 (n = 20)	107.5 ± 42.5 (n = 20)	−5.8 ± 23.2 (n = 20)	121.8 ± 34.8 (n = 18)	112.9 ± 46.4 (n = 18)	−8.9 ± 30.9 (n = 18)	.742
TG, mg/dL	212.6 ± 177.2 (n = 23)	203.7 ± 132.9 (n = 23)	−8.9 ± 177.2 (n = 23)	212.6 ± 115.2 (n = 30)	203.7 ± 106.3 (n = 30)	−8.9 ± 70.9 (n = 30)	.895

DBP = diastolic BP; SBP = systolic BP; TC = total cholesterol; TG = triglycerides.

[a]Values presented as mean ± SD.

[b]Independent sample *t* test.

[c]Unable to perform test or calculate confidence interval owing to n = 1 in non-pharmacist clinic.

size and limited time frame to determine significant physical health outcomes, also fails to prove positive correlation between physical health monitoring and physical health improvement. To better support clinical practice in this area, further research with a larger sample size and longer follow up is required.

The only statistically significant difference between groups was diastolic BP, where the pharmacist-group maintained diastolic BP of approximately 82 mm Hg, and the non-pharmacist clinic lost 5 mm Hg on average. Table 3 shows that the non-pharmacist clinic had a much wider SD than the pharmacist clinic for postintervention diastolic BP. A closer review of the data showed that, post intervention, 2 of the patients in the non-pharmacist clinic had a drop in diastolic BP by greater than 20 mm Hg. These 2 patients both had high systolic BP, indicating hypertension. Potentially these patients had their hypertension managed using anti-hypertensives during this study resulting in a lower diastolic BP average in this cohort. However, this study was not designed to look at the interventions made to address physical health.

While not statistically significant, the pharmacist-group lost weight on average, while the non-pharmacist-group gained weight. At the time, evidence was emerging for the use of metformin to combat weight gain caused by antipsychotics[16-18]; and in conjunction with dietary and lifestyle advice, having a pharmacist in the clinic may have encouraged earlier adoption of this prescribing trend. Again, however, this study did not look at interventions, and there is no data to support this hypothesis. Total cholesterol and LDL were lower in the pharmacist-group, but this again was not statistically significant. These results are similar to what was observed in the aforementioned US study.[12]

As discussed, the role of pharmacists working in other specialist clinics has been well documented.[9,10] Taking a cohort of hypertension patients, for example, having a pharmacist in clinic improves BP control.[19] However, it is important to note that the physical health concerns of patients using clozapine are diverse. For example, some, but not all, clozapine patients will have elevated lipids. Only a proportion of the cohort would require interventions to manage their lipids, but any improvement seen would be averaged alongside the cohort that did not need any intervention. If we look at the baseline mean BP, the groups both had normal BP, but individuals in these groups had hypertension. There were insufficient numbers to separate the cohort based on physical illnesses (ie, diabetes); ideally future studies in this area should be powered to have sufficient patients in the different physical illness subgroups.

Compared to the US study,[12] the types of interventions made by the pharmacist were not assessed. Although pharmacist interventions were documented, there was no comparable information in the control group. Furthermore, documentation of non-psychotropic medications was poor in the control group, making it difficult to determine if physical health interventions (eg, commencing metformin) were being made in this group.

This study adds important findings to a small body of literature that suggests that the implementation of pharmacists into mental health clinics improves physical health monitoring. It is unclear, however, whether this translates to improvement in associated outcomes.

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