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Clozapine clinical toolkit optimizes inpatient clozapine monitoring

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Abstract

Introduction: Clozapine is the most effective antipsychotic in the management of treatment-resistant schizophrenia; however, its use is challenging due to the risk of severe adverse effects. Despite the risks associated with clozapine, there is no mandatory monitoring in Canada beyond hematologic testing for agranulocytosis surveillance. This study focuses on the development, implementation, and evaluation of a clozapine clinical toolkit (CTK) targeted at optimizing inpatient clozapine use.

Methods: A comprehensive literature review was conducted to identify clozapine best practices, experts were consulted, and a comprehensive clozapine CTK was developed and implemented at a large Canadian tertiary hospital in December 2018. To evaluate the CTK, a retrospective chart review was conducted to assess for change in guideline-concordant monitoring pre- and post- CTK implementation. Patients were included if they were > 18 years of age and received clozapine during inpatient admission. Results were analyzed using descriptive and inferential statistics.

Results: Among the charts reviewed, 185 and 113 admissions met the pre- and post-CTK inclusion criteria, respectively. Staff used the CTK in the care of 96% of clozapine patients post implementation, and its use resulted in improvements in guideline-concordant monitoring for agranulocytosis and myocarditis.

Discussion: Implementation of the clozapine CTK increased the concordance of clozapine monitoring with best practice recommendations. Future research is necessary to assess the impact of the CTK on clinical outcomes and patient satisfaction.

Keywords: clozapine, monitoring, interdisciplinary, psychiatry

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Introduction

Clozapine use poses a multitude of challenges due to potential severe adverse effects, such as agranulocytosis and myocarditis, and the monitoring required to mitigate them.[1] There is a lack of standardized monitoring to support safe care of patients prescribed clozapine in inpatient settings.[2] In Canada, there is a mandatory nationwide system of monitoring registries for agranulocytosis surveillance; however, there is no formalized system for monitoring other clozapine-induced adverse effects, such as myocarditis.[3] This contrasts with evidence-based recommendations that emphasize integrated approaches that combine hematological monitoring with clinical assessment(s) to target clozapine adverse effects.[4,5]

Existing evidence suggests adverse effects, monitoring requirements, and inadequate clinician training are barriers to safe clozapine use.[6] An international guideline provides recommendations to personalize clozapine dosing titration.[7] This guideline provides specific recommendations for clozapine dosing and monitoring during initiation, and these extend beyond the mandatory requirements, but does not include clinical tools to support their implementation. Ally and Stallman demonstrated that implementation of a brief two-page clozapine decision support tool (DST) led to improved clozapine monitoring.[8] To date, there is no published literature on the impact of an integrated, evidence-based clozapine clinical toolkit (CTK) that provides both education and guidance on clozapine monitoring during inpatient treatment. The focus of this paper is to describe the development, implementation, and evaluation of a CTK in a large Canadian tertiary hospital. The primary outcome was to assess for change in guideline-concordant clozapine monitoring pre- and post-CTK implementation.

Methods

CTK Development

The CTK was developed using an action research approach, a methodology commonly used to promote transformative change in health care environments.[9] It is a systematic process of inquiry conducted by and for those taking action in collaboration with researchers.[10] The integration of clinical and scientific knowledge with user perspectives fosters a comprehensive and practical approach to intervention development.[9] Action research is characterized by iterative cycles of planning, acting, evaluating, and reflecting.[9]

Planning

Clozapine CTK planning began with a comprehensive assessment of clozapine best practices. A literature search was completed to determine evidence-based prescribing and monitoring of patients on clozapine. The search engines utilized included PubMed, EMBASE, Wiley Online Library, ClinicalKey, and Google Scholar. Studies were included in the analysis if they were conducted in an adult inpatient psychiatry unit; published in the last 10 years; and originated from Canada, the United States, Australia, or the United Kingdom.

The results of the literature search were summarized and reviewed with clinical experts to inform the CTK development. The CTK was codeveloped by 2 interdisciplinary teams of researchers and clinicians located in 2 tertiary teaching hospitals in Vancouver, British Columbia. The team holds expertise in psychiatry, clinical pharmacy, nursing, education, research methodology, and change management; specifically, the team included health care professionals from nursing, pharmacy, psychiatry, and cardiology.

Throughout the planning and development of the CTK, best-practice standards for clozapine prescribing and monitoring were incorporated. Monitoring parameters were classified as best practice if they aligned with evidence-based recommendations for clozapine monitoring.[5,11–17] For items that lacked clear recommendations across guidelines, clinician experts were consulted. Figure 1 summarizes the best-practice standards that were integrated into the CTK. Monitoring for clozapine-induced constipation was also a key CTK component, but data related to constipation was not captured in this study.

CTK Elements

The CTK consists of 6 key elements, including (1) an online course for clinicians, (2) an interdisciplinary practice guideline, (3) a preprinted order (PPO) set for standardized ordering of clozapine and monitoring, (4) a nursing monitoring flowsheet to support nurses to proactively monitor for clozapine adverse effects, (5) a discharge summary sheet for communication with outpatient providers, and (6) a patient-specific clozapine education brochure (Figure 2). The interdisciplinary guideline describes the purpose of the CTK as well as includes each point-of-care tool (ie, PPO, nursing monitoring flowsheet, and discharge summary sheet) along with a detailed description of how each component should be implemented in practice. These tools became a mandatory component for clozapine use on the psychiatry ward at the study hospital.

A free, 30-minute, online, asynchronous course was developed to improve physician, pharmacist, and nursing knowledge and

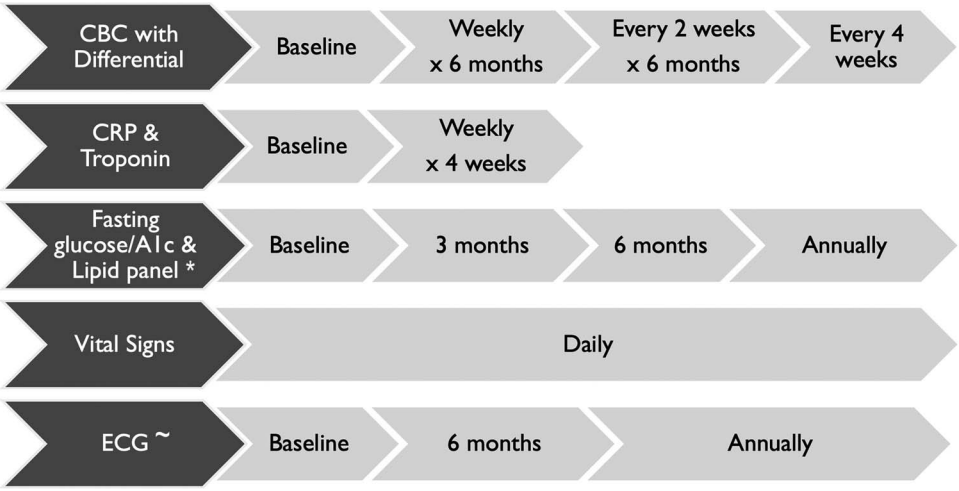

FIGURE 1: Monitoring guideline recommendations

CBC = complete blood count with differential; CRP = C-reactive protein; ECG = electrocardiogram.
*Required to be assessed within the first week of starting a patient on clozapine.
~Required to be assessed within 24 hours of starting a patient on clozapine.

confidence related to clozapine care. The course includes several modules related to clozapine prescribing, effectiveness, adverse effects, and required monitoring and is now a mandatory component of new staff orientation.

Staff Preparation and CTK Implementation

Prior to CTK implementation, background education on clozapine as well as all elements of the CTK were provided to nurses, pharmacists, and psychiatrists via online education modules, in-person in-services, and one-on-one support. This education was provided by a clinical pharmacy specialist, clinical nurse specialist, and nurse educators. Additionally, in the 4 months leading up to implementation, the CTK team attended leadership and clinical meetings to socialize the toolkit and address potential facilitators and barriers to uptake. The CTK was implemented on December 5, 2018.

CTK Evaluation: Data Collection

To evaluate the CTK, a retrospective chart review of all adult patients ($\geq$ 18 years) who received clozapine during an inpatient admission were reviewed. Data was collected during two time periods. The pre-CTK implementation data was collected from December 4, 2016, to December 4, 2018, and the post-CTK implementation data collection period was January 5, 2019, to January 5, 2020. Data sources included patient information from the electronic medical record, paper charts, and inpatient pharmacy order entry software. To determine whether care provided was concordant with best practice standards, data was collected on 4 key domains:

1. Clinical adoption of the CTK: percentage of patients with completed clozapine PPOs, monitoring flow sheets, clozapine discharge summary sheets.
2. Prescribing practices: Patient status (new start vs restart vs continuation and confirmation of medication adherence), clozapine initiation regimen (dose and frequency), and bloodwork frequency.
3. Monitoring practices: bloodwork ordered and obtained (ie, complete blood count with differential (CBC-D), C-reactive protein (CRP), hemoglobin A1c, and lipid panel), diagnostics ordered (ie, electrocardiogram), vital signs monitoring, and signs and symptoms of infection and myocarditis monitoring (ie, fever, muscle aches, sore throat, headache, diarrhea, chest pain, heart rate above 120 beats per minute or increased more than 30 beats per

FIGURE 2: Clozapine clinical toolkit components

TABLE 1: Patient demographics

Variable		Pre-CTK ($n = 185$)	Post-CTK ($n = 113$)	p-value[a]
Sex, *N* (%)	Male	112 (61)	75 (66)	.312
Age, mean (SD)	Years	42 (14)	42 (13.6)	—
Ethnicity, *N* (%)	Caucasian	110 (59)	78 (69)	.097
	Other	75 (40.5)	35 (31)	
Discharge diagnosis, (%)	Schizophrenia	96 (52.2)	57 (50.4)	.772
	Other	89 (47.8)	56 (49.6)	
Duration of admission, median (range)	Days	24 days (1–144 days)	20 days (1–144 days)	.277[b]
Clozapine status, *N* (%)	New start	28 (15)	23 (20)	—
	Restart	64 (35)	39 (35)	—
	Continuation	88 (47)	45 (40)	—
	Unable to determine	5 (3)	6 (5)	—
Frequency of bloodwork, *N* (%)	Weekly	92 (50)	72 (64)	—
	Every 2 weeks	7 (4)	13 (12)	—
	Every 4 weeks	32 (17)	14 (12)	—
	Assumed weekly	54 (29)	14 (12)	—

CTK = clinical toolkit.
[a]$p < .05$ are statistically significant.
[b]The exception was the independent sample *t*-test used for the admission days comparison. The difference is nonsignificant.

minute from baseline, shortness of breath, peripheral edema, fatigue, light-headedness).
4. Specialist referral: consults to medical specialty health care providers if applicable (eg, cardiology consults for patients with suspected myocarditis).

Baseline monitoring was calculated as proportion of total admissions for which each monitoring parameter was obtained. For patients who were readmitted multiple times, each admission was included as a separate event. For ongoing monitoring parameters throughout admission, we defined the following recommendations for each monitoring parameter:

- CBC-D weekly, every 2 or 4 weeks, depending on patient-specific requirement dictated by Health Canada and identified in the patient chart (if not noted, then assumed weekly).[4]
- CRP and troponin weekly for 4 weeks for new starts or restarts.

Adherence to ongoing monitoring parameters was then determined as a proportion of admissions in which 50% or more of recommended bloodwork was completed. The cut-off of 50% adherence was chosen to allow for comparison of monitoring practices between the pre- and post-CTK implementation groups and does not reflect a clinical benchmark.

CTK Evaluation: Statistical Analysis

The data was analyzed using descriptive and inferential statistics. During the analysis stage, raw data was deidentified and aggregated. Both pre and post findings were compared to assess aggregate level changes across the 4 key domains. The pre and post findings were compared using basic chi-square analysis for which $p < .05$ was statistically significant except for the admission day comparisons, which were analyzed using independent sample *t*-tests. The data was retained and protected in accordance with University of British Columbia Providence Health Care and Vancouver Coastal Health Research Ethics Boards (H19-03897).

Results

The cohort comprised 298 unique patient admissions, 185 in the pre-CTK and 113 in the post-CTK groups, respectively. The cohort was predominately male Caucasian with a mean age of 42 years and a primary diagnosis of schizophrenia (Table 1).

Clinical Adoption of the CTK

The CTK was used for 96% of patients prescribed clozapine post implementation. The nursing monitoring flowsheet was completed in its entirety for 37% of patients and partially completed for 58% of patients. The discharge form was used for 36% of admissions, and the patient/caregiver brochure was documented to be distributed in 12% of admissions in the post-CTK cohort. No data on CTK adoption was gathered for the preimplementation admissions as the CTK components did not exist during that time.

Prescribing Practices

Clozapine prescribing was similar between the pre- and post-CTK groups (Table 1). The average daily clozapine dose prescribed was 158 mg in the pre-CTK group and 130 mg in the post-CTK group. The frequency of bloodwork, which refers to required hematological monitoring for agranulocytosis surveillance, was documented as the following in the pre- and post-CTK groups, respectively: once weekly

TABLE 2: Proportion of admissions adhering to best practice for baseline orders and ongoing monitoring

Variable	Pre-CTK ($n = 185$), n (%)	Post-CTK ($n = 113$), n (%)	p-value[a]
Baseline orders			
CBC-D	171 (92.4)	110 (97.3)	.076
CRP	56 (30.3)	65 (57.5)	<.001
Troponin	54 (29.2)	62 (54.9)	<.001
Fasting glucose/hemoglobin A1c	96 (51.9)	70 (61.9)	.090
Fasting lipid panel	95 (51.4)	69 (61.1)	.102
ECG	123 (66.5)	68 (60.2)	.271
Ongoing monitoring (proportion of admissions with monitoring adherence rates of 50% or more)			
CBC-D	140 (75.7)	103 (91.2)	<.001
CRP	69 (37.3)	90 (81.1)	<.001
Troponin	72 (38.9)	91 (81.3)	<.001

CBC-D = complete blood count with differential; CRP = C-reactive protein; CTK = clinical toolkit; ECG = electrocardiogram.
[a]$p < .05$ are statistically significant.

(50% and 64%), every 2 weeks (4% and 12%), every 4 weeks (17% and 12%), and assumed to be once weekly based on weekly bloodwork ordered in-hospital and no other available documentation (29% and 12%).

In the post-CTK analysis, there was a significant increase in baseline monitoring for CRP and troponin adhering to best practice. Table 2 summarizes the proportion of admissions prior to and after the CTK implementation for which baseline monitoring parameters were ordered according to best-practice standards.

Monitoring Practices

Table 2 summarizes the proportion of admissions for which each monitoring parameter was obtained according to best-practice guidelines on an ongoing basis throughout the patient's hospital admission. Prior to the CTK, 75.7% of hospital admissions had ongoing CBC-D monitoring at a rate of 50% or more compared with 91.2% admissions post-CTK implementation ($p < .001$). CRP monitoring adhering to best practice in 50% or more of admissions was 37.3% pre-CTK implementation compared with 81.1% post-CTK implementation ($p < .001$). Troponin monitoring adhering to best practice in 50% or more of admissions was 38.9% pre-CTK implementation compared with 81.3% post-CTK implementation ($p < .001$).

Prior to the CTK, symptom monitoring for infection was documented in 4% of admissions, and 1% of admissions adhered to recommended symptom monitoring for myocarditis. After the CTK, 96% of admissions were adequately monitored for signs and symptoms of infection and myocarditis.

Follow-up

The researchers aimed to collect data on patient consults with specialty providers but faced retrospective challenges, leading to its omission.

Discussion

Implementation of a comprehensive interdisciplinary toolkit, including clinician education and training, resulted in overall guideline-concordant care of patients on clozapine. This is the first study to summarize the impact of an interdisciplinary CTK on inpatient clozapine monitoring in a large Canadian tertiary hospital. This work aligns with prior research demonstrating the effectiveness of a clozapine DST to improve clinician adherence to best-practice standards for clozapine monitoring.[8] The clozapine DST assessed by Ally et al was a brief 2-page guideline implemented in a long-stay mental health facility compared with the comprehensive multimodal CTK implemented on an acute inpatient psychiatry ward. Thus, the optimal clozapine clinical tool may vary depending on practice site.[8]

The most substantial changes between the pre- and post-CTK groups were the changes in documented monitoring for signs and symptoms of infection and myocarditis. Prior to CTK implementation, clinicians likely monitored signs of myocarditis and agranulocytosis without documenting. The implementation of the CTK created a formalized, systematic approach to clozapine use, and the point-of-care tools embedded within the CTK created a forced function for best practice use of clozapine.

Another considerable change was the substantial increase in the proportion of admissions in the post-CTK group with ongoing CRP and troponin monitoring that adhered to best practice. Prior to the CTK implementation, there was no clear local guidance on when to assess the CRP and troponin in patients on clozapine. CRP and troponin monitoring, based on evidence-based recommendations, were built into the clozapine PPO and nursing monitoring flowsheet. Thus, the structure and automaticity created by the CTK supported improvements in monitoring these aspects of clozapine care.[5] The utilization of the clozapine discharge

form was low, and utilization of the education brochure was difficult to capture as it was not always documented within patients' charts. Both are areas for improvement.

The CTK did require funding and clinician time for development and implementation. Additionally, sustainability of the CTK hinges on the clinical pharmacy specialist covering the inpatient psychiatry wards to update and revise the CTK as needed. Adaptation to other sites should consider these factors; however, given that the CTK components already exist, adaptation to other sites should be less labor-intensive than the initial CTK creation.

When the CTK was implemented at the study hospital, physician orders and chart documentation, including pharmacy and nursing monitoring, were all paper-based. After the period of data collection for this study, the study hospital transitioned to a fully electronic health record (EHR), and the CTK has been successfully integrated into that system. Future studies assessing the impact of the CTK when used within an EHR would be beneficial to provide evidence of the adaptability of the CTK.

Although this study has several strengths, there are some limitations to consider. First, our retrospective design may be impacted by misclassification bias and subject to missing or incomplete records. Second, there is potential for confounding in that factors may have been present that were not possible to capture. Although multiple data sources were consulted, there were a few cases in which limited or incomplete data was all that was available, resulting in assumptions needing to be made (ie, frequency of bloodwork monitoring at baseline). Additionally, this retrospective chart review did not gather data on the impact of the CTK on monitoring for clozapine-induced constipation and did not evaluate if proactive monitoring led to proactive management strategies. It would be useful to repeat the chart review to assess the impact of the CTK on these factors as well as to assess if clozapine utilization has been sustained.

Given the limited scope of the retrospective chart review and the relatively short study duration period post-CTK implementation, it was not possible to determine if the CTK had an impact on clinical outcomes (eg, detection of myocarditis), nor was it possible to determine patient satisfaction with the patient components of the CTK (ie, patient information brochure). Additionally, barriers to clozapine monitoring adhering to best practice were not captured. For example, physicians may have altered the frequency of monitoring practices based on their own opinion, or patients may have refused specific types of monitoring (eg, bloodwork) based on their clinical state. Future studies that explore these aspects would be useful to better understand the holistic impact of the CTK and barriers to its use.

Conclusion

The use of the CTK at a large Canadian tertiary hospital increased guideline-concordant clozapine practices. The success of the CTK is linked to a clozapine order set, which provides a standardized approach to laboratory and clinical monitoring for signs and symptoms of myocarditis and infection. Future work could evaluate the impact of the CTK on clinical outcomes, such as rates of myocarditis detection, and acceptability and feasibility of the CTK implementation at other sites, including those with EHRs.

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