Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Clozapine Treatment of Hospitalized Patients: A Review of Clinical Practice Guidelines and Safety

DATE: 20 December 2010

CONTEXT AND POLICY ISSUES

Clozapine is an atypical antipsychotic that is indicated for use in treatment-resistant schizophrenia.[1] In addition to its dopaminergic effects, it has potent anticholinergic, adrenolytic, antihistaminic and antiserotoninergic activity.[1] Related to its risks for adverse effects, clozapine use has been limited to those with treatment-resistant schizophrenia who fail to achieve an adequate clinical response or experience intolerable adverse effects with other antipsychotics.[1]

Patients treated with clozapine are at risk for numerous adverse effects, some of which can be serious and possibly life-threatening.[2-4] These effects include bowel perforation, myocarditis, diabetes, death, seizures and agranulocytosis.[1-5] In addition, some of clozapine's adverse effects may be due to its anticholinergic effects, such as dry mouth, sedation, constipation, drooling and orthostatsis.[6]

Clozapine treatment is generally reserved for those with severe illness.[7] Given the potential for numerous adverse effects associated with clozapine use, it is important to identify guidelines that can be used to aid in the careful monitoring of inpatients initiating clozapine therapy. This review will examine the recent clinical guidelines for monitoring adult inpatients initiating clozapine therapy and identify the risks associated with clozapine therapy.

RESEARCH QUESTIONS

1. What are the clinical guidelines for monitoring adult hospitalized patients initiating clozapine therapy to adult hospitalized patients?

2. What are the risks associated with clozapine therapy to adult hospitalized patients?

KEY MESSAGE

The key areas to monitor that were consistently reported in the identified guidelines for the initiation of clozapine therapy include the hematologic, cardiovascular, metabolic, gastrointestinal and central nervous systems. Based upon the identified literature, the most serious risks associated with clozapine therapy for adult hospitalized patients include agranulocytosis, myocardial infarction, myocarditis, weight gain, fever, seizure, and increased risk of death.

METHODS

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 11, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and November 23, 2010. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS

The literature search identified one relevant systematic review, [6] and four non-randomized studies.[8-11] No relevant randomized controlled trials (RCTs) or guidelines that were clearly evidence-based were identified.

Three additional systematic reviews were identified, but were not included in this rapid review.[12-14] A Cochrane systematic review by Asenjo et al. (2010)[12] was excluded because the majority of the studies included in the review were not conducted in hospital settings. A review by Ramaswamy et al. (2006)[13] investigated the presence of an increased risk of diabetes due to the consumption of atypical antipsychotics. The review was excluded because the number of clozapine users was not clearly distinguished in the overall sample. A review by Citrome et al. (2007)[14] was excluded because it was unclear whether the studies included in the review were conducted in inpatient or outpatient settings.

Although there were no guidelines identified for clozapine initiation in hospitalized patients that appeared to be evidence-based, general guidelines or recommendations concerning the use of clozapine for hospitalized adult patients have been generated internationally. Of the seven guidelines included, four were developed in Australia,[15-18] two were developed the United States of America,[19,20] and one was developed in the United Kingdom.[21] Details of these guidelines can be found in the Appendix.

Systematic reviews and meta-analyses

A Cochrane review conducted by Essali et al. (2009)[6] compared the clinical efficacy and adverse effects of clozapine with typical antipsychotic drugs for patients with schizophrenia. The authors searched multiple databases for RCTs. Fifty of the 52 included RCTs were conducted in hospital settings. All studies included in the review were subject to a formal quality assessment to determine risk of bias. These studies compared clozapine to chlorpromazine, haloperidol, clopenthixol, loxapine, perphenazine, and thioridazine. A total of 4746 patients were included from the 52 trials. The duration of the included trials varied. Forty-four of the trials were up to 12 weeks (short-term), seven trials were longer than 26 weeks (long-term), and one study reported

outcomes for up to 12 weeks and for 13 to 26 weeks (medium-term). A meta-analysis of 13 short-term RCTs (n= 1031) was conducted to compare clozapine to haloperidol and chlorpromazine. In this meta-analysis, clozapine was associated with an increased risk of blood problems (RR= 7.09, 95% CI 2.0 to 25.6). Blood problems were defined as any blood problem requiring a participant to withdraw from a trial, leukopenia (white cell count < 3000 per mm^3), or neutropenia (granulocyte count < 15000 per mm^3). The risk of abnormal erythrocyte sedimentation rates was higher in the clozapine group compared to chlorpromazine in one study (n= 62) (RR= 10.78, 95% CI 2.8 to 41.9). All other pooled estimates were generated from a mixture of short-term, medium-term, and long-term studies. Pooled results from 16 RCTs (n= 1527) demonstrated that clozapine was associated with an increased risk of drowsiness when compared to haloperidol and chlorpromazine (RR= 1.23, 95% CI 1.1 to 1.3). Excess salivation occurred more frequently during the use of clozapine across 17 RCTs (n= 1479) (RR= 2.25, 95% CI 2.0 to 2.6) compared to haloperidol, chlorpromazine and loxapine.[6] Across five RCTs (n= 590) patients gained more weight on clozapine in (RR= 1.28, 95% CI 1.1 to 1.5) compared to haloperidol and chlorpromazine. Increases in body temperature were more frequent in the clozapine group as well across nine RCTs (n= 1147) (RR= 1.57, 95% CI 1.3 to 2.0) compared to haloperidol and chlorpromazine. Finally, one study (n=87) reported that more participants in the clozapine group had abnormal blood glucose than participants in the chlorpromazine group (weight mean difference = 1.00, 95% CI 0.4 to 1.6). The authors concluded treatment-resistant individuals demonstrated better responses on clozapine compared to typical antipsychotics. In terms of adverse of effects, the authors noted clozapine caused more drowsiness and weight gain than typical antipsychotics. The generalizability of this review to adult hospitalized patients could potentially be limited by the inclusion of one study with adolescents and children and the inclusion of two studies with patients in the community among the 52 studies included in the meta-analysis.

Non-randomized studies

Four non-randomized studies were identified that were not included in the systematic reviews previously summarized in this report.

Praharaj et al. (2010)[11] conducted a prospective hospital-based non-randomized study in India to determine the change in salivary flow rate for patients with schizophrenia on clozapine. A sample of 20 male inpatients with diagnosed schizophrenia was started on clozapine. Unstimulated salivary flow rate was assessed at baseline and then weekly for four weeks. Three patients dropped out for unknown reasons. A significant increase in salivary flow was observed at the third (t[16]= -2.3888, P= 0.030, Cohen's d = 0.87) and fourth week (t[16] = -2.363, P= 0.031; d = 0.83). There was no correlation between salivary flow rate and clozapine dose. The authors concluded that there was a significant increase in salivary flow rate from baseline after starting clozapine and that the effect size was moderate. Limitations of this study include the number of participants, four week duration, lack of explanation for dropouts in the study, and the inclusion of only male patients.

Dutt et al. (2010)[10] examined the adverse effects and clinical profile of patients treated with clozapine. The authors conducted a retrospective study reviewing the case records of 51 inpatients of a hospital psychiatric unit in India. The study included all patients admitted to the psychiatric inpatient unit over a six year period who started on or continued on clozapine. The mean duration of inpatient stay was 62.94 days (SD= 36.38). The most common adverse effect was sialorrhoea (excess saliva), which was experienced by 58.8 % (30/51) of patients. Other adverse effects that were experienced included sedation by 47% (24/51), constipation by 15.6%

(8/51), severe hypotension by 2% (1/51), urinary incontinence by 2% (1/51), and urinary retention by 2% (1/51) of patients. The authors concluded that clozapine leads to a decrease in psychopathology and the most frequent adverse event was sialorrhoea. Limitations of this study included the lack off a comparison group, duration of inpatient stay, and that there was no distinction made between clozapine initiators and those continued on clozapine.

Chung at al. (2008)[9] investigated the incidence, patient characteristics and predictors of clozapine-induced fever in a sample of 227 inpatients at a psychiatric unit in Hong Kong. This retrospective study involved a review of case notes for patients newly started on clozapine over a 45 month period. The incidence of clozapine-induced fever was 13.7% (31/227 patients). The mean day of onset of fever was 13.7 days (SD= 7.1 days) and the mean duration of fever was 4.7 days (SD= 3.0 days). The authors suggested when managing patients with clozapine induced fever, a complete blood examination, liver and renal function tests, blood culture, chest x-ray and investigation of creatine kinase should be performed. The authors concluded that clozapine induced fever is common, in particular, during the first three weeks of therapy. Limitations of this study include the use of an arbitrary definition of fever as a temperature of 38ºC, which might lead to a slight underestimation of the incidence of clozapine-induced fever. In addition, there was no comparison group included. As well, ten cases of fever for which other causes were identified or could not be ruled out were excluded.[9]

Bai et al. (2006)[8] conducted a retrospective chart review to determine if the initial response to clozapine is related to weight change. The researchers reviewed the charts of 96 hospitalized patients with schizophrenia in a Taiwanese psychiatric hospital who were treated with clozapine for an eight year period. Patients were weighed monthly for eight years. Fifty-five patients received clozapine for the entire eight year period of the study. The average weight gain was 11.7 kg (SD= 1.6 kg). The authors suggested that given the long-term health risks associated with excess weight gain, for patients with lower baseline BMI and a good initial clinical response, weight change and associated metabolic syndrome symptoms should be closely monitored. It is important to note that 24% of patients were concomitant users of mood stabilizers (13/55) and 9% of patients were concomitant users of other antipsychotics (5/55), which could potentially impact weight gain as well. One limitation of this study was that the sample did not include treatment resistant schizophrenics, the indication for which clozapine is used. In addition, variables that could confound the relationship between clozapine and weight gain were not reported. As well, possible adverse events due to clozapine use such as measures of metabolic syndrome (e.g. blood glucose, waist circumference, blood lipids, and blood pressure) were not reported.

Guidelines and recommendations

No evidence-based guidelines were identified; however, recommendations from guidelines of potential interest are summarized in the appendix.

Limitations

The systematic review identified included RCTs only, which could be insufficient in duration to obtain a comprehensive picture of the safety concerns or the risks associated with chronic clozapine use in hospitalized patients. In addition, the authors of the systematic review and meta-analysis indicated many of the studies included were industry funded. Generally the quality of reporting for the studies included in the reviews was described as being poor. No studies provided clear descriptions of sequence generation and allocation concealment.

Blinding was often conducted but in an inadequate manner and reporting biases were common. The findings of the systematic review could potentially be affected by the limitations of the included studies.

The non-randomized studies were mostly retrospective studies without comparison groups, which relied on records or the recall of individuals, which can be inaccurate and subject to bias. In addition, the non-randomized studies had sample sizes that ranged from 20 to 227 patients and limited durations of follow-up. Furthermore, some study populations were restricted by gender or ethnicity, which could limit the generalizability of their findings. Within the studies clozapine users frequently discontinued treatment. However, no accounts or reasons for discontinuation were provided.

No clearly evidence-based guidelines were identified and the guidelines that were included in the appendix had multiple limitations. The majority of the guidelines did not provide references or information on how the guidelines were developed. Only three of seven guidelines included a complete reference list, one guideline stated the product monograph as the sole reference, and three guidelines did not provide any references. In addition, there was no information on the grade of the evidence used for the guidelines. Finally, there was a considerable amount of variability in terms of the suggested time frames for monitoring specific measures that appeared in multiple guidelines. For example, in numerous guidelines it was recommended that the blood glucose levels be monitored. However, the definition of levels at which the clinical staff should be concerned varied and there were differences in the suggested duration and/or frequency of monitoring of blood glucose levels.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The literature search did not identify any clinical guidelines for monitoring adult hospitalized patients initiating clozapine therapy that were clearly evidence-based. Non-evidence-based recommendations suggest monitoring the cardiovascular, central nervous, gastrointestinal, hematologic and metabolic health/systems along with various drug interactions for adult hospitalized patients using clozapine.

There are multiple risks associated with clozapine therapy for adult hospitalized patients, the most serious of which are agranulocytosis, myocardial infarction, myocarditis, weight gain, fever, seizure, and increased risk of death. The included systematic review identified an increased risk of blood problems, weight gain, sialorrhea, and increased body temperature associated with clozapine use. Non-randomized studies reported clozapine use was associated with increased risk of fever, weight gain, sialorrhea, and sedation. The identified risks from the included systematic review and nonrandomized studies are consistent with those identified in the Canadian product monograph for clozapine. No other relevant risks were identified.

The findings of this report have implications for clinical practice. There is some evidence to suggest that extensive monitoring of adult hospitalized patients is necessary during the initiation of clozapine therapy. According to the identified recommendations, it is important for clinical staff to be aware of the risks of clozapine therapy in this patient population and to monitor multiple organ systems throughout the use of clozapine therapy in hospitalized patients.

Clozapine therapy is indicated for treatment-resistant schizophrenia. A clear understanding of this condition and what categorizes a patient as treatment resistant may ensure that clozapine is used in the population for which it is approved in Canada. This could help to limit exposure of

clozapine to those patients in which the potential clinical benefit might outweigh the risk of serious adverse effects.

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APPENDIX: Summary of the Included Guidelines

Five of the guidelines were designed solely for the purpose of managing or monitoring of patients using clozapine,[15,16,19-21] and two of the guidelines were intended for antipsychotic monitoring with additional instructions for clozapine monitoring.[17,18] Generally, the guidelines did not clearly state how they were developed. All of the guidelines recommended extensive monitoring at baseline and ongoing throughout clozapine treatment. Because of the detailed nature of the guidelines, a brief summary has been provided with a quality assessment of the evidence and key outcomes or areas for monitoring.

Organization, Title, Country	Year	Recommendations for monitoring adult hospitalized patients using clozapine	Quality Assessment				
			Objectives and Population stated	Methods to develop stated	Based on a systematic review	Sources of Evidence for the Guidelines Provided	Key Outcomes or Areas to Monitor
Western Australian Psychotropic Drugs Committee **Antipsychotic Drug Guidelines**[18] Australia	2006	For patients who have had poor/ partial response or unacceptable side effects with at least two other atypical antipsychotics use clozapine A wide range of monitoring schedules from weekly, biweekly, quarterly, and biannually	No	Yes	No	Expert Opinion	ECG, FBS, FBC, BP, urea, electrolyte, liver function, BMI, waist/hip ratio, and Troponin I
Graylands Hospital Drug Bulletin **Antipsychotic Monitoring**[17] Australia	2006	Provides monitoring recommendations for antipsychotic use at baseline, 1-2 weeks, monthly for six months, at 3 months, quarterly, biannually, and annually	No	No	No	Peer-reviewed journal articles and guidelines	BMI, blood sugar level, fasting lipid profile, ECG, full blood picture, urea and electrolytes, liver function test, BP and pulse

Australian Psychiatry **A clinical monitoring system for clozapine**[16] Australia	2006	Provide forms for monitoring at initiation, the first 18 weeks of clozapine use, and monitoring at three month intervals for up to 36 months	No	No	No	Peer-reviewed journal articles and medical handbooks	Initiation: cardiovascular disease, bone marrow disorders, renal/hepatic, prostatic hypertrophy, narrow angle glaucoma, diabetes, and dyslipidaemia Week 1 and beyond: Full blood examination, blood groups, for women when necessary monitor human chorionic gonadotropin, liver function tests, urea, electrolytes, troponin I or creatine phosphokinase, metabolic syndrome measures, cardiac measures, and physical measures

CNS Drugs **Monitoring the Safe Use of Clozapine:** **A Consensus View from Victoria, Australia**[15] Australia	2007	Provide recommendations to extend monitoring beyond just haematological adverse events. Suggestions for monitoring at baseline, weekly up to 18 weeks, beyond 18 weeks, at six and 12 months, ongoing, and additional monitoring if suspected cardiac complications	Yes	Yes	No	Peer-reviewed journal articles and expert opinion	Baseline: Clinical history and examination, weight, BP, HR, ECG, Transthoracic echocardiogram, Troponin and CK-MB level, Lipid profile and blood glucose level, WBC count and differential (repeat in 1 week if in the amber range), Liver function tests 0-18 weeks**:** WBC count and differential, Clinical evaluation, ECG, plasma troponin and CK-MB levels days 7 and 14 >18 weeks: WBC count and differential 6 and 12 months: Lipid profile, blood glucose level, Liver function tests, Transthoracic echocardiogram Ongoing: WBC count and differential (monthly), blood glucose (biannually), transthoracic echocardiogram (annually), lipid profile (annually), weight, BP, HR, troponin and liver function test (as required) Additional: Chest x-ray, inflammatory markers, selenium level[15]

Veterans Health Administration **Clozapine Patient Management Protocol (CPMP)**[19] United States of America	2008	Suggest monitoring of clozapine at a various stages When initiating clozapine to minimize the likelihood of adverse effects, clozapine treatment should be initiated at very low doses and titrated gradually In addition, the authors provide guidelines concerning an adequate time frame for non-response to clozapine along with suggestions for ongoing monitoring	Yes	No	No	Based on the product monograph	Agranulocytosis, granulocytopenia, cardiac problems, pulmonary embolism, hyperglycemia, anticholinergic toxicity, seizures or seizure disorder, sleep apnea, renal impairment, sedation, sialorrhea, hypotension, fever, EKG repolarization, unexpected death, and hematologic monitoring
Manchester Mental Health and Social Trust **Guidelines for Inpatient Initiation of Clozapine**[21] England	2009	The authors provide these guidelines because of the adverse events associated with clozapine use and the requirement for intensive physical monitoring during the initial stages of treatment. They advise clozapine is commenced on an inpatient unit The authors provide advice for initiation monitoring, management of adverse events, blood monitoring, contraindications, cautions and ongoing monitoring	Yes	No	No	No	Hypotension with cardiovascular collapse, myocarditis /cardiomyopathy, severe hyperthermia, neutropenia, and seizures. Drug interactions- other antipsychotics, benzodiazepines, and cardiac medications.

County of Santa Barbara Alcohol, Drug and Mental Health Services **Clozapine Prescribing and Monitoring**[20] United States of America	2009	Provide criteria for clients who should be considered for clozapine initiation. In addition, they provide suggestions for monitoring for drug interactions, and white blood cell and absolute neutrophil counts at various stages of therapy.	Yes	No	No	No	agranulocytosis; seizure/myoclonus; myocarditis; marked hypotension; respiratory depression; increased glucose, lipids, and/or weight; fever; blood monitoring including white blood cell count and differential count

CBC= Complete Blood Count; FBS= Fasting Blood Glucose, AST=aspartate aminotransferase); ECG= Electrocardiogram; FBC= Full Blood Count; BP= Blood Pressure; BMI= Body Mass Index; HR= Heart Rate;