Diagnostic Characteristics of Clozapine-Induced Myocarditis Identified by an Analysis of 38 Cases and 47 Controls

Kathlyn J. Ronaldson, MSc, DPhil; Andrew J. Taylor, MBBS, FRACP, PhD; Paul B. Fitzgerald, MBBS, MPM, FRANZCP, PhD; Duncan J. Topliss, MBBS, FRACP, MD, FACE; Maros Elsik, BSc (Med), MBBS, FRACP; and John J. McNeil, MBBS, FRACP, MSc, PhD, FAFPHM

Objective: To analyze cases of clozapine-induced myocarditis for clinical and diagnostic trends.

Method: A case definition was developed by a multidisciplinary group using reports of myocarditis with clozapine submitted to the Australian Therapeutic Goods Administration. The definition uses for diagnosis either histology or the combination of new signs of cardiac dysfunction combined with a cardiac-specific diagnostic parameter occurring within 45 days of starting clozapine. Potential cases of clozapine-related myocarditis occurring between January 1993 and September 2008 and a comparative group of long-term clozapine users were documented from the patients' medical records.

Results: Thirty-eight of 59 reviewed cases met the case definition. Three patients died, and the diagnosis for these was confirmed on cardiac histology. Nearly all of the remaining patients had persistent tachycardia and elevated troponin level. The time to onset was 14–22 days in all except 2 patients. Of the patients who survived, 66% (23 cases) had eosinophilia occurring 0–7 days (mean, 4.0) after the peak in troponin. C-reactive protein (CRP) level was elevated to above 100 mg/L (952 nmol/L) in 79% (23 cases), and some had elevated levels of CRP when troponin level was still normal. None of the control group (47 patients) met the case definition.

Conclusions: Eosinophil counts should not be relied on for diagnosis of clozapine-related myocarditis, but elevated CRP may be an early indicator of developing myocarditis. Patients starting clozapine should be actively monitored for myocarditis during the first 4 weeks, with extra care taken during week 3.

J Clin Psychiatry 2010;71(8):976–981

See also Commentary on page 982.

Submitted: *January 7, 2009; accepted March 6, 2009.*
Online ahead of print: *March 9, 2010 (doi:10.4088/JCP.09m05024yel).*
Corresponding author: *Kathlyn Ronaldson, MSc, DPhil, Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Hospital, Melbourne, Victoria 3004, Australia (kathlyn.ronaldson@med.monash.edu.au).*

In 1999, the publication by Kilian et al[1] of an Australian case series of myocarditis with clozapine provided strong evidence that this relationship was causal, especially given the estimated high incidence of 1 in 500 in the first month of clozapine use. This evidence was reinforced 18 months later by a data-mining study conducted on the international database of adverse drug reactions maintained by the World Health Organization.[2] In this study, Coulter et al[2] found that clozapine was significantly more frequently associated with myocarditis than any other drug. In subsequent publications,[3,4] it has been proposed that the incidence may be more than 2% of patients starting clozapine.

Clozapine is recognized as the most effective antipsychotic available for treatment-resistant schizophrenia,[5,6] but its use is limited to third-line therapy because of its adverse reactions, including agranulocytosis, neutropenia, and myocarditis. Mandatory full blood count monitoring is effective in reducing the incidence of agranulocytosis, but despite introduction by the sponsor of a cardiac monitoring program in Australia in December 1999, the occurrence of clozapine-related myocarditis and death from this cause has not been prevented.

With the exception of a case series[3] from Queensland, the publications to date either have been individual case reports[7–16] or have described cases collected through a national spontaneous adverse drug reactions reporting program.[1,17–21] Published cases have not adhered to a common single case definition, or any case definition at all. Hence, published reports provide a rough guide but not a reliable indicator of clinical and diagnostic trends to assist in monitoring and diagnosis. Because of the potential risk of serious cardiac damage with myocarditis and death from arrhythmia and other complications in the acute phase, it is important to make the diagnosis as early as possible to enable timely drug withdrawal; conversely, because of the often unique benefit of the drug, the diagnosis should not be assumed without reliable evidence.

Because of the clinical need to characterize clozapine-associated myocarditis further, we developed and validated a case definition. On the basis of this definition, we documented 38 cases from the patients' medical records and analyzed them for trends in clinical and diagnostic parameters.

METHOD

A case definition (Table 1) that maximizes specificity at the expense of sensitivity was developed by a multidisciplinary group, including individuals with specialist expertise in cardiology, pharmacology, pharmacovigilance and epidemiology using 116 reports of myocarditis submitted to the Australian Therapeutic Goods Administration.

For the case analysis, cases of clozapine-related myocarditis were identified from reports submitted to the

Therapeutic Goods Administration between January 1993 and September 2008, from cases advised directly to the researchers, and from cases in the National Coroners' Information Service database. A comparative group comprised patients starting clozapine close in time to a case occurring at the same health service. These patients had taken clozapine for at least 6 months without manifest cardiac disease.

Documentation of each patient included the date of birth, sex, clozapine start and end dates, dose of clozapine taken each day, baseline pathology results and results obtained during the course of clozapine treatment and until resolution of myocarditis for the cases, and signs and symptoms recorded in the progress notes. Documentation for each case was reviewed by the study steering group for compliance with the case definition for clozapine-related myocarditis (see Table 1).

Approval for the study was obtained from the Human Research Ethics Committees of the following institutions or health services: Monash University, Barwon Health, Bayside Health, Bendigo Health, Department of Human Services, Department of Justice, Eastern Health, Mercy Health, North West Mental Health, Peninsula Health, Southern Health (all from Victoria, Australia); and, Northern Sydney Central Coast Health (from New South Wales, Australia). The approvals covered access to medical records without patient consent. In addition, an Access Agreement was signed with the Victorian Institute of Forensic Medicine for access to the National Coroners' Information Service database and a Deed of Confidentiality and Conflict of Interest with the Therapeutic Goods Administration for access to original case reports.

RESULTS

Compliance With the Case Definition

Of 59 cases reviewed, 38 met the case definition. Three cases were fatal and for these the diagnosis was made by cardiac histology at autopsy. For the remaining 35 cases, the clinical criteria for myocarditis were met by the presence of documented sustained tachycardia in 32 cases and by basal lung crepitations and/or peripheral edema in 3 cases. In 30 cases, the cardiac specific diagnostic parameters were satisfied by at least 1 troponin I or T measurement greater than or equal to twice the upper limit of normal. In each of these cases, the patient had a documented normal troponin level at baseline. The 5 cases without raised troponin level had diagnostic confirmation by evidence of left ventricular impairment by echocardiography (4 cases) or gated blood pool scan (1 case). In 1 patient, the diagnosis of myocarditis was confirmed by magnetic resonance imaging.[22]

Twenty-one potential cases were excluded for the following reasons: the time to onset was more than 45 days (3 cases), other disease states may have caused confounding (4 cases), insufficient data were available to make an assessment (2 cases), or the clinical and diagnostic criteria were not met by the data (12 cases).

Table 1. Case Definition for Clozapine-Related Myocarditis

- Onset of new symptoms within 45 days of commencing clozapine
- PLUS
  - Histologic evidence of myocarditis at postmortem or on myocardial biopsy in the absence of other plausible explanations, including
    - Confirmed viral infection or
    - Exposure to other likely causative agents within an appropriate timeframe
- OR
  - New signs of cardiac dysfunction (eg, persisting tachycardia [heart rate > 100 bpm for ≥ 24 hr], third heart sound, basal crepitations, peripheral edema) with, or without, febrile systemic illness
- PLUS
  - At least ONE of the following diagnostic abnormalities with or without eosinophilia:
    - Elevated troponin I and/or troponin T levels (≥ 2 times the upper limit of normal)
    - Elevated CK-MB levels (≥ 2 times the upper limit of normal)
    - Evolutionary electrocardiographic changes (involving ≥ 1 mm ST segment depression or T wave inversion in 2 or more contiguous leads, excluding lead aVR) consistent with myocarditis, with no other obvious cause
    - Chest X-ray evidence of heart failure
    - Evidence of left or right ventricular systolic dysfunction by echocardiogram, gated pool blood scan, magnetic resonance imaging, or contrast ventriculogram
    - Magnetic resonance imaging diagnostic of myocarditis
  - In the absence of alternative plausible etiologies:
    - Confirmed viral infection
    - Exposure to other likely causative agents within an appropriate timeframe
    - Other likely explanation for these findings, including
      - Acute myocardial infarction
      - Neuroleptic malignant syndrome
      - Pneumonia or other pulmonary infection
      - Pulmonary embolism
      - Other (eg, severe sepsis)
  - Of these other likely explanations, only confirmed myocardial infarction and neuroleptic malignant syndrome, in the absence of histologic evidence of myocarditis, were automatic exclusions. The presence of the other named alternative diagnoses required documentation consistent only with myocarditis and not with the other diagnosis.

Abbreviations: aVR = limb lead augmented vector right, bpm = beats per minute, CK-MB = creatine kinase-MB.

Characteristics of the Cases

The characteristics of the confirmed cases are presented in Table 2 and the diagnostic features in Table 3. Echocardiography (29 cases) or gated blood pool scan (1 case) was performed 0–5 days after stopping clozapine. Of these 30 patients, 22 had left ventricular impairment with ejection fraction ranging from the lower limit of normal to 30%. All except 2 of 18 cases with baseline echocardiography had deterioration in cardiac function from baseline.

Two patients, 1 of whom died, had no symptoms associated with myocarditis. Eighteen patients had persistent fever for up to 6 days before troponin was found to be elevated or other diagnostic measures indicated myocarditis. Several of these had normal troponin after onset of fever. Other symptoms associated with myocarditis were sore throat, vomiting, diarrhea, headache, dyspnea, and neck pain. The variety in clinical presentation is illustrated by the 5 case histories in Table 4.

Peripheral eosinophilia developed in 66%[23] of the nonfatal cases (see Table 3), but a notable feature was a delay in the increase in eosinophil count, with the peak occurring

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 2. Characteristics of the 38 Cases

Characteristic	Value	Range	Outliers
Gender, n			
Male	27		
Female	11		
Age, y	38 ± 13[a]	22–73	
Duration of clozapine, d[b]	17.6 ± 2.3[a]	14–22	26 and 33
Dose at onset, mg/d	232 ± 69[a]	100–400	50[c] and 750
Outcome, n			
Fatal	3		
Survived	35		

[a]Mean ± SD.
[b]Duration of clozapine used as a surrogate for time to onset of myocarditis.
[c]The dose had been reduced from 100 mg/d with the onset of illness.

Table 3. Diagnostic Features of the 38 Cases of Myocarditis

	No. of Cases		
Parameter	Present	Absent	Unknown
Tachycardia (heart rate > 100 bpm)[a]	34	4	0
Heart rate ≥ 120 bpm	30	8	0
Fever (> 37°C)	33	5	0
Chest pain	22	16	0
Troponin I/T level ≥ 2ULN	31	5	2
Left ventricular impairment by cardiac imaging	22	8	8
ECG abnormalities	29	7	2
T-wave abnormalities	27	9	2
ST-elevation/depression	14	22	2
CK-MB level > ULN	2	5	31
Creatine kinase level > ULN	11	25	2
Eosinophil count > ULN	23	12	3[b]
Eosinophil count ≤ 0.1×10^9/L	6	29	3[b]
C-reactive protein level > 100 mg/L	23	6	9
ESR > 50 mm/hr	7	7	24
White blood cell count > ULN	22	16	0
Neutrophil count > ULN	27	11	0
Monocyte count > ULN	12	26	0

[a]Persistent for ≥ 24 hours.
[b]Data missing for 3 fatal cases.
Abbreviations: bpm = beats per minute, CK-MB = creatine kinase-MB, ECG = electrocardiogram, ESR = erythrocyte sedimentation rate, ULN = upper limit of normal.

from 0 to 7 days (mean ± SD, 4.0 ± 2.2) after the maximum observed troponin I or T value. Because of this delay, none of the fatal cases developed eosinophilia. In 5 instances, C-reactive protein (CRP) level was above 50 mg/L (476 nmol/L), while troponin level was still normal. In a further 9 cases, the first CRP determination was more than 150 mg/L on the day troponin level was first found to be elevated.

Case Recovery

Except for the fatal cases and 1 who appeared well throughout, all identified cases of clozapine-associated myocarditis experienced improvement in constitutional symptoms following withdrawal of clozapine. Recovery was reflected by return of heart rate to less than 100 beats per minute (29 cases) and a fall in troponin level to normal (25 cases) or an incomplete reduction (3 cases). All except 1 of the 35 nonfatal cases had documented return of either heart rate or troponin levels to within the normal range. The exception had a fall in troponin I level to half of the maximum with no further determinations.

Table 4. Case Vignettes[a]

Case 1: The heart rate of a patient rose to 133 (baseline 100) bpm after 16 days of clozapine. Troponin I level was not raised above normal, but echocardiography showed deterioration in ejection fraction from a baseline of > 59% to 40%–59%. CRP rose to a maximum of 190 mg/L

Case 2: A patient died while asleep after taking clozapine (current dose 750 mg/d) for 33 days. Hypersensitivity myocarditis was diagnosed by histology at autopsy. Although the patient had been hospitalized from the time of starting clozapine, there had been no indication of physical illness. Weekly blood tests were due the following day

Case 3: A patient developing a fever with tachycardia of 120 bpm after 17 days of clozapine had normal troponin the following day, although CRP was elevated to 113 mg/L. Another normal troponin level was followed by an elevated value on day 21. Myocarditis was further confirmed by echocardiographic evidence of new left ventricular dysfunction

Case 4: After taking clozapine for 20 days, a patient had basal crepitations but only brief periods with a heart rate of 100 beats/min or more. Troponin I level was 5.6 µg/L (ULN 0.5), CRP 224 mg/L, creatine kinase 587 U/L and left ventricular ejection fraction 20%–39%. Pulmonary embolism, bacterial infection, and neuroleptic malignant syndrome were investigated and excluded

Case 5: A patient developed a sore throat, stiff joints, neck pain, fever, tachycardia, and chest pain on clozapine day 15. Despite the indications of neuroleptic malignant syndrome, creatine kinase was not elevated; maximum recorded was 61 U/L. Further, no infectious cause was identified. Troponin was 0.11 µg/L (ULN 0.03); CRP, 475 mg/L; and left ventricular ejection fraction, 30%–35%

[a]Age and gender are not provided to protect the identity of the individuals.
Abbreviations: bpm = beats per minute, CRP = C-reactive protein, ULN = upper limit of normal.

Follow-up cardiac imaging more than 5 days after clozapine cessation was available for 17 cases: 12 showed normal cardiac function, 4 showed improvement, and 1 was unchanged. The patient without improvement 7 days after stopping clozapine nevertheless had normalization of heart rate and troponin level.

Comparative Group

Forty-seven of 69 patients reviewed met the criteria for the comparative group. These 47 patients were aged 19–73 years (mean ± SD, 37 ± 13), and 32 were male and 15 female. Table 5 presents the results of investigations relevant to the exclusion or diagnosis of myocarditis in this group, and Figure 1 compares the rates of 5 features for cases and controls. The odds ratio for eosinophilia 14–28 days after starting clozapine for cases with myocarditis versus the comparative group was 3.29 (95% CI, 1.21–9.02; $P = .009$). The sensitivity of eosinophilia for a diagnosis of myocarditis was 61% and specificity, 68%. Eight control patients had both eosinophilia and tachycardia.

DISCUSSION

Study Strengths

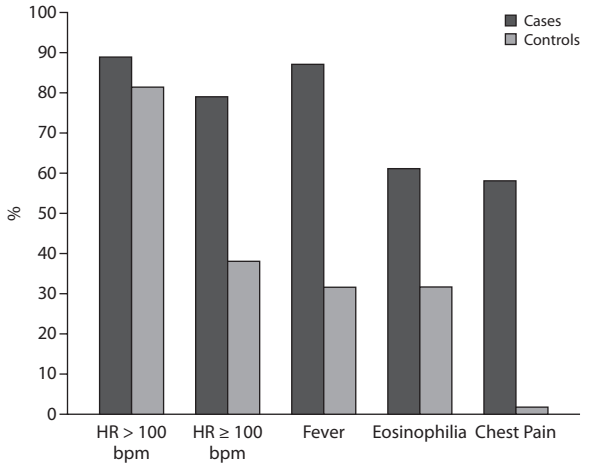
A number of factors of the Australian context have allowed us to obtain detailed documentation of the initiation of clozapine for both the cases and the controls and for the clinical presentation of myocarditis in the patients in whom it developed. Clozapine is typically initiated in a hospital, with close monitoring of the patient's vital signs, minor

Table 5. Diagnostic Features of the Comparative Group of 47 Patients Who Took Clozapine for ≥ 6 Months Without Manifest Cardiac Disease

Parameter	No. of Patients		
	Present	Absent	Unknown
Tachycardia (heart rate > 100 bpm)[a]	26	6	15
Heart rate ≥ 120 bpm	12	20	15
Fever (> 37°C)	6	13	28
Chest pain	1	46	0
Troponin I/T level > ULN (clozapine days 12–21)	0	20	27
Eosinophil count > ULN (clozapine days 14–28)	14	30	3
Left ventricular impairment by cardiac imaging after clozapine day 45	0	28	19
C-reactive protein level > 50 mg/L	1	6	40

[a]One or more episodes; no limit on duration.
Abbreviations: bpm = beats per minute, ULN = upper limit of normal.

Figure 1. Percentage of Cases and Controls With Each of 5 Diagnostic Characteristics[a,b]



[a]Cases in which the patient died were included in the category of no eosinophilia.
[b]Calculations for controls excluded those for whom data were missing, meaning that the denominator changed with each calculation.

side effects, as well as hematologic and cardiac parameters. Much of the literature about clozapine-related myocarditis has been generated from Australia, and it is well recognized in this country. The well supported adverse reaction monitoring system has led to reports being accumulated from across Australia and has in turn generated added awareness of this serious adverse effect.

This is the first study to systematically document multiple cases of clozapine-induced myocarditis from patient medical records. Clozapine initiation commonly causes a variety of minor signs and symptoms, some of which, including tachycardia, eosinophilia, and fever, may confound the diagnosis of myocarditis. We have established a case definition that distinguishes between myocarditis and these other benign conditions, as demonstrated by none of the comparative group meeting the case definition. The suitability of the case definition is further supported by the rapid recovery of the surviving cases in this group following withdrawal of clozapine. From this foundation, we have been able to examine cases of myocarditis and identify clinical characteristics of myocarditis that can inform monitoring and early diagnosis in the future.

Time to Onset

This analysis has used the duration of clozapine as a surrogate for the time to onset, and the duration of clozapine in 36 of 38 cases was 14–22 days. The possibility of bias with respect to time to onset of myocarditis in this study should not be overlooked. All except 1 case were identified to the researchers because they were recognized by a treating clinician in the first instance. Clinicians are more likely to recognize cases occurring earlier rather than later in the course of clozapine because of a heightened level of alertness to adverse reactions in the early stages of a new treatment, because of the cardiac monitoring protocol with checks at days 7 and 14, and because, although most start clozapine in hospital, few are hospitalized for more than 3 weeks after initiation. In published cases, the time to onset is typically 7–35 days. It is possible that time to onset is a function of rate of dose titration, but this is yet to be investigated.

Heart Rate as a Diagnostic Characteristic

It should be noted that tachycardia (heart rate > 100 beats/min) as a diagnostic feature of cases was required to persist for at least 24 hours. However, when tachycardia was recorded in a control patient, data on persistence were usually not available and were not documented. Hence, the comparison of frequency of heart rate of more than 100 beats per minute for cases and controls places a stricter requirement on cases (Figure 1). For the comparison of frequency of heart rate of 120 or more beats per minute, persistence was not a criterion for either group.

With regard to the validity of persistence of tachycardia as a diagnostic feature, it was supported by conjunction in time with symptoms of illness and the presence of cardiac-specific diagnostic measures, followed by resolution of these, including tachycardia, on withdrawal of clozapine.

Eosinophil Count, C-Reactive Protein Level, and Fever

A recently published review advises determining eosinophil count as a means to diagnosis of clozapine-related myocarditis.[23] In the present series, 66% of the nonfatal cases experienced eosinophilia, and, surprisingly, the elevation in eosinophil count was delayed for as long as 7 days after the peak in troponin I/T levels. Checking for eosinophilia would not assist in the early diagnosis of myocarditis and, most importantly, would not prevent fatalities. Furthermore, overreliance on peripheral eosinophil count could result in clozapine withdrawal in a patient without myocarditis, as indicated by the 32% incidence of eosinophilia in the comparative group.

In contrast, there are indications that CRP may be the first measurable parameter to herald the onset of a disease process. While it is a nonspecific inflammatory marker, elevations above 50 mg/L would be a reason to monitor

© Copyright 2010 Physicians Postgraduate Press, Inc.

the health of the patient more closely, particularly by daily electrocardiography (ECG) and troponin determinations. Similar monitoring advice could be associated with the development of fever, and a normal troponin determination after the development of fever does not mean that myocarditis has been excluded; rather, the fever may be part of an evolving myocarditis prodrome.

Limitations

A limitation of this case analysis is that it was constrained by the investigations that the treating clinician of each individual patient chose to conduct. For instance, it was not possible to fully explore the value of CRP as an early indicator of myocarditis. Similarly, daily eosinophil counts would have assisted in the characterization of the observed delay in the development of eosinophilia.

Other Countries

Countries other than Australia, and perhaps New Zealand,[21] have reported very few cases of myocarditis considering clozapine usage. Various causes have been postulated including genetic differences and high ozone in the breathed atmosphere of the southern hemisphere.[24] A plausible reason, however, is that cases have been missed in other countries. The presentation of myocarditis is nonspecific. It may resemble influenza or there may be no symptoms. Added to this are patient factors, such as psychiatric illness, which typically is poorly controlled at the time of clozapine initiation, making it difficult for patients to communicate symptoms they feel. Without a preceding high level of awareness of the association and hence active investigation for myocarditis, it very likely will be missed, especially if clozapine is initiated without the clinical scrutiny inherent in hospitalization.

A recent analysis[25] of data from a health maintenance organization in the United States found a higher rate of mortality from sudden cardiac death in community patients treated with clozapine than with any other antipsychotic. The study included no data on time to onset, but it is at least feasible that myocarditis may have contributed to the excess of deaths.

Monitoring

Not all centers internationally routinely initiate clozapine with the patient hospitalized, but weekly blood count monitoring is mandatory in several countries (Australia, Canada, New Zealand, United Kingdom, and United States) during the first 18 weeks. Diagnosis of myocarditis would be improved if the collected blood were also used to check cardiac parameters (troponin I or T) and CRP and an ECG taken at baseline and at 7, 14, 21 and 28 days. Whether the patient is treated in the community or as an inpatient, he or she should be seen by a physician and examined for signs and symptoms of illness at each of these intervals. Although chest pain was present in only 58% of cases in this study, it may be 1 useful indicator. Those with elevated CRP or indications of illness not conclusively diagnosed as having another cause should be closely monitored over the next few days. Further, patients and their carers should also be advised to report *any* illness, between the dates of routine tests, to a physician during this critical 4-week period. If troponin level is elevated or a new ECG abnormality is detected, clozapine should be discontinued pending further investigation.

CONCLUSION

In the absence of a gold standard for the diagnosis of clozapine-associated myocarditis, our case definition is a simple algorithm that can assist clinicians to identify clozapine-related myocarditis while excluding those with benign rises in eosinophil counts and heart rate. This analysis of 38 cases found that the typical time to onset of clozapine-related myocarditis is 14–22 days after starting clozapine and that eosinophil counts are a poor tool for diagnosis. Patients starting clozapine should be actively monitored for myocarditis during the first 4 weeks, with extra care taken during week 3. Rises in CRP level and development of fever may be early indicators of myocarditis and daily ECG and troponin measurements in the presence of fever or following a CRP level of more than 50 mg/L may be diagnostically useful.

Drug name: clozapine (FazaClo, Clozaril, and others).
Author affiliations: Department of Epidemiology and Preventive Medicine, Monash University (Drs Ronaldson, McNeil, and Elsik); and the Heart Centre (Dr Taylor), Monash Alfred Psychiatric Research Centre (Dr Fitzgerald), and Department of Endocrinology and Diabetes (Dr Topliss) the Alfred Hospital, Melbourne, Victoria, Australia.
Potential conflicts of interest: None reported.
Funding/support: A salary was paid to Dr Ronaldson in 2006 and 2007 from a grant from the Australian National Health and Medical Research Council.
Acknowledgments: The authors are grateful for the assistance of individuals at each of the following health services: from Victoria, Barwon Health (Dr T. Callaly, Mr W. Kuluris, Ms D. Grapsas), Bayside Health (Ms K. Hirth, Ms C. Forrester, Ms A. Given, Ms L. Scarff, Ms L. Hughes, Ms A. La Trobe, Ms J. Giuliani, Mrs D. Elliott), Bendigo Health (Dr P. Chopra, Ms S. Maynard), Eastern Health (Assoc Prof P. Katz, Ms J. Jolly, Ms A. McClaren), North West Mental Health (Dr K. Morton, Ms Gisella Campanelli, Ms A. Hammoud, Ms A. Gilchrist, Mr A. Cox, Ms H. Manos), Peninsula Health (Assoc Prof R. Newton, Mr G. Dobson), Southern Health (Dr S. Damodaran, Ms A-M Foster, Ms L. Rouda, Mr D. Graham, Mr A. Koca), Thomas Embling Hospital (Dr A. Brennan), and Werribee Mercy Mental Health Service (Dr S. Jespersen, Assoc Prof D. Stevenson, Mrs K. Hodge, Ms F. Gleeson, Ms K. Gray); and from New South Wales, Northern Sydney Central Coast Health (Dr M. Paton, Dr L. Newton, Mr J. Glen, Mr J. Bajuk, Ms A. Steele, Mrs P. Wheeler).

REFERENCES

1. Kilian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. *Lancet*. 1999;354(9193):1841–1845.
2. Coulter DM, Bate A, Meyboom RH, et al. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ*. 2001;322(7296):1207–1209.
3. Reinders J, Parsonage W, Lange D, et al. Clozapine-related myocarditis and cardiomyopathy in an Australian metropolitan psychiatric service. *Aust N Z J Psychiatry*. 2004;38(11–12):915–922.
4. Tirupati S. Clozapine and heart in the Hunter region. *Aust N Z J Psychiatry*. 2006;40(1):97.
5. Freedman R. The choice of antipsychotic drugs for schizophrenia. *N Engl J Med*. 2005;353(12):1286–1288.
6. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis.

Lancet. 2009;373(9657):31–41.
7. Bandelow B, Degner D, Kreusch U, et al. Myocarditis under therapy with clozapine. *Schizophr Res*. 1995;17(3):293–294.
8. Reid P. Clozapine rechallenge after myocarditis. *Aust N Z J Psychiatry*. 2001;35(2):249.
9. Annamraju S, Sheitman B, Saik S, et al. Early recognition of clozapine-induced myocarditis. *J Clin Psychopharmacol*. 2007;27(5):479–483.
10. Pieroni M, Cavallaro R, Chimenti C, et al. Clozapine-induced hypersensitivity myocarditis. *Chest*. 2004;126(5):1703–1705.
11. Kakar P, Millar-Craig M, Kamaruddin H, et al. Clozapine induced myocarditis: a rare but fatal complication. *Int. J Cardiol*. 2006;112(2):e5–e6.
12. Fineschi V, Neri M, Riezzo I, et al. Sudden cardiac death due to hypersensitivity myocarditis during clozapine treatment. *Int J Legal Med*. 2004;118(5):307–309.
13. Merrill DB, Ahmari SE, Bradford J-ME, et al. Myocarditis during clozapine treatment. *Am J Psychiatry*. 2006;163(2):204–208.
14. Varambally S, Howpage P. Acute myocarditis associated with clozapine. *Australas Psychiatry*. 2007;15(4):343–346.
15. Belloni E, De Cobelli F, Esposito A, et al. Myocarditis associated with clozapine studied by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2007;9(3):591–593.
16. Rathore S, Masani ND, Callaghan PO. Clozapine-induced effusoconstrictive pericarditis: case report and review of the literature. *Cardiology*. 2007;108(3):183–185.
17. Haas SJ, Hill R, Krum H, et al. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993–2003. *Drug Saf*. 2007;30(1):47–57.
18. Hägg S, Spigset O, Bate A, et al. Myocarditis related to clozapine treatment. *J Clin Psychopharmacol*. 2001;21(4):382–388.
19. Degner D, Bleich S, Grohmann R, et al. Myocarditis associated with clozapine treatment. *Aust N Z J Psychiatry*. 2000;34(5):880.
20. La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med*. 2001;345(3):224–225.
21. Hill GR, Harrison-Woolrych M. Clozapine and myocarditis: a case series from the New Zealand Intensive Medicines Monitoring Programme. *N Z Med J*. 2008;121(1283):68–75.
22. Friedrich MG, Strohm O, Schulz-Menger J, et al. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. *Circulation*. 1998;97(18):1802–1809.
23. Berk M, Fitzsimons J, Lambert T, et al. Monitoring the safe use of clozapine: a consensus view from Victoria, Australia. *CNS Drugs*. 2007;21(2):117–127.
24. Devarajan S, Kutcher SP, Dursun SM. Clozapine and sudden death. *Lancet*. 2000;355(9206):841, author reply 843.
25. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;360(3):225–235.