Government of **Western Australia**
South Metropolitan Health Service
Fiona Stanley Fremantle Hospitals Group

A retrospective review of clozapine-induced myocarditis and cardiomyopathy

Frances Paterson, Amanda Green
Department of Pharmacy, Fremantle Hospital
Contact: **frances.paterson@health.wa.gov.au**

Background

- Post marketing reports have implicated clozapine in causing serious cardiac adverse effects including myocardial infarction, myocarditis, pericarditis and cardiomyopathy.
- Clozapine product information states global reports of myocarditis and cardiomyopathy are rare (<0.1%) in the first month of treatment and very rare (<0.01%) thereafter, however the reported incidence in the literature varies.[1,2,3,4]
- The reason for this increased incidence is unknown, sparking interest in the symptoms, diagnosis, risk factors and required monitoring.

Aim

To review cases of serious cardiac adverse effects including myocarditis and cardiomyopathy in patients taking clozapine, over a 5 year period at a metropolitan mental health service.

Methods

- A retrospective report from Clopine Central®* identified all patients who had experienced clozapine therapy interruptions or cessation between January 2013 and February 2018.
- Patients with cardiac related complications were identified from this report. A detailed review of all myocarditis and cardiomyopathy cases was undertaken by a clinical pharmacist.
- Medical records were recalled and reviewed for each of the patients identified with myocarditis or cardiomyopathy with intent to identify any common features amongst those patients.
- Patient data was obtained from medical notes, discharge summaries, medication charts, iSOFT Clinical Manager* and Stocca*.

Results

- Over the five year period, 159 patients were registered with Clopine Central® and were treated with clozapine.
- A total of 65 therapy interruptions (from the Clopine Central® Therapy Events Report) were identified for 47 patients. (see Table 1)
- There were 12 cardiac related therapy interruptions. (see Figure 1)
- Seven patients experienced interruption or cessation of clozapine therapy associated with myocarditis or cardiomyopathy.
- The incidence of myocarditis was 3.1% and onset was within four weeks in all cases.
- C-reactive protein and troponin were elevated in all five myocarditis patients.
- Other clinical indicators included elevated body temperature, tachycardia and changes to echocardiogram and electrocardiography from baseline.
- Cardiomyopathy was present in 1.3% of all clozapine patients reviewed, with cases occurring up to 14 years after clozapine therapy commencement.
- There were no fatalities identified in this cohort.

Table 2: Patient information for clozapine-induced myocarditis

Patient and Diagnosis	Therapy Event(s)	Time to event	Symptoms reported	Echocardiogram (ECHO)	Electrocardiography (ECG) changes	Patient Outcome
73yo Female Chronic paranoid schizophrenia	Myocarditis *Mild viral myocarditis (low clinical suspicion of clozapine-induced myocarditis)*	24 days	NIL	Reduced Left Ventricular Ejection Fraction (LVEF) (63%)	NIL	Clozapine ceased. Repeat ECHO was normal and troponin returned to baseline.
32yo Male Chronic paranoid schizophrenia	Myocarditis *Heart failure with reduced ejection fraction*	19 days	Mild chest discomfort (tightness) and coryzsal symptoms	Reduced LVEF (21%) Severe reduction in systolic function	Sinus tachycardia	Clozapine ceased. Recent ECHO results returned to baseline.
56yo Female Chronic schizoaffective disorder	Myocarditis *Likely acute myocarditis secondary to clozapine*	18 days	Sweating, lethargy, and mild abdominal pain	Unchanged LVEF (60%) Mild dilation of ascending aorta	T wave inversion	Clozapine ceased. Repeat ECHO returned to baseline.
38yo Male Organic Delusional Disorder post brain injury	Myocarditis *Early myocarditis - detected before cardiac function affected*	18 days	Constipation	Unremarkable	NIL	Clozapine ceased. Detected before cardiac function affected.
31yo Male Schizophrenia	Myocarditis *Likely febrile illness however unable to exclude myocarditis*	19 days	Shortness of breath, diarrhoea, myalgia and a non-productive cough	Reduced LVEF (59%) Moderate mitral regurgitation (increased severity from baseline)	NIL	Clozapine ceased.

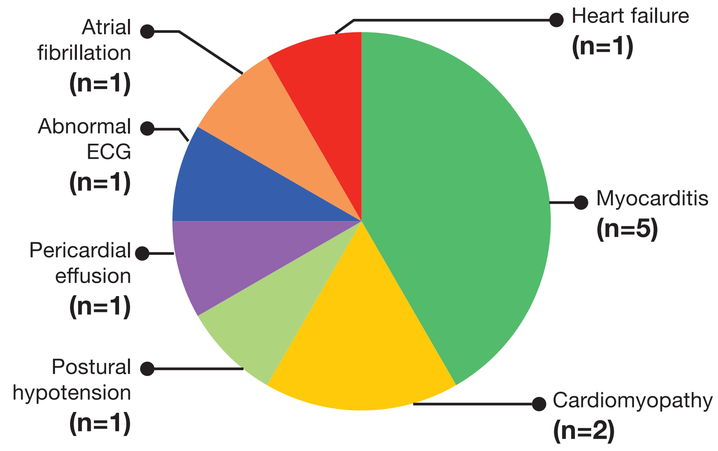
Table 3: Patient information for clozapine-induced cardiomyopathy

Patient and Diagnosis	Therapy Event(s)	Time to event	Symptoms reported	Echocardiogram (ECHO)	Electrocardiography (ECG) changes	Patient Outcome
46yo Male Chronic schizophrenia	Cardiomyopathy *Heart failure secondary to clozapine*	11 years	Shortness of breath, cough, intermittent palpitations, fatigue, dysuria and diarrhoea	Reduced LVEF (15%) Dilated cardiomyopathy and hypokinesis of both ventricles	NIL	Clozapine ceased. Diagnosis of heart failure.
32yo Male Chronic paranoid schizophrenia	Cardiomyopathy *Mild left ventricular impairment due to chronic clozapine-induced dilated cardiomyopathy.*	14 years	NIL	Unchanged LVEF (48%) Mild systolic dysfunction	NIL	Clozapine continues.

Table 1: Therapy interruptions identified from Clopine Central®

Therapy interruptions	No of therapy interruptions recorded	Percentage of total therapy interruptions	Percentage of all Clozapine patients
Myocarditis	**5**	**7.70%**	**3.10%**
Cardiomyopathy	**2**	**3.10%**	**1.30%**
Cardiac Complications	**4**	**6.20%**	**2.50%**
Postural Hypotension	**1**	**1.50%**	**0.60%**
Non-Compliance	33	50.80%	20.80%
Sedation	5	7.70%	3.10%
Other medical reasons not listed	2	3.10%	1.30%
Inadequate Response	2	3.10%	1.30%
Death of Patient	2	3.10%	1.30%
Neutropenia	2	3.10%	1.30%
Other side-effects not listed	1	1.50%	0.60%
Seizures	1	1.50%	0.60%
Weight Gain	1	1.50%	0.60%
Switched brands of Clozapine	1	1.50%	0.60%
Hypersalivation	1	1.50%	0.60%
Personal Reasons	1	1.50%	0.60%
Family/Carer Objections	1	1.50%	0.60%
Total	**65 therapy interruptions**		**159 patients**

Figure 1: Cardiac related therapy interruptions identified from Clopine Central®



Discussion

- The true incidence of myocarditis and cardiomyopathy associated with clozapine use may be underrepresented due to the non-specific nature of presentation. This could account for the variability of frequency found in published data. (See Table 4)
- Early detection of myocarditis, supportive management and cessation of clozapine are crucial for positive patient outcomes.
- Ongoing monitoring is essential for detection and management of cardiomyopathy, which can occur at any stage of treatment.

Table 4: Comparative rates of myocarditis and cardiomyopathy

	Literature Reports[2,3,4]	Product Information[1]	Fremantle Hospital Jan 2013 - Feb 2018
Myocarditis	**0.7-4%**	**0.1-1%**	**3.1%**
Cardiomyopathy	**0.02-0.1%**	**n/a**	**1.3%**

Conclusion

The rates of clozapine-induced myocarditis and cardiomyopathy identified in this review are significantly higher than the rates stated in product information. Future studies across Australian mental health services would be beneficial in an effort to identify factors behind the apparent increased incidence of this complication in Australia.

References

1. MIMS. Clopine. 2012 [cited 2018 May 3]. In: MIMS Online database [Internet]. Available from: https://www-mimsonline-com.au.smhslibresources.health.wa.gov.au
2. 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: 47–57.
3. Remington G, Lee J, Agid O, Takeuchi H, Foussias G, Hahn M, Fervaha G, Burton L, Powell V. Clozapine's critical role in treatment resistant schizophrenia: ensuring both safety and use. Expert Opinion on Drug Safety 2016; 15(9): 1193-1203. Doi:10.1080/14740338.2016.1191468
4. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999; 354: 1841–1845

***Clopine Central® is a patient monitoring system for patients taking clozapine, iSOFT Clinical Manager is an electronic patient information system and Stocca is a clinical pharmacist patient's notes program**