## It is illegal to post this copyrighted PDF on any website. An Unmet Need: A Clozapine-Induced

## Myocarditis Screening Protocol

**To the Editor:** Clozapine is the only antipsychotic approved for treatment-resistant schizophrenia, and clinicians should confidently be able to recognize and manage potential side effects of the medication, including myocarditis.<sup>1</sup> Clozapine-induced myocarditis was reported in 1999 in a series<sup>2</sup> of 15 cases (out of 8,000 patients prescribed clozapine: 0.19%), all within 3 weeks of starting clozapine. Five of these 15 patients died of clozapine-induced myocarditis.<sup>2</sup> Similar reports<sup>3</sup> from other countries, including Germany, Switzerland, Sweden, Australia, Canada, and the United States, soon followed. More recent reports<sup>4</sup> from Australia suggest incidence rates between 1.1% and 5%. Clozapine-induced myocarditis is included in the US Food and Drug Administration boxed warnings on clozapine use, along with 4 other categories of adverse effects.

Despite this warning, there is no monitoring protocol for myocarditis in the package insert for clozapine in the United States even though there is an extensive federally mandated monitoring protocol for clozapine-induced neutropenia. Additionally, published treatment guidelines<sup>5</sup> do not currently recommend a monitoring protocol for clozapine-induced myocarditis. This lack of a protocol is especially important because myocarditis is commonly missed in clinical practice; its presentation tends to be nonspecific, ranging from fever and rising troponin and C-reactive protein (CRP) levels to evidence of heart failure and in some cases death. Furthermore, it is possible that some individuals may have elevations in markers such as troponins and CRP that abate with no need for intervention.

**Methods:** As part of a study investigating attitudes toward prescribing clozapine, we surveyed community psychiatrists from the online Listserv of the American Association of Community Psychiatrists (AACP). The survey was sent out in 3 waves: November 10, 2015; December 8, 2015; and August 8, 2016. The survey included 25 questions. One question specifically addressed whether prescribers used a myocarditis screening protocol.

**Results:** Of the 57 responses to the survey (8.1% of the total AACP Listserv), all respondents had prescribed clozapine in the past, and 90% had prescribed clozapine in the last month. Only 5 respondents (9%) reported using a myocarditis screening protocol when initiating clozapine.

**Discussion and Conclusion:** Clozapine-induced myocarditis is a rare but serious risk of clozapine use. Despite having incidence rates similar to, if not higher than, clozapine-induced neutropenia, there are no similarly mandated monitoring protocols in place. Our data from a representative group of community psychiatrists (of note, there are no currently published studies systematically assessing attitudes regarding clozapine use among this group, who are likely to be more frequent prescribers of clozapine) suggest that despite frequent clozapine use, there are no standard protocols in place to screen for myocarditis. In our clinical practice, we use a modified protocol described in Ronaldson et al.<sup>4</sup> Education regarding known associations between clozapine and risk for myocarditis is important, including concurrent use of medications such as sodium valproate, increased rate of clozapine dose titration, and increased age.<sup>4,6,7</sup>

individuals with myocarditis, we recommend obtaining baseline levels of these biomarkers as well as weekly assessments of CRP and troponin levels for the first 6 weeks that a patient is treated with clozapine. As autopsy reports have shown eosinophilic infiltration on histologic report, eosinophil count and percentage may be an additional biomarker to consider along with CRP and troponins.<sup>3</sup> Vital signs must be monitored as well to assess for fever, tachycardia, and deviations in blood pressure from baseline. Unlike the Ronaldson protocol,<sup>4</sup> we do not routinely obtain baseline echocardiograms since they are not routinely available at our clinical setting, could delay clozapine initiation, and, as such, could significantly limit clozapine use.

In line with the Ronaldson protocol,<sup>4</sup> we suggest that clozapine should be stopped if troponins are twice the upper limits of normal or if CRP is > 100 mg/L. Mild elevations in troponins or CRP in the setting of persistent abnormal tachycardia and signs or symptoms consistent with an infectious process should warrant daily troponin and CRP measurements until these features resolve. Any concerns for clozapine-induced myocarditis may warrant a cardiology consultation, with the understanding that there are no current treatments for myocarditis except for removing the offending agent and other supportive approaches. Of note, there have been cases<sup>8</sup> of successful rechallenge in patients treated with clozapine who developed myocarditis. A standard protocol is an unmet need and should be viewed as a tool for clinicians to more safely prescribe clozapine.

## REFERENCES

- 1. Stroup TS, Gerhard T, Crystal S, et al. Geographic and clinical variation in clozapine use in the United States. *Psychiatr Serv.* 2014;65(2):186–192.
- Kilian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. *Lancet*. 1999;354(9193):1841–1845.
- Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand*. 2015;132(4):231–240.
- Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust N Z J Psychiatry. 2011;45(6):458–465.
- Buchanan RW, Kreyenbuhl J, Kelly DL, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements. Schizophr Bull. 2010;36(1):71–93.
- 6. Pui-yin Chung J, Shiu-yin Chong C, Chung KF, et al. The incidence and characteristics of clozapine-induced fever in a local psychiatric unit in Hong Kong. *Can J Psychiatry*. 2008;53(12):857–862.
- 7. Tham JC, Dickson RA. Clozapine-induced fevers and 1-year clozapine discontinuation rate. *J Clin Psychiatry*. 2002;63(10):880–884.
- Cook SC, Ferguson BA, Cotes RO, et al. Clozapine-induced myocarditis: prevention and considerations in rechallenge. *Psychosomatics*. 2015;56(6):685–690.

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