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Letter to the editor

Clozapine-induced myocarditis in Canada: Evidence from spontaneous reports

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Dear Editor:

Treatment resistance has been estimated to occur in 25–30% of patients with schizophrenia (Kane, 1996), and clozapine represents the only antipsychotic with proven efficacy and a clinical indication for use in this population (Remington et al., 2017). Despite this, the use of clozapine is commonly delayed or even avoided (Latimer et al., 2013). Historically, this was driven by concerns over agranulocytosis, with the requisite hematological monitoring also considered a barrier to clozapine initiation. While the mortality rate related to agranulocytosis has steadily declined with routine monitoring, other serious and potentially lethal side effects have been identified (Remington et al., 2016).

Myocarditis is an inflammation of the heart that can lead to severe complications including death (Raedler, 2010). Several antipsychotic medications have been associated with myocarditis, although reports involving clozapine are the most common (Coulter et al., 2001), and monitoring protocols for clozapine-induced myocarditis (CIM) have been recently introduced (Ronaldson et al., 2011). A recent case report highlighted myocarditis amongst several potentially fatal outcomes associated with clozapine (Li et al., 2018). In response, Dawson and colleagues examined the Australian Therapeutic Goods Administration (TGA) database for reports of CIM (Dawson et al., 2018). Findings demonstrated fewer than 5 annual reports of CIM prior to the year 2000, a figure that soared to more than 130 reports in 2016. Despite this increase, there was no evidence of an increased number of reported deaths due to CIM.

Similar to the Australian TGA database, the Canada Vigilance Program is a post-market database of suspected adverse reactions to health products marketed in Canada since 1965. The program's database uses the Medical Dictionary for Regulatory Activities (MedDRA version 21.0) to categorize adverse reaction terms. We hypothesized that spontaneous Canadian reporting of CIM would reflect a pattern similar to Australian reporting. Using a search strategy similar to Dawson and colleagues, the Canada Vigilance Program database was searched from January 1, 1965 to the latest data release (June 30, 2018) for the adverse reaction term 'myocarditis' related to the active ingredient 'clozapine'. The number of reports and outcome were recorded.

The number of annual reports for suspected CIM is presented in Fig. 1. There were no reported cases prior to 1997, and fewer than 5 reports annually between 1997 and 2001. This increased in 2002 (n = 6), with a marked increased in the last several years. The most reports (n = 47) were submitted in 2017; however, this number has already been approached in the first six months of 2018 (n = 31). The most common outcome noted at the time of report was 'unknown' (n = 157), followed by 'recovered/resolved' (n = 75), 'not recovered/not resolved' (n = 24), 'death' (n = 14), 'recovering/resolving' (n = 7), and 'recovered/resolved with sequelae' (n = 6). Death was noted in 4.9% of reports, the most deaths to date were reported in 2008 (n = 4), and the last death was reported in 2016 (n = 1).

We sought to examine adverse reaction reports related to CIM in Canada. Confirming our hypothesis, we found a progressive increase in the number of reports in the Canada Vigilance Program database, a pattern resembling trends in the Australian TGA database. This likely reflects adoption of monitoring protocols for CIM as the increase is observed earlier in Australia, where guidelines were implemented before Canada. In contrast, CIM monitoring guidelines were not in place until 2014 at our Centre and monitoring in Canada remains confined to a limited number of sites.

These results must be viewed within the limitations of post-market data. Such data likely underestimate the number of adverse reactions since they depend on voluntary reporting. Even when submitted, reports may be incomplete, inaccurate, and not followed up in terms of outcomes. The Canadian database also permits submission by anyone, which in turn can impact the certainty of key information such as an established versus suspected diagnosis. Along similar lines, Canadian data indicate no reports of death in the last several years. Certainly one interpretation might attribute this decrease to closer monitoring for myocarditis leading to earlier detection and drug discontinuation. Alternatively, it may be that outcomes are more frequently identified and reported near the time of myocarditis onset whereas final outcomes are less frequently reported.

Prospective studies examining CIM are required to clarify key information such as demographic factors, titration schedules, and monitoring practices that best predict fatal and non-fatal CIM. In the interim, current data suggest that CIM occurs rarely and typically within the first month of treatment (Ronaldson et al., 2012). Existing monitoring protocols appear to be enhancing CIM detection and, in doing so, mitigating fatal outcomes. Hopefully, increased attention to CIM is not associated with an unintended consequence of further delays in initiation or complete avoidance of treatment with clozapine (Remington et al., 2016).

Conflict of interest

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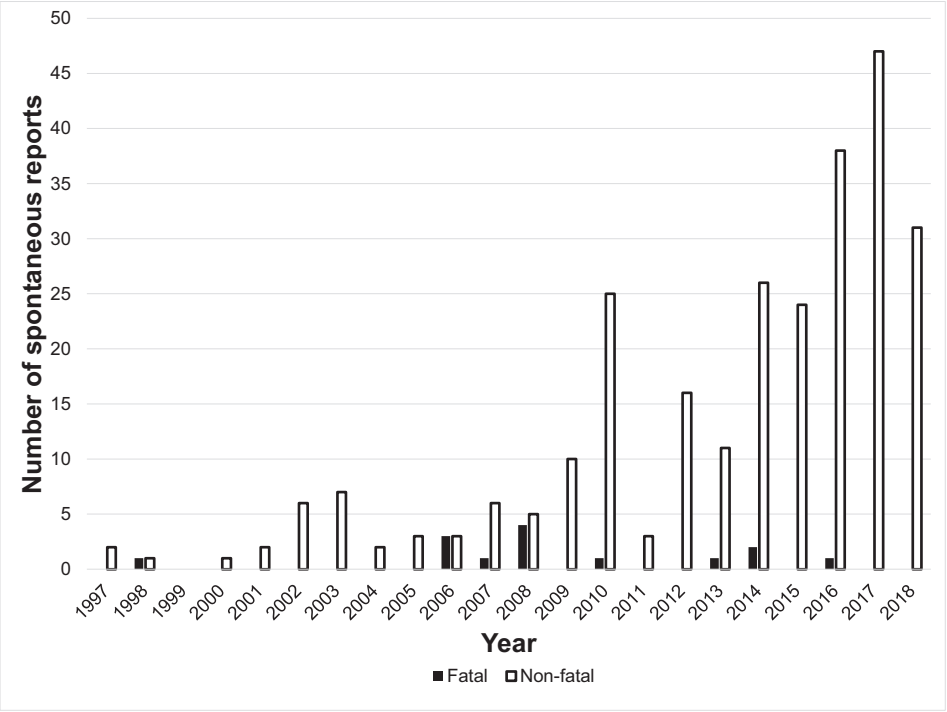

Fig. 1. Number of spontaneous reports submitted to the Canada Vigilance Program database between January 1, 1965 and June 30, 2018 for suspected clozapine-induced myocarditis. Black bars represent the number of reports with fatal outcomes and white bars represent the number of reports without fatal outcomes.

CRediT authorship contribution statement

Nicholas H. Neufeld: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Gary Remington:** Conceptualization, Supervision, Writing - review & editing.

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