

**Supplementary Table 11.** Contribution of Australians to the field of clozapine-induced myocarditis

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Putting clozapine-induced myocarditis on the radar of the drug agencies

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- In 1999, Kilian et al.<sup>90</sup> placed clozapine-induced myocarditis on the radar of drug agencies.
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First Australian comment on the role of rapid titrations in the 2007 guideline

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- In 2007, a comment was included in a consensus guide for the safe use of clozapine by Australian experts:<sup>150</sup> “Some groups have found that abnormalities are more likely to be associated with more rapid titration (Pantelis C, unpublished observations). There are, nevertheless, no current data or studies to definitively support this notion.”
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Bringing attention to the role of rapid titration in 2012 by Ronaldson et al.<sup>96</sup>

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- In a case-control study, Ronaldson et al.<sup>96</sup> was the first to describe clozapine-induced myocarditis in Australia as significantly associated with rapid titration. Rapid titration was defined on the basis of each additional 250 mg of clozapine administered in the first nine days with an OR of 1.26 (CI 1.02 to 1.55).
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Bringing attention to the role of valproate by Ronaldson et al.<sup>96</sup>

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- Ronaldson et al.<sup>96</sup> was also the first who described clozapine-induced myocarditis due to valproate co-administration as associated with an OR of 2.59 (CI 1.51 to 4.42). This is one of the most consistent findings in studies of clozapine-induced myocarditis.<sup>151</sup>
  - Valproate can behave as an inhibitor during early titration before the inductive effects of valproate on norclozapine predominate.<sup>152</sup>
  - In 13 patients with clozapine-induced myocarditis from 2 case series with blood levels,<sup>153,154</sup> 8 patients took valproate and behaved as clozapine PMs.
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Bringing attention to the confounding role of co-infections

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- Regarding the diagnosis of clozapine-induced myocarditis diagnosed in a referral to an Australian hospital, Winckel et al.<sup>155</sup> found:
    - 65% (13/20) did not meet criteria for myocarditis.
    - 25% (5/20) had upper respiratory infections, which may explain the myocarditis.They proposed that this diagnosis included cases of inflammation that did not strictly meet the diagnosis of myocarditis and cases with concomitant viral infections.
  - Meeting or not meeting the criteria for a diagnosis of clozapine-induced myocarditis is not important. Any inflammation during clozapine titration is extremely worrisome. It does not matter whether it is secondary to rapid clozapine titration or has another cause; all inflammation releases cytokines that decrease clozapine metabolism.<sup>46</sup> As a matter of fact, patients with undiagnosed inflammation cannot tolerate normal titrations and can develop additional clozapine-induced inflammation, making titration very risky.<sup>46</sup>
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Bringing attention to the role of co-medication with quetiapine

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- A small case-control study<sup>156</sup> in Australia found significant increases of quetiapine co-prescription in 29% of the 24 myocarditis cases versus 18% of the 121 controls (This provided an OR=1.79, slightly higher than the valproate OR=1.69).
  - In VigiBase data on clozapine-induced myocarditis through 2021,<sup>67</sup> quetiapine co-prescription increased the risk for:
    - seriousness OR 2.83 (95% CI 1.82 to 4.40) and
    - lethality 2.12 (95% CI 1.03 to 4.35).
  - Quetiapine, in overdoses or rapid titrations, may cause myocarditis by itself.<sup>157</sup>
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CI, confidence interval; OR, odds ratios; PM, poor metabolizer