

## Supplementary Table 6. Clozapine-induced myocarditis

### First descriptions

- In 1980, Danish authors<sup>85</sup> published in Danish the first case of clozapine-induced myocarditis in a patient started on 300 mg/day (rapid titration by a doctor).
- In 1992, US authors<sup>86</sup> described the “first rapid titration by a patient” (a lethal intentional overdose using 2,000 mg). They found eosinophilic myocarditis.
- Two years later, the same eosinophilic myocarditis was described in Danish by Jensen and Gøtzsche,<sup>87</sup> who first proposed it was an “allergic” myocarditis.
- Eosinophilic myocarditis is the typical presentation of clozapine-induced myocarditis.<sup>88</sup>

### Drug agencies

- In 1993, the British agency first described clozapine as a possible cause of myocarditis.<sup>89</sup>
- In 1999, an article by Killian et al.<sup>90</sup> reviewed 23 cases from the Australian drug registry and placed clozapine-induced myocarditis on the radar of the drug agencies.
- This article prompted skeptical reviews by investigators from Vigibase<sup>91</sup> and the FDA.<sup>92</sup> In 2002, the FDA included the warning in the US package insert.
- It is unfortunate that the drug agencies did not pay attention to a comment on Killian’s cases by Canadians<sup>93</sup> who stated that “in all cases, daily clozapine doses were increased rapidly” and that the Australian titrations were much faster than their Canadian titrations.
- In a review of reports to the Swedish drug agency, Scandinavian investigators<sup>94</sup> related myocarditis to hypersensitivity myocarditis and other clozapine-induced eosinophilic syndromes.

### Unusually high incidence of clozapine-induced myocarditis in Australia

- In 2012, two crucial articles defending two extreme positions on clozapine-induced myocarditis were published by Continental Europeans<sup>95</sup> and Australians.<sup>96</sup>
- Authors from the Netherlands<sup>95</sup> brought attention to an incidence rate of 0.7%–1.12% in Australia versus 0.07% worldwide. This difference was replicated in a 2020 meta-analysis (2% in 9 Australian samples vs 0.3% in 15 non-Australian samples).<sup>97</sup>
- In the Australian case-control study, Ronaldson et al.<sup>96</sup> found that clozapine-induced myocarditis in Australia was significantly associated with rapid titration (rapidity 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), while valproate co-administration was associated with an OR of 2.59 (CI 1.51 to 4.42).
- Since 2012 these two positions may have become further apart. In their 2015 review literature, Ronaldson et al.<sup>98</sup> proposed that the Australian experience is the correct one since the real incidence of myocarditis is around 3% and “that a similar incidence would be found in other jurisdictions, if a practice of routine monitoring for myocarditis was adopted.”
- Ronaldson’s estimates are obviously wrong, according to the Danish registry. Rohde et al.<sup>99</sup> found no deaths in the first 2 months of clozapine treatment. According to the theory of Ronaldson et al.,<sup>98</sup> Danish psychiatrists overlooked approximately 97 (3% of 3,262) cases of clozapine-induced myocarditis but, surprisingly, none of them died.<sup>100</sup>

### A hypersensitivity reaction associated with rapid titration

- In 2015 two articles,<sup>101,102</sup> independently commenting on the myocarditis review by Ronaldson et al.,<sup>98</sup> proposed that clozapine-induced myocarditis is a hypersensitivity reaction associated with rapid titration of clozapine and analogous to the lamotrigine-induced Stevens-Johnson syndrome.

CI, confidence interval; FDA, Food and Drug Administration; OR, odds ratios