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Response to 'The association of clozapine and haematological malignancies needs to be replicated by other studies and more importantly by analyses of subsamples from VigiBase'

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We have read with interest the reply by *De Leon* et al. (Leon, las Cuevas, Sanz, & Verdoux, 2020*a*) about our work assessing the association between clozapine and haematological malignancies (Chrétien et al., 2020) in VigiBase®. We are grateful that *De Leon* et al. showed such interest in our study and we think that their remarks merit further explanations to be fully addressed. We agree that pharmacovigilance databases suffer several limitations that we previously discussed. However, the use of disproportionality analysis in pharmacovigilance databases represents a major tool to detect safety signals and adapt management guidelines, especially for rare events and have shown extremely valuable in the past (Faillie, 2019). Using a similar methodology in VigiBase®, *De Leon* et al. recently highlighted a significant association between clozapine and pneumonia compared to other second-generation antipsychotics, that also represent an important piece of information for psychiatrists (De Leon, Sanz, & De las Cuevas, 2020; Leon, Sanz, Norén, & las Cuevas, 2020*b*). The risk of false positive in VigiBase® requires a rigorous approach of such analyses and the existence of a pathophysiological pathway underlying the association is of the highest importance to prevent researchers from misleading conclusions.

We agree with *De Leon* et al. that analysing more subsamples from VigiBase® could have strengthened our previous in-depth analysis with multiple settings of analyses in VigiBase® and we therefore provide here Bayesian shrinkage observed-to-expected ratio in sub-groups of the full de-duplicated VigiBase® population for all adult age groups and across Africa, the Americas, Asia, Europe and Oceania. Our results showed a reduction in the likelihood of being due to report artefacts or case duplication (Table 1).

De Leon et al. seem to consider problematic that more adverse effects are reported with clozapine than with risperidone, quetiapine or olanzapine. Fortunately, disproportionality analyses are specifically designed to overcome this issue, as it compares the proportion of reports of an adverse effect reported for a single drug with the proportion of reports of the same adverse effect for all other drugs or for a selected panel of control drugs. Moreover, at the moment of the study, clozapine was barely suspected to be a cause of haematological malignancies, which allowed us to exclude a notorious bias. We are confused by *De Leon* et al. advising the use of Bayesian shrinkage statistics rather than disproportionality analyses as Bayesian shrinkage statistics are disproportionality analyses themselves (Norén, Hopstadius, & Bate, 2013). When a p value does not reach the 0.05 threshold, it is assumed that no specific association was demonstrated (in the case of a two-sided Bayesian test, the correspondence is the lower-end of a 95% credibility interval, e.g. the IC_{025}). In VigiBase®, this is even more important as the risk of false positive is of concern, as highlighted by *De Leon* et al.

We believe our negative control fits its purpose in regard to our statistical hypothesis. While using 'all other considered drugs' as a negative control could have a real interest in a cohort of schizophrenic patients, it is extremely hazardous in pharmacovigilance databases. Indeed, 'all other considered drugs' represent the background of the disproportionality analysis and their measurement of disproportionality is *de facto* the inverse of the signal for the drug of interest. Thus, 'all other considered drugs' would systematically have a negative association with the adverse effect of interest and would not discriminate between false- and true-positive associations (i.e. they would not fit the purpose of 'negative controlling') (Faillie, 2019).

Table 1. Disproportionality analyses in VigiBase® of lymphomas and leukaemias in clozapine treated patients: analyses of subsamples

		Lymphomas			Leukaemias		
		N	IC	95% CI	*N*	IC	95% CI
Age (years)	18–44	143	1.63	(1.35–1.83)	75	1.09	(0.71–1.37)
	45–64	289	1.73	(1.53–1.87)	116	1.22	(0.91–1.44)
	65–74	36	1.94	(1.39–2.34)	28	1.31	(0.68–1.76)
	⩾75	8	1.72	(0.51–2.52)	15	1.83	(0.96–2.44)
Region	Africa	0	*		0	*	
	Americas	197	2.04	(1.81–2.21)	147	1.57	(1.29–1.76)
	Asia	2	*		1	*	
	Europe	295	1.70	(1.51–1.84)	121	1.00	(0.69–1.21)
	Oceania	78	1.09	(0.72–1.36)	27	0.77	(0.13–1.22)

N, number of cases; CI, confidence interval.
Lymphomas were retrieved using the associated Standardized MedDRA Query; Leukaemias were retrieved using the associated High Level Term; the interaction constant was the Information Component (IC), a Bayesian shrinkage observed-to-expected disproportionality analyses method; a lower end of the 95% CI higher than 0 was significant. Total de-duplicated reports in VigiBase®: 22.092.938; *disproportionality analysis were computed if at least five cases were reported.

We do agree with *De Leon* et al. that it would have been of interest to explore the effect of duration of the treatment, but this data was quite inconsistent in the base and we chose not to describe it.

Finally, we are aware that pharmacovigilance retrospective studies using large databases provide a low level of evidence. However, they represent major tools to detect rare and delayed adverse events that cannot be detected in randomized controlled trials. This is the reason why at the time of the publication we could not advise clozapine discontinuation, but rather a careful evaluation of the benefit–risk taking into account potential risk factors of haematological malignancies at the discretion of the physician. We also advised, in accordance with the summary of products characteristics and current guidelines (Keating et al., 2017), the use of the lowest effective posology, as our study showed a potential dose-effect. 'Scaring patients' was never our intention. Appropriate and loyal information must always be provided to patients in regard to the available level of evidence for potential adverse effects they may encounter.

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Conflict of interest. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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