

# Tramadol and hyponatraemia – new aspects of an old signal

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## Background

In 2016, the PRAC, at the European Medicines Agency, reviewed a signal of hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) with tramadol, an opioid analgesic. Causality was not established, since reports were relatively few, concerned mostly elderly patients and were confounded by therapy or other factors.[1] These arguments are not entirely convincing; the relatively few cases may be explained by extensive underreporting of hyponatraemia.[2] And since hyponatraemia is largely predominant in the elderly population, and is a symptom of various spontaneous or drug-induced conditions, it is inevitable that the reports concern these patients, primarily.

## Aim

To investigate if VigiBase, the WHO global database of individual case safety reports, included cases suggestive of causality between tramadol and hyponatraemia.

## Methods

VigiBase data until 04-02-2018 for the broad MedDRA SMQ 'Hyponatraemia/SIADH', and tramadol as suspected, included 278 unique cases. Our analysis focused on cases with time-to-onset available, or where tramadol was the only reported drug, in the structured data. From these, cases with potentially confounding drugs (i.e. drugs with hyponatraemia and/or SIADH as known ADRs[3], and other opioids) started within 2 months before or after tramadol initiation, were excluded. The remaining cases were reviewed case by case.

## Results

The case-by-case review included 118 cases. Ages ranged between 20-106 years (median 77), with 35 patients younger than 65 years. Time-to-onset distribution was: within one day (21 cases), 2-14 days (71), 15-30 days (8) and >30 days (6). Seventy-nine patients recovered after withdrawal but fluid or sodium corrections, or other drug withdrawals, were co-reported for 45 of these. One well-described positive rechallenge was identified. Tramadol was sole-suspect in 63 cases and in 26 the sole-reported drug. Potentially confounding conditions, such as surgery, were described in around 25% of cases. In another 25% of cases, not recently diagnosed conditions like hypothyroidism and diabetes were reported, which were more likely risk factors than confounders. Fifty-five patients were co-treated with drugs known to cause hyponatraemia (e.g. antidepressants, diuretics and ACE-inhibitors). However, in 16 cases these were long-term drugs and were taken over many months or years in some cases, and hyponatraemia occurred only after tramadol initiation. In five cases, tramadol was reported as suspected of having interacted with the co-medications.

## Conclusion

VigiBase cases that support causality between tramadol and hyponatraemia were found. The key cases usually concerned elderly and predisposed patients, but young individuals were also identified. Causality was supported by the time-to-onset pattern, cases with positive dechallenge and one positive rechallenge.

## References

1. Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the PRAC meeting 4-8 July 2016. Available from: <https://www.ema.europa.eu/en/committees/prac/prac-agendas-minutes-highlights>. Accessed: May 2019.
2. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatraemia. *Am J Kidney Dis.* 2008 Jul;52(1):144-53.
3. Electronic Medicines Compendium. Available from: <http://www.medicines.org.uk/emc>. Accessed: May 2019.

