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Attributing Hyponatraemia to Treatment with Antipsychotic Medications

Meulendijks et al.[1] recently published in *Drug Safety* a review of the available evidence on antipsychotic-induced hyponatraemia. The authors are to be commended for drawing attention to a condition that is not uncommon in individuals with psychosis and serious enough to merit clinical concern. They reviewed 4 studies and 91 published case reports and/or case series of 120 subjects. Even though the review did not include a fairly recent study[2] that found no association between antipsychotic drug treatment and hyponatraemia in a large sample of individuals with psychosis (n = 328), the authors provided a balanced and nuanced review of this complex medical condition.

Unfortunately, the same cannot be said for the abstract. The implications of the most substantive passages in the abstract are misleading and contradict the review itself. In their abstract, the authors state that "A causality assessment was performed on all case reports using Naranjo's adverse drug reaction probability scale" and then go on to state that the results of this causality assessment "… indicated possible causality in most cases (80%), probable causality in a significant amount of cases (19%) and unlikely causality in one case (1%)." The implication here is that hyponatraemia among individuals being treated with antipsychotics is nothing but an adverse drug reaction; however, there is nothing in the review that can be taken as empirical evidence of causality. It is unfortunate that the authors introduced the language of probabilistic statistics into their abstract without any qualifying comments or disclaimers. The authors themselves acknowledge that "We identified no clinical studies that have investigated hyponatraemia as an adverse reaction associated with antipsychotic treatment. Although several preliminary studies found no association between antipsychotic treatment and hyponatraemia, a great deal of evidence is available in the form of case reports." Yet the abstract asserts that in 99% of the cases the observed hyponatraemia was 'probably or possibly' caused by treatment with antipsychotic medications.

For nearly a century now it has been recognized that schizophrenia itself elevates the risk of hyponatraemia apart from any exposure to antipsychotic medication,[3-5] and very recent neuroanatomical findings suggest that the degree of fluid dysregulation in these patients may be proportional to discrete changes in hippocampal and amygdala shape.[6] The Meulendijks et al.[1] review is based primarily (70%) on cases of schizophrenia, a population that introduces numerous overlapping risk factors for hyponatraemia (both disease- and treatment-related) making it impossible to attribute causality without employing a much more empirically-based approach than was used by the authors. It is important that limitations to inferences being presented in an abstract be clear to prevent misinterpretation of clinical and research applications drawn by the media, patients, families, clinicians and others. There are too many examples in the medical literature showing deleterious effects on patient care that persist for as long as 15 years, resulting from methodological flaws that were slow to be recognized.[7]

Hopefully, interested readers of the Meulendijks et al.[1] review will move beyond the abstract and delve into the body of the review where the authors provided a balanced and nuanced review of this complex medical condition.

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References

1. Meulendijks D, Mannesse CK, Jansen PAF, et al. Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. Drug Saf 2010; 33 (2): 101-14
2. Jessani M, Montgomery J, Fedde JD, et al. Lack of association between antipsychotics and hyponatremia in chronic schizophrenia. Schizophr Res 2006; 83: 307-9
3. Hoskins RG, Sleeper FH. Organic functions in schizophrenia. Arch Neurol Psychiatry 1923; 30: 123-40
4. Targowla R. Des troubles fonctionnel du rein dans les maladies mentales. L'excretion del'eau (Kidney malfunction and mental illness: water excretion). Bull Mem Soc Med Hop Paris 1923; 47: 711-5
5. Barahal HS. Water intoxication in a mental case. J Psych Quat 1938; 12: 767-71
6. Goldman MB. The mechanism of life-threatening water imbalance in schizophrenia and its relationship to the underlying psychiatric illness. Brain Res Rev 2009; 61: 210-20
7. Moore TJ. Deadly medicine: why tens of thousands of heart patients died in America's worst drug disaster. New York: Simon & Schuster, 1995

The Authors' Reply

We thank Dr Josiassen and colleagues for their interest in our systematic review on antipsychotic-induced hyponatraemia that was recently published in *Drug Safety*.[1] We appreciate the opinion that the review draws attention in a balanced and nuanced manner to the serious condition of hyponatraemia. Dr Josiassen brings up a few issues that we would like to address. Firstly, it is pointed out that the study by Jessani et al.[2] was not included in the review. The title of this article suggests that the study includes information on patients with hyponatraemia; however, the study analyses the correlation between sodium levels and antipsychotic drug dosage in mostly normonatraemic individuals. We did not include this study because it did not meet our inclusion criteria; no sodium levels and information about drug treatment are mentioned for individual hyponatraemic patients. We should note that the main result of this study, the fact that no association was found between antipsychotic drug dosage and sodium levels, is in accordance with our results.

We regret that the writer brings forward the issue of the way our results were presented in the abstract. We attempted to summarize our results in the abstract in such a way that they reflect what is discussed in the full text. Furthermore, we did so in accordance with the *Drug Safety* 'Instructions for Authors' and item 1b of the STROBE statement: ''Title and abstract provide information and balanced summary of what was done and what was found.''[3] In reporting on the results of the causality assessment for which the Naranjo algorithm was used, we used the definitions originally used by Naranjo et al.[4] The Naranjo algorithm is a validated and widely accepted method for assessing causality in the setting of suspected drug-related adverse reactions. We regret that the definitions for possible outcomes (unlikely, possible, probable and certain), which reflect the degree of causality between drug treatment and a suspected adverse reaction in single cases, gave the writer the impression of ''language of probabilistic statistics''. This is an association that is far from the original reason to use this tool.

Another point Dr Josiassen makes is that schizophrenia itself is a risk factor for the occurrence of hyponatraemia. This idea is supported by research that has been done by Goldman,[5] and, as thoroughly discussed in the review, we share this point of view. We should note that in scoring the case reports we deducted points for all cases with schizophrenia or 'psychosis' in the medical history because we did consider this as an 'other possible cause' (as well as other relevant co-morbidity and co-medication). The fact that another important risk factor is present in the population treated with antipsychotics certainly complicates studying a potential relation between drug treatment and an adverse drug reaction. The cases that describe elevation of sodium after dechallenge of the suspected drug as well as recurrence of hyponatraemia at rechallenge may, however, indicate that not all cases of hyponatraemia in schizophrenia should be discarded as disease-related morbidity. Furthermore, in another recent publication on the issue of antipsychotic-induced hyponatraemia, using a case-control study on the WHO database (VigiBase), we concluded that antipsychotic use may be associated with reporting of hyponatraemia.[6]

What arises from this discussion is that more research is needed in this area, which starts with physicians and researchers being aware of the different factors that may contribute to hyponatraemia in psychiatric patients.

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References

1. Meulendijks D, Mannesse CK, Jansen PAF, et al. Antipsychotic-induced hyponatraemia: a systematic review of the published evidence. Drug Saf 2010; 33: 101-14
2. Jessani M, Montgomery J, Fedde JD, et al. Lack of association between antipsychotics and hyponatremia in chronic schizophrenia. Schizophr Res 2006; 83: 307-9
3. von Elm E, Altman DG, Egger M, et al., for the STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008 Apr; 61 (4): 344-9
4. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981 Aug; 30 (2): 239-45
5. Goldman MB. The mechanism of life-threatening water imbalance in schizophrenia and its relationship to the underlying psychiatric illness. Brain Res Rev 2010; 61: 210-20
6. Mannesse CK, van Puijenbroek EP, Jansen PAF, et al. Hyponatraemia as an adverse drug reaction of antipsychotics: a case-control study in VigiBase. Drug Saf 2010; 33: 569-78