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Letter to the Editor

### A Retrospective, Uncontrolled Study is Not Suitable for Evaluating the Efficacy of Onabotulinumtoxin A in Chronic Migraine

Josef Finsterer

Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: Josef Finsterer

#### Letter to the Editor

We read with interest the article by Waliszewska-Prosół *et al.* regarding a retrospective, multicenter observational study on the efficacy of onabotulinumtoxin A (BoNT-A) <sup>[1]</sup>. The study examined a cohort of 479 Polish patients who had failed at least two prior oral prophylactic therapies, aiming to identify clinical predictors of treatment response, defined as a reduction in monthly headache days (MHDs) of >50% <sup>[1]</sup>. At the nine-month follow-up, a reduction of 5.9 in MHDs, an improvement of 53 points in the Migraine Disability Assessment Scale (MIDAS) score, a reduction in MHDs of more than 50% in 27% of patients, and the resolution of medication-overuse headache in 41% of patients were observed. A positive family history of migraine and more than four prior failures of prophylactic drug therapy were identified as predictors of a poor response <sup>[1]</sup>. While the study is noteworthy, certain aspects warrant discussion.

One initial point concerns the retrospective study design <sup>[1]</sup>. Retrospective designs have various drawbacks, such as lower data quality, missing data, the inability to establish causality (only associations can be determined), susceptibility to recall and selection bias, difficulties in controlling for confounding factors, and a generally lower level of evidence compared to prospective studies <sup>[2]</sup>.

A second point is that the MIDAS questionnaire has significant limitations regarding accuracy and practical applicability in everyday life <sup>[3]</sup>. Its main weakness is that the instrument requires patients to recall pain and days lost due to illness over a three-month period. This can lead to estimates or the forgetting of details <sup>[3]</sup>. Furthermore, questions regarding a 50% loss in productivity are difficult to define, resulting in widely varying responses from affected individuals <sup>[3]</sup>. Additionally, the score is of limited use for evaluating patients who experience only a few, albeit severe, attacks <sup>[3]</sup>. It does not capture overall quality of life but is limited to documenting days lost or days with restricted activity, while failing to account for the significant psychological or emotional burdens associated with migraine <sup>[3]</sup>. Additionally, many patients feel that the score does not adequately reflect the impact on their personal lives <sup>[3]</sup>.

A third point is that the study in question was uncontrolled <sup>[1]</sup>. Uncontrolled studies have the critical disadvantage of being unable to establish causal relationships; consequently, it is difficult to determine whether the observed outcome is truly attributable to the treatment or if other external factors played a role <sup>[4]</sup>. External variables, such as changes in the participants' diet, lifestyle, or environment, can influence the results. Moreover, participants often show improvement simply because they believe they are receiving an effective treatment. Since many diseases and symptoms improve spontaneously over time, uncontrolled studies carry the risk that natural recovery might be mistakenly attributed to the efficacy of the drug or therapy. Furthermore, individuals often participate in clinical studies only when their symptoms are at their most severe. However, since these symptoms often return to a less severe baseline level, this can create the appearance of treatment success <sup>[4]</sup>. Without blinding or random assignment to different groups, researchers and participants can unconsciously influence data collection and interpretation, thereby distorting the study's conclusions <sup>[4]</sup>.

The fourth point is that none of the enrolled patients had ever taken CGRP inhibitors <sup>[5]</sup>, which block calcitonin gene-related peptide. Were patients who had taken CGRP inhibitors specifically excluded from the study? The effect of BoNT-A was to be compared with that of a control group of patients treated with CGRP inhibitors.

**Declarations**

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**Consent to Participation:** Not applicable.

**Consent for Publication:** Not applicable.

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**Availability of Data and Material:** All data are available from the corresponding author.

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