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ORIGINAL COMMUNICATION

Differences in treatment of anti-NMDA receptor encephalitis: results of a worldwide survey

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Abstract The objective of the study was to identify differences in treatment strategies for anti-NMDA receptor encephalitis based on specialty of treating physicians, geographic location, and years in practice. We conducted an anonymous worldwide electronic survey through the Practice Current section of Neurology® Clinical Practice to appraise differences in decisions about first- and second-line treatment and timing for initiation of second-line treatment for anti-NMDA receptor encephalitis. 399 participants answered all questions of the survey and were included in the analysis. 261 (65%) were adult neurologists, 86 (22%) were neurologists treating children, and 52 (13%) were pediatric rheumatologists. 179 (45%) responders practiced in the US. The majority agreed on the use of steroids and/or IVIg for first-line therapy and rituximab alone as second line. Differences in initial treatment regimen based on specialty included increased use of plasma exchange by adult neurologists (27%) and rituximab by pediatric rheumatologists (29%) ($\chi^2(4) = 27.43$, $p < 0.001$). Trainees opted for plasma exchange (35%) and junior faculty picked rituximab (15%) more as part of first line ($\chi^2(4) = 13.37$, $p = 0.010$). There was greater usage of anti-metabolites for second-line therapy outside of the US (15%) ($\chi^2(4) = 11.67$, $p = 0.020$). US physicians also utilized second-line treatment earlier than their mostly European counterparts (14 vs. 23% used later than 2 weeks; $\chi^2(1) = 4.96$, $p = 0.026$). Although treatment patterns were similar, differences observed across specialties and geographic locations may guide the development of consensus-driven guidelines by multi-disciplinary task forces. These guidelines may promote treatment trials of immunomodulators in autoimmune encephalitides.

Keywords Anti-NMDA receptor encephalitis · Treatment · Immunotherapy

Introduction

Anti-NMDA receptor (anti-NMDAr) encephalitis is increasingly recognized as the most common form of immune-mediated encephalitis [1] and has generated considerable attention in the neuroscience community since the initial studies that described it between 2005 and 2007 [2, 3].

While the spectrum of clinical manifestations and sensitivity of diagnostic tests have been described [4, 5], data on the efficacy of treatment strategies are lacking and all evidence is class IV [6]. No open label trial has been conducted, and choices are influenced by results of large retrospective studies [5], individual preference and anecdotal experience. Common protocols include tumor removal (when present), and various combinations of immunomodulators including high-dose corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange

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(PLEX), rituximab, cyclophosphamide, and anti-metabolite agents (such as mycophenolate and azathioprine). Treatment is usually considered a two-stage process; second-line medications are often given in case of a lack of clinical improvement or worsening of status after a variable amount from time of first-line treatment administration. There are expert opinion statements regarding the use of a comprehensive immunotherapy regimen consisting of a second-line agent such as rituximab upfront with first line at the time of diagnosis [7]. Such comprehensive "induction" regimens are justified by the severity of the disease, which can be fatal or lead to considerable morbidity if not treated early and aggressively [8].

Anti-NMDAr encephalitis is diagnosed in all age groups and the management of these patients often requires a multi-disciplinary approach. In North American pediatric hospitals, rheumatologists often assist neurologists with immunomodulation efforts.

We hypothesized that there are differences in treatment strategies for anti-NMDAr encephalitis, based on specialty of treating physicians, geographic location, and years in practice.

Methods

Survey

The electronic survey consisted of three clinical and six demographic questions (supplemental data). Clinical questions included: (1) Treatment of choice for first line, (2) Timing of initiation of second-line treatment; (3) Treatment of choice for second-line. Demographic questions were: (1) Subspecialty and population treated (neurologists treating adults only, neurologists treating children or pediatric rheumatologists); (2) Years in practice; (3) Primary work setting; (4) Level of training; (5) Practice in the US or outside and (6) in what state or country.

In the introduction to the survey, it was stated that the survey questions applied to newly diagnosed patients and not to relapses and that tumor removal, when present, was considered part of the first-line treatment for all the available options.

The survey was administered through an online survey development cloud-based software and did not allow or request responders to provide identifiable personal information. A link to the questionnaire was available on the Neurology® journals webpages (including Neurology®, Neurology: Clinical Practice®, Neurology: Genetics® and Neurology: Neuroimmunology & Neuroinflammation®) and in the Practice Current dedicated webpage [9]. Members of the American Academy of Neurology (AAN) also received a link to the survey by email in the form of AAN e-News and AAN Editors' Picks; members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) received a link to the survey by email through their mailing list. Practice Current was also advertised by a feature article in Neurology Today [10]. Internet Protocol (IP) address was collected to ensure authenticity of individual responses. No award or compensation was offered to responders.

A total of 455 responses were collected from December 2, 2015 to August 23, 2016. 399 complete questionnaires (where all questions were answered) were included in the analysis.

The study was certified as exempt from review by Children's National Health System institutional IRB.

Statistical analysis

Frequency distributions were reported for all clinical and demographic variables.

We used Pearson's Chi squared and Fisher Exact tests to analyze the differences in treatment variables according to the following demographic variables: specialty of treating physicians (adult neurology, pediatric neurology or pediatric rheumatology); practice within the United States or outside; and years in practice (in training; less than 10 years; 10 or more years).

For the sake of statistical analyses, and in order to group cells that had too few responses, treatment variable responses were clustered a priori according to the following answers: (1) First-line treatment: (a) high-dose steroids and/or IVIg; (b) PLEX alone or in combination with steroids and/or IVIg; (c) rituximab with any combination of steroids/PLEX and IVIg; (2) Interval between first and second-line treatment: (a) 2 weeks or less; or (b) 3 or 4 weeks; (3) Second-line treatment: (a) rituximab alone; (b) rituximab combined with cyclophosphamide; (c) cyclophosphamide alone; (d) any first-line medication alone or in combination, excluding rituximab; (e) anti-metabolites (azathioprine or mycophenolate).

Adjusted standardized residuals were generated to identify the responses accounting for group differences (adjusted residual Z scores >1.96 were considered statistically relevant). A p value <0.05 was considered statistically significant; p values were not significant unless stated in body of work or in figures. Statistical analyses were conducted using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Response rates

Frequencies of clinical and demographic variables are summarized in Table 1.

Table 1 Frequency of demographic and clinical variables for 399 complete responses

Demographic	*n* (%)	Clinical	*n* (%)
Specialty		**1st line treatment**	
Adult neurology	261 (65)	High-dose steroids and/or IVIg	261 (65)
Child neurology	86 (22)	PLEX ± High-dose steroids ± IVIg	98 (25)
Pediatric rheumatology	52 (13)	Rituximab ± PLEX ± High-dose steroids ± IVIg	40 (10)
Years in practice		**2nd line treatment**	
In training	102 (26)	Rituximab	225 (56)
Less than 10	149 (37)	Cyclophosphamide	9 (2)
10 or more	148 (37)	Rituximab + cyclophosphamide	62 (15)
Level of training		Any combination of 1st line treatment	62 (15)
Faculty/board certified physician	261 (65)	Anti-metabolites (azathioprine or mycophenolate)	41 (10)
Resident/fellow	102 (26)	**Interval between 1st and 2nd line treatment**	
Advanced practice practitioner	29 (7)	2 weeks or less	324 (81)
Practice in US		3 or 4 weeks	75 (19)
Yes	179 (45)		
No	220 (55)		

261 responders (65%) identified themselves as adult neurologists, 86 (22%) as practitioners that took care of children as a standard part of their practice and 52 (13%) as pediatric rheumatologists. 102 (26%) were trainees, 261 (65%) faculty/board certified physicians and 29 (7%) advanced practice providers. 149 (37%) of survey takers have been in practice for 10 years or more, 148 (37%) for less than 10 years and 102 (26%) were still in training.

The majority of responders utilize high-dose steroids and/or IVIg for first-line treatment ($n = 261$, 65%) and rituximab alone for second-line treatment ($n = 225$, 56%). Other choices for first-line included: PLEX alone or in association with high-dose steroids and/or IVIg ($n = 98$, 25%); rituximab in combination with PLEX and/or high-dose steroids and/or IVIg ($n = 40$, 10%). Other choices for second-line treatment were: cyclophosphamide alone ($n = 9$, 2%); rituximab in combination with cyclophosphamide ($n = 62$, 15%); repeating any combination of first-line treatments ($n = 62$, 15%); and anti-metabolites ($n = 41$, 10%).

The interval between first- and second-line treatments was 2 weeks or less for 81% of participants ($n = 324$) and 3 or 4 weeks for 19% of them ($n = 75$).

Respondents were from 57 countries. Europe represented 44% of responses ($n = 97$) outside of the US. Most represented individual nations outside of the US were Brazil (19 responses), Italy and Spain (17 responses each) United Kingdom (15 responses), Germany and Saudi Arabia (11 responses each) and India (10 responses). The remaining countries had less than 10 responses each.

Group differences based on specialty

The majority of responders across specialties (67% of adult neurologists, 67% of neurologists that take care of children, and 56% of pediatric rheumatologists) chose high-dose steroids and/or IVIg as first-line treatment. The use of PLEX and rituximab for first line resulted different based on specialty of treating practitioners ($\chi^2(4) = 27.43$, $p < 0.001$): 27% percent of adult neurologists chose PLEX alone or in combination with IVIg and/or high-dose steroids, compared to 15% of pediatric rheumatologists and 21% of child neurologists. 29% of pediatric rheumatologists recommend to include rituximab in the first-line treatment, versus 6% of adult neurologists and 12% of child neurologists (Fig. 1). PLEX usage by adult neurologists and initial rituximab by pediatric rheumatologists were the cells with significant residuals in this analysis.

We also observed several treatment pattern differences in choice of second-line treatments ($\chi^2(8) = 23.12$, $p = 0.003$). While rituximab alone received the majority of responses from all specialties, neurologists that take care of children chose it less (with significant adjusted residual) than adult neurologists and pediatric rheumatologists (46 vs. 57 vs. 67%). Pediatric rheumatologists opted to repeat any combination of first-line treatments less (with significant adjusted residual) than adult neurologist and child neurologists (6 vs. 16 vs. 19%). Pediatric rheumatologists utilized anti-metabolites (azathioprine or mycophenolate) less (with significant adjusted residual) than adult neurologists and child neurologists (2 vs. 12 vs. 10%). Adult neurologists used cyclophosphamide alone less than

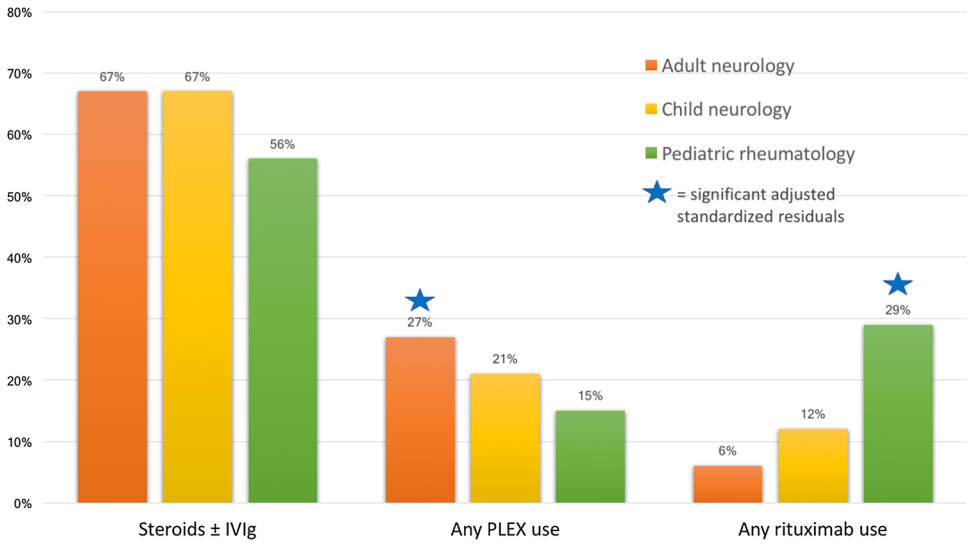

Fig. 1 First-line treatment responses grouped by specialty. Relative frequency of responses to the question about first-line treatment of choice grouped by specialty, highlighting consensus for high-dose steroids and/or IVIg and differences for the use of PLEX and Rituximab ($\chi^2(4) = 27.43$, $p < 0.001$). Significant residuals are represented by a *star* above the respective *bar*

pediatric rheumatologists (1 vs. 7%) but not much differently than child neurologists (3%). Cyclophosphamide variation had a significant residual in this analysis although there were a small number of overall responses for this intervention. We found no major differences for the combination of rituximab and cyclophosphamide (Fig. 2).

We also found no statistically significant differences across specialties for the interval between first- and second-line treatment, with the majority recommending initiation of second-line therapy after 2 weeks or less from initial treatment.

Group differences comparing United States and other countries

We observed agreement on the choices of first-line treatments between US and other countries. The majority recommended high-dose steroids and/or IVIg (63 vs. 67%) as initial therapy.

Second-line treatments were given earlier by physicians residing in the US ($\chi^2(1) = 4.96$, $p = 0.026$). Only 14% of US practitioners recommend second-line treatment three or four weeks after first-line, compared to 23% of non-US responders.

Choice of second-line therapy agent seemed to differ based on location of the respondents ($\chi^2(4) = 11.67$, $p = 0.020$). Participants across the world agree with the choice of rituximab alone as second-line treatment (60% of US responses vs. 53% of other countries), but survey takers outside of the US utilize anti-metabolites more often than US responders (15 vs. 5%). This discrepancy in anti-metabolite usage was the only cell with significant residual in this analysis. No other statistically significant differences were found for other second-line options (Fig. 3). These

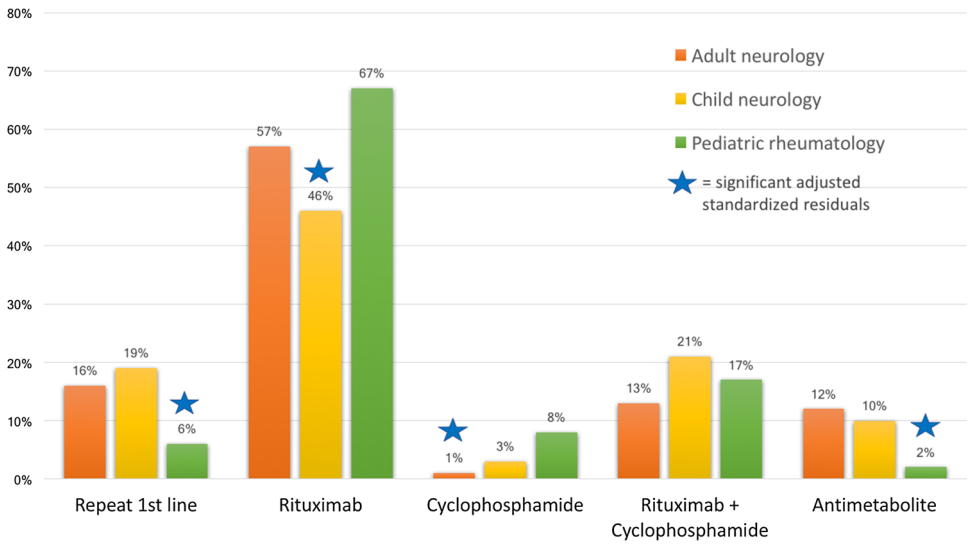

Fig. 2 Second-line treatment responses grouped by specialty. Relative frequency of responses to the question about second-line treatment grouped by specialty, showing differences in all groups except for combined cyclophosphamide and rituximab ($\chi^2(8) = 23.12$, $p = 0.003$). Significant residuals are represented by a *star* above the respective *bar*

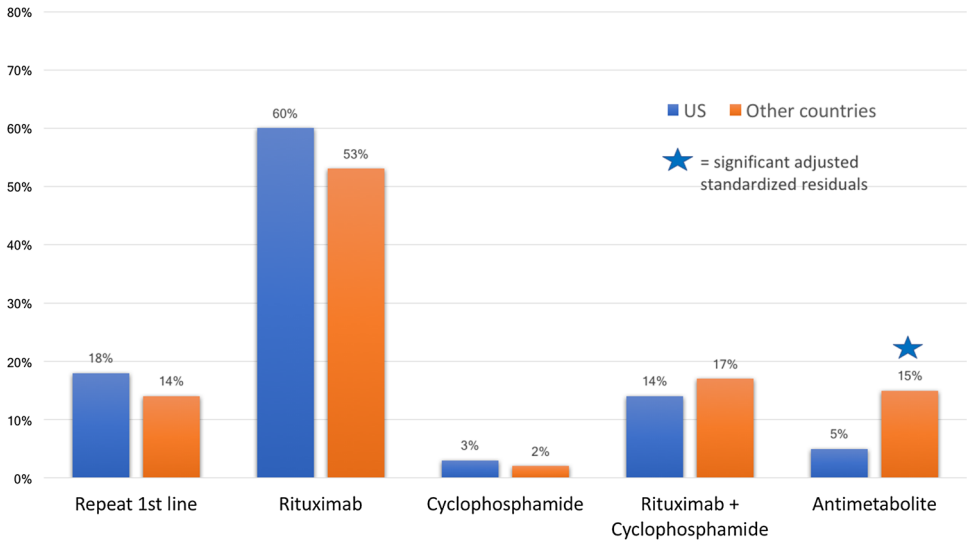

Fig. 3 Second-line treatment responses comparing United States vs. other countries. Relative frequency of responses to the question about second-line treatment comparing US vs. other countries, revealing overall consensus except for the use of anti-metabolites (more frequent outside of the US) ($\chi^2(4) = 11.67$, $p = 0.020$). Significant residuals are represented by a *star* above the respective *bar*

results were similar in a subanalysis that excluded pediatric rheumatologists and studied responses only from adult and pediatric neurologists.

Group differences based on years in practice

There were differences in first-line treatment choices when analyzed by years in practice ($\chi^2(4) = 13.37$, $p = 0.010$). The majority of responders in all experience groups chose high-dose steroids and/or IVIg as first-line treatment (59% of trainees, 69% of physician in practice for 10 years or more and 66% of those in practice for less than 10 years). The two cells that had significant residuals were PLEX and rituximab usage: trainees recommend PLEX alone or in combination with high-dose steroids and/or IVIg more often than both physician groups (35 vs. 19 vs. 22%, respectively); physicians in practice for less than 10 years recommended the use of combination therapy including rituximab as initial therapy more often than trainees and senior physicians (15 vs. 6 vs. 8%, respectively). We did not observe pattern differences for second-line therapy choice or the interval between first- and second-line when analyzing by experience.

Discussion

For the first time in such a large-scale survey, we provided a snapshot of current treatment strategies for anti-NMDAr encephalitis and appraised differences among specialties (adult neurology, child neurology, and pediatric rheumatology), length of professional experience (training, less than 10 years and 10 or more years) and between the United States and other countries. Given the current lack of evidence on the effectiveness and superiority of any treatment regimen, [11] our findings can contribute to the ongoing discussion on immunotherapy for the most prevalent form of immune-mediated encephalitis.

For first-line treatment, while the majority of respondents agreed on the use of the widely available and relatively well-tolerated high-dose steroids and/or IVIg, adult neurologists seemed more comfortable with initial PLEX usage than the other groups. This could potentially be attributed to the fact that this technique is generally considered more invasive and, therefore, may be reserved upfront for particularly severe cases or older children in pediatric institutions. It is worth noting that the efficacy of PLEX, and potentially IVIg, may be limited for this disease, considering that removal of circulating antibodies may work systemically, but this cannot alter the pathological process that happens inside the central nervous system where abundant intra-thecal production of autoantibodies occurs and infiltrates of plasma cells and plasmablasts have been previously described [12].

Rituximab is the second-line treatment of choice for the majority of responders in all specialty groups, but we found that pediatric rheumatologists recommend its use more often than the other groups both as part of a comprehensive initial immunotherapy regimen and as second-line treatment. This may be the result of more familiarity and comfort with this monoclonal antibody, which they routinely utilize for a variety of rheumatic diseases [13, 14]. Additionally, pediatric rheumatologists may only be consulted for more severe presentations or after failure of traditional first-line agents. Meanwhile, rituximab's usage in neurological diseases such as multiple sclerosis, neuromyelitis optica, peripheral neuropathies, or myasthenia gravis is relatively more recent [15] and skewed towards the adult population. The observed differences may also be influenced by a younger age of pediatric rheumatologists that participated in the survey.

In the largest available retrospective cohort study of anti-NMDAr encephalitis [5] (577 patients of which 211 were children), 76% of patients who received second-line treatment (23% of total patients) and did not have a teratoma were prescribed rituximab. The authors concluded that the use of second-line therapy resulted in better outcome and reduced the risk of relapses. The relative paucity of experience with this drug in children with primary neurological diseases may also account for the fact that for second-line therapy child neurology respondents in our survey tended to repeat first-line treatments (or resort to PLEX) and use rituximab less frequently than the other groups. In our group analysis, PLEX is considered a first-line treatment (as per convention in seminal papers), while it is possible that some child neurologists may consider it a "second-line" agent and use it as an escalation therapy, potentially contributing to the observed differences. Along the same lines, we observed that pediatric rheumatologists chose cyclophosphamide alone more often as a second-line therapy perhaps due to its usage as standard of care in a variety of life threatening rheumatic diseases that affect the brain such as neuropsychiatric lupus and primary CNS vasculitis. Yet, only a minority of physicians (independent of specialty) recommend its usage, probably due to its slow mechanism of action and significant side-effect profile [16].

When we compared second-line treatment strategies between US and other countries we found general consensus on first-line and second-line treatments, with the exception of anti-metabolites which were prescribed more often outside of the US. In the case of azathioprine, it is possible that Europe's historical background with the medication and longer experience may account for the difference. Interestingly, a previous survey of gastroenterologists about the treatment of inflammatory bowel diseases found that azathioprine is prescribed more frequently in Europe than in North America [17]. Respondents from outside of the US that reside in countries with a single health payer system may also have greater barriers to accessing rituximab, due to its cost, than oral anti-metabolites.

Responders from the US utilized second-line agents earlier than their counterparts in other parts of the globe, again potentially owing to access to these immunomodulators. The decision to intervene sooner with second tier medications seems supported by the evidence that early first-line treatment resulted in better outcome and fewer relapses [5, 18], but requires confirmation with further studies analyzing the specific contribution of a shorter interval between therapies in relation to outcomes and time to recovery.

In terms of differences based on years in practice, we observed that trainees included PLEX in the first-line treatment regimen more than the other experience groups. It is possible that the comfort level with more aggressive treatments is more prevalent during training when residents are supervised and take care of sicker patients in ICU settings. Studies have shown that trainees are more confident than faculty about the correctness of their diagnoses [19] and that the ability to "slow down" or temper treatment decisions often comes with experience [20]. The other experience difference we observed was that young faculty chose a comprehensive first-line immunotherapy regimen that included rituximab more than older respondents. Current evidence on the effectiveness of this approach is based on expert opinion [7] and requires confirmation with further studies.

Limitations

Our survey study's sample size was limited to representation of members from AAN or CARRA and readers of the Neurology® group journals and may not be entirely representative of global practice. Indeed, the pediatric rheumatologists that completed our survey make up less than 20% of the boarded pediatric rheumatologists in North America; both them and neurologists who participated may be a self-selected group with more comfort with autoimmune encephalitides (AE). Moreover, we did not ask survey takers to document how many cases of AE they have treated. Due to anonymity of the respondents, another possible limitation of the research design is the possibility that the responses were inaccurate or misrepresented [21]. Further surveys with a different sampling technique may be necessary to better examine the reproducibility of the associations we highlight.

Conclusions

This study provides current information about "real-life" differences in treatment strategies for anti-NMDAr encephalitis. Clinical trials may be difficult to fund and initiate due to the heterogeneity and severity of many patients and the costs and side-effect profiles of second-line agents. A potential approach to enhance the care of patients with NMDAr encephalitis may include ad hoc taskforces (representing different specialties such as neurology, rheumatology, psychiatry, pharmacology), developing standardized consensus-driven treatment regimens (treatment arms) that can be utilized in clinical care and whose outcomes can then be prospectively assessed. We believe that our survey data may serve as an additional resource for such work groups.

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Compliance with ethical standards

Ethical standards The present study was certified as research exempt from IRB review by Children's National Health System Institutional Review Board Committee in accordance with article 45 CFR 46.101(b)—Category 2 (Research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior). The manuscript does not contain clinical studies or patient data.

Conflicts of interest The authors declare that they have no conflict of interest.

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