Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease

In the article, "INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease", Meyer et al. reported that low-dose naproxen did not significantly reduce the progression of a composite indicator of presymptomatic Alzheimer Disease (AD)—the Alzheimer Progression Score (APS)—in a 2-year double-blind randomized placebo-controlled trial that enrolled 195 cognitively intact elderly participants with a family history of AD. In response, Dr. Ashford posits that the observed epidemiologic association of nonsteroidal anti-inflammatory drugs (NSAIDs) with decreased risk of AD may be related to the effect of these drugs on gamma-secretase rather than on inflammation, citing previous work showing that flurbiprofen and ibuprofen lower amyloidogenic Abeta42 independently of cyclooxygenase activity. He postulates that several years of treatment may be required to observe a benefit and wonders whether ibuprofen may be a better drug to test than naproxen. He also highlights the need for better tools to more accurately assess treatment effects in early AD. Responding to these comments, Drs. Breitner et al. noted that a meta-analysis of 6 prospective studies showed no significant differences in apparent risk modification of AD between gamma secretase-modifying and non-gamma secretase-modifying NSAIDS and suggested no difference between exposure to naproxen vs ibuprofen. Although they acknowledge that INTREPAD lacked an initially estimated degree of power, they note that the APS captured significant progression of apparent AD signs over the course of the trial and allowed a reasonably precise estimate of a lack of treatment effect, with naproxen also having no benefit on any of the APS components. With the largely unimpressive results of antiamyloid treatment strategies to date in AD, interest in alternative therapeutic targets, including anti-inflammatory strategies, is likely to continue growing in the coming years.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2020;94:593. doi:10.1212/WNL.0000000000009182

Reader response: INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease

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Neurology® 2020;94:593–594. doi:10.1212/WNL.0000000000009184

I read with interest the Null Hypothesis article by Meyer et al.[1] In 2001, Weggen et al.[2] suggested that flurbiprofen and ibuprofen had an effect on gamma secretase not shared by other cyclooxygenase inhibitors. This finding, along with several other failed studies of anti-inflammatory mechanisms in Alzheimer disease (AD), suggests that the widely replicated epidemiologic findings of nonsteroidal anti-inflammatory drug (NSAID) benefit for decreasing AD risk could be related to the effect on gamma-secretase, not inflammation. A flurbiprofen study failed to show a benefit for patients with AD,[3] but a considerable number of studies suggest that the NSAID-related benefit requires years of treatment before dementia develops, which the study by Meyer et al.[1] was appropriately targeting. However, the question remains as to whether ibuprofen is the drug to test, not naproxen.

Author disclosures are available upon request (journal@neurology.org).

Accurate measurement in early AD is also problematic. The failure to find an effect with the Alzheimer Progression Score, with quite large variability bars, suggests that tools for much more accurate assessments of early AD effects are needed.

1. Meyer PF, Tremblay-Mercier J, Leoutsakos J, et al. INTREPAD: a randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease. Neurology 2019;92:e2070–e2080.
2. Weggen S, Eriksen JL, Das P, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature 2001;414:212–216.
3. Green RC, Schneider LS, Amato DA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA 2009;302:2557–2564.

Author response: INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease

John Breitner (Montreal) and Pierre-Francois Meyer (Montreal)
Neurology® 2020;94:594. doi:10.1212/WNL.0000000000009185

We thank Dr. Ashford for his comment on our article "INTREPAD: A randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease."[1] Dr. Ashford raises 2 important points: whether a gamma-secretase-modifying (GSM) NSAID such as ibuprofen would likely have given different results and whether the Alzheimer progression score outcome was sufficiently precise to reveal efficacy.

A meta-analysis of 6 prospective studies[2] compared apparent Alzheimer disease (AD) risk modification in 13,499 older persons (70,863 person-years) exposed to various NSAIDs vs unexposed but showed no appreciable differences in risk modification comparing individuals exposed to GSM vs non-GSM NSAIDs. This analysis specifically suggested no difference in apparent risk reduction with exposure to naproxen vs ibuprofen. Considering these results, together with those of the flurbiprofen trials, we doubt that naproxen's lack of GSM activity explains the results of INTREPAD.[3]

The second point relates to statistical power. Our study addressed this issue directly. We acknowledged that INTREPAD lacked an initially estimated degree of power. But we pointed out that the Alzheimer progression score revealed a significant progression of apparent AD signs over the trial interval. The estimated confidence interval around the treatment-related change rate ratio suggested <5% likelihood that naproxen reduced AD progression by more than 36%. This conclusion was bolstered by the lack of apparent benefit on any of the 12 APS components.

1. Meyer PF, Tremblay-Mercier J, Leoutsakos J, et al. INTREPAD: a randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease. Neurology 2019;92:e2070–e2080.
2. Weggen S, Eriksen JL, Das P, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature 2001;414:212–216.
3. Green RC, Schneider LS, Amato DA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA 2009;302:2557–2564.

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Editors' note: New onset refractory status epilepticus research: What is on the horizon?

In the article, "New onset refractory status epilepticus research: What is on the horizon?", Gofton et al. reviewed the current state of knowledge in new-onset refractory status epilepticus (NORSE) and proposed a roadmap of future collaborative research. In response, Dr. Sethi seeks the authors' recommendation regarding which patients with NORSE should be treated immediately with immunomodulatory agents, given that autoantibodies implicated in many cases of NORSE may not be readily detectable and test results may be unavailable for weeks. He also wonders whether allopregnanolone may be a treatment option for these patients. Replying to these comments, Gofton et al. noted the absence of current guidelines in this area but noted that early immunotherapy may be indicated in patients with biomarkers or risk factors for autoimmunity or tumors potentially associated with autoimmune encephalitis. The authors emphasize that early immunomodulatory therapy seems to be associated with better outcomes in patients with NORSE, and therefore, it could also be an important consideration in those without a clear etiology and no contraindications to immunotherapy. Gofton et al. also noted that there is limited evidence on treatment of NORSE with allopregnanolone but highlighted the STATUS trial (A Study with SAGE-547 for Super-Refractory Status Epilepticus) of brexanolone, which did not reach its primary endpoint. In the absence of definitive evidence, the optimal treatment of NORSE remains uncertain, relying on the clinical judgment of the treating physicians.

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Neurology® 2020;94:595. doi:10.1212/WNL.0000000000009186

Reader response: New onset refractory status epilepticus research: What is on the horizon?

Nitin K. Sethi (New York)
Neurology® 2020;94:595. doi:10.1212/WNL.0000000000009188

I read with interest the Contemporary Issues article by Gofton et al.[1] on new-onset refractory status epilepticus (NORSE). Treatment for patients with NORSE includes traditional anticonvulsant therapy and intravenous anesthetic for status epilepticus. In addition, many patients are administered with immunotherapies, such as IV methylprednisolone, IV immunoglobulin, plasma exchange, rituximab, or cyclophosphamide. Autoantibodies-induced cases of NORSE may respond to immunogenic therapy, but—at the onset of NORSE—many of these autoantibodies are not readily detectable, and it may take weeks for the results to come back. Do the authors have any recommendation on which patients with NORSE should be immediately treated with immune modulators? In addition, are there any data for treatment of NORSE with allopregnanolone?

1. Gofton TE, Gaspard N, Hocker SE, Loddenkemper T, Hirsch LJ. New onset refractory status epilepticus research: what is on the horizon? Neurology 2019;92:802–810.

Author disclosures are available upon request (journal@neurology.org).

Author response: New onset refractory status epilepticus research: What is on the horizon?

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Neurology® 2020;94:596. doi:10.1212/WNL.0000000000009187

We thank Dr. Sethi for the comment on our Contemporary Issues article.[1] There are currently no guidelines and early immunotherapy may be indicated for patients with biomarkers or risk factors for autoimmunity (e.g., extreme delta with or without brushes, suggestive of anti-NMDA receptor antibody encephalitis,[2] a personal or family history of autoimmunity), or tumors that are known to be associated with autoimmune encephalitis.[3] There are limited data to date, and the decision to treat with immunomodulatory treatments is ultimately a clinical one pending further research. Any patient without a clear etiology for NORSE within the first 72 hours of presentation and without a clear contraindication to immunosuppression warrants careful consideration for treatment with immunotherapy. Current evidence suggests that earlier treatment is associated with better clinical outcomes.[4] This comment may also draw further attention to the current autoantibody testing limitations; we hope that improved and faster testing may become available.

Current data for treatment of NORSE with allopregnanolone are limited to conference presentations and published case series.[5] The STATUS Trial of brexanolone (an intravenous formulation of allopregnanolone) in the treatment of super-refractory status epilepticus did not reach its primary endpoint of successful weaning of third-line agents.[6]

1. Gofton TE, Gaspard N, Hocker SE, Loddenkemper T, Hirsch LJ. New onset refractory status epilepticus research: what is on the horizon? Neurology 2019;92:802–810.
2. Steriade C, Hantus S, Moosa ANV, Rae-Grant AD. Extreme delta - with or without brushes: a potential surrogate marker of disease activity in anti-NMDA-receptor encephalitis. Clin Neurophysiol 2018;129:2197–2204.
3. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
4. Khawaja AM, DeWolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE)–The potential role for immunotherapy. Epilepsy Bhav 2015;47:17–23.
5. Rosenthal ES, Claassen J, Wainwright MS, et al. Brexanolone as adjunctive therapy in super-refractory status epilepticus. Ann Neurol 2017;82:342–352.
6. Sage therapeutics reports top-line results from phase 3 STATUS trial of brexanolone in super-refractory status epilepticus. In: sage therapeutics [online]. Available at: investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-reports-top-line-results-phase-3-status-trial. Accessed May 18, 2019.

Author disclosures are available upon request (journal@neurology.org).