



# Letter to the Editor

## Is CGRP Receptor Blockade Cardiovascularly Safe? Appropriate Studies are Needed

With great interest, we read the publication by Depre and colleagues<sup>1</sup> describing that inhibition of the canonical CGRP receptor does not seem to worsen myocardial ischemia contrary to theoretical concerns.<sup>2</sup> In a randomized, double-blind, placebo-controlled study the authors did not find evidence for an adverse effect of the CGRP receptor antibody erenumab on exercise time during a treadmill test in patients with stable angina. Although we certainly appreciate the endeavor to address this important issue, we are concerned that the study population, the study design, and the interpretation of the results do not allow for such a reassuring conclusion.

While the authors rightly indicate that it is currently not clear to which extent CGRP is relevant in maintaining blood flow in case of myocardial and cerebral ischemia, we do not agree with their argument stating that “the concentrations of exogenous CGRP required to increase total exercise time or protect against myocardial ischemia far exceed the endogenous physiological levels of CGRP that are released during a response to ischemia.” This is because it is not the *systemic plasma* concentration that is relevant in this perspective, but the actual concentration of CGRP *at the neuro-vascular junction*, where CGRP is released. Obviously, the plasma concentration is likely to be several log units lower than the junctional concentration due to dilution and hydrolysis. Further, we feel that the argument that erenumab does not contract the human isolated coronary artery *per se*<sup>3</sup> does not add to the introduction, since the question that should be answered here is whether inhibition of the actions of CGRP is potentially harmful in myocardial ischemia.

More importantly, the patients included in this study suffered from stable angina pectoris, which often is caused by a stenosis of the epicardial conducting portions of the coronary artery. As we pointed out earlier,<sup>2</sup> the importance of CGRP in the proximal, epicardial portions of the coronary artery bed seems limited, while CGRP is a highly effective vasodilator in the intramyocardial, smaller (distal) sections of the coronary artery bed. Thus, it is unfortunate that a patient population with, most likely, mainly diseased proximal coronary arteries, was chosen for this study, despite the advantage of a clear-cut definition of these patients. Although stable angina pectoris due to epicardial stenosis may occur in both men and women, this is typically considered a “male” form of cardiac pathology,<sup>4</sup> as illustrated by the fact that 78% of patients included in the current study were male. In contrast, in females, who are the majority of migraine sufferers and thus also the majority of the population likely to use erenumab or related drugs in future, coronary artery disease often presents as diffuse atherosclerosis, without an angiographically detectable stenosis.<sup>4–6</sup> These observations indicate that coronary microvascular dysfunction plays a more important role in angina pectoris in female patients and that blocking the effects of CGRP in female patients may have different effects than in male patients.

An essential concern of this study is based on pharmacokinetic and pharmacodynamic considerations. The authors rightly indicate that plasma concentrations obtained 30 min after intravenous infusion of 140 mg erenumab (the time interval until the start of the

---

*Conflict of Interest:* AMvdB received research grants and/or consultation fees from Amgen/Novartis, Lilly/CoLucid, Teva, and ATI.

CMV received consultation fees from Lilly/CoLucid.

treadmill test) will provide “a substantial margin over concentrations achieved by subcutaneous administration of 140 mg.” In contrast, their claim that “the use of 140 mg intravenous dose of erenumab ensured rapid and robust blockade of the CGRP receptor” is not substantiated by any evidence. It should be taken into account that, before a receptor blocking antibody can effectively occupy the receptor where it is binding to, the antibody should first have access to the receptor biophase. In this case, erenumab was infused intravenously and thus reached the blood vessel wall from the luminal side. The CGRP receptor is located in the smooth muscle wall,<sup>5</sup> thus it may take several hours before the receptor was reached by erenumab at sufficiently high concentrations to induce an effective blockade of the CGRP receptor, especially given the large molecular size (150 kDa) of erenumab. This is well beyond the time the treadmill test had finished. A way to verify whether blockade has been achieved (at least in skin blood vessels) is by assessing blockade of capsaicin-induced increases in dermal blood flow. The earliest time point for such measurements that has been published, to the best of our knowledge, for erenumab is 2 days after intravenous administration,<sup>6</sup> which is about 100-fold longer than the period applied in the current study. Thus, we feel that evidence for significant blockade of the canonical CGRP receptor should have been provided to substantiate the statement that CGRP receptor blockade was reached *during* the treadmill study, since otherwise the interpretation of the current study is questionable.

Taken together, we would politely urge the authors to provide evidence for the fact that vascular CGRP receptor blockade has been achieved 30 min after intravenous infusion of erenumab, since this is a crucial part of the study. Further, we plead for cardiovascular safety studies on patients and/or experimental animals with microvascular disease, as such a group may better represent the patients at cardiovascular risk after the use of erenumab. Even if the

antibodies against CGRP or its receptor would not increase the risk for cardiovascular ischemia, there will be cases of patients with ischemic complaints, even without a causal relationship. Appropriate studies in relevant subjects may avoid sudden distress, such as happened with the triptans in the past.

A. Maassen van den Brink, PhD; E. Rubio-Beltrán, MSc; D. Duncker, MD, PhD; C.M. Villalón, PhD  
Division of Pharmacology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands (A. Maassen van den Brink and E. Rubio-Beltrán); Department of Experimental Cardiology, Erasmus MC, Rotterdam, The Netherlands (D. Duncker); Department Pharmacobiology, Cinvestav-Coapa, Tlalpan, Mexico City, Mexico (C. Villalón)  
e-mail: a.vanharen-maassenvandenbrink@erasmusmc.nl

## REFERENCES

1. Depre C, Antalík L, Starling A, et al. A randomized, double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina. *Headache*. 2018;58:715-723.
2. MaassenVanDenBrink A, Meijer J, Villalón CM, Ferrari MD. Wiping out CGRP: Potential cardiovascular risks. *Trends Pharmacol Sci*. 2016;37:779-788.
3. Rubio-Beltrán E, Labastida A, De Vries R, et al. Effects of AMG 334 on human isolated coronary artery. *Cephalalgia*. 2016;36:S41.
4. Humphries KH, Pu A, Gao M, Carere RG, Pilote L. Angina with “normal” coronary arteries: Sex differences in outcomes. *Am Heart J*. 2008;155:375-381.
5. Maas AH, van der Schouw YT, Regitz-Zagrosek V, et al. Red alert for women’s heart: The urgent need for more research and knowledge on cardiovascular disease in women: Proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J*. 2011;32:1362-1368.
6. Duncker DJ, Koller A, Merkus D, Canty JM Jr. Regulation of coronary blood flow in health and ischemic heart disease. *Prog Cardiovasc Dis*. 2015;2015:409-422.
7. Chan KY, Edvinsson L, Eftekhari S, et al. Characterization of the calcitonin gene-related peptide receptor antagonist telcagepant (MK-0974) in human isolated coronary arteries. *J Pharmacol Exp Ther*. 2010;334:746-752.
8. Vu T, Ma P, Chen JS, et al. Pharmacokinetic-pharmacodynamic relationship of erenumab (AMG 334) and capsaicin-induced dermal blood flow in healthy and migraine subjects. *Pharm Res*. 2017;34:1784-1795.

**HEADACHE: The Journal of Head and Face Pain** (ISSN 0017-8748 Print; 1526-4610 Online), is published in the months of January, February, March, April, May, June, July, September, October, November on behalf of the American Headache Society by Wiley Subscription Services, Inc., a Wiley Company, 111 River St., Hoboken, NJ 07030-5774, USA. Postmaster: Send all address changes to **HEADACHE**, John Wiley & Sons Inc., C/O The Sheridan Press, PO Box 465, Hanover, PA 17331, USA.

Submit manuscripts electronically at: <http://mc.manuscriptcentral.com/headache>

**Copyright and Copying (in any format):** Copyright © 2018 American Headache Society. All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means without the prior permission in writing from the copyright holder. Authorization to copy items for internal and personal use is granted by the copyright holder for libraries and other users registered with their local Reproduction Rights Organisation (RRO), e.g. Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA ([www.copyright.com](http://www.copyright.com)), provided the appropriate fee is paid directly to the RRO. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for republication, for creating new collective works or for resale. Permissions for such reuse can be obtained using the RightsLink "Request Permissions" link on Wiley Online Library. Special requests should be addressed to: [permissions@wiley.com](mailto:permissions@wiley.com)

**Information for subscribers:** *Headache: The Journal of Head and Face Pain* is published in 10 issues per year. *Headache* is free with membership to the American Headache Society. Institutional subscription prices for 2018 are: Print & Online: US\$802 (US), US\$1293 (Rest of World), €842 (Europe), £662 (UK). Prices are exclusive of tax. Asia-Pacific GST, Canadian GST/HST and European VAT will be applied at the appropriate rates. For more information on current tax rates, please go to [www.wileyonlinelibrary.com/tax-vat](http://www.wileyonlinelibrary.com/tax-vat). The price includes online access to the current and all online backfiles to January 1st 2014, where available. For other pricing options, including access information and terms and conditions, please visit [www.wileyonlinelibrary.com/access](http://www.wileyonlinelibrary.com/access).

**Delivery Terms and Legal Title:**

Where the subscription price includes print issues and delivery is to the recipient's address, delivery terms are Delivered at Place (DAP); the recipient is responsible for paying any import duty or taxes. Title to all issues transfers Free of Board (FOB) our shipping point, freight prepaid. We will endeavour to fulfil claims for missing or damaged copies within six months of publication, within our reasonable discretion and subject to availability.

**Back issues:** Single issues from current and recent volumes are available at the current single issue price from [cs-journals@wiley.com](mailto:cs-journals@wiley.com). Earlier issues may be obtained from Periodicals Service Company, 351 Fairview Avenue - Ste 300, Hudson, NY 12534, USA. Tel: +1 518 822-9300, Fax: +1 518 822-9305, Email: [psc@periodicals.com](mailto:psc@periodicals.com).

**Disclaimer:** The Publisher, American Headache Society and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, American Headache Society and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, American Headache Society and Editors of the products advertised.

**Publisher:** *Headache: The Journal of Head and Face Pain* is published by Wiley Periodicals, Inc., 350 Main St, Malden, MA 02148-5020, +1 781 388 8250.

**Journal Customer Services:** For ordering information, claims and any enquiry concerning your journal subscription please go to [www.wileycustomerhelp.com/ask](http://www.wileycustomerhelp.com/ask) or contact your nearest office.

**Americas:** Email: [cs-journals@wiley.com](mailto:cs-journals@wiley.com); Tel: +1 781 388 8598 or +1 800 835 6770 (toll free in the USA & Canada).

**Europe, Middle East and Africa:** Email: [cs-journals@wiley.com](mailto:cs-journals@wiley.com); Tel: +44 (0) 1865 778315.

**Asia Pacific:** Email: [cs-journals@wiley.com](mailto:cs-journals@wiley.com); Tel: +65 6511 8000.

**Japan:** For Japanese speaking support, Email: [cs-japan@wiley.com](mailto:cs-japan@wiley.com)

**Visit our Online Customer Help** available in 7 languages at [www.wileycustomerhelp.com/ask](http://www.wileycustomerhelp.com/ask).

**Production Editor:** Jennifer Spofford (email: [HEAD@wiley.com](mailto:HEAD@wiley.com))

Wiley's Corporate Citizenship initiative seeks to address the environmental, social, economic, and ethical challenges faced in our business and which are important to our diverse stakeholder groups. Since launching the initiative, we have focused on sharing our content with those in need, enhancing community philanthropy, reducing our carbon impact, creating global guidelines and best practices for paper use, establishing a vendor code of ethics, and engaging our colleagues and other stakeholders in our efforts. Follow our progress at [www.wiley.com/go/citizenship](http://www.wiley.com/go/citizenship)

View this journal online at [wileyonlinelibrary.com/journal/HEAD](http://wileyonlinelibrary.com/journal/HEAD)

Wiley is a founding member of the UN-backed HINARI, AGORA, and OARE initiatives. They are now collectively known as Research4Life, making online scientific content available free or at nominal cost to researchers in developing countries. Please visit Wiley's Content Access - Corporate Citizenship site: <http://www.wiley.com/WileyCDA/Section/id-390082.html>

Printed in the USA by The Sheridan Group.

**Society Contact Information:** American Headache Society, 19 Mantua Road, Mt. Royal, NJ 08061. Tel: +1 856 423 0043; Fax: +1 856 423 0082; email: [ahshq@talley.com](mailto:ahshq@talley.com); Website: [www.americanheadachesociety.org](http://www.americanheadachesociety.org)

The Journal is indexed by Academic Search, Academic Search Premier, Biological Abstracts, BIOSIS, BIOSIS Previews, CAS: Chemical Abstracts Service, CINAHL: Cumulative Index to Nursing & Allied Health Literature, CSA Biological Sciences Database, Current Contents: Clinical Medicine, EBSCO Publishing Embase, HEED: Health Economic Evaluations Database, IBIDS: International Bibliographic Information on Dietary Supplements, Index Medicus/MEDLINE, InfoTrac Journal Citation Reports/Science Edition, MEDLINE, Neuroscience Citation Index, Neurosciences Abstracts, PASCAL Database, Psychology & Behavioral Sciences Collection, PsycINFO/Psychological Abstracts, PSYNDEX, Science Citation Index, Science Citation Index Expanded, VINITI.

*Headache: The Journal of Head and Face Pain* accepts articles for Open Access publication. Please visit <http://olabout.wiley.com/WileyCDA/Section/id-828081.html> for further information about OnlineOpen.

For submission instructions, subscription and all other information visit [www.headachejournal.org](http://www.headachejournal.org)

It is a condition of publication that manuscripts submitted to this journal have not been published and *will not be simultaneously submitted or published elsewhere*. By submitting a manuscript, the authors agree that the copyright for their article is transferred to the American Headache Society if and when the article is accepted for publication. The copyright covers the exclusive rights to reproduce and distribute the article, including

# HEADACHE

The Journal of Head and Face Pain  
Official Publication of the American  
Headache Society

"...to improve the lives of headache sufferers"

[www.AmericanHeadacheSociety.org](http://www.AmericanHeadacheSociety.org)

ISSN 0017-8748

## American Headache Society Board of Directors

2018-2020

### PRESIDENT

Kathleen B. Digre, MD, FAHS

### PRESIDENT-ELECT

Peter J. Goadsby, MD, PhD, FAHS

### TREASURER

Andrew C. Charles, MD, FAHS

### SECRETARY

Todd J. Schwedt, MD, MSCI, FAHS

### IMMEDIATE PAST PRESIDENT

R. Allan Purdy, MD, FAHS

### BOARD MEMBERS-AT-LARGE

Jessica Ailani, MD, FAHS

Dawn C. Buse, PhD, FAHS

Deborah I. Friedman, MD, MPH, FAHS

Morris Levin, MD, FAHS

Matthew S. Robbins, MD, FAHS

Robert E. Shapiro, MD, PhD

Stewart J. Tepper, MD, FAHS

Bert B. Vargas, MD, FAHS

### AMERICAN MIGRAINE FOUNDATION CHAIR

David W. Dodick, MD, FAHS

### EDITOR HEADACHE

Thomas N. Ward, MD, FAHS

### EXECUTIVE EDITOR OF HEADACHE

Jason Roberts, PhD

### CORPORATE LIAISON

Barry S. Baumel, MD

### CHAIR, SPECIAL INTEREST SECTIONS

Mia Minen, MD, FAHS

### CHAIR, AAN HEADACHE SPECIAL INTEREST

Morris Levin, MD, FAHS

### IHS REPRESENTATIVE

R. Allan Purdy, MD, FAHS

### PAN AMERICAN LIAISON

Fabiola Dach, MD, PhD

### PAN ASIAN LIAISON

Toshi Shimizu, MD, PhD

### PAST PRESIDENT ADVISORS

Robert B. Daroff, MD, FAHS

Elizabeth W. Loder, MD, MPH, FAHS

Richard B. Lipton, MD, FAHS

Lawrence C. Newman, MD, FAHS

Joel R. Saper, MD, FAHS

Stephen D. Silberstein, MD, FAHS

Paul Winner, DO, FAHS

### CHIEF EXECUTIVE OFFICER

Linda McGillicuddy



**Editorial Board**

**Editor-in-Chief**  
Thomas N. Ward, MD Hanover, NH

**Senior Editorial Advisors**  
Robert B. Daroff, MD Cleveland, OH, USA  
Anne Ducros Montpellier, France  
Michel Ferrari, MD Leiden, The Netherlands  
Peter J. Goadsby, MD, PhD, DSc London, United Kingdom  
Donald Penzien, PhD Winston-Salem, North Carolina  
John Rothrock, MD Washington, DC, USA

**Associate Editors**  
Steven M. Baskin, PhD Stamford, CT, USA  
Rebecca Burch, MD Boston, MA, USA  
Gregory Dussor, PhD Dallas, Texas, USA  
Deborah Friedman, MD Dallas, TX, USA  
Amy Gelfand, MD, San Francisco, California, USA  
Christopher Gottschalk, MD New Haven, CT, USA  
Laine Greene Halifax, Nova Scotia, Canada  
Lyn Griffiths, PhD Gold Coast, Australia  
Andrew Hershey, MD, PhD, Cincinnati, OH, USA  
Robert Kaniecki, MD Pittsburgh, PA, USA  
Abouch Krymchantowski, MD, PhD Rio de Janeiro, Brazil  
Morris Levin, MD San Francisco, CA  
Dan Levy Boston, MA, USA  
Elizabeth Loder, MD Boston, MA, USA  
Vincent Martin, MD Cincinnati, OH, USA  
Brian E. McGeeney, MD Boston, MA, USA  
Mia Minen, MD New York, NY  
Julio Pascual, MD, PhD Oviedo, Spain  
B. Lee Peterlin, DO Baltimore, MD, USA  
Luiz P. Queiroz, MD Florianopolis, Brazil  
Paul B. Rizzoli, MD Boston, MA, USA  
Matthew S. Robbins, MD Bronx, NY  
Noah Rosen, MD Great Neck, New York, USA  
Todd J. Schwedt, MD Phoenix, AZ, USA  
Jonathan Smith, MD Lexington, KY, USA  
Todd A. Smitherman, PhD Oxford, MS, USA  
Till Sprenger, MD Basel, Switzerland  
Jerry W. Swanson, MD, MHPE Rochester, MN, USA  
Deborah E. Tepper, MD Sandwich, MA, USA  
Stewart J. Tepper, MD Lebanon, NH, USA  
Gretchen E. Tietjen, MD Toledo, OH, USA  
Marcelo M. Valença, MD, PhD Recife, Brazil  
Shuu-Jiun Wang, MD Taipei, Taiwan  
Randall E. Weeks, PhD Stamford, CT, USA

**Assistant Editors**  
Jennifer Hranilovich, MD Boston, MA, USA  
Saad Kanaan, MD Boston, MA, USA  
Amanda Maccone, MD Lebanon, NH, USA

**Headache Currents Editor-in-Chief**  
Stewart J. Tepper, MD Lebanon, NH, USA

**Online Editor**  
Todd Schwedt, MD Phoenix, AZ, USA

**Associate Provider Editor**  
Lynda J Krasenbaum MSN, ANP-BC  
New York, NY, USA

**Supplement Editors**  
R. Allan Purdy, MD Halifax, Nova Scotia, Canada  
Alan Rapoport, MD Los Angeles, California

**Abstracts and Citations Editors**  
Wade Cooper, DO Ann Arbor, Michigan, USA  
Robert Kaniecki, MD Pittsburgh, PA, USA  
Frederick R. Taylor, MD Minneapolis, MN, USA

**Book/Media Review Editor**  
R. Allan Purdy, MD Halifax, Nova Scotia, Canada

**Expert Opinion Section Editor**  
Randolph W. Evans, MD Houston, TX, USA

**Residents and Fellows Section Editors**  
Morris Levin, MD San Francisco, CA  
Matthew S. Robbins, MD Bronx, NY

**Statistical Consultant**  
Timothy Houle, PhD Boston, MA, USA

**Design & Methods Advisor**  
Dana Turner Boston, MA, USA

**Editorial Office**  
Jason Roberts, PhD  
Executive Editor, Headache Ottawa, Ontario, Canada  
Email: journal@ahsnet.org

**AHS Executive Office**  
Linda McGillicuddy  
American Headache Society CEO  
Mount Royal, NJ USA  
Copyright © 2018 by the American Headache Society

# HEADACHE

## The Journal of Head and Face Pain

http://mc.manuscriptcentral.com/headache

Official Publication of the American Headache Society  
www.headachejournal.org

Volume 58, Number 8

September 2018

	Page
<b>Guest Editorials</b>	
<b>The Importance of Statistical Power Calculations . . . . .</b>	<b>1187</b>
Dana P. Turner, MSPH, PhD; Timothy T. Houle, PhD	
<b>Have You Got the Power? Why Statistical Power Calculations Are Critical to Research Design . . . . .</b>	<b>1192</b>
Serena L. Orr, MD, MSc, FRCPC; Andrew D. Hershey, MD, PhD, FAHS	
<b>Research Submissions</b>	
<b>Predictors of First-Line Treatment Success in Children and Adolescents Visiting an Infusion Center for Acute Migraine . . . . .</b>	<b>1194</b>
Serena L. Orr, MD, MSc, FRCPC; Marielle A. Kabbouche, MD; Paul S. Horn, PhD; Hope L. O'Brien, MD, FAHS, FAAN; Joanne Kacperski, MD; Susan LeCates, MSN, APRN, CNP; Shannon White, DNP, CNP; Jessica Weberding, MSN, CNP; Mimi N. Miller, MSN, APRN, CNP; Scott W. Powers, PhD, ABPP, FAHS; Andrew D. Hershey, MD, PhD, FAHS	
<b>Aura in Cluster Headache: A Cross-Sectional Study . . . . .</b>	<b>1203</b>
Ilse F. de Coe, MD; Leopoldine A. Wilbrink, MD; Gaby D. Ie, MD; Joost Haan, MD, PhD; Michel D. Ferrari, MD, PhD	
<b>Structured Clinical Documentation to Improve Quality and Support Practice-Based Research in Headache . . . . .</b>	<b>1211</b>
Steven Meyers, MD; Kelly Claire Simon, ScD; Stuart Bergman-Bock, MD; Franco Campanella, DO; Revital Marcus, MD; Angela Mark, MD; Thomas Freedom, MD; Susan Rubin, MD; Irene Semenov, DO; Rebekah Lai, BS; Laura Hillman, BBA; Samuel Tideman, MS; Anna Pham, BS; Roberta Frigerio, MD; Demetrius M. Maraganore, MD	
<b>Migraine and Non-Migraine Headaches Following Diagnostic Catheter-Based Cerebral Angiography . . . . .</b>	<b>1219</b>
Adnan I. Qureshi, MD; Nishath Naseem, MD; Muhammad A. Saleem, MD; Anvita Potluri, MD; Faisal Raja, MD; Shawn S. Wallery, MD	
<b>Measures of Functioning in Patients With Episodic Migraine: Findings From a Double-Blind, Randomized, Placebo-Controlled Phase 2b Trial With Galcanezumab . . . . .</b>	<b>1225</b>
David W. Ayer, PhD; Vladimir Skljarevski, MD; Janet H. Ford, PhD; Allen W. Nyhuis, MS; Richard B. Lipton, MD; Sheena K. Aurora, MD	
<b>Images From Headache</b>	
<b>Central Skull Base Osteomyelitis Presenting Only With a Severe Headache . . . . .</b>	<b>1236</b>
Pahn K. Choi, MD; Ji Y. Chung, MD; Hyun G. Kang, MD, PhD	
<b>Brief Communications</b>	
<b>Orthostatic Headache After Suboccipital Craniectomy Without CSF Leak: Two Case Reports . . . . .</b>	<b>1238</b>
Monique M. Montenegro, MD; Jeremy K. Cutsforth-Gregory, MD	
<b>Cerebral Venous Thrombosis in Spontaneous Intracranial Hypotension: A Report on 4 Cases and a Review of the Literature. . . . .</b>	<b>1244</b>
Dan Zhang, MD; Jin Wang, MD; Qiaowei Zhang, MD; Feifang He, PhD; Xingyue Hu, MD, PhD	



Scan this QR code with your smartphone to listen to the most recent Headache Journal podcast.



# Qudexy<sup>®</sup> XR

(topiramate) extended-release capsules



## Eliminating barriers with Qudexy<sup>®</sup> XR

With the Platinum Pass, it has never been easier to prescribe Qudexy<sup>®</sup> XR. Help patients start, stay and save on therapy today!



**Get Your Patients Started on Qudexy<sup>®</sup> XR Today!**  
Visit [hcp.QudexyXR.com](http://hcp.QudexyXR.com) or call Access Pathways<sup>®</sup> at 1-855-282-4887.

\*Restrictions apply. Medicare, Medicaid, and other federal and state health care program patients are not eligible.

Qudexy and Access Pathways are registered trademarks of Upsher-Smith Laboratories, LLC.  
© 2018 Upsher-Smith Laboratories, LLC, 6701 Evenstad Drive, Maple Grove, MN 55369 113236.02

**UPSHER-SMITH**

Partners in Health Since 1919

**DOCKET  
ALARM**

Find authenticated court documents without watermarks at [docketalarm.com](http://docketalarm.com).