9th Annual Meeting: Experimental Therapeutics

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New Treatments for Dystonia?

- Doctor's perspective
  Why do we need new treatments?
  Botulinum toxins are very effective
  DBS surgery is also effective

- The patient's perspective
  Are you trying to find something better?
  Numerous studies show satisfaction varies
  Approximately 1 in 3 patients discontinue BoNT

- The clueless cynic's perspective
  Nothing new is being developed

Experimental Therapeutics

EXPERT OPINION ON DRUG DISCOVERY
2019, VOL. 14, NO. 9, 893–900
https://doi.org/10.1080/17460441.2019.1623785

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

New approaches to discovering drugs that treat dystonia

Sarah Pirio Richardson[a,b] and H. A. Jinnah[c]

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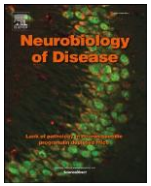
Neurobiology of Disease 130 (2019) 104526

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Review

The neurobiological basis for novel experimental therapeutics in dystonia

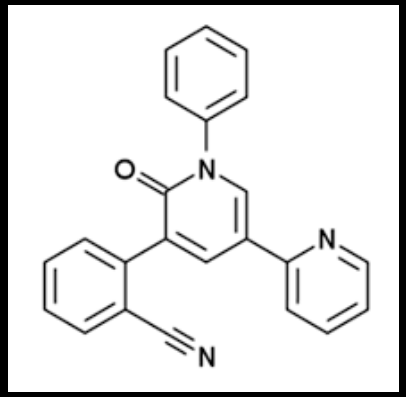
Check for updates

Anthony M. Downs[a,1], Kaitlyn M. Roman[a,1], Simone A. Campbell[a], Antonio Pisani[b,c], Ellen J. Hess[a,d], Paola Bonsi[b,*]

Glutamate Receptors

- Widely distributed in brain
  basal ganglia
  cerebellum
- Numerous animal studies implicate GluR in dystonia
- *GRIN2B* (NMDA receptor) linked with human dystonia
- Pilot study of riluzole in cervical dysotnia

Perampanel: AMPA Receptor



- Non-competitive antagonist
- Pre-clinical studies
  animal studies implicate AMPA receptors
  several dystonia models showed benefit
- Perampanel is already available as anti-convulsant

SAFE-per-CD Trial

Movement Disorders
CLINICAL PRACTICE
DRUG TRIALS

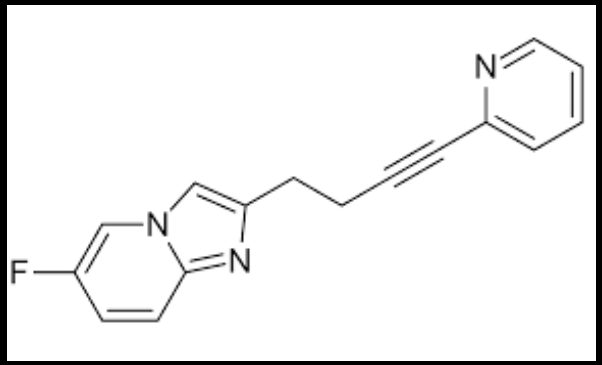
An Open-Label Phase 2a Study to Evaluate the Safety and Tolerability of Perampanel in Cervical Dystonia

Susan H. Fox, MRCP,PhD,[1,2,3,] Matthew Swan, MD,[4] Hyder A. Jinnah, MD, PhD,[5] Maria E.T. de Freitas, MD,[1,2,3] Lais M. de Oliveira, MD,[1,2,3] Duha Al-Shorafat, MD,[1,2,3] Hubert H. Fernandez, MD,[6] Katie Kompoliti, MD,[7] and Cynthia Comella, MD[7]*

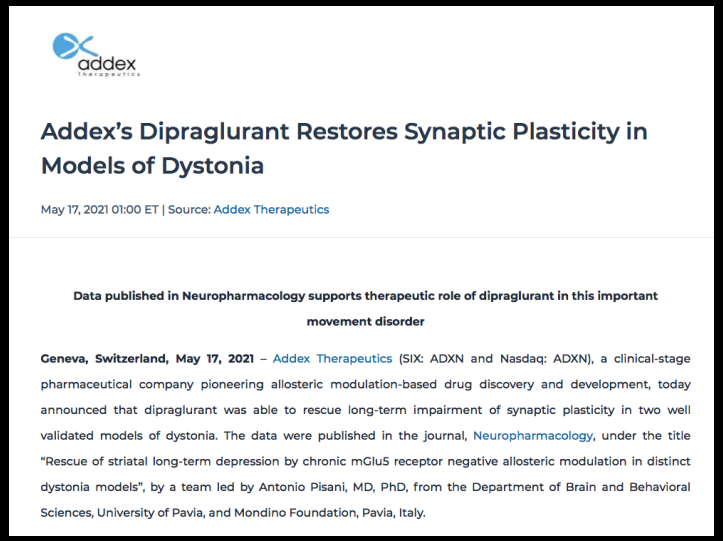
- Phase 2a, open label, multicenter
- 25 subjects with CD
  studied at end of BoNT cycle
  titrated 2-12 mg/day
  tolerability, TWSTRS, CDIP-58, CGI

Dipraglurant: mGluR5

- Negative allosteric modulator (mGLUR5)
- Pre-clinical studies
  animal models implicate mGLUR5
  several dystonia models implied benefit
- Reduces levodopa-induced dyskinesias
  rodent and primate models
  patients with Parkinson disease



Addex & Dystonia



addex Therapeutics

Addex's Dipraglurant Restores Synaptic Plasticity in Models of Dystonia

May 17, 2021 01:00 ET | Source: Addex Therapeutics

Data published in Neuropharmacology supports therapeutic role of dipraglurant in this important movement disorder

Geneva, Switzerland, May 17, 2021 – Addex Therapeutics (SIX: ADXN and Nasdaq: ADXN), a clinical-stage pharmaceutical company pioneering allosteric modulation-based drug discovery and development, today announced that dipraglurant was able to rescue long-term impairment of synaptic plasticity in two well validated models of dystonia. The data were published in the journal, Neuropharmacology, under the title "Rescue of striatal long-term depression by chronic mGlu5 receptor negative allosteric modulation in distinct dystonia models", by a team led by Antonio Pisani, MD, PhD, from the Department of Brain and Behavioral Sciences, University of Pavia, and Mondino Foundation, Pavia, Italy.

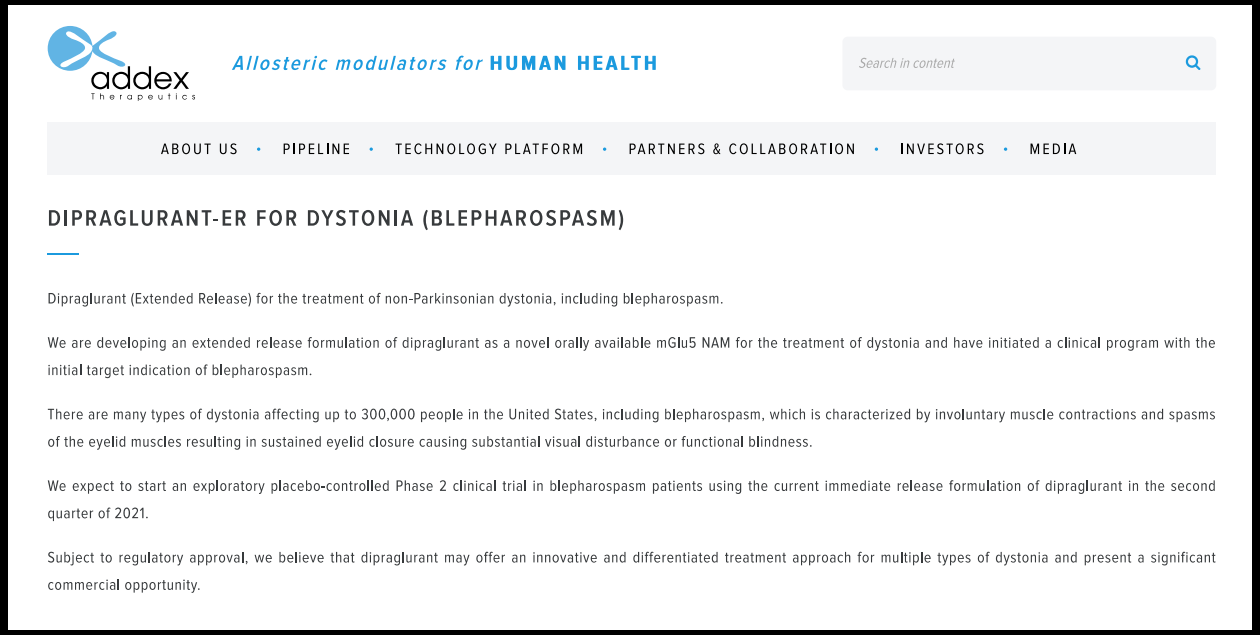
addex therapeutics

PRESS RELEASE

Addex Dipraglurant Reduces Motor Abnormalities in a Preclinical Model Relevant for Several Rare types of Dystonia

Dipraglurant, a novel oral small molecule negative allosteric modulator of mGlu5 receptor, on track for Phase 2 clinical testing in the second half of 2013

Addex Trial: Blepharospasm



addex Therapeutics

Allosteric modulators for **HUMAN HEALTH**

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DIPRAGLURANT-ER FOR DYSTONIA (BLEPHAROSPASM)

Dipraglurant (Extended Release) for the treatment of non-Parkinsonian dystonia, including blepharospasm.

We are developing an extended release formulation of dipraglurant as a novel orally available mGlu5 NAM for the treatment of dystonia and have initiated a clinical program with the initial target indication of blepharospasm.

There are many types of dystonia affecting up to 300,000 people in the United States, including blepharospasm, which is characterized by involuntary muscle contractions and spasms of the eyelid muscles resulting in sustained eyelid closure causing substantial visual disturbance or functional blindness.

We expect to start an exploratory placebo-controlled Phase 2 clinical trial in blepharospasm patients using the current immediate release formulation of dipraglurant in the second quarter of 2021.

Subject to regulatory approval, we believe that dipraglurant may offer an innovative and differentiated treatment approach for multiple types of dystonia and present a significant commercial opportunity.

- Phase 2
- Double blind
- Subjects with BSP
- Expected start: 2021

Anti-Cholinergics

Progress in Neurobiology 127–128 (2015) 91–107

Contents lists available at ScienceDirect

Progress in Neurobiology

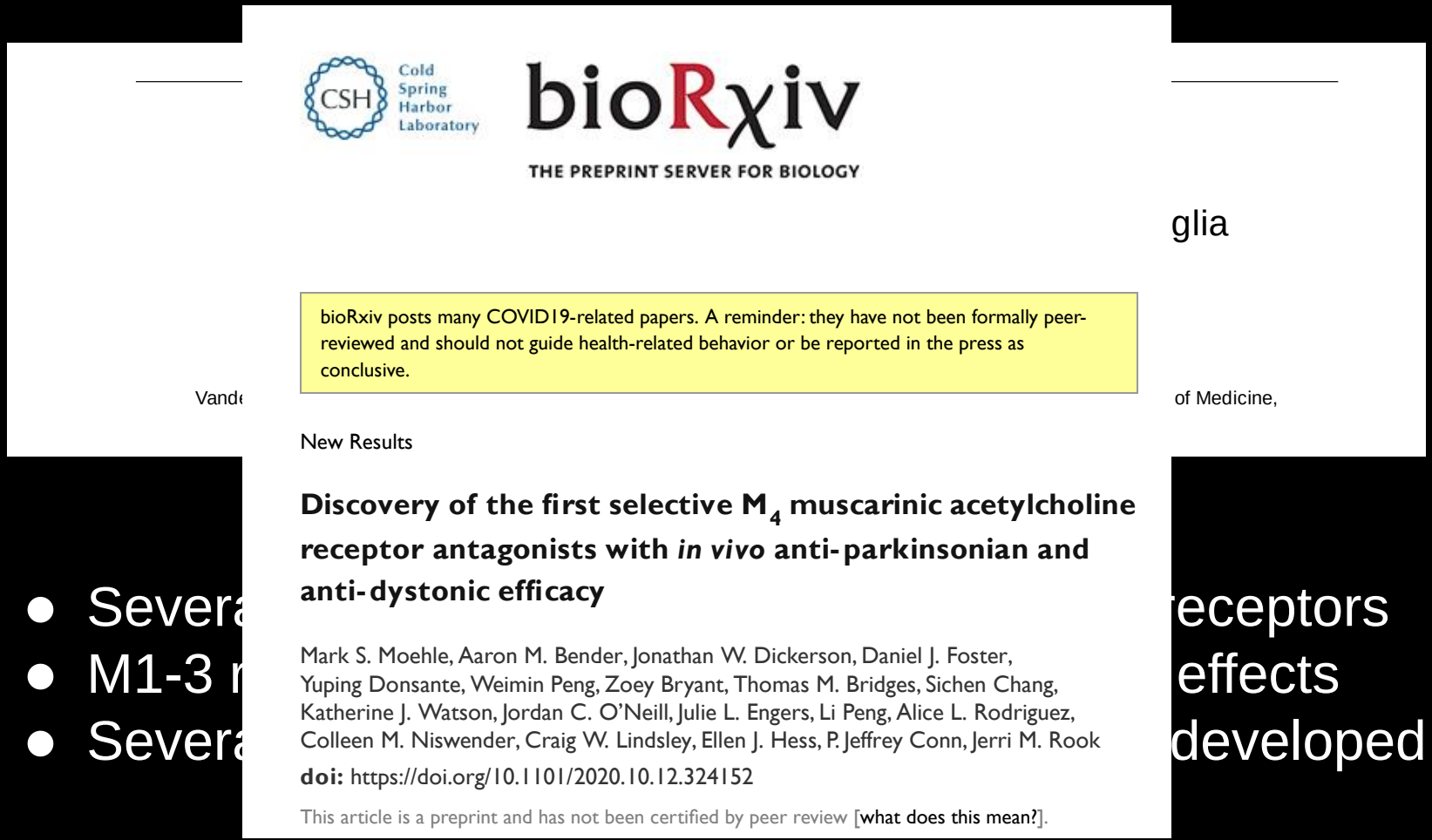
journal homepage: www.elsevier.com/locate/pneurobio

Striatal cholinergic dysfunction as a unifying theme in the pathophysiology of dystonia

K.L. Eskow Jaunarajs [a], P. Bonsi [b], M.F. Chesselet [c], D.G. Standaert [a,**], A. Pisani [b,d,*]

- Anticholinergics effective for many types of dystonia
- Side effects are terrible, so they are hard to use
- Available anticholinergics are non-selective
- Can we make better ones that are more selective?

Anti-Cholinergics: M4 Receptor



Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

glia

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

Vande

of Medicine,

New Results

Discovery of the first selective M_4 muscarinic acetylcholine receptor antagonists with *in vivo* anti-parkinsonian and anti-dystonic efficacy

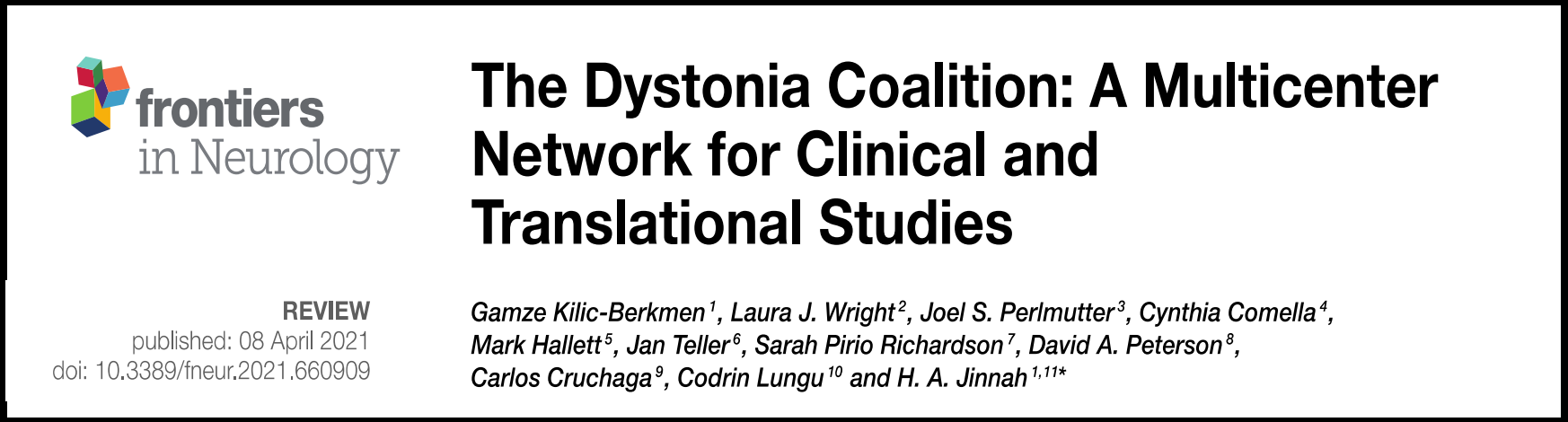
Mark S. Moehle, Aaron M. Bender, Jonathan W. Dickerson, Daniel J. Foster, Yuping Donsante, Weimin Peng, Zoey Bryant, Thomas M. Bridges, Sichen Chang, Katherine J. Watson, Jordan C. O'Neill, Julie L. Engers, Li Peng, Alice L. Rodriguez, Colleen M. Niswender, Craig W. Lindsley, Ellen J. Hess, P. Jeffrey Conn, Jerri M. Rook

doi: https://doi.org/10.1101/2020.10.12.324152

This article is a preprint and has not been certified by peer review [what does this mean?].

- Severa receptors
- M1-3 r effects
- Severa developed

Only 3 Examples in 15 Minutes



frontiers in Neurology

The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies

REVIEW
published: 08 April 2021
doi: 10.3389/fneur.2021.660909

*Gamze Kilic-Berkmen[1], Laura J. Wright[2], Joel S. Perlmutter[3], Cynthia Comella[4], Mark Hallett[5], Jan Teller[6], Sarah Pirio Richardson[7], David A. Peterson[8], Carlos Cruchaga[9], Codrin Lungu[10] and H. A. Jinnah[1,11]**

- Existing treatments & limitations
- Some new treatments being developed
- ClinTrials.Gov: 16 recent or active trials
- Importance of being ready for trials