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"
Review

The neurobiological basis for novel experimental therapeutics in dystonia

Anthony M. Downs, Kaitlyn M. Roman, Simone A. Campbell, Antonio Pisani, Ellen J. Hess, Paola Bonsi
Glutamate Receptors

- Widely distributed in brain
  - basal ganglia
  - cerebellum

- Numerous animal studies implicate GluR in dystonia

- \textit{GRIN2B} (NMDA receptor) linked with human dystonia

- Pilot study of riluzole in cervical dystonia
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

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

Susan H. Fox, MRCP, PhD, Matthew Swan, MD, Hyder A. Jinnah, MD, PhD, Maria E.T. de Freitas, MD, Lais M. de Oliveira, MD, Duha Al-Shorafat, MD, Hubert H. Fernandez, MD, Katie Kompoliti, MD, and Cynthia Camella, MD

- 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

**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
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

- 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?
Several investigators have honed in on M4 receptors that regulating. Within severe movements, University of Medicine and Biology VU6021625, summarized a model showing M4 receptors do not engage the basal ganglia of dystonia. Two recent studies from the Cold Spring Harbor Laboratory reported that the role of M4 receptors in the basal ganglia has been explored. The discovery of the first selective M4 muscarinic acetylcholine receptor antagonists with in vivo anti-parkinsonian and anti-dystonic efficacy has been reported. This article is a preprint and has not been certified by peer review [what does this mean?].

**Discovery of the first selective M₄ 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

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.
Only 3 Examples in 15 Minutes

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

Gamze Kilic-Berkmen¹, Laura J. Wright², Joel S. Perlmutter³, Cynthia Comella⁴, Mark Hallett⁵, Jan Teller⁶, Sarah Pirio Richardson⁷, David A. Peterson⁸, Carlos Cruchaga⁹, Codrin Lungu¹⁰ and H. A. Jinnah¹¹*

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