Treatment of orthostatic hypotension in Multiple System Atrophy
New Clinical Studies

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Disclosure

Lundbeck Pharmaceutical
• Consultant
• Member of the Advisory Board
Off-label Drug Use

Atomoxetine

Class:
Norepinephrine Transporter Blocker
What happen when the autonomic nervous system fails?

Dizziness
Lightheadedness
Fatigue
Weakness
Fainting

…upon standing improves after sitting down
Symptomatic orthostatic hypotension?

Symptoms +

Drop in systolic blood pressure $\geq 20 \text{ mm Hg}$
Or diastolic blood pressure of $\geq 10 \text{ mm Hg}$
within 3 minutes
Why do we have to treat orthostatic hypotension?

If left untreated...
- Increases the risk of falls
- Impaired quality of life
- Reduced daily activities
- Impaired cognitive abilities
What is the ideal Treatment?

A medication that increases sympathetic activity only when the sympathetic nerves are activated

Standing
MULTIPLE SYSTEM ATROPHY IS A DISEASE THAT SPARED PERIPHERAL SYMPATHETIC NERVES

Central Autonomic Failure (Multiple System Atrophy, MSA)

Blood vessel

Spinal cord

Collateral ganglion

Sympathetic ganglion

Sympathetic Nerves Fibers are spared
Potential Treatment
Norepinephrine Transporter Inhibitor
Atomoxetine

Atomoxetine commercially available for the treatment of attention deficit hyperactivity disorder in children and adults
Proof-of-concept study
Atomoxetine increased blood pressure in Multiple System Atrophy

Shibao C., Biaggioni I et al.
Hypertension 2007
Second study. Experimental Approach

- **baseline**
- **post-medication**

- **BP q 5 min**

**DRUG**

- PLACEBO (no active medication)
- ATOMOXETINE 18 mg
- MIDODRINE 5-10 mg
Atomoxetine preferentially improved standing blood pressure compared with midodrine

Ramirez CE & Shibao et al. Hypertension 2014

69 patients with Orthostatic hypotension
Atomoxetine but not midodrine significant decreased lightheadedness

Ramirez CE & Shibao et al. Hypertension 2014
Multiple system atrophy (MSA)
Parkinson disease (PD)
Pure Autonomic Failure (PAF)
Unknown diagnosis (early)
Conclusion and Future directions

Atomoxetine use for the treatment of attention deficit disorder in children improved upright blood pressure and orthostatic symptoms compared with midodrine

Patients with multiple system atrophy had a better response than other patients with orthostatic hypotension

Our goal is to repurpose atomoxetine for the treatment of orthostatic hypotension in multiple system atrophy
Norepinephrine Transporter Blockade, Autonomic Failure (NETAF) (NETAF)

This study is currently recruiting participants. (see Contacts and Locations)

Verified December 2016 by Vanderbilt University Medical Center

Sponsor:
Vanderbilt University Medical Center

Collaborator:
New York University School of Medicine

Information provided by (Responsible Party):
Cyndya Shibao, Vanderbilt University Medical Center

ClinicalTrials.gov identifier:
NCT02784535

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Last updated: December 28, 2016
Last verified: December 2016

History of Changes

Locations

United States, New York

Dysautonomic Center at NYU Langone Medical Center
New York, New York, United States, 10016
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United States, Tennessee

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Nashville, Tennessee, United States, 37232
Contact: Bonnie Black, RN III 615-343-6862 bonnie.black@vanderbilt.edu
Principal Investigator: Cyndya A Shibao, MD
Preliminary report

N=11 subjects completed both phases

72% enrolled patients requested their treating physician to change OH current therapy to atomoxetine after participation in the trial
Is there benefit of a longer acting NET-inhibitor?
TD-9855
Structure and Chemical Formula

4-[2-(2,4,6-trifluorophenoxy)methyl]phenyl]piperidine
• Longer half life of TD-9855 results in a more consistent 24 hour steady state occupancy of NET than atomoxetine

Sauer et al., Clinical Pharmacokinetics, 2008
Lo et al., Poster at ASCPT 2015
TD-9855 Phase 2 in Neurogenic Orthostatic Hypotension (nOH)

This study is currently recruiting participants. (see Contacts and Locations)
Verified July 2016 by Theravance Biopharma R & D, Inc.
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Principal Investigator: Italo Biaggioni, MD
TD-9855: BP Response in Patient with MSA and nOH

- 62 yo female diagnosed with MSA 2 years prior.
- Severe nOH. Unable to stand for more than a minute
Future directions

• Better understand the hemodynamic effects of NET-inhibitors (short and long acting)
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Our patients