Norepinephrine transport inhibition and vasovagal syncope – POST6 Study

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on behalf of the POST6 Investigators

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Libin Cardiovascular Institute of Alberta
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Heart Rhythm Congress (Birmingham UK)
October 2018
Physiologic model of VVS & Drug Targets

- **Physiological Stress**
  - Volume Depletion
  - Catecholamines

- **Baroreceptor activation or inactivation**

- **CNS Reflex**
  - Vagal Stimulation
  - Sympathetic Withdrawal

- **Drug Targets**
  - Salt & Water
  - Fludrocortisone
  - Beta-Blockers
  - SSRI - Paroxetine
  - Midodrine

- Pacemakers
- Scopolamine
New Drugs for Syncope in Last 25 Years

This is a complete list
Norepinephrine Transporter Inhibition Prevents Tilt-Induced Pre-Syncope

Christoph Schroeder, MD,* Andreas L. Birkenfeld, MD,* Antje F. Mayer,* Jens Tank, MD,* Andre Diedrich, MD, PhD,† Friedrich C. Luft, MD,* Jens Jordan, MD*

- "Meta-Analysis" of 3 studies of 2 different NET inhibitors
- "Healthy" controls


Placebo  – 9/18 fainted
Reboxetine  – 1/18 fainted

A Norepinephrine Synapse

Slide courtesy of Alex Nackenoff (Vanderbilt)
A Norepinephrine Synapse
Tyrosine hydroxylase (TH) and norepinephrine transporter (NET) proteins in VVS patients

Gautam Vaddadi et al. Circ Arrhythm Electrophysiol. 2011;4:711-718

**NET in VVS with normal BP**

**TH in VVS with low BP**
- Sibutramine
- Open-label study
- “worst of the worst” fainters
- **Marked reduction in fainting rates**
- Sibutramine no longer on the Canadian Market
Prevention of Syncope Trial (POST) 6: Assessment of Atomoxetine to Prevent Vasovagal Syncope
Assessment of Atomoxetine to Prevent Vasovagal Syncope

- Prospective placebo-controlled RCT; parallel design
- Acute NET blockade
  - atomoxetine 40 mg po bid x 2 doses
- N=58 vasovagal syncope patients randomized, 2 dropouts)

- ENDPOINT: Tilt Table Test induced syncope
- INCLUSION: Fainting and Calgary S3 score

- Multicenter Canadian RCT
  - Calgary, Hamilton, Sherbrooke, Montreal
- Timeline: July 2015 – January 2018
Randomly assign

Placebo
- Pill at night and in the morning
- Tilt table test
- Faint?

Atomoxetine
- Pill at night and in the morning
- Tilt table test
- Faint?
## POST6: Study Population

<table>
<thead>
<tr>
<th>Item</th>
<th>On average...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>56 (39 women)</td>
</tr>
<tr>
<td>Age</td>
<td>37±14</td>
</tr>
<tr>
<td>Faints in prior year</td>
<td>3 (pretty bad)</td>
</tr>
<tr>
<td>Lifetime faints</td>
<td>12 (really bad)</td>
</tr>
<tr>
<td>Syncope Score</td>
<td>3 (definite diagnosis)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>77 bpm</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>116 mmHg</td>
</tr>
</tbody>
</table>
**POST6: Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 27)</th>
<th>Active Pill (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean ±SD</strong></td>
<td>38 ± 14</td>
<td>35 ± 14</td>
</tr>
<tr>
<td><strong>Female, n</strong></td>
<td>18 (67%)</td>
<td>22 (79%)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², median (IQR)</strong></td>
<td>25 (21.3-30)</td>
<td>25.1 (22.6-28.3)</td>
</tr>
<tr>
<td><strong>Syncope history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age of onset, years, median (IQR)</strong></td>
<td>14 (9-22)</td>
<td>17 (11-27)</td>
</tr>
<tr>
<td><strong>Lifetime spells, median (IQR)</strong></td>
<td>11 (4-20)</td>
<td>12 (5-36)</td>
</tr>
<tr>
<td><strong>Spells in previous year, median (IQR)</strong></td>
<td>3 (1-6)</td>
<td>3 (2-6.75)</td>
</tr>
<tr>
<td><strong>Duration of symptoms, years, median (IQR)</strong></td>
<td>17 (7-30)</td>
<td>13.5 (3.25-25)</td>
</tr>
<tr>
<td><strong>Calgary Syncope Score, median (range)</strong></td>
<td>3 (-2, 6)</td>
<td>3 (-2, 6)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mmHg, median (IQR)</strong></td>
<td>115 (111-131)</td>
<td>118 (107-134)</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min, median (IQR)</strong></td>
<td>75 (65-84)</td>
<td>78 (73-83)</td>
</tr>
</tbody>
</table>
POST6: Syncope

Syncope-Free Survival

\[ p = 0.012 \]

Syncope-free Survival (%) vs Tilt Time (min)

ATOM
PLAC

POST 6
Presyncope-Free Survival

Presyncope-free Survival (%)

Tilt Time (min)

\[ p = 0.660 \]
<table>
<thead>
<tr>
<th>Item</th>
<th>Placebo</th>
<th>Atom</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>27</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Syncope %</td>
<td>63%</td>
<td>28%</td>
<td>0.009</td>
</tr>
<tr>
<td>Syncope-free survival %</td>
<td>65%</td>
<td>30%</td>
<td>0.024</td>
</tr>
<tr>
<td>Presyncope %</td>
<td>78%</td>
<td>72%</td>
<td>0.76</td>
</tr>
<tr>
<td>Presyncope-free survival %</td>
<td>22%</td>
<td>24%</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Atomoxetine does not prevent the *vasovagal reflex* ... but does prevent *vasovagal syncope*
## Syncope vs Presyncope

<table>
<thead>
<tr>
<th>Trough Vital Signs</th>
<th>Presyncope</th>
<th>Syncope</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>72</td>
<td>57</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>95</td>
<td>62</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.3</td>
<td>1.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke vol index (ml/m²)</td>
<td>26</td>
<td>29</td>
<td>0.30</td>
</tr>
<tr>
<td>SVR index</td>
<td>2034</td>
<td>2109</td>
<td>0.98</td>
</tr>
</tbody>
</table>

### Diagram:

**Presyncope vs. Syncope**

- **CI** (Cardiac Index) increases
- **HR** (Heart Rate) increases
- **BP** (Blood Pressure) increases
- **SV** (Stroke Volume) decreases
- **SVR** (Systemic Vascular Resistance) increases
## Placebo vs Atomoxetine

### Presyncope & Syncope Patients

<table>
<thead>
<tr>
<th>Trough vital signs</th>
<th>Placebo</th>
<th>Atom</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>55</td>
<td>76</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>58</td>
<td>93</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac index (L/m(^2))</td>
<td>1.4</td>
<td>2.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke vol index (ml/m(^2))</td>
<td>28</td>
<td>28</td>
<td>0.95</td>
</tr>
<tr>
<td>SVR index</td>
<td>2034</td>
<td>2019</td>
<td>0.96</td>
</tr>
</tbody>
</table>

ATOM vs. Placebo

- \(\uparrow\text{Cl}\)  \(\rightarrow\text{SV}\)  \(\rightarrow\text{SVR}\)
- \(\uparrow\text{HR}\)  \(\rightarrow\text{BP}\)

**POST 6**

Atomoxetine preserves BP by preserving HR
POST6: Conclusions

▪ NET inhibition with Atomoxetine
  — Prevents tilt-induced vasovagal syncope
  — Does not prevent tilt-induced presyncope

▪ Atomoxetine physiologically:
  — Does not increase vascular resistance
  — Functions as a pharmacological pacemaker
    ▪ Works more just when needed

▪ Future clinical trial is needed
  — Clinical syncope will be the endpoint
Acknowledgements

- POST6 Investigators
- POST6 Patients
- POST Office
  - University of Calgary Syncope Coordinating Center led by Robert S Sheldon MD PhD
- Cardiac Arrhythmia Network of Canada