Clinical Development Programs for Disease-Modifying Agents for Peripheral Neuropathy: Public Workshop

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Panel 3: Structural and Functional End Points

Quantitative Autonomic Assessment
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Overview:

In spite of the clear association of autonomic neuropathy (AN) with multiple symptoms and impairments, the substantial effects of AN on the quality of life and the unquestionable link between AN and deaths related to cardiovascular dysfunction, the quantitative assessment of AN has often been limited or omitted from previous multicenter studies of neuropathy.
Structural or Functional Deficits in the Autonomic Nervous System (partial list)

Cardiovascular
   e.g., tachycardia, exercise intolerance, cardiac denervation, orthostatic hypotension, exercise intolerance

Neurovascular
   e.g., sudomotor deficits, impaired skin blood flow

Gastrointestinal
   e.g., gastroparesis, diarrhea, constipation

Genitourinary
   e.g., erectile dysfunction, cystopathy, neurogenic bladder

Pupillary
   e.g., faulty dilation, Argyll-Robertson pupil
AN – Several Phenotypes

• One component of a generalized neuropathy (e.g., diabetic polyneuropathy)

• Primary autonomic neuropathy (e.g., amyloidosis, autoimmune autonomic neuropathy)

• Distal small fiber sensory polyneuropathy (SFSN)
Complexities Associated with the Quantitative Assessment of AN

• Autonomic nerves are composed of small diameter axons and, except for skin, they are relatively inaccessible.

• The impact of AN often includes effects on a combination of both parasympathetic and sympathetic axons.

• Most measures of AN are focused on changes in an end organ following deficits in innervation – these tests are influenced by a number of non-neural confounders.

• The sheer scope and range of the available tests and the complexity of their analysis complicates simple estimates of sensitivity, specificity and clinical value.
Measures of AN that are Feasible for Clinical Research Fall into Two Categories

• **Questionnaires** (partial list) – Medline search AN + questionnaires
  103 hits past 5 years
  
  Survey of Autonomic Symptoms (SAS)  Zilliox et al., 2011
  Orthostatic Hypotension Questionnaire (OHQ)  Kaufman et al., 2012
  Composite Autonomic Symptom Score (Compass 31)  Sletten et al., 2012

• **Objective, Quantitative Measures** (partial list)
  
  Heart rate variability
  Valsalva maneuver
  Baroreflex sensitivity
  Measures of sudomotor function
  Pupillary response characteristics
Early and Simple Evaluations (CAN)

Ewing et al., 1970

- Valsalva maneuver
- Heart rate change with deep breathing*
- Heart rate response to standing
- Blood pressure response to standing
- Blood pressure response to sustained hand grip

* Earliest reports linking HRV and breathing can be traced to publications in the mid 1800s

Characterized heart rate response to deep breathing, Valsalva ratio, R-R interval to standing, beat-to-beat blood pressure changes, and QSART measures as having high sensitivity and specificity, and commented that they are safe, valuable and cost effective tests.

In contrast, this review characterized sustained hand grip and sympathetic skin responses as having limited sensitivity and specificity – with confounders not fully defined.

Finally, they characterized the thermoregulatory sweat test (TST) as having high sensitivity, but low specificity, and poorly understood reproducibility.
2009 Polyneuropathy Task Force (evidence based)
American Academy of Neurology (AAN)
American Academy of Neuromuscular and Electrodiagnostic Medicine
American Academy of Physical Medicine and Rehabilitation

Recommendations:

• The assessment of heart rate variability, including changes induced by manipulation of blood pressure - Sensitivity reported to be 97.5 for parasympathetic deficit in diabetic subjects - similar to NCV studies.

• The use of the quantitative sudomotor axon reflex test (QSART) - Sensitivity to distal sudomotor loss 75 to 90%.

• To achieve the highest diagnostic accuracy, they recommended the use of a composite autonomic scoring system (CASS) which includes QSART, orthostatic blood pressure, heart rate response to tilt and deep breathing, the Valsalva ratio, and beat-to-beat blood pressure measurements.
Table 1—Reported prevalence of CAN

<table>
<thead>
<tr>
<th>Author</th>
<th>Date of publication</th>
<th>Diabetes type</th>
<th>Subjects (n)</th>
<th>Test(s) used</th>
<th>% Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharpey-Schafer and Taylor (26)</td>
<td>1960</td>
<td></td>
<td>337</td>
<td>Valsalva maneuver</td>
<td>21</td>
</tr>
<tr>
<td>Ewing et al. (27)</td>
<td>1974</td>
<td>Mixed with autonomic symptoms</td>
<td>124</td>
<td>Handgrip test</td>
<td>18</td>
</tr>
<tr>
<td>Morley et al. (28)</td>
<td>1977</td>
<td>Adult diabetic patients</td>
<td>70</td>
<td>Heart rate variation</td>
<td>11</td>
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<tr>
<td>Hilsted and Jensen (29)</td>
<td>1979</td>
<td>Insulin-treated</td>
<td>126</td>
<td>Heart rate variation</td>
<td>40</td>
</tr>
<tr>
<td>Mackay et al. (30)</td>
<td>1980</td>
<td></td>
<td>287</td>
<td>Heart rate variation</td>
<td>30</td>
</tr>
<tr>
<td>Ewing et al. (31)</td>
<td>1980</td>
<td>Mixed with autonomic symptoms</td>
<td>73</td>
<td>Valsalva maneuver</td>
<td>47</td>
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<tr>
<td>Ewing et al. (32)</td>
<td>1980</td>
<td>Mixed with autonomic symptoms</td>
<td>61</td>
<td>Handgrip</td>
<td>54</td>
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<tr>
<td>Hulper and Wilms (33)</td>
<td>1980</td>
<td></td>
<td>92</td>
<td>Postural BP</td>
<td>17</td>
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<tr>
<td>Dyrberg et al. (34)</td>
<td>1981</td>
<td>Insulin-dependent</td>
<td>73</td>
<td>Heart rate variation</td>
<td>27</td>
</tr>
<tr>
<td>Xuei et al. (35)</td>
<td>1981</td>
<td>Newly diagnosed non-insulin-dependent</td>
<td>506</td>
<td>At least two of the following: heart rate variation in response to 1) rest 2) single deep breath 3) Valsalva maneuver or 4) standing</td>
<td>17</td>
</tr>
<tr>
<td>O’Brien et al. (36)</td>
<td>1991</td>
<td>Insulin-dependent</td>
<td>506</td>
<td>At least three of the following: CV of heart rate variation, low- and mid-frequency bands of spectral analysis, MCR, Valsalva maneuver, or lying-to-standing</td>
<td>7.7</td>
</tr>
<tr>
<td>Ziegler et al. (24)</td>
<td>1992</td>
<td>Newly diagnosed insulin-dependent</td>
<td>130</td>
<td>Greater than two of the following: coefficient of variation of heart rate variation, low- and mid-frequency bands of spectral analysis, MCR, Valsalva maneuver, or lying-to-standing</td>
<td>25.3</td>
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<tr>
<td>Ziegler et al. (24)</td>
<td>1992</td>
<td>Insulin-dependent</td>
<td>647</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Non-insulin-dependent</td>
<td>524</td>
<td></td>
<td>34.3</td>
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<tr>
<td>Kennedy et al. (25)</td>
<td>1995</td>
<td>Insulin-dependent</td>
<td>290</td>
<td>Heart rate variation</td>
<td>90</td>
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<td>DCCT Research Group (37)</td>
<td>1998</td>
<td>Insulin-dependent, primary cohort 1–5 years’ duration; secondary cohort 1–15 years’ duration</td>
<td>1,441</td>
<td>Heart rate variation</td>
<td>1.6–6.2</td>
</tr>
</tbody>
</table>

Vinik et al., 2003

Tables 1-3 listed 42 separate studies of CAN dating back to 1960

Total of 40 studies used either heart rate variation or Valsalva or both
The Toronto Consensus Panel on Diabetic Neuropathy – Bernardi et al., 2011

Recommendations re: Cardiac Autonomic Dysfunction

- Heart rate variability (time and frequency domain)
- Baroreflex sensitivity
- Muscle sympathetic nerve activity
- Plasma catecholamines
- Heart sympathetic imaging
As always – “the devil is in the details”
e.g., R-R variation can be measured in multiple ways which impact sensitivity and reproducibility

Power Spectral Analysis
Low 0.04 - 0.15Hz – sympathetic and vagal activity
High frequency 0.15 to 0.04 Hz – vagal activity

Karamitsos et al., 1998
The DCCT/EDIC Study (Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications) – Pop-Busui et al., 2013

• Evaluated the association between CAN and left ventricular structure and function in 966 participants in the DCCT/EDIC study.

• CAN was defined by specific deficit in R-R variation or by a composite index that included R-R variation, Valsalva ratio, and blood pressure upon standing (original autonomic end points in the DCCT study).

• The study confirmed that CAN was associated with increased LV hypertrophy with concentric remodeling independent of age, sex, and other factors.
Sensory axons branching from the epidermal neural plexus

Nolano, Provitera, Caporaso et al., 2010

Explored the quantification of sweat gland innervation and pilomotor nerves
Emerging Techniques

• Further refinement of the analysis of autonomic fibers and structures in skin biopsies.

• Enhanced nerve conduction procedures focused on the assessment of nerve conduction velocity in small diameter and thinly myelinated axons.

• Non-invasive measures of deficits in nerves using the MRI technique of diffusion tensor imaging.

• Refinements in smooth muscle physiology.

• Greater use of imaging techniques to detect changes in end-organ structure driven by AN.