Basiskurs Schmerztherapie; Parkvilla Wörth, Pörtschach

**** 25 Jahre ****

Chronisch regionales Schmerzsyndrom (CRPS I/II, Morbus Sudeck)

Michael Stanton-Hicks
MB; BS, Dr. med, FRCA, FCAI (hon), ABPM, FIPP
Department of Pain Management
Center for Neurological Restoration
Shaker Pediatric Rehabilitation
Cleveland Clinic
Ambroise Paré as surgeon to Charles IX, during multiple bloodletting for smallpox, caused nerve injury that led to causalgic Sx 1557
Weir Mitchell
“symptom amplification” causalgia
“Gunshot Wounds and other Injuries”
with Moorhouse and Keen 1864

Paul Sudeck
“..über die akute Knockenatrophie..”
1900

René Leriche
Related pain to SNS dysfunction
1879-1955
WORKSHOP

REFLEX SYMPATHETIC DYSTROPHY

OCTOBER 15-17, 1988

Schloßhotel Rettershof

6233 Kelkheim/TS.
participants

- Wilfrid Jänig
- Martin Zimmermann
- Terrence Murphy
- Edmond Charlton
- William Roberts
- Martin Kolzenberg
- Hans Nolte
- Ilmar Jurna
- Jennifer Kelly
- Hermann Kreuscher
- Peter Wilson
- Karen McCann
- Gabor Racz
- Ronald Tasker

- Stephen Butler
- Erik Torbjörk
- Prithvi Raj
- Ulf Egle
- Robert Boas
- Helmut Blumberg
- Stephen Abram
- David Haddox
- Hannington-Kiff
- Christopher Glynn
- Albert van Steenberge
- Hans Gebershagen
- Michael Stanton-Hicks
Orlando concensus conference 1993
Reflex sympathetic dystrophy: changing concepts and taxonomy.

Stanton-Hicks M, Jänig W, Hassenbusch S, Haddox JD, Boas R, Wilson P
Taxonomy CRPS - 1994 IASP

- Terms Reflex Sympathetic Dystrophy and Causalgia lost clinical utility

- Taxonomy emphasizes clinical characteristics
  - Complex: varied clinical features
  - Regional: majority of cases involve a region of the body, usually an extremity
  - Pain: essential to the diagnosis
  - Syndrome: repetitive nature of clinical features

A favorable response to a sympatholysis is **NOT** required for the diagnosis of CRPS.

Merskey H and Bogduk N eds. IASP Press 1994
Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients.

Veldman PH₁, Reynen HM, Arntz IE, Goris RJ.

"...In its early phase, reflex sympathetic dystrophy is characterised by regional inflammation, which increases after muscular exercise. Pain was present in 93% of patients, and hypoaesthesia and hyperpathy were present in 69% and 75% respectively..."

"...Tremor was found in 49% and muscular incoordination in 54% of patients. Sympathetic signs such as hyperhidrosis are infrequent and therefore have no diagnostic value..."
“Budapest” Criteria
at least 1 SYMPTOM in 3 of 4 categories and 1 SIGN in 2 or more categories. (SENS. 0.99: SPEC. 0.68)

Harden et al. Pain (2010);150: 268-274

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SYMPTOM</th>
<th>SIGN</th>
</tr>
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<tbody>
<tr>
<td>SENSORY</td>
<td>Hyperesthesia, allodynia</td>
<td>hyperalgesia (PP) allodynia – mech. / thermal / deep</td>
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<td>VASOMOTOR</td>
<td>Δ skin / color</td>
<td>&gt; 1° C / Δ skin color</td>
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<tr>
<td></td>
<td>Δ temperature</td>
<td></td>
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<tr>
<td>SUDOMOTOR EDEMA</td>
<td>Δ sweating / edema</td>
<td>Δ sweating / edema</td>
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<tr>
<td>MOTOR TROPHIC</td>
<td>motor dysfunction ↓ ROM</td>
<td>motor function ↓ ROM (weak, dystonia, tremor) / trophic</td>
</tr>
<tr>
<td></td>
<td>Δ trophic</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms

- Inflammation
- Neurogenic inflammation
- Vasculopathy
- Immune dysfunction
- Genetic
Inflammation

Inflammatory mediators at injury site

- Cytokines: IL6, TNFα, osteoprotegerin
- Neuropeptides: CGRP, SP, VIP
- Eicosanoids: PGE2
Inflammatory Aspects


**Inflammation in CRPS: role of the sympathetic supply.**

Schlereth T¹, Drummond PD², Birklein F³

- Pro-inflammatory cytokines
- Adaptive immunity - autoantibodies to β₂-adrenergic and muscarinic 2 receptors
- Cold skin – noradrenaline, endothelin/NO disturbance
- Neurogenic inflammation – CGRP, NK1
- Up-regulation of keratinocytes
α₁ AR immunoreactivity on keratinocytes, BV’s and sweat glands

PGP 9.5 red
α₁- AR green

Finch et al Pain Medicine 2014; 15: 1945
CNS

- Sensitization – NMDA, NK-1 receptors
  Ji RR. Trends Neurosci. 2003; 26: 696-705

- Activated glia “drive” allodynia and hyperalgesia – CRPS
  Milligan and Watkins Nat Rev Neurosci 2009


  Wang X1,2, Zhang Y3, Peng Y4, Hutchinson MR5, Rice KC6, Yin H4, Watkins LR3
Activation of cutaneous immune responses in complex regional pain syndrome.

Birklein F, Drummond PD, Li W, Schlereth T, Albrecht N, Finch PM, Dawson LF, Clark JD, Kingery WS.

PERSPECTIVE:
The results of this study support the hypotheses that CRPS involves activation of the innate immune system, with keratinocyte and mast cell activation and proliferation, inflammatory mediator release, and pain.

- TNF-a, IL-6 are elevated in skin blister fluid
- tryptase (mast cells)
- exaggerated sympathetic signaling
- keratinocytes
- $\alpha_1$-adrenoceptors
Emerging Rx: IVIG

Complex regional pain syndrome, prototype of a novel kind of autoimmune disease

*Goebel and Blaes 2013; 12: 682*

- IgG serum autoantibodies against autonomic receptors
- CRPS includes an autoantibody-mediated autoimmune process
- Suggests novel Rx modalities in future
A CRPS-IgG-transfer-trauma model reproducing inflammatory and positive sensory signs associated with complex regional pain syndrome.

Tékus V¹, Hajna Z¹, Borbély É¹, Markovics A¹, Bagoly T¹, Szolcsányi J², Thompson V³, Kemény Á¹, Helyes Z², Goebel A⁴

- Serum IgG from Chronic CRPS, normal pts. and saline mice with hind limb incision
- CRPS IgG caused extreme inflammation at 8 days
- Normal controls and saline had no effect
Genetic Factors

- HLA-DR2 in caucasian women
  - *Mailis and Wade* 1994

- HLA DR13 relation to dystonia
  - *Van de Beek et al* 2003

- HLA-DQ8 & HLA-B62 associated with CRPS ± dystonia
  - *Van Rooijen et al* 2012
Pathophysiology CRPS

Brain

Central Sensitisation
- allodynia
- dystonia
- autonomic dysfunction

Inflammation
- IL6
- TNFα

Blood vessel
- NO/endothelial dysfunction

Mast cells

CNS

Spinal cord

Neuropeptides
- cGRP

Nerve damage

Tissue damage
- Genetic
- Immune acquired
Levels of Evidence

- Level 1: Meta-analysis or systematic reviews.
- Level 2: One or more well-powered randomized, controlled trials.
- Level 3: Retrospective studies, open-label trials, pilot studies.
- Level 4: Anecdotes, case reports, clinical experience, etc.

Core Treatment Algorithm

MVF, GMI
  - Reactivation
  - Contrast Baths
  - Desensitization
  - Exposure therapy

Edema control
  - Flexibility (active)
  - Isometric strengthening
Correction of postural abnormalities
  - Dx & Rx of secondary MFPS

Stress loading
  - Isotonic strengthening
  - ROM – gentle – resistant
  - General aerobic conditioning
  - Postural normalization & balanced use

Ergonomics
  - Movement therapies
  - Normalization of use
  - Vocational / Functional Rehabilitation
Interdisciplinary Management

Guzman J et al., BMJ 2001; 322: 1511–6
The algorithms were discussed in Milan

SIG, Pain & SNS : “A comprehensive analysis of CRPS treatment: the new, the old. what works and what doesn’t”

*World Congress, IASP, Milan, August 25 –31, 2012*
A COMPREHENSIVE ANALYSIS OF CRPS TREATMENT: The New, The Old, What Works and What Doesn’t

UPDATING THE TREATMENT ALGORITHM

AUGUST 26 & 27, 2012 - MILAN, ITALY

PROGRAM CHAIRMEN
Joshua P. Prager, MD, MS  Michael Stanton-Hicks, MD

PROGRAM Co-CHAIRS
Candy McCabe, RGN, MSc, PhD  Anne Louise Oaklander, MD, PhD

SPEAKERS
Ralf Baron, MD
Frank Birklein, MD
Daniel Carr, MD
Andreas Goebel, MD, PhD
Frank Huygen, MD
Marilyn Jacobs, PhD
Ralph-Thomas Kiefer, MD
Max Klein, PhD
Franklin Kozin, MD
Robert Levy, MD, PhD
Andre Machado, MD, PhD
Angela Mailis-Gagnon, MD, MSc

Donald Manning, MD, PhD
Candy McCabe, RGN, MSc, PhD
Harold Merskey, MA, DM
Lorimer Moseley, PhD
Anne Louise Oaklander, MD, PhD
Joshua P. Prager, MD, MS
Roberto Perez, PhD
Srinivasa Raja, MD
Michael Stanton-Hicks, MD
Navil Sethna, MD, ChB
J.J. Van Hilten, MD, PhD
Marissa Vrolijk de Mos, MD

Milan 2012
15th World Congress on Pain
problems of management

- Non-uniform Rx strategies
  - wide range of practice habits
  - patient heterogeneity

- Scale of treatment options
  - limited evidence
  - always something new

- Non responders
  - mismatch of treatment with patient
different CRPS symptoms have different mechanisms

• Changes in color, temperature, edema due to malfunction/pathology of microcirculation

• Changes in bones due to osteoclast/blast dysregulation

• Pain can be nociceptive and/or neuropathic

• Regional changes in muscle, skin, hair, nails
Subject viewing non-reflective surface with painful limb hidden

• Daly and Bialocerkowski: **meta-analysis**

⇒ good quality level 2 evidence


Anticonvulsants

- Gabapentin: mild effect (level 2)
  - Adult case series and pediatric case report
  - 1 DBRCT: mild effect with improvement in sensory deficits
- pregabalin, topiramate, zonisamide, levetiracetam, carbamazepine, oxcarbazepine etc.

Antidepressants

- TCA’s, SSRI’s, SSRNα’s
  - NNT = 3 for TCA in neuropathic pain
  - There is no evidence that antidepressants are effective in reducing pain in patients with CRPS-I (level 4)
Psychological interventions

- Psychological/social issues: Important

- Rationale
  - Utility in non-CRPS
  - ? direct interaction with pathophysiological mechanisms
    - Sympathetic/catecholamines
      - Both anxiety and anger expressiveness have been found to be significantly stronger in CRPS patients than in non-CRPS
  - Inflammatory mediators

Antihypertensives and α-Adrenergic Antagonists

- **Nifedipine:**
  - 2 uncontrolled case series found doses of up to 60 mg/day useful for CRPS (level 4)

- **Phenoxybenzamine:**
  - Treatment of complex regional pain syndrome type I with oral phenoxybenzamine: rational and case reports
  - α₁ & α₂ non-competitive block

*Kingery WS et al., Pain 1997;73:123–39
Muizelaar JP et al., Clin Neurol Neurosurg 1997;99:26–30
Inchiosa M, Kizelshteyn G Pain Pract 2008; 8; 125-132
Inchiosa M, Anesthesiology Research and Practice 2013, Article 978615,*
Sympathetic Blocks


Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Price D Long S, Wilsey B, Rafii A

Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study

Successful treatment of CRPS 1 with anti-TNF

A Double Blind, Randomized, Placebo Controlled Trial of Anti-TNFα Chimeric Monoclonal Antibody in CRPS
Effect of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: a randomized controlled trial. BMC Musculoskelet Dis 2008; 20

Groeneweg GI, Huygen FJ, Niehof SP, Wesseldijk F, Bussmann JB, Schasfoort FC, Stronks DL, Zijlstra FJ

n=24
Rx, 20 mg po /daily
for 10 weeks

<table>
<thead>
<tr>
<th>Tadalafil</th>
<th>Placebo</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>start</td>
<td>end</td>
<td>start</td>
</tr>
<tr>
<td>Pain intensity VAS (0-100mm)</td>
<td>61.3 ± 14.1</td>
<td>52.3 ± 19.1</td>
<td>57.0 ± 12.1</td>
</tr>
</tbody>
</table>
Biphosphonates


Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study.

Varenna M¹, Adami S, Rossini M, Gatti D, Idolazzi L, Zucchi F, Malavolta N, Sinigaglia L.

- n=82, neridronate IV 4 X for 10 days
- @ 20 days VAS ↓ 4.6 cf. 2.2
- @ 1 year – no CRPS pts. had CRPS Sx
Free Radical Scavengers

- Vitamin C prevents CRPS (level 1)
- 4 RCTs, 3 UE (wrist) and 1 LE (ankle)
  - A minimum dose of 500 mg/day is recommended
- Limited to prophylaxis immediately after fx

Zollinger PE et al., J Bone Joint Surg Am. 2007 Jul;89(7):1424-31
Shibuya N et al., J Foot Ankle Surg. 2013 Jan-Feb;52(1):62-6

DMSO (50% cream 5 x/day for 2 months) significant pain vs. placebo (level 2)
It is likely that 600 mg tab of N-acetylcysteine TID will \(\downarrow\) CRPS Sx (level 3)

Perez RS et al., Pain 2003, 102:297-307
Hyperbaric Oxygen (level 2)

- DBRCT, 15 x 90-minute sessions, 5 d/wk
- 37 patients HBO vs. normal air
- 34 patients room air (2.4 Atm. P)

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After session 15</th>
<th>Day 45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBO</td>
<td>Control</td>
<td>HBO</td>
</tr>
<tr>
<td>VAS pain (score)</td>
<td>6.81 ± 1.44a</td>
<td>6.44 ± 1.43</td>
<td>4.83 ± 1.4a,b</td>
</tr>
<tr>
<td>Wrist flexion (degrees)</td>
<td>40.54 ± 19.74a</td>
<td>38.23 ± 15.8</td>
<td>50.54 ± 19.03a,b</td>
</tr>
<tr>
<td>Wrist extension (degrees)</td>
<td>36.08 ± 14.19</td>
<td>41.76 ± 12.48</td>
<td>40.54 ± 14.03</td>
</tr>
<tr>
<td>Wrist circumference (cm)</td>
<td>18.90 ± 0.84a</td>
<td>18.67 ± 0.66</td>
<td>18.02 ± 0.84a,b</td>
</tr>
</tbody>
</table>

*aStatistically significant difference between the results after the 15th therapy session and day 45 (P < 0.001; within the HBO group).
*bStatistically significant difference between the HBO and control groups (P < 0.001).

neuromodulation

- SCS - when CMM has either failed or when confronted with florid CRPS
- Intrathecal ziconotide for complex regional pain syndrome: seven case reports

Kapural L, Lokey K, Fiekowsky S, Stanton-Hicks M, Sapienza-Crawford A,
Webster L Pain Pract 2009; 9: 296
severe CRPS pain
D1 = square
D5 = circle

Pain with SCS “ON”
- reversal of dipoles D1 & D5

SCS “OFF”
Partial sustained pain relief

Pahapill P Neuromodulation 2014; 17: 22-27
Why SCS?

- CRPS
  - Peripheral adrenergic-nociceptor coupling
  - DRG $A_\beta$-adrenergic coupling in CRPS II
  - Peripheral ischemic pathology
  - $\alpha_1$-adrenoceptor population on keratinocytes, mast cells and immune cells
  - Neuropeptide release in DH & periphery (SP, CGRP, VIP)
  - Inhibition of inflammatory response
Neuromodulation of $\alpha_1$-adrenoceptor sites

Jänig and Baron Lancet Neurology 2003
Stimulation of the dorsal route ganglion for the management of complex regional pain syndrome: a prospective case series.

CRPS of the Foot

- 8 patients – prospective, randomized controlled trial

- Average Pain Reduction (VAS): 
  75.0% Foot
  65.0% Overall

* Data courtesy of JP Van Buyten, I Smet, L Liem, M Russo, F Huygen 2014
CRPS of the Foot

- 60 year-old male
- CRPS type-1 after minor fracture
- Pain in left leg and foot showing signs of severe erysipelas.

* Data courtesy of JP Van Buyten & I Smet.
Data from van Buyten et al

- **Baseline VAS**
  - Overall: 67 mm
  - Leg: 69 mm
  - Foot: 91 mm

- **Single lead at L5 DRG**

* Data courtesy of JP Van Buyten & I Smet.*
CRPS of the Foot

data from Van Buyten et al.
Emerging: Botulinum Toxin

- DBPRCT, 25 pts
  - 0.2ml or 5 units per site
  - Limit: 40 sites or 200 U
  - spontaneous pain, brush allodynia, and cold pain thresholds

- LSB with BTx-A in 9 CRPS patients with SMP
  → pain relief 71 days vs. < 10 days for bupivacaine

Ranoux D et al., **Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain.** Ann Neurol. 2008 Sep; 64(3): 274-83

Carroll I et al., **Sympathetic block with botulinum toxin to treat complex regional pain syndrome.** Ann Neurol 2009 Mar; 65(3): 348-51
Scrambler therapy (Calmare)


**Scrambler Therapy for Chronic Pain.**
Abdi S, Smith TJ, Marineo G.


**Scrambler Therapy for the management of chronic pain.**
Majithia N1, Smith TJ2, Coyne PJ3, Abdi S4, Pachman DR5, Lachance D6, Shelerud R7, Cheville A7, Basford JR7, Farley D8, O'Neill C5, Ruddy KJ5, Sparadeo F9, Beutler A5, Loprinzi CL10.

**CONCLUSION:**
The positive findings from preliminary studies with Scrambler Therapy support that this device provides benefit for patients with refractory pain syndromes. Larger, randomized studies are required to further evaluate the efficacy of this approach.
research pathways

(Claude Bernard) Lerchès
Livingstone
Alexander
Bonica
Jänig
Baron Kiel Group
Drummond
Birkelein
Sudeck
Goris
Dutch Group
Huygen
Bläa
Goebel
Oaklander

1860 - 1900
1940 - 1980
2000 - 2016

NEUROPATHOLOGY
AUTONOMIC
IMMUNE
AUTOIMMUNE
INFLAMMATORY
INFLAMMATORY
CRPS in Children
Functional restoration algorithm

SYMP. BLOCK
CONT’T. RA
SCS

ROM
STRESS LOADING
POSTURAL CORRECTION
AEROBIC XC’s

GAMES
WATER THERAPY
FUNCTIONAL REHAB

FLEXIBILITY
EDEMA CONTROL
ISOMETRICS

REACTIVATION
CONTRAST BATHS
DESENSITIZATION
EXPOSURE THERAPY

MUSIC THERAPY
COGNITIVE BEHAVIORAL
GROUP THERAPY
PSYCHOLOGICAL COUNSELING
OF PATIENT / PARENTS
SCHOOLING
Response to Treatment

- > 87% functional improvement
- > 90% respond to physical and behavioral modalities
- Sympathetic block may affect treatment in 6% *(CCF experience)*
- TEC or SCS used to modify allodynia for PT in 6% *(CCF experience)*
Recurrence

- 30% within 6 months
- Most resolve with further Rx

Katholi BR, Daghstani SS, Banez G. Non-invasive treatments for pediatric complex regional pain syndrome: a focused review PM R 2014; 6: 926

CRPS data at 1 month

- Pain
  - Pre-Trx: 8
  - 1 mo FU: 2

- Physical
  - Pre-Trx: 15
  - 1 mo FU: 5

- Anxiety
  - Pre-Trx: 10
  - 1 mo FU: 5

- Social
  - Pre-Trx: 15
  - 1 mo FU: 10
Adolescent Pain Severity and BAPQ Composite Scores at Admission and 1-year Follow-Up

- **Pain Rating (0-10)**
- **BAPQ: Social Functioning**
- **BAPQ: Physical Functioning**
- **BAPQ: Pain Specific Anxiety**

Legend:
- Admission
- 1-year f.u.
Spinal cord stimulation in adolescents with complex regional pain syndrome type I (CRPS-I).


An effective treatment of severe complex regional pain syndrome type I in a child using high doses of intrathecal ziconotide.

03/2002

15 y.o. girl with ankle sprain

• Rx: AE's, AD's, opiates

– TEC - PT / OT 6 weeks

– D/C due to SE's

– Extended trial SCS - 6 weeks

– Sx resolved

08/2003

SCS implant – due returning

09/2005

"rolled ankle" – Sx returned

IT trial fentanyl/bup/clonidine – adverse SE's

– IT ziconotide trial - 21 mcg/d

– 2 weeks, walking with crutches. Implanted Synchromed pump

02/2014

Explanted SCS

01/2016

24.2 mcg/d – finished college, married
Complex regional pain syndrome I in children: a multidisciplinary approach and invasive techniques for the management of non-responders

### Therapies & Results at 12 mos.

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Capsaicin 8% patch</td>
<td>✔</td>
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**12 mos. f/u**

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<tr>
<th>VAS</th>
<th>0</th>
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<th>1</th>
<th>0</th>
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<th>0</th>
<th>1</th>
<th>0</th>
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<th>0</th>
</tr>
</thead>
</table>

**Functional Disability Inventory (FDI) - MINOR Meds**

<table>
<thead>
<tr>
<th>“CRPS-free weeks”</th>
<th>20</th>
<th>21</th>
<th>19</th>
<th>8</th>
<th>30</th>
<th>32</th>
<th>24</th>
<th>48</th>
<th>21</th>
<th>39</th>
</tr>
</thead>
</table>

**School absence - NO**

*Rodriguez-Lopez et al 2015, Epub*
Pathophysiology

Inflammation
- TNFα
- IL-6
- (Immune modulator)
- Infliximab
- thalidomide
- IVIG

Movement Disorder
- tremor
- dystonia
- IT Baclofen UE’s
- SCS

Hypoxia
- NO/ endothelin dysfunction
- O₂ radicals
- vasoconstriction
- NO donation
- eNO synthase
- Isosorbidedinitrate
- PDE-5 inhibition
- Tadalafil
- Neuromodulation
- O2 radical scavengers

Central sensitization
- DH
- microglia
- astrocytes
- locus coeruleus
- anticonvulsants
- antidepressants
- minocycline
- WP9QY
- naltrexone (TLR4)
- Phenoxybenzamine (α₁α₂)
- neuromodulation

Autonomic
- blood vessels
- sweat glands
- keratinocytes
- mast cells
- NE’s
- α₁ antagonists
- Ca+ blockers
- phenoxybenzamine neuromodulation

Psychologic
- no pre-morbid Hx
- Beerthuizen et al 2011
- Psychologic interventions
- MVF
- GMI