Novel Options for Treating Snoring and OSA

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Overview

Provent™, Theravent™: EPAP
Orofacial exercises
Acupuncture
Didgeridoo

Tongue implants
Magnetic implants
Tongue resection procedures
SMILE
Lingual tonsillectomy/midline glossectomy
Submucosal lingualplasty (Robinson)
Robotic-assisted surgery
Hypoglossal nerve stimulation

Overview—Not Discussed

Innovations in positive airway pressure therapy

Palate procedures
Relocation pharyngoplasty
Expansion sphincter pharyngoplasty
Lateral pharyngoplasty
Palatal advancement pharyngoplasty
Etc.

Disclosures

The following personal financial relationships with commercial interests relevant to this presentation:

Medical Advisory Board
Medical Advisory Board
Consultant
Consultant
Intellectual Property Rights
Intellectual Property Rights

Apnex Medical
ReVENT Medical
Inspire Medical Systems
Split Rock Scientific
Berendo Scientific
Magnap
**Provent™**

FD cleared for treatment of OSA
Requires prescription
High Resistance (studies) and Standard Resistance

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**Provent™: Nasal Expiratory Resistor**

Inspiration

Expiration

Valve opens

Valve closes, directing air through small air channels, increasing resistance and creating expiratory positive airway pressure

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**Provent™: Proposed Mechanisms of Action**

Upper airway dilation during expiration

End-expiration may be time when airway most prone to collapse

Increase in Functional Residual Capacity

Decrease in airway collapsibility due to increase in tracheal traction/tug

Hypercapnia and increased ventilatory drive

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**Provent™: 1 week and 3 Month Outcomes**

Berry SLEEP 2011

AHI >10; no other previous treatments; total N=250

PSGs at 1 week and 3 mo with sham vs. active device

(expiratory resistance <1 vs. 80 cm H2O/L/s at 100 L/s)

<table>
<thead>
<tr>
<th></th>
<th>1 week</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI—Active</td>
<td>13.8 to 5.0*</td>
<td>14.4 to 5.6*</td>
</tr>
<tr>
<td>AHI—Sham</td>
<td>11.1 to 11.6</td>
<td>10.2 to 8.3</td>
</tr>
<tr>
<td>Response (AHI reduction &lt; 50% OR AHI &lt; 10)</td>
<td>62% (active) vs. 27% (sham) at 1 week 51% vs. 22% at 3 months</td>
<td></td>
</tr>
</tbody>
</table>

Reduction in AHI particularly in REM and supine sleep

Less benefit with baseline AHI > 30

Kryger JCSM 2011: if efficacious, use at 3 mos = 12 mos

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**Theravent™**

Lower resistance than Provent

Randomized trial of Theravent vs. external nasal dilator strips

One of few snoring studies with objective assessment or comparison to alternative tx

FDA-cleared for treatment of snoring

Does not require prescription

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**Oral Pressure Therapy**

(Attune/Winx™)

ATLAST study (2012)

6 centers, 63 subjects, prospective

Clinical success: AHI ≥50% reduction, <20

Success 41%

Symptoms improved

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**Orofacial Exercises**

Guimarães AJRCCM 2009

Exercises drawn from speech therapy targeting the tongue, palate, and lateral pharyngeal walls

Randomized trial of daily (30 mins, divided 3-5 x day) exercises vs. sham (nasal breathing and irrigations) for 3 months

AHI 15-30, BMI < 40 kg/m²
Orofacial Exercises

“Response” unclear, but 67% shift to mild or no OSA
Benefits more pronounced in REM
No change in BMI

Change in AHI associated with change in neck circumference
Ongoing research: simplifying regimen (ID most beneficial exercises) and evaluation including imaging and $P_{crit}$

Didgeridoo

Australian aboriginal wind instrument
Playing requires continuously vibrating lips with circular breathing (inhaling through nose, expelling air through mouth with cheeks and tongue)
Study designed after German instructor noted improvement in snoring, daytime sleepiness in some students

N=25; AHI 15-30; BMI < 30
RCT to didgeridoo vs. observation
Active: $\geq 20$ mins/day $\times \geq 5$ days/week $\times 4$ months

Didgeridoo higher AHI at baseline
Decrease in AHI in both groups, but greater in didgeridoo
Larger study helpful
Tongue Implants—Aspire

N=10; AHI 15-50
AHI 22.8 to 11.8 (p = 0.007)
ESS and snoring improved
Problems: device malfunctions (n=5)
Similar results in US (AAO-HNS 2008) and Europe (Pavelec Laryng 2011)
IP: Philips Respironics

MULTI-LEVEL UPPER AIRWAY IMPLANTS FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA: TOLERANCE IN CANINES AND FINITE ELEMENT ANALYSIS

V. Pavelec, LENTE, Plzen, Czech Republic, JM Anderson, Case Western Reserve University, Cleveland OH, USA; P Buscemi, ReVENT Medical, Inc. Cupertino CA, USA; N deVries, Saint Lucas Andreas Hospital, Amsterdam Netherlands; E Gillis, ReVENT Medical Inc., Cupertino CA, USA; RM Kellman SUNY Upstate Medical University of New York, NY, USA; E Kezirian, University of California San Francisco, San Francisco CA, USA; LM Nelson, San Jose CA, USA; J Peauroi, VDX-Predclinical, Davis, CA, USA; BW Rotenberg, University of Western Ontario, London, Canada; T Verse, Asklepios Klinik Harburg, Hamburg, Germany; RP Walker, Loyola University, Chicago, IL, USA

Presentation for X World Congress on Sleep Apnea
August 30, 2012

Magnetic Implants—Apneon

Nelson Oto-HNS 2005
Dogs (hounds)—magnetic implants placed in tongue base and posterolateral pharynx, oriented to repel
In vitro: forces similar to 10-12 cm H\textsubscript{2}O PAP
Dogs: decrease in Pcrit 10 cm H\textsubscript{2}O (-22.5 to -33)
IP: Philips Respironics
What is the Link between Obesity and OSA?
Why is Obesity Associated with Worse Outcomes after Most Procedures?

Fat Is Deposited in Tongue in Obese Subjects
(Nashi et al, Laryngoscope 117:1467, 2007)

Correlation of Percent Tongue Fat with BMI
(Nashi et al, Laryngoscope 117:1467, 2007)

Table 7: Midline Glossectomy Results

<table>
<thead>
<tr>
<th>Study</th>
<th>BMI (Mean)</th>
<th>AHI (Mean)</th>
<th>Proportionality</th>
<th>RR Test</th>
<th>LSA Test</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haffajee et al 2010</td>
<td>27.7</td>
<td>36</td>
<td>0.043 (36)</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Werkmeister et al 2012</td>
<td>27.7</td>
<td>36</td>
<td>0.043 (36)</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Newhouse et al 2012</td>
<td>27.7</td>
<td>36</td>
<td>0.043 (36)</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Horwitz et al 2010</td>
<td>27.7</td>
<td>36</td>
<td>0.043 (36)</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Sato et al 2008</td>
<td>27.7</td>
<td>36</td>
<td>0.043 (36)</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
</tbody>
</table>
| Response to surgery in 50% (37/74)
Higher AHI and BMI than samples in other case series
Kezirian EJ, Goldberg AN. Archives Oto—HNS 2006

Source: Kezirian EJ, Goldberg AN. Archives Oto—HNS 2006
SMILE
Submucosal Minimally Invasive Lingual Excision
Anterior incision and submucosal resection of tissue using Coblation (Arthrocare)
Not FDA-cleared indication for use—obtain consent

Maturo SC, Mair EA Ann ORL 2006
Cadaver
Pediatric series (obstructive macroglossia—Trisomy 21, B-W)

Friedman Oto-HNS 2008
Adult OSA

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Table 2
Comparison of postoperative versus preoperative polysomnography and subjective indicators of disease severity

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Unsuccessful</th>
<th>Successful</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFBOT</td>
<td>28 (58.3%)</td>
<td>20 (41.7%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Coblation</td>
<td>17 (35.6%)</td>
<td>31 (64.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Lingual Tonsillectomy/Partial Glossectomy

No analysis of BMI
Friedman Oto-HNS 2008

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Lingual Tonsillectomy/Partial Glossectomy

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Intraoperative, 2 weeks, 4 weeks, 2 months

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LT/MLG Outcomes: Suh Oto-HNS 2013
Lingual tonsillectomy/midline glossectomy + palate surgery (UPPP or ESP)
n = 50 (8F/42M); age = 43 ± 8 years; BMI 30.9 ± 4.0 kg/m²
AHI 55.3 to 26.9; 56% success (≥50% AHI reduction, <20)
Better outcomes:
  4+ lingual tonsils (73% success rate)
  Baseline AHI < 60 (69%)
  Modified Mallampati Position 3 (vs. MMP 4; 76%)
Lower complications than SMILE (2 cases of delayed bleeding, no hypoglossal weakness or need for transcervical control of bleeding)

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Submucosal Lingualplasty

Robinson Clin Oto 2003
Multiple refinements
Direct approach to tongue base
Not FDA-cleared indication for use
**SML: Gunawardena Oto-HNS 2013**

Submucosal lingualplasty + palate surgery (UPPP ± PA)

n = 27 (5F/22M); age = 51 ± 2 years; BMI 30 ± 1 kg/m²

11/27 with previous HP procedures (RF, GA, HS)

AHI 44.0 to 12.5; 74% success (≥50% AHI reduction, <15)

Similar improvements in ODI, LSAT, sleep architecture

ESS 8.3 to 5.8

No change in BMI

**Robotic-Assisted Surgery**

da Vinci System

Intuitive Surgical

Urology, GYN, CT, and General Surgery

Minimally invasive, improved access, decreased morbidity

OSA: lingual T

FDA-approved with little data (Vicini)

**Vicini Head Neck 2012**

AHI 36 to 16; ESS 12.6 to 7.7

Resection: 13.5 ± 8.2 ml (< 7 ml poor)

Baseline AHI mid-50s

Resection: 2.3±0.4 g (no correlation with outcomes)
Hypoglossal Nerve Stimulation Technologies

Three companies in this area: Apnex Medical, ImThera, and Inspire Medical Systems.

Apnex Inspire ImThera

<table>
<thead>
<tr>
<th>Stimulation cuff placement</th>
<th>Protrusor branch</th>
<th>Main trunk → protrusor branch</th>
<th>Main trunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing lead?</td>
<td>Yes (subcutaneous)</td>
<td>Yes (between intercostals)</td>
<td>No</td>
</tr>
<tr>
<td>Stimulation timing</td>
<td>Inspiration</td>
<td>Inspiration</td>
<td>Continuous (rotate on 3-4 contacts)</td>
</tr>
<tr>
<td>BMI selection (Feasibility study)</td>
<td>&lt;40 (Australia) / &lt;37 (US)</td>
<td>&lt;35 then &lt;32</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Other selection criteria</td>
<td>AHI 20-100 0-2+ tonsils</td>
<td>Part I: AHI &gt; 20 Part II: AHI 20-50 DISE: no complete concentric collapse AHI &gt; 20 0-2+ tonsils MMP 1-3</td>
<td></td>
</tr>
</tbody>
</table>

Acute Effects – Sleep Titration PSG (Apnex HGNS®)

Maximal Inspiratory Flow ($V_{max}$) vs. Stimulation Current Amplitude


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Acute Upper Airway Effects - Intraoperative Fluoroscopy
Apnex Medical HGNS® System
HGNS resulted in anterior displacement of the tongue base which caused opening of hypopharynx/oropharynx in all subjects
HGNS opened the airway at multiple levels (i.e., both retrolingual and retropalatal) in majority of subjects
- Soft palate movement
- Retropalatal space opening
http://sleep-doctor.com/blog

Inspire Medical: Upper Airway Stimulation (UAS)
Part 1: responders (n=6) vs. non-responders (n=14)
No change in AHI overall
Groups differed by AHI, BMI, DISE findings
Part 2: revised selection criteria, incl DISE (n=8)
Decrease in ODI in responders
Improved ESS and FOSQ
Van de Heyning Laryngoscope 2012
Vanderveken JCSM 2013
http://sleep-doctor.com/blog

Inspire Medical Pivotal Trial: Strollo NEJM 2014
- Single arm
- 12 centers: US, Europe
- Safety
- Efficacy
  - AHI
  - ODI
  - FOSQ
  - ESS
  - % sleep O2 <90%
- Key Entry Criteria
  - Failed CPAP
  - AHI 20-50
  - BMI < 32
  - Age: 20 - 70
  - Minimal central/mixed OSA
  - DISE: no CCC palate
http://sleep-doctor.com/blog

Study Schematic and Timeline
Screening (PSG) Therapy ON Randomized Withdrawal (n = 46) Long term Follow-Up
Implant
Titration PSG
PSG
PSG
BL 0M 1M 12M 13M
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Conclusions

New technologies and techniques that are either available or on the horizon may change the landscape of OSA treatment.

Additional research will enhance our understanding of how and why these treatments do or do not offer benefits over treatments available currently.

Acupuncture

Acupuncture → 5-HT, endorphin release, suppress inflammation.

Freire Sleep Medicine 2007
AH1 15-30; no previous tx
N=36 (26 for analysis)
Randomized to active, sham, control
Active or sham acupuncture weekly x 10

Acupoints selected “based on their specific characteristics, such as points that tonify the whole energy of the subject...for somnolence...throat diseases...rhinitis...[or] to move the ‘stagnations’ in the whole body.”
Acupuncture: Freire Sleep Medicine 2007

Table 3

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Baseline</th>
<th>12-week</th>
<th>After</th>
<th>Baseline</th>
<th>12-week</th>
<th>After</th>
<th>Baseline</th>
<th>12-week</th>
<th>After</th>
</tr>
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<tbody>
<tr>
<td>Acupuncture</td>
<td></td>
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<tr>
<td>Manual</td>
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<td>EA 10 Hz</td>
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<td></td>
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<tr>
<td>EA 2 Hz</td>
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<tr>
<td>Control</td>
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</tbody>
</table>

Freire Acupuncture Medicine 2010

AHI 15-30; no previous tx
N=40
Randomized to MA, EA 2 Hz, EA 10 Hz, or control
Many of same acupoints for MA, but some were different
EA had fewer points, some distant but some in neck and into genioglossus
One treatment, followed by repeat PSG

Acupuncture: Immediate Effects

Manual acupuncture (MA) releases beta-endorphin, electroacupuncture (EA) also releases ACTH
Low frequency EA activates more somatic afferents than higher frequency EA (10 Hz or 20 Hz)

Neuromuscular Stimulation: Revisiting Technology from the Past

Hypoglossal nerve stimulation
Medtronic—Inspire I
Implantable pulse generator (IPG) is connected to a transfascial sensor by means of a sensor lead. A stimulation lead connected the IPG with a half-cuff electrode around the HGN.
Improved OSA but device malfunctions
Inspire I—Good News, Bad News

Eight patients at 4 centers
Improvements in AHI (52 to 22.6), $V_{\text{max}}$

Device malfunction (n=5) ≥ 6 months following implantation

Financial support for replacement parts withdrawn.

Treatment was suspended in these cases and was abandoned after internal power supply depleted in remaining patients

Define feasible and optimal parameters of stimulation

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Apnex Medical HGNS® System
Feasibility Study Objective

To examine the safety, feasibility, and efficacy of the Apnex Medical HGNS® system in treating OSA at 12 months following implantation

(6 month outcomes: Eastwood PR et al. Treating obstructive sleep apnea with hypoglossal nerve stimulation Sleep 2011; 34:1479-1486.)

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Apnex Feasibility Trial: Kezirian J Sleep Res 2013
(6 Month Australian Results: Eastwood SLEEP 2011)

• Single arm
• Multi-Center
  – 4 US, 4 AUS
• Primary Endpoint
  – Safety
• Efficacy Endpoints
  – AHI
  – FOSQ
  – ESS
  – PSQI

• Key Entry Criteria
  – Failed CPAP
  – AHI > 20
  – BMI < 40/37
  – Age: 20 - 70
  – Minimal central/mixed OSA

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Study Schematic and Timeline

Screening (PSG)
Implant
Titration PSG
Therapy “ON”
Long term Follow-Up
BL 0M 1M 6M 12M 36M

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Apnea-Hypopnea Index

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>26</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.7 ± 17.7</td>
<td>23.3 ± 16.1</td>
<td>21.3 ± 18.0</td>
<td>20.8 ± 16.3</td>
</tr>
<tr>
<td>Median</td>
<td>42.2</td>
<td>19.4</td>
<td>14.2</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Impact of Body Mass Index on Change in AHI

<table>
<thead>
<tr>
<th>BMI&lt;35</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (Events/Hr)</td>
<td>1.5x IQR</td>
<td>3rd Quartile</td>
<td>Median 1st Quartile</td>
</tr>
</tbody>
</table>

P < 0.001

Other PSG Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline n=32 Mean (SD)</th>
<th>12 mo n=26 Mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arousal Index (events/hr)</td>
<td>43.8 (17.7)</td>
<td>25.4 (11.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ODI4% (events/hr)</td>
<td>20.4 (17.2)</td>
<td>12.0 (14.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total sleep time (TST) (min)</td>
<td>347.4 (71.9)</td>
<td>362.5 (60.4)</td>
<td>0.77</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>77.2 (12.4)</td>
<td>82.2 (10.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Time in N1 (% TST)</td>
<td>28.8 (11.4)</td>
<td>19.8 (8.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time in N2 (% TST)</td>
<td>49.1 (7.9)</td>
<td>50.8 (8.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>Time in N3 (% TST)</td>
<td>9.3 (7.6)</td>
<td>12.9 (8.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Time in REM (% TST)</td>
<td>12.8 (6.5)</td>
<td>16.5 (5.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Self-Reported Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 mo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>12.0 (4.6)</td>
<td>7.4 (3.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FOSQ</td>
<td>14.3 (2.0)</td>
<td>17.2 (2.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SAQLI</td>
<td>3.2 (1.1)</td>
<td>5.0 (1.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PSQI</td>
<td>10.5 (3.0)</td>
<td>7.7 (4.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>BDI</td>
<td>15.3 (9.1)</td>
<td>8.9 (8.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Improvements in daytime sleepiness, sleep-related quality of life, sleep disturbance, & depression symptoms
**ImThera: Targeted Hypoglossal Neurostimulation (THN)**

N=13; single center
Decrease in AHI, ArI, and ODI
Higher proportion of events supine with treatment
No change in sleep architecture
Response rate 77% (10/13)
Trends toward improvement in ESS and fatigue at 12 months

Mwenge Eur Resp J 2013

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**Safety Outcomes (Serious AEs)**

<table>
<thead>
<tr>
<th>Event Descriptions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Device Explants</td>
<td>Device explanted without sequelae</td>
</tr>
<tr>
<td>• 1 Infection/Hematoma</td>
<td>Underwent multilevel pharyngeal surgery and subsequently had an explant. Second subject decided to withdraw before system activation and requested explant. Both underwent device explant without sequelae.</td>
</tr>
<tr>
<td>• 2 Elective Explants</td>
<td></td>
</tr>
<tr>
<td>2 Cuff Dislodgements</td>
<td>Occurred early in postoperative period. Surgical revision and re-placement required. Both subjects continued in the study with no further sequelae.</td>
</tr>
</tbody>
</table>

Inspire Medical: one explant for infection
ImThera: device and technical failures early (IPG, leads, external charger); no explants