LEARNING OBJECTIVES

- Explain epidemiology, etiology, and standard of care of anxiety
- Discuss Alpha-Stim administration, indications, and mechanism of action
- Analyze primary literature to determine efficacy of Alpha-Stim in anxiety and place in therapy

ANXIETY

- Definition
- Etiology
- Epidemiology
- Standard of Care

BACKGROUND

- Anxiety disorder encompasses psychiatric disorders that involve fear or worry
  - Generalized anxiety disorder (GAD)
  - Panic disorder
  - Specific phobias
  - PTSD
  - Social anxiety
  - Obsessive-compulsive disorder (in DSM-IV)

Causes distress and interferes with daily life

EPIDEMIOLOGY

- National prevalence: 40 million in US, or 18% experience an anxiety disorder in any given year
- WHO: 1 in 3 globally suffer from anxiety and are most common mental disorders worldwide
- Only 1/3 of those suffering from an anxiety disorder receive treatment

Prevalence of anxiety disorders (% of population), by WHO Region

Source: https://adaa.org/understanding-anxiety
PATHOPHYSIOLOGY

Psychological Theories
• Worry & anxiety as form of self-protection
• Conditioned response to neutral stimuli rather than only aversive stimuli
• Exaggerated response to danger cues and reduced response to safety cues

Neurobiological Theories
• Fear conditioning centered in amygdala
• GABA or glutamate dysregulation
• Serotonin dysregulation
• CRF, ACTH and cortisol

STANDARD OF CARE: GAD

First-line
• SSRI
• SNRI

Second-line
• TCA
• MAOI

Adjunctive
• Buspirone
• Hydroxyzine

ALPHA-STIM

Administration
Indications
Mechanism of action

WHAT IS ALPHA-STIM?

Cranial electrotherapy stimulation which delivers low current in pulsed microcurrents through cranium to treat depression, anxiety, and insomnia

FDA approval in 1979 for treatment of depression, anxiety, and insomnia
• Has also been studied in pain, headaches, fibromyalgia, smoking cessation, and opiate withdrawal

Image: https://www.alpha-stim.com/healthcare-professionals/treating-pain/
MECHANISM OF ACTION

Neurotransmitters

- Increased catecholamine levels in men and women and increased thyroxine production in men
- Increase in platelet monoamine oxidase-B activity and plasma GABA concentration
- CSF and plasma increase in serotonin


MECHANISM OF ACTION

Electrical stimulation

- EEG changes in healthy males showed downward shift in alpha mean frequency
- Attenuation of beta band on EEG

ASSESSMENT QUESTION

Which is not recommended for continuous treatment of generalized anxiety disorder?

a) Paroxetine
b) Hydroxyzine
c) Clonazepam
d) Venlafaxine

TRIALS


BARCLAY TH, ET AL.

A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression

Design

- 5 week double-blind parallel group
- Patients to treat themselves daily for 1 hour
- Logged day, time, and duration of treatment
- $30 fee to participate
- Alpha-Stim 100 μA, 0.5 Hz

Objective

Test CES on various anxiety disorders with and without comorbid depression

Endpoint

- HAM-A and HAM-D21 at weeks 1, 3, and 5
  - Intervention: 57
  - Sham group: 51
Inclusion
- Ages 18-65
- DSM-IV criteria for anxiety disorder
- If comorbid depression, anxiety as primary diagnosis
- Lower end of mild on HAM-A
- If on antidepressants, stable dose for 3 months prior and still exhibiting anxiety

Exclusion
- Risk for suicide or attempted within 12 months
- Hospitalization for psychiatric condition
- Alcohol or substance abuse
- Seizure disorders
- Pacemaker
- Pregnant or breastfeeding
- History of poor treatment adherence

Baseline Characteristics
- 62% male
- Mean age 42 years old
- 64% prescribed medication
- Duration of prior pharmacotherapy 17 years
- GAD 63%
- Specific phobia 5%
- PTSD 11%
- Panic disorder 25%
- OCD 11%
- Depression 20% (n=23)

Author's Conclusions Critique
- CES is an effective treatment for anxiety and comorbid depression
- No adverse effects were seen
- Favorable risk/reward ratio supporting use of CES in evidence-based practice
- Limitations: small number of participants with both anxiety and depression
- Small sample size overall
- Short follow-up period
- Lower end of mild HAM-A baseline scores
- Entry fee may have increased placebo effect
- No adjustment of current performed

ASSESSMENT QUESTION
Which is not an indication for use of cranial electrotherapy stimulation?
- a) Neuropathic pain
- b) Sleep-onset insomnia
- c) Generalized anxiety disorder
- d) Borderline personality disorder
**Effects of cranial electrotherapy stimulation on preoperative anxiety, pain and endocrine response.**

**Design**
- Female patients undergoing thyroidectomy
  - Double-blinded
  - Alpha-Stim 100 μA, 0.5 Hz
  - Treated for 20 minutes on night before and morning of surgery

**Objective**
- Determine if CES could decrease preoperative anxiety, injection pain of rocuronium, postoperative pain and stress hormone levels

**Endpoint**
- 5 point Likert scale for anxiety; ACTH, cortisol, glucose; postoperative pain at 1, 4, 12, and 24 hours

**Intervention**
- CES group
  - 25

**Sham group**
- 25

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**Baseline Characteristics**

**Anxiety scores in patients given CES compared with those given no pretreatment**

<table>
<thead>
<tr>
<th>Anxiety score</th>
<th>Control group n (%)</th>
<th>CES group n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 (12)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>2</td>
<td>6 (24)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>3</td>
<td>10 (40)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>4</td>
<td>6 (24)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Anxiety score, CES vs. control, p = 0.016 (Chi-squared test)

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**Author’s Conclusions**
- Psychological stress was significantly decreased in patients receiving two CES interventions compared to control group
- Useful for patients with severe anxiety and risk factors precluding use of sedatives
- Limitations: placebo effects due to sham treatment
- Use of Likert scale
- Small sample size
- Female demographics

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**A Comparative Study of Anxiety Disorders Treatment with Paroxetine Associated with Cranial Electrotherapy Stimulation**

**Design**
- 6 week parallel group trial in China
  - One week washout period, then treatment with 10-20mg/day paroxetine
  - Alpha-Stim current adjusted to just below reported sensory threshold, treated for 1 hour daily

**Objective**
- Explore additive effect of CES in treatment of anxiety disorders

**Endpoint**
- HAM-A at weeks 0, 4, 6, and 8; WHOQOL-BREF and CGI-SI at weeks 0 and 6

**Intervention**
- CES group
  - 60

**Control group**
- 60

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**Baseline Characteristics**

**Exclusion**
- Serious renal disease
- BMI ≥ 25
- Pregnancy
- Psychiatric medications

**Baseline Characteristics**
- 100% female
- Height 160 cm (63 in)
**LING LU ET AL.**

Comparison of HAM-A scores before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Group</td>
<td>25±4.2</td>
<td>19.4±2.5</td>
<td>14.8±4.4</td>
<td>8.3±3.7</td>
</tr>
<tr>
<td>Control Group</td>
<td>24.5±4.3</td>
<td>19.2±3.1</td>
<td>15.2±3.8</td>
<td>12.4±3.5</td>
</tr>
</tbody>
</table>

*p >0.05 >0.05 >0.05 <0.01*

Other findings:
- CGI-S scores significantly decreased from week 0 to week 6 for both groups with a significantly greater decrease in the CES group (t=-2.652, p<0.05).
- WHOQOL-BREF scores from week 0 to week 6 significantly increased for both groups with no difference between groups except for the physical domain.

**Author’s Conclusions**
- CES with paroxetine showed more improvement than paroxetine alone.
- Physical domain of quality of life benefit.
- Limitation: Follow-up time short.

**Critique**
- Used higher HAM-A baseline score.
- CES initiation alongside paroxetine initiation confounds.
- Adjustment of current consistent with manufacturer recommendations.
- Differences in baseline characteristics.

**Ling LU et al.** Medical Innovation of China. 2014;11(8):80-82.

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**BYSTRITSKY A, ET AL.**

A pilot study of cranial electrotherapy stimulation for generalized anxiety disorder

**Design**
- 6 week open-label trial
- Adjusted current just below reported threshold of sensation (all chose 300 μA)
- Treated for 1 hour daily for 6 weeks
- Treatment recorded in logs, reviewed at assessments every 3 weeks

**Objective**
- Test CES in the treatment of GAD

**Endpoint**
- CGI-I and HAM-A
  - Response to treatment: 50% reduction on HAM-A; score of 1 or 2 on CGI-I
  - Symptom remission: score ≤ 7 on HAM-A; score of 1 or 2 on CGI-I

**Inclusion**
- Ages 18-64
- Current diagnosis of GAD, confirmed with Mini-International Neuropsychiatric Interview
- HAM-A score ≥ 16
- HAM-D 17 score < 17

**Exclusion**
- Primary DSM-IV diagnosis for Axis I disorder other than GAD
- Mental retardation, pervasive developmental disorder, neurologic impairment
- Current or recent (6 months) history of drug or alcohol abuse, suicide attempt, or personality disorder
- Pregnancy or breastfeeding

**Baseline Characteristics**
- 75% female
- Age 43 years old
- HAM-A at baseline ~21
- 42% had been on pharmacotherapy for at least 3 months

**Anxiety score, p=0.01, t=3.083 (Paired t-test)**

**Author’s Conclusions**
- CES may improve anxiety symptoms associated with GAD
- Limitations: small, pilot, open-label study
- 3 patients dropped out due to side effects (dizziness, headache)

**Critique**
- Clinically significant decreased HAM-A scores but findings limited by lack of sham group and small sample size.

**BYSTRITSKY A, ET AL.**

Comparison of HAM-A scores before and after treatment

<table>
<thead>
<tr>
<th>HAM-A score at baseline</th>
<th>HAM-A score at endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.25 ± 5.82</td>
<td>12.67 ± 5.47</td>
</tr>
</tbody>
</table>

**BYSTRITSKY A, ET AL.**

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CRITIQUE

Dosing regimens fixed at low current
Sham devices not ideal as control groups
Small trials
Applicability

ASSESSMENT QUESTION

AS is a 34-year-old Caucasian women with complaints of persistent, excessive, and uncontrollable worry which has caused her significant functional and social distress like skipping social events. She also has difficulty falling asleep, difficulty concentrating, and constant restlessness.

No significant PMH; Medications: MVI daily

Which of the following would you start for initial treatment of her GAD?

a) Duloxetine
b) Paroxetine
c) Alpha-Stim
d) Hydroxyzine

CONCLUSIONS

Alpha-Stim CES shows some potential in treating psychiatric disorders like anxiety and depression, but should be used as adjunctive therapy rather than first-line treatment

Currently unknown which anxiety disorders CES would show most benefit in, but is relatively safe to use in all anxiety disorders

Expensive with comparatively small benefit over standard therapy, attempt psychotherapy and pharmacotherapy first

Overall, psychosocial and pharmacotherapy before Alpha-Stim in anxiety disorders

ACKNOWLEDGEMENTS

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Dr. Stephen Slubar, PharmD

REFERENCES

APPENDICES

HAM-A: 14-item clinician-administered assessment for anxiety symptoms
- <17 = mild anxiety
- 18-24 = mild-moderate anxiety
- ≥25 = moderate-severe anxiety

HAM-D17: 17-item clinician-administered assessment for depression symptoms
- <9 = normal
- 10-13 = mild depression
- 14-17 = mild-moderate depression
- ≥18 = moderate-severe

ASA: American Society of Anesthesiologists classifications
- ASA1: a normal, healthy patient
- ASA2: a patient with a mild systemic disease, such as obesity, treated hypertension, cigarette smoker
- ASA3: a patient with a severe, systemic disease (not life-threatening)
- ASA4: a severe, systemic disease that is a constant threat to life

CGI-S: Clinical Global Impression – Severity: 1 to 7; 1 is normal, 7 is extremely ill

WHOQOL-BREF: 26-item instrument used to measure physical health, psychological health, social relationships, and environment