Neurological Devices Advisory Panel
Electroconvulsive Therapy (ECT) Devices
515(i) Reclassification

FDA
Center for Devices and Radiological Health
January 27-28, 2011
1. Regulatory Considerations  
   Marjorie Shulman

2. ECT Clinical and Regulatory Background  
   Bradley Cunningham, LCDR, USPHS, Branch Chief

3. FDA Assessment of ECT  
   Strategy and Methodology: Anna Georgiopoulos, MD

4. FDA Safety Review  
   Adverse Events Analysis: Anna Georgiopoulos, MD  
   Cognitive and Memory Adverse Events: Peter Como, PhD  
   Cognitive Meta-Analyses: Cara Krulewitch, CNM, PhD, FACNM  
   Neuropathological Changes and Death: Allison Komiyama, PhD

5. FDA Effectiveness Review  
   Lawrence Park, MD

6. Key Risk Identification and Mitigation Factors  
   Lawrence Park, MD
FDA Assessment of ECT

Anna Georgiopoulos, M.D.
Medical Officer
FDA/CDRH/ODE/DONED
FDA Assessment of ECT

- Safety Review
  » Analysis of docket and adverse events database
  » Analysis of scientific literature for adverse events
  » Review of published systematic reviews, meta-analyses, and practice guidelines
  » Systematic review of randomized controlled trials (RCTs)
  » Meta-analysis of pertinent RCTs

- Effectiveness Review
  » Review of published systematic reviews, meta-analyses, and practice guidelines
  » Systematic review of RCT data
  » Meta-analysis of pertinent RCTs

- Key Risk Identification

- Consideration of Mitigation Factors for Key Risks
FDA Safety Review
FDA Safety Review Sources

- Public docket
- Manufacturer docket
- Manufacturer and User Facility Device Experience (MAUDE) database
- FDA Literature Review
  - Published reports of adverse events
  - Clinical research studies (including RCTs)
  - Systematic reviews
  - Meta-analyses
  - Practice guidelines
FDA Safety Review Sources

- **Public docket**
- **Manufacturer docket**
- **Manufacturer and User Facility Device Experience (MAUDE) database**
- **FDA Literature Review**
  - Reports of adverse events (published reports)
  - Systematic reviews
  - Meta-analyses
  - Practice guidelines
  - Clinical research studies (including RCT’s)
Public Docket

- FDA issued Federal Register Notice [FDA-2009-N-0392] announcing the opening of a public docket to receive information and comments regarding the current classification efforts related to ECT devices opened September 10, 2009
- Closed on January 9, 2010
- 3,045 responses
Public Docket: Categories of Analysis

- Respondent type
- Affiliate institution/organization
- U.S. or outside U.S.
- Use of form letter
- Number of individuals represented in comment
- Position on reclassification
- ECT effect reported
- Adverse event reported
- Supporting evidence provided
- Special population reported
Public Docket Respondent Type

- Consumers: 1,798
- Medical, Mental Health Providers: 342
- Current / Former ECT Practitioners: 109
- Alternative Therapies Practitioners: 141
- Organization Representatives: 124
- Recipients of ECT: 71
- Relatives / Friends of ECT Recipients: 6
- Duplicates / Not Responsive: 6
- Other: 71
- Not Identified: 6
Public Docket Responses

- Oppose reclassification to Class II: 79%
- Support reclassification to Class II: 14%

- 92 group submissions (form letters)
  - 6462 oppose reclassification
  - 462 support reclassification
Public Docket Adverse Events Reports (by frequency)

- Memory (529)
- Cognitive decline (357)
- Brain damage (298)
- Death/reduced life span (126)
- Worsening psychiatric condition (88)
- Decreased function/QOL (82)
- Apathy (54)
- Suicidality (43)
- Seizures (28)

- Physical trauma (21)
- Cardiac (20)
- Emotional trauma (20)
- Incoordination/balance (19)
- Motor symptoms (18)
- Pain (15)
- Headache (13)
- Speech difficulty (12)
- Dental/oral trauma (10)
Public Docket Adverse Events Reports (continued)

- Loss of creativity (9)
- Stroke (5)
- Vision problems (5)
- Sleep disturbance (4)
- Coma (4)
- Nausea/vomiting (4)
- Respiratory (4)
- Substance abuse (4)
- Hypertension (3)
- Burns (2)
- Falls (2)
- Homicidality (2)

- Nerve damage (1)
- Fibromyalgia (1)
- Hair loss (1)
- Immune compromise (1)
- Incontinence (1)
- Ruptured aneurysm (1)
- Sensory symptoms (1)
- Tinnitus (1)
- Other/unspecified (3)
Public Docket: Other Reported Concerns

- Inadequate informed consent (291)
- Use as punishment (213)
FDA Safety Review Sources

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  - Meta-analyses
  - Practice guidelines
  - Clinical research studies (including RCT’s)
FDA requested information on: indications for use, device description, device labeling, risks, alternative practices and procedures, summary of preclinical and clinical data, and a bibliography

2 manufacturers responded

Both supported reclassification to Class II
Manufacturer Docket
Adverse Events (alphabetical order)

- Brain damage (including structural injury, brain cell injury, hippocampal damage)
- Cardiac arrhythmias
- Cognitive adverse events
  - Short-term confusion
  - Short-term memory loss
  - Long-term (persistent or permanent) memory loss
  - Risk of everyday or semantic memory loss
- Complications of pre-existing medical conditions
- Death
- Device malfunction (electrical hazards, risk of excessive dose administration)
- Prolonged seizures
- Skin burns
Manufacturer Docket: Proposed Mitigating Factors

- Reduce frequency of treatments during a course (i.e., increasing the time between treatments)
- Temporary or permanent interruption of treatments
- Reduce stimulus dose (using dose titration to determine minimal effective treatment levels)
- Electrode placement (i.e. right unilateral placement)
- Use of general anesthesia
- Management (minimization) of psychotropic medications
- Use of brief pulse or ultrabrief pulse waveform stimulus
- Electroencephalography (EEG) monitoring to determine seizure length and quality
FDA Safety Review Sources

- Public docket
- Manufacturer docket
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- FDA Literature Review
  - Reports of adverse events (published reports)
  - Systematic reviews
  - Meta-analyses
  - Practice guidelines
  - Clinical research studies (including RCTs)
MAUDE Reports

- From August 1996 – December 7, 2010
- 151 original adverse events reports
  - 135 voluntary reports
  - 16 user facility reports
## MAUDE (by frequency)

<table>
<thead>
<tr>
<th>By Adverse Event #</th>
<th>Adverse Event</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>117</td>
<td>Memory loss</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>General emotional / psychiatric</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>General motor</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>General functional disability</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Cognitive</td>
<td>Including learning disabilities</td>
</tr>
<tr>
<td>20</td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Pain</td>
<td>All types</td>
</tr>
</tbody>
</table>
## MAUDE (continued)

<table>
<thead>
<tr>
<th>By Adverse Event #</th>
<th>Adverse Event</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Burns</td>
<td>One from faulty wire, and nonconductive gel use</td>
</tr>
<tr>
<td>13</td>
<td>Neurological</td>
<td>All types not in other categories</td>
</tr>
<tr>
<td>10</td>
<td>Ineffective</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Brain damage</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sleep disturbance</td>
<td>Including nightmares</td>
</tr>
<tr>
<td>8</td>
<td>Visual change</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Forced treatment</td>
<td></td>
</tr>
<tr>
<td>By Adverse Event #</td>
<td>Adverse Event</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>6</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Personality change</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Mechanical malfunction</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Improper consent</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Death</td>
<td>1 instance reported within 2 months of ECT treatment</td>
</tr>
<tr>
<td>2</td>
<td>Auditory complaint</td>
<td>1 hyperacusity; 1 hypoacusity</td>
</tr>
<tr>
<td>By Adverse Event #</td>
<td>Adverse Event</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>2</td>
<td>Dental/oral</td>
<td>1 dental injury; 1 tongue laceration</td>
</tr>
<tr>
<td>2</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Suicide</td>
<td>1 suicide attempt; 1 completed</td>
</tr>
<tr>
<td>2</td>
<td>Urinary complaint</td>
<td>1 frequency; 1 incontinence</td>
</tr>
<tr>
<td>2</td>
<td>Anesthesia related</td>
<td>Complications of anesthesia</td>
</tr>
<tr>
<td>1 each</td>
<td>Coma, miscarriage, pulmonary</td>
<td></td>
</tr>
</tbody>
</table>
FDA Safety Review Sources

- Public docket
- Manufacturer docket
- Manufacturer and User Facility Device Experience (MAUDE) database
- **FDA Literature Review**
  - Published reports of adverse events
  - Clinical research studies (including RCTs)
  - Systematic reviews
  - Meta-analyses
  - Practice guidelines
FDA Literature Search Strategy: Safety and Effectiveness

- PubMed, CINAHL and PsycINFO (through September 7, 2010)
- Search terms: “major depression,” “electroconvulsive therapy,” “bipolar depression,” “schizophrenia,” “schizoaffective psychosis,” “schizoaffective disorder,” “catatonia,” “mania,” and “mixed states”
- Cross referenced with public and manufacturer dockets, practice guidelines, published systematic reviews and meta-analyses
<table>
<thead>
<tr>
<th>Topic Area</th>
<th>Number of Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroconvulsive Therapy</td>
<td>9,952</td>
</tr>
<tr>
<td>Major Depression (MD)</td>
<td>12,317</td>
</tr>
<tr>
<td>Schizophrenia (S)</td>
<td>63,845</td>
</tr>
<tr>
<td>Catatonia (C)</td>
<td>1,220</td>
</tr>
<tr>
<td>Mania (M)</td>
<td>24,536</td>
</tr>
<tr>
<td>Mixed Disorder/State (MXD)</td>
<td>144</td>
</tr>
<tr>
<td>Mood Disorder (MOD)</td>
<td>5,413</td>
</tr>
<tr>
<td>ECT and (MD or S or BD or SD or C or M or MXD or MOD), limit to English language</td>
<td>1,984</td>
</tr>
<tr>
<td>Limit to clinical trial, Cochrane review, controlled clinical trials, meta analyses, randomized controlled clinical trials, systematic reviews, research study, cohort study, case-control study, cross-sectional study, case study, observational study and case report.</td>
<td>1,231</td>
</tr>
</tbody>
</table>
Objective

- Identification of all reported adverse events in the literature

Methods

- Two independent members of the review team (psychiatric clinical reviewers) examined the citation, abstract and articles to identify potentially suitable studies
- Disagreements settled by entire team
All Reported Adverse Events
(from all sources; by approximate frequency of report)

- Memory dysfunction\(^1,2\)
- Cognitive dysfunction\(^1,2\)
- Neuropathological changes (brain damage) \(^1,2\)
- Death/reduced life span\(^1,2\)
- Onset/exacerbation of psychiatric symptoms
- General motor dysfunction
- General functional disability
- Pain/discomfort\(^2\)
- Prolonged seizures\(^2\)

\(^1\) Focus of FDA literature review
\(^2\) Identified key risk, mitigation factors proposed
All Reported Adverse Events (continued)

- Physical trauma$^2$
- Skin burns$^2$
- Neurological symptoms
- Pulmonary complications$^2$
- Sleep disturbance
- Visual disturbance
- Nausea
- Alterations in blood pressure$^2$
- Cardiovascular complications$^2$
- Stroke$^2$
- Auditory complications
- Dental/oral trauma$^2$
- Suicidality
- Homicidality
- Substance abuse
- Urinary complaints
- Coma
- Adverse reaction to anesthetic/neuromuscular blocking agents$^2$

$^1$ Focus of FDA literature review
$^2$ Identified key risk, mitigation factors proposed
Identification of Potentially Significant Adverse Events

- Substantiated by comprehensive review of all sources of data
- Significant adverse events defined as:
  » Sufficient evidence of significant frequency
  » Sufficient evidence of significant severity
- Evidence of being associated with ECT device use
Potentially Significant Adverse Events (alphabetical order)

- Adverse reaction to anesthetic agents/neuromuscular blocking agents
- Alterations in blood pressure
- Cardiovascular complications
- Cognitive dysfunction
- Death/reduced life span
- Dental/oral trauma
- Device malfunction
- Memory dysfunction
- Neuropathological changes (brain damage)
- Onset/exacerbation of psychiatric symptoms
- Pain/discomfort
- Physical trauma
- Prolonged seizures
- Pulmonary complications
- Skin burns
- Stroke
- Suicidality
## Potentially Significant Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Severity</th>
<th>Association with ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia-Related</td>
<td>Rare, similar to other procedures using general anesthesia</td>
<td>Mild-Severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Alterations in Blood Pressure</td>
<td>Common</td>
<td>Mild-Severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Uncommon</td>
<td>Mild-Severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Cognitive Dysfunction</td>
<td>Common</td>
<td>Mild-Severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Death/Reduced Life Span</td>
<td>Rare</td>
<td>Severe</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Dental / Oral Trauma</td>
<td>Uncommon</td>
<td>Mild-moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Memory Dysfunction</td>
<td>Common</td>
<td>Mild-severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuropathological Changes</td>
<td>Rare</td>
<td>Mild-severe</td>
<td>No</td>
</tr>
</tbody>
</table>
### Potentially Significant Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Severity</th>
<th>Association with ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset/Exacerbation of Psychiatric Symptoms</td>
<td>Uncommon</td>
<td>Mild-moderate</td>
<td>Only established for manic switching (uncommon)</td>
</tr>
<tr>
<td>Pain / Discomfort</td>
<td>Common</td>
<td>Mild-moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Physical Trauma</td>
<td>Uncommon</td>
<td>Mild-moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Prolonged Seizure</td>
<td>Uncommon</td>
<td>Mild-moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>Pulmonary Complications</td>
<td>Rare</td>
<td>Moderate-severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin Burns</td>
<td>Rare</td>
<td>Mild</td>
<td>Yes</td>
</tr>
<tr>
<td>Stroke</td>
<td>Rare</td>
<td>Mild-severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Suicidality</td>
<td>Rare, no increase from non-ECT psychiatric populations</td>
<td>Severe</td>
<td>No</td>
</tr>
</tbody>
</table>
Focused Review of Adverse Events

Based on frequency of reports, estimated frequency of occurrence, potential severity of adverse events, and amount of evidence in the literature, an in depth review of the following adverse events was conducted:

» Cognitive and memory dysfunction
» Neuropathological changes (brain damage)
» Death
Focused Review of Adverse Events

» Cognitive and memory dysfunction
  – Peter G. Como, PhD
  – Cara Krulewitch, CNM, PhD, FACNM

» Neuropathological changes (brain damage)
  – Allison Komiyama, PhD

» Death
  – Allison Komiyama, PhD
Cognitive and Memory Adverse Events: FDA Systematic Literature Review

Peter G. Como, Ph.D.
Neuropsychologist/Lead Reviewer
FDA/CDRH/ODE/DONED
Cognitive and Memory Adverse Events: Methodological Challenges

- Literature has yielded mixed results
  - Methodological issues:
    - Use of non-standardized cognitive tests
    - Numerous cognitive test batteries available – impacts ability to conduct meta-analyses
    - Timing of cognitive assessment
    - Lack of long-term data (> 6 months)
- Impact of depression on cognitive function
  - Degree to which ECT ameliorates symptoms of depression influences cognitive test performance
- Recent data limited by lack of double-blind, sham-controlled trials
FDA Safety Literature Review: Published Articles

- 3 published practice guidelines
  - APA, 2001; NICE, 2003; NICE, 2009

- 5 published systematic reviews
  - NICE, 2003; Rose, 2003; Fraser, 2008; Gardner, 2008; NICE, 2009

- 4 published meta-analyses
  - UK ECT Review Group, 2003; Greenhalgh, 2005; Semkovska, 2010; Semkovska, in press)
FDA Safety Literature Review: Published Articles (continued)

- RCTs
  - FDA systematic literature review
  - FDA meta-analyses
    - Time to reorientation (seconds)
    - Global cognitive impairment (Mini Mental State Examination-MMSE)
    - Retrograde personal (autobiographical) memory (Autobiographical Memory Interview – AMI)
Inclusion of only prospective randomized controlled trials (crossover designs included if analyzable pre-crossover data)

Use of standardized neuropsychological tests

Statistical comparisons:

» Compare outcomes between subjects randomized to various ECT treatment conditions:
  - Electrode placement
  - Energy dose
  - Frequency of treatment
  - Waveform
  - Brief pulse vs. ultra brief pulse
FDA Safety Literature Review: Clinical Research Studies (continued)

» ECT vs. sham ECT
» ECT vs. other treatment (drug, placebo)
» Pre- and Post-ECT (non-randomized)

● Total of 68 studies identified which met above criteria
Impairment in orientation, memory and global cognitive function immediately after ECT and up to 6 months

- Autobiographical memory most common
- Limited evidence that memory and cognitive adverse effects may not last beyond 6 months

Greater risk of memory or cognitive impairment with:

- Sine wave compared to brief pulse ECT
- Bilateral and dominant hemisphere electrode placement
- High energy dose ECT

Raising electrical stimulus increases effectiveness of unilateral ECT but with greater memory and cognitive impairment
Subjective reports of memory loss more persistent (lasting >6 months) than results from objective measures.

Memory and cognitive impairment contribute to considerable distress to those affected.

Cognitive effects of ECT do not differ by psychiatric diagnosis.

Factors other than ECT likely impact cognitive function:
- Individual variability
- Relief of depression
- Use of medications
FDA Systematic Review: Cognitive Domains

- **Orientation**
  - Person, place, time; time to re-orientation following ECT

- **Executive function:**
  - Attention/concentration
  - Mental tracking, planning
  - Problem-solving
  - Response inhibition, set-shifting
  - Working memory (capacity to hold information in short term storage to execute cognitive response)

- **Global Cognitive Function**
  - Composite score on tasks of multiple cognitive functions (e.g., MMSE)

- **Global Memory**
  - Composite score on standardized memory battery (e.g., Wechsler Memory Scale)
Anterograde Memory
- Capacity to encode, store and retrieve verbal and non-verbal information

Retrograde Memory
- Capacity to retrieve information encoded prior to initiation of ECT treatment:
  - Personal (autobiographical) – past personal information and events
  - Impersonal – historical or factual information

Subjective Memory
- Patient self-report of perceived memory problems
FDA Systematic Review: Cognitive Assessment Time Points

• Acute effects: immediately post-ECT (within 24 hours)
• Subacute effects: 24 hours to less than 2 weeks
• Medium-term effects: 2 weeks to less than 3 months
• Longer-term effects: 3 months to less than 6 months
• Long-term effects: 6 months or greater
FDA Systematic Review: Energy Dosage Definition

- Low Dose = 1 - 1.5x ST
- Moderate Dose = 1.5 - 3x ST
- High Dose = > 3x ST

(ST = seizure threshold)
FDA Systematic Review: Electrode Placement Definition

- Bilateral (BL)
  - Bitemporal (BT)
- Bifrontal (BF)
- Unilateral (UL)
  - Unilateral nondominant (ULND)
  - Right unilateral (RUL)
- Left unilateral (LUL)
  - Unilateral dominant (ULD)
FDA Systematic Review Results: Time to Reorientation

- Longer disorientation with bilateral electrode placement and with high dose ECT
- Available data do not demonstrate evidence of persistent disorientation
FDA Systematic Review Results: Executive Function

- No differences among any of the ECT treatment parameters
  » Single study suggested greater executive dysfunction with LUL vs RUL
- Improvement or no statistically significant change from baseline at up to 6 months after ECT
FDA Systematic Review Results: Global Cognitive Function

- Bilateral ECT was associated with greater impairment compared to right unilateral ECT
- No consensus on change from baseline up to 2 weeks, but apparent improvement or no change from baseline by 3 to <6 months
- Dose effects generally not significant
FDA Systematic Review Results: Global Memory Function

- No significant differences by dose or waveform, or with real vs. sham ECT
- Bilateral ECT is associated with greater global memory impairment up to ~ 3 months (limited evidence)
- No change from baseline up to 6 months
FDA Systematic Review Results: Anterograde Verbal Memory

- Inconsistent results: effect of ECT vs sham ECT
- Greater risk of memory impairment with:
  - Sine wave compared to brief pulse ECT
  - Bilateral and dominant hemisphere electrode placement
  - High energy dose ECT
Change from baseline:

» After ~1 week of ECT verbal memory may return to baseline and might improve (right unilateral, low/moderate energy dose)

» After ~2 weeks of ECT verbal memory function following bilateral electrode placement may return to baseline and improve

At 6 months post-ECT, there is limited data to support evidence of verbal memory impairment
FDA Systematic Review Results: Anterograde Non-Verbal Memory

- ECT is associated with greater impairment compared to sham ECT immediately after treatment.
- No differences with respect to electrode placement.
- Brief pulse ECT *may* be associated with greater impairment compared to ultra brief pulse ECT.
- After 2 weeks of ECT, there is no conclusive evidence to support any differences among any of the ECT treatment parameters.
- Conclusive evidence of no significant changes from baseline in the short-term.
- Limited data suggests that in the longer term (3 to 6 months), non-verbal memory function *may* return to baseline levels.
FDA Systematic Review Results: Retrograde Impersonal Memory

• Immediately post-ECT, bilateral electrode placement may be associated with greater impairment

• Inconsistent results with respect to electrode placement, pulse or energy dose from 24 hours to 3 months

• No differences between sham ECT and ECT, electrode placement or pulse wave at 6 months

• Change from baseline inconsistent up to 6 months at which time no significant change is present
FDA Systematic Review Results: Retrograde Personal Memory

- Immediately post-ECT, bilateral ECT may be associated with greater impairment
- Conclusive evidence of impairment within 24 hrs to 2 weeks with bilateral ECT; limited evidence with respect to effects of sine pulse or high energy dose
  - Evidence to suggest a decline from baseline during this period
- Limited data to suggest differences among any of the ECT treatment parameters in the medium term
- Single study at 3 months examined maintenance ECT vs medication
- Single study at 6 months which demonstrated possible return to baseline with unilateral ECT but continued decline with BL placement and sine wave pulse
Patients typically report memory impairment immediately following ECT.

Bilateral ECT associated with greater impairment compared to unilateral ECT subacutely.

By 6 months, no differences with electrode placement, waveform, or sham vs. real ECT.

Improvement or no change from baseline noted at 6 months after ECT.
FDA Literature Review
Summary – Cognitive Adverse Events

- ECT is associated with cognitive and memory impairment
- Degree and duration of impairment appears domain-specific and related to certain ECT treatment parameters
- Greater risk of cognitive and memory impairment with:
  - Bilateral and dominant hemisphere electrode placement
  - High energy dose ECT
FDA Literature Review

Key Impaired Cognitive Domains

- Disorientation – transient and generally resolves within minutes after seizure termination

- General memory dysfunction:
  - Anterograde memory loss
  - Retrograde autobiographical memory loss
    - BL ECT associated with greater autobiographical memory impairment than UL ECT
      - Limited evidence to suggest deficits may return to pre-ECT baseline performance at 6 months
Summary of Evidence Regarding Cognitive and Memory Dysfunction Associated with ECT (Non-Randomized Pre-Post Comparisons)

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Change Relative to Pre-Treatment Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediately post-ECT</td>
</tr>
<tr>
<td>Time to reorientation</td>
<td>▼</td>
</tr>
<tr>
<td>Executive function</td>
<td>—</td>
</tr>
<tr>
<td>Global cognitive function</td>
<td>▼</td>
</tr>
<tr>
<td>Global memory function</td>
<td>▼</td>
</tr>
<tr>
<td>Anterograde memory Verbal</td>
<td>▼</td>
</tr>
<tr>
<td>Anterograde memory Non-verbal</td>
<td>—</td>
</tr>
<tr>
<td>Retrograde memory Impersonal</td>
<td>▼</td>
</tr>
<tr>
<td>Retrograde memory Personal</td>
<td>▼</td>
</tr>
<tr>
<td>Subjective memory</td>
<td>N/A</td>
</tr>
</tbody>
</table>

↑ = improved from baseline; ▼ = declined from baseline; — = no change from baseline.; ± = depends on treatment parameter
RED = conclusive evidence in the literature; BLUE = limited/equivocal evidence in the literature
FDA Safety Meta-Analyses: Cognition and Memory

Cara Krulewitch, C.N.M., Ph.D., F.A.C.N.M.
Branch Chief
OSB/DEPI/EERB2
FDA Safety Meta-Analysis: Methodology

- Evaluated acute, sub-acute and medium term cognitive adverse effects
- Published data were insufficient to evaluate longer-term effects through formal meta-analyses
- Selection criteria used
  - At least two groups and at least two studies
  - Same or cross-validated measures
  - Sufficient published data for analysis
    - Number of patients per group
    - Standard deviation
- DerSimonian and Laird Random Effects Model
FDA Safety Meta-Analyses: Study Elements

- Electrode Placement
  - Right Unilateral
  - Bilateral

- Energy Level
  - Low (< 2x seizure threshold)
  - Moderate (2-4x seizure threshold)

- Cognitive Domains
  - Orientation (Time to Reorientation)
  - Global Cognitive Function (MMSE)
  - Retrograde Personal Memory (AMI)
FDA Safety Meta-Analyses: Limitations of Meta-Analysis

- Limited to studies with adequate data
- Dependent on the quality of the studies included
- Publication bias
- Temporal bias
There were two to five studies that met all criteria for each of the three study element groups, limiting the generalizability of the findings.

Findings should be viewed with caution.
Time to Reorientation (Seconds)
Unilateral Low (ULL) vs Bilateral Moderate (BLM)
(with 95% Confidence Intervals)
MMSE Acute Changes (% Change) 
Unilateral Low (ULM) vs Bilateral Moderate (BLM) (with 95% Confidence Intervals)

Sackeim '00 (JECT) 
-3.9
-6.1
-16.1

Sobin '95 
-4.7
-11.6
-18.5

Overall 
-4.2
-9.8
-15.5

Difference ULM - BLM
MMSE at 2 Months (% Change)
Unilateral Moderate (ULM) vs Bilateral Moderate (BLM)
(with 95% Confidence Intervals)
Autobiographical Memory Interview Subacute (1 day-2 weeks)(% Change)
Unilateral Moderate (ULM) vs Bilateral Low (BLL)
(with 95% Confidence Intervals)

-29
-27
-25
-23
-21
-19
-17
-15
-13
-11
-9

Difference in Score ULM - BLL

Sackeim '00 (JECT)

-25.7
-18.6
-11.5

Sobin '95

-28.2
-20.2
-12.2

Overall

-24.6
-19.3
-14.0
Autobiographical Memory Interview Pre/Post Treatment by Energy Level
(Percent of Score Pretreatment Score)
(with 95% Confidence Intervals)
Summary of Findings

- Bilateral lead placement has a larger adverse effect on time to reorientation, MMSE and AMI compared to unilateral lead placement.
- Energy level does not have a significant effect on these measures when comparing pre-treatment to post-treatment measurements.
Neuropathological Changes and Death

Allison Komiyama, Ph.D.
Neurobiologist
FDA/CDRH/OSEL
Neuropathological Changes

- Brain lesions
- Neurodegeneration
  - Neuron “death,” “destruction” or “loss”
- DNA damage to brain cells
- Gross loss
- Glial proliferation
- Neuroproliferation
- Gross gain
Potential Mechanisms of Injury

- Direct Injury
  - Electrical stimulus
  - Brain heating
  - Burns
  - Anoxia

- Indirect Injury
  - Seizure induction
FDA Literature Search Strategy: Neuropathological changes


- Studies that did not focus on neuroanatomy, electroshock that was not electroconvulsive in nature or studies that looked solely at status epilepticus or kindling were not included in this review
Neuropathological Changes
Types of Evidence

- Autopsy and Neuroimaging
- Immunohistochemical
- Biomarkers of Injury
Pathology Data

No gross pathological changes seen in human and non-human primate ECT-treated subjects

(Scalia et al. 2007)

92 year old former ECT patient

(Dwork et al. 2009)

8 ECS and 8 sham treated macaques
Treated for 6 weeks, 4x/week
Neuroimaging Data

Hippocampal volume increases in ECT patients

TABLE 3. Differences in Hippocampal Volume (µL) Pre-ECT and Post-ECT (n = 12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-ECT</th>
<th>Post-ECT</th>
<th>r</th>
<th>df</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hippocampus</td>
<td>3109</td>
<td>3242</td>
<td>0.97</td>
<td>11</td>
<td>-3.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>2905</td>
<td>3054</td>
<td>0.98</td>
<td>11</td>
<td>-6.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total volume (right + left)</td>
<td>6014</td>
<td>6296</td>
<td>0.99</td>
<td>11</td>
<td>-6.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Immunohistochemical Data
Evidence of Neuroproliferation in Primates after ECS

(Perera et al. 2007)
Biomarkers for Damage

- Biomarker evidence that ECT does not lead to a brain inflammatory response, brain cell leakage, neuronal damage or blood-brain barrier dysfunction

- Cerebrospinal Fluid (CSF)
  - Zachrisson et al., 2000
    - CSF-tau protein
    - CSF-neurofilament
    - CSF-S-100 beta protein
Biomarkers for Damage (continued)

- Human blood serum
  - Giltay et al. 2001
    - C-reactive protein (CRP)
    - Alkaline phosphatase (ALP)
    - Lactate dehydrogenase (LDH)
    - Alanine aminotransferase (ALT)
    - Aspartate aminotransferase (AST)
    - Creatine kinase (CK)
  - Berrouschot et al., 1997; Agelink et al., 2001; Palmio et al., 2010
    - Neuron-specific enolase (NSE)
    - Protein S-100
Panel Question

Regarding neuropathological changes, the manufacturer and public dockets both indicated “brain damage” as a potential risk associated with ECT. However, FDA’s review of the literature did not identify evidence of gross anatomical, histological, or immunohistochemical evidence, or evidence from biomarkers of injury, to support this association. Please discuss whether the existing clinical data support brain damage as a potential risk of ECT and if so, how this risk can be mitigated.
Death

- Mortality rate estimates (APA 2001; Watts et al. 2010):
  - 1:10,000 patients or 1:80,000 treatments
  - Rate similar to that associated with minor surgery (APA 2001; Badrinath et al. 1995; NICE 2003)

- ECT used in CA (Kramer 1985, 1999):
  1977-1982: 1.12:10,000 people received ECT
    - 0.2 deaths per 10,000 treatments
  1984-1994: 28,437 patients received 160,847 treatments
    - 0.19 deaths per 10,000 treatments
Death

- Decline in mortality rates in recent years (Nuttall et al. 2004)
  - 2,279 patients received 17,394 treatments
  - 21 patients (0.92%) experienced complications
    - Majority were cardiac arrhythmias
  - 18 deaths within 30 days of the last treatment, none thought to be related to ECT
Panel Question

To inform the FDA’s decision on reclassification, the key risks presented by ECT must be identified, and a determination must be made regarding how and whether sufficient information exists to establish controls to mitigate those risks. The FDA has identified the following key risks of ECT (in alphabetical order) in the FDA’s review of the Public Docket, the Manufacturer Docket, the Manufacturer and User Facility Device Experience (MAUDE) Database, and in FDA’s literature review:
Panel Question (continued)

a. Adverse reaction to anesthetic agents/neuromuscular blocking agents
b. Alterations in blood pressure
c. Cardiovascular complications
d. Cognition (disorientation and confusion)
e. Death
f. Dental/oral trauma
g. Device malfunction
h. Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory)
i. Pain/somatic discomfort
j. Physical trauma
k. Prolonged seizures
l. Pulmonary complications
m. Skin burns
n. Stroke
Panel Question (continued)

Is this a complete and accurate list of the key risks presented by ECT?

Comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks are among the key risks presented by ECT.
FDA Effectiveness Review

Lawrence Park, A.M., M.D.
Medical Officer
FDA/CDRH/ODE/DONED
Opinion regarding reclassification to Class II
- Oppose reclassification to Class II: 79%
- Support reclassification to Class II: 14%

Reporting effect of ECT
- Positive: 471 (15%) respondents
- Negative: 1857 (61%) respondents
FDA Effectiveness Systematic Review and Meta-Analysis

- Literature Review (by indication)
  - Methodology similar to safety literature review
    - Review of published systematic reviews, meta-analyses and practice guidelines
    - FDA independent systematic review and meta-analyses
  - Limited to RCTs

- Meta-Analyses
  - Clinical research studies (RCTs)
  - Two or more comparison groups
  - Assessment by standardized ratings instruments
    - Hamilton Rating Scale for Depression (HRSD) for depression
    - Brief Psychiatric Rating Scale (BPRS) for schizophrenia
FDA Effectiveness Literature Review: Clinical Research Studies

- **Depression (Bipolar and Unipolar)**
  - ECT vs. sham treatment
  - ECT vs. placebo
  - ECT vs. antidepressants
  - Variation in electrode placement
  - Variation in energy dose
  - Variation in frequency of treatment
  - Variation in pulse width

- **Schizophrenia**
  - ECT vs. sham treatment
  - ECT vs. antipsychotics

- **Acute Mania/Mixed States**
  - ECT vs. sham
  - ECT vs. mood stabilizers

- **Catatonia, Schizoaffective Disorder: few/no RCTs**
FDA Effectiveness Review: Published Systematic Reviews, Meta-Analyses, Practice Guidelines

- **10 published systematic reviews**

- **7 published meta-analyses**

- **3 published practice guidelines**
Depression: Summary of Published Systematic Reviews and Meta-Analyses

- ECT effectiveness is demonstrated only for the period immediately post-ECT to one month
- ECT is more effective than sham or placebo
- ECT is more effective than some antidepressants
- Limited evidence that ECT is more effective than repetitive transcranial magnetic stimulation
- Limited evidence to support the effectiveness of ECT for elderly patients
- The overall response rate of ECT estimated to be 72%
Depression: Summary of Published Systematic Reviews and Meta-Analyses (continued)

- Bilateral (BL) ECT is more effective than unilateral (UL),
- Moderate and high dose UL ECT may be as effective at low dose BL ECT
- Low dose UL ECT may be no more effective than sham
- For UL ECT,
  » increasing energy dosage increases effectiveness, and
  » increases memory and cognitive impairment
- Presence of psychotic symptoms may predict better response
Schizophrenia: Summary of Published Systematic Reviews and Meta-Analyses

- ECT effectiveness is demonstrated only for the period immediately post-ECT to one month.
- Conflicting data suggest ECT may be more effective than antipsychotic medication for acute episode.
- ECT associated with greater likelihood of being discharged from hospital.
- Limited evidence that ECT may reduce relapses.
Other Indications: Summary of Published Systematic Reviews and Meta-Analyses

- **Bipolar Mania**
  - Limited evidence that ECT may be effective

- **Bipolar Mixed States**
  - Limited evidence that ECT may be effective

- **Catatonia**
  - Lack of RCTs

- **Schizoaffective Disorder**
  - No evidence that ECT is effective at any time point
FDA Effectiveness Review: Practice Guidelines

- American Psychiatric Association (APA) Task Force on ECT (2001)
- Third report of the Royal College of Psychiatrists’ Special Committee on ECT (2004)
- National Institute for Health and Clinical Excellence (NICE 2003; NICE 2009)
FDA Effectiveness Review: Practice Guidelines

- Severe depression (unipolar and bipolar)
- Schizophrenia
- Acute mania (and bipolar mixed states)
- Catatonia
FDA Effectiveness Review: Practice Guidelines Clinical Setting

- Primary Use
  - A need for rapid, definitive response because of the severity of a psychiatric or medical condition
  - When the risks of other treatments outweigh the risks of ECT
  - A history of poor medication response or good ECT response in one or more previous episodes of illness
  - The patient’s preference
Secondary Use

» Treatment resistance to medications
  - For depression, after one or more antidepressant trials
  - For mania, after one or more mood stabilizer trials with adjunctive atypical antipsychotic treatment
  - For clozapine resistant schizophrenia
  - For lorazepam resistant catatonia
» Intolerance to or adverse effects with pharmacotherapy that are deemed less likely or less severe with ECT

» Deterioration of the patient’s psychiatric or medical condition creating a need for a rapid, definitive response
If response or remission has been achieved with ECT, antidepressants (including lithium augmentation) should be started or continued to prevent relapse.

ECT should not be recommended for an individual with moderate depression or who has not responded well to a previous course of ECT.

Comprehensive informed consent process.

FDA Effectiveness Review: Practice Guidelines Clinical Setting (continued)
“On balance, the evidence supports the conclusion that modern ECT is among those treatments effective for the treatment of select severe mental disorders, when used in accord with current standards of care, including appropriate informed consent.”

FDA Effectiveness Systematic Review and Meta-Analysis: Studies Identified

- **Depression:**
  - ECT vs. Sham: 11 RCTs
  - ECT vs. Placebo: 6 RCTs
  - ECT vs. Antidepressants: 18 RCTs
  - Electrode Placement by Energy Dose: 22 RCTs
  - Frequency (2x vs. 3x per week): 6 RCTs
  - Pulse Width (brief vs. ultrabrief pulse): 2 RCTs

- **Schizophrenia (ECT vs. Sham):** 10 RCTs

- **Mania (ECT vs. Sham):** 6 RCTs
FDA Systematic Review and Meta-Analysis: ECT vs. Sham for Depression

- **Systematic Review**
  - **Acute (immediately post-ECT)**
    - Sufficient evidence to conclude that ECT may be more effective than sham
  - **At one month or longer**
    - There is no evidence that ECT is superior to sham

- **Meta-analysis (5 studies)**
  - Mean improvement in HRSD for subjects treated with ECT was about 7.1 points (95% confidence interval [CI]: -0.1, 14.2)
FDA Meta-Analysis:
ECT vs. Sham for Depression

Wilson63
Lambourn78
Johnstone80
Brandon84
Jagadeesh92

Overall estimate:
7.1 (95% CI: -0.1, 14.2)
FDA Systematic Review and Meta-Analysis: ECT vs. Placebo for Depression

- **Systematic Review**
  - **Acute (immediately post-ECT)**
    - Conclusive evidence to show that ECT is more effective than placebo
  - **Long term (6 months post-ECT)**
    - 1 study demonstrated that ECT was more effective than placebo

- **Meta-analysis could not be conducted**
FDA Systematic Review and Meta-Analysis: ECT vs. Antidepressants for Depression

- **Systematic Review**
  - Immediately to one month post-ECT
    - Conflicting evidence regarding ECT and antidepressants
  - Greater than one month post-ECT
    - Sufficient evidence to conclude that ECT is more effective than antidepressants

- **Meta-analysis (8 studies)**
  - Mean improvement in HRSD for subjects treated with ECT was about 5 points (95% CI: 0.8, 9.1) greater than antidepressants
FDA Systematic Review and Meta-Analysis: Electrode Placement in Depression

- Systematic Review
  - Immediately post-ECT to 2 weeks
    - No significant difference between BL and RUL, or BF and RUL
    - 1 study showed that UL ultrabrief pulse (UBP) significantly more effective than BL UBP
  - Medium term (two weeks to three months)
    - Conclusive evidence of no significant difference between BL and UL electrode placement
FDA Systematic Review and Meta-Analysis: Electrode Placement in Depression

- **Systematic Review**
  - Immediately post-ECT to 2 weeks
    - No significant difference between BL and RUL, or BF and RUL
    - 1 study showed that UL ultrabrief pulse (UBP) significantly more effective than BL UBP
  - Medium term (two weeks to three months)
    - Conclusive evidence of no significant difference between BL and UL electrode placement

- **Meta-analysis (5 studies)**
  - Dosage unspecified: Mean improvement in HRSD for subjects treated with BL ECT about 4 points (95% CI: -0.6, 8.6) greater than UL ECT
FDA Systematic Review and Meta-Analysis: Energy Dose in Depression

- **Systematic Review**
  - High energy stimulation may be more effective than low to moderate energy stimulation (especially with RUL electrode placement)
  - Up to 6 months
    - Conclusive evidence that a significant difference is seen pre- to post-treatment across all groups.
  - 6 month and greater
    - One study demonstrated improvement out to 6 months

- **Meta-analysis (4 studies)**
  - In BL low or moderate dose vs. UL high dose, mean improvement in HRSD for subjects treated with BL ECT about 0.2 points (95% CI: -2.2, 2.6) greater than UL ECT
FDA Systematic Review and Meta-Analysis: Treatment Frequency (2x vs. 3x per week) for Depression

- **Systematic Review**
  - 1-4 weeks post-ECT
    - No significant between groups differences
    - Significant difference seen pre- to post- treatment across all groups (2x/week and 3x/week)
  - 3x/week treatment
    - Conclusive evidence that 3x/wk associated with more rapid improvement in depression symptoms
    - Conclusive evidence that 3x/wk associated with more severe memory problems.

- **Meta-analysis (3 studies)**
  - Mean improvement in HRSD for subjects receiving 3x/week was about 1.1 (95% CI: -5.0, 7.2) point greater than 2x/week
FDA Systematic Review and Meta-Analysis: Brief Pulse vs. Ultrabrief Pulse Waveform for Depression

- Systematic Review (2 studies)
  - RUL 6x ST vs. BL 2.5x ST (BP=1.5 ms or UBP=0.3 ms) (n=90)
    - 1 week post ECT
    - UBP BL ECT associated with significantly less improvement than other groups
  - BL 1.5x ST UBP vs. UL 6x ST UBP
    - 1 and 6 weeks post ECT (n=81)
      - No significant between groups difference between the two groups
      - UL UBP group required fewer treatments to achieve response/remission
FDA Systematic Review and Meta-Analysis: ECT vs. Sham for Schizophrenia

- **Systematic Review**
  - In monotherapy (without antipsychotic medications), no conclusive evidence that ECT is superior to sham immediately post-ECT to 8 weeks
  - In adjunctive therapy (with antipsychotic medications), conclusive evidence that ECT is not superior to sham at any time point
  - However, ECT may increase the speed of response

- **Meta-analysis (3 studies)**
  - Mean improvement in BPRS score of subjects treated with ECT was about 2.3 (95% CI: -3.7, 8.3) points greater than those treated with sham
FDA Systematic Review and Meta-Analysis: Acute Mania

- Systematic Review
  - ECT vs. sham design
    - ECT significantly better than sham immediately post-ECT
  - ECT vs. lithium
    - ECT as effective as lithium for post-ECT mania
Effectiveness Summary Slide

- **Depression**
  - In the acute and sub-acute phase, ECT is more effective than sham or placebo
  - After 1 month post-treatment, ECT is more effective than antidepressants
  - High dose UL ECT may be as effective as low-moderate dose BL ECT
  - No significant difference seen in effectiveness between 2x/week and 3x/week ECT, though 3x/week is associated with faster response

- **Schizophrenia**
  - ECT does not appear more effective than sham or antipsychotic medications

- **Mania**
  - Limited data suggest that ECT is superior to sham and as good as lithium
Identification of Key Risks and Potential Mitigating Factors
Identification of Key Risks

- Substantiated by comprehensive review of all sources of data
- Sufficient evidence of significant frequency
- Sufficient evidence of significant severity
- Evidence of being associated with ECT device use
Key Risks

- Medical/Physical
  - Adverse reaction to anesthetic agents/neuromuscular blocking agents
  - Alterations in blood pressure
  - Cardiovascular complications
  - Death
  - Dental/oral trauma
  - Pain/discomfort
  - Physical trauma
  - Prolonged seizures
  - Pulmonary complications
  - Skin Burns
  - Stroke

- Cognition and Memory Dysfunction

- Device Malfunction
To inform the FDA’s decision on reclassification, the key risks presented by ECT must be identified, and a determination must be made regarding how and whether sufficient information exists to establish controls to mitigate those risks. The FDA has identified the following key risks of ECT (in alphabetical order) in the FDA’s review of the Public Docket, the Manufacturer Docket, the Manufacturer and User Facility Device Experience (MAUDE) Database, and in FDA’s literature review:
Panel Question (continued)

a. Adverse reaction to anesthetic agents/neuromuscular blocking agents
b. Alterations in blood pressure
c. Cardiovascular complications
d. Cognition (disorientation and confusion)
e. Death
f. Dental/oral trauma
g. Device malfunction
h. Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory)
i. Pain/somatic discomfort
j. Physical trauma
k. Prolonged seizures
l. Pulmonary complications
m. Skin burns
n. Stroke
Panel Question (continued)

Is this a complete and accurate list of the key risks presented by ECT?

Comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks are among the key risks presented by ECT.
Key Risks

- Medical/Physical
  - Adverse reaction to anesthetic agents/neuromuscular blocking agents
  - Alterations in blood pressure
  - Cardiovascular complications
  - Death
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  - Pain/discomfort
  - Physical trauma
  - Prolonged seizures
  - Pulmonary complications
  - Skin Burns
  - Stroke

- Cognition and Memory Dysfunction

- Device Malfunction
## Key Risks: Medical/Physical

<table>
<thead>
<tr>
<th>Key Risk</th>
<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
</tr>
</thead>
</table>
| Adverse reaction to anesthesia          | Anesthetic agents, neuromuscular blockers  
Frequency: rare  
Severity: severe | -Pre-ECT assessment (medical, family history)  
-Appropriate procedure monitoring  
-Appropriate clinical management |
| Alterations in blood pressure           | Hypertension or hypotension  
Frequency: common  
Severity: mild-severe | -Pre-ECT assessment (BP, EKG, echocardiogram)  
-Appropriate procedure monitoring  
-Appropriate clinical management |
| Cardiovascular complications            | Arrhythmias or Ischemia  
Frequency: uncommon  
Severity: severe  
Known common risk of ECT. | -Pre-ECT assessment (BP, EKG, echocardiogram, holter)  
-Appropriate procedure monitoring  
-Appropriate clinical management |
<table>
<thead>
<tr>
<th>Key Risk</th>
<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Resulting from other pathophysiological processes</td>
<td>- Medical work-up and management per each underlying specific key risk</td>
</tr>
<tr>
<td></td>
<td>Frequency: rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severity: severe</td>
<td></td>
</tr>
<tr>
<td>Dental/oral trauma</td>
<td>Dental fractures, dislocations, lacerations, prosthetic damage</td>
<td>- Pre-ECT dental assessment</td>
</tr>
<tr>
<td></td>
<td>Frequency: uncommon</td>
<td>- Removal of prostheses</td>
</tr>
<tr>
<td></td>
<td>Severity: mild-moderate</td>
<td>- Use of mouth protection (bite blocks)</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>Frequency: common</td>
<td>- Use of analgesic medications</td>
</tr>
<tr>
<td></td>
<td>Severity: mild-moderate</td>
<td></td>
</tr>
<tr>
<td>Physical trauma</td>
<td>Fractures, soft tissue injury</td>
<td>- Use of general anesthetic agents and neuromuscular blocking agents</td>
</tr>
<tr>
<td></td>
<td>Frequency: uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severity: mild-severe</td>
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</tbody>
</table>
# Key Risks: Medical/Physical

<table>
<thead>
<tr>
<th>Key Risk</th>
<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged seizures</td>
<td>Frequency: uncommon Severity: moderate-severe</td>
<td>- Pre-ECT neurological evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- EEG monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Availability of seizure treatment during procedure</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>Apnea, aspiration Frequency: rare Severity: high</td>
<td>- Pre-ECT assessment (chest x-ray, pulmonary function tests)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Appropriate procedure monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Appropriate clinical management</td>
</tr>
<tr>
<td>Skin burns</td>
<td>Burns at electrode site Frequency: uncommon Severity: mild</td>
<td>- Skin preparation and electrode contact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Use of conductivity gel</td>
</tr>
<tr>
<td>Stroke</td>
<td>Frequency: rare Severity: high</td>
<td>- Pre-ECT assessment (neuro-imaging, vascular studies)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Appropriate procedure monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Appropriate clinical Management</td>
</tr>
</tbody>
</table>
Potential Mitigating Factors:
Acceptance of Risk and Informed Decision Agreement

- Written Informed Consent
- Inclusion of checklist of risks of treatment
- Checklist elements
  - All known risks of ECT
  - Likelihood of occurrence
  - Potential severity
- Review by treating physician and patient
- Initialing of each risk by both physician and patient to acknowledge review of the risk
- Documentation to be kept with standard written informed consent documentation
- Criteria for patient capacity to consent for treatment unchanged
Panel Question

Below are potential regulatory controls FDA could apply to ECT to mitigate medical/physical risks of ECT (i.e. adverse reaction to anesthetic agents/neuromuscular blocking agents, alterations in blood pressure, cardiovascular complications, death, dental/oral trauma, pain/somatic discomfort, physical trauma, prolonged seizures, pulmonary complications, skin burns, stroke):
Panel Question (continued)

a. Restricting ECT device use to physicians with specific training and/or experience with the administration of ECT;

b. Physician labeling recommendations for:
   i. pre-ECT assessment (including pertinent history, physical examination, EKG, echocardiogram, chest x-ray, pulmonary function tests, lab tests, and neuroimaging)
   ii. ECT procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)
Panel Question (continued)

iii. The appropriate use of general anesthesia, neuromuscular blocking agents by a licensed anesthesiologist during the ECT procedure

iv. pre-ECT dental assessment and the use of mouth protection (bite blocks)

v. Electroencephalography (EEG) monitoring during and after the procedure

vi. Adequate skin preparation and the use of conductivity gel during electrode placement
c. Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment

d. Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new indications for use (IFU)
Panel Question (continued)

Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the medical/physical risks of ECT.
Key Risks: Memory and Cognitive Dysfunction

- Risks:
  - Immediate post-treatment cognitive dysfunction (disorientation)
  - General memory dysfunction
    - anterograde memory loss
    - retrograde autobiographical memory

- Course:
  - Disorientation appeared to be transient and generally resolved in a matter of minutes after the procedure
Key Risks: Memory and Cognitive Dysfunction (continued)

» All memory domains, except autobiographical memory, appeared to resolve days to weeks after the completion of a course of ECT treatment

» Autobiographical memory deficits were more persistent
  - Approximately 76-77% performance with RUL ECT
  - 58-67% performance with BL ECT at the one- to two-week time point.
  - Limited evidence suggested that autobiographical memory deficits may approach baseline at six months
## Potential Mitigating Factors: Cognitive and Memory Dysfunction

<table>
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<tr>
<th>Key Risk</th>
<th>Risk Characterized</th>
<th>Potential Mitigation Factors</th>
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| **Cognition** | Disorientation generally occurs post-treatment, but typically resolves minutes after completion of treatment. | - Exclusive use of square wave, direct current, brief pulse waveform stimulus  
- Use of ultrabrief pulse (0.3 msec) stimulus  
- Exclusive use of unilateral nondominant electrode placement  
- Use of bifrontal electrode placement  
- Frequency of treatment no greater than twice weekly during a course of ECT |
| **Memory** | Generally memory dysfunction occurs, but resolves over time. Autobiographical memory dysfunction is longer lasting, with limited data suggesting complete resolution at 6 months. | - Exclusive use of square wave, direct current, brief pulse waveform stimulus  
- Use of ultrabrief pulse (0.3 msec) stimulus  
- Exclusive use of unilateral nondominant electrode placement  
- Use of bifrontal electrode placement  
- Frequency of treatment no greater than twice weekly during a course of ECT |
Mid-Course Mitigation Strategies

- Switch BL to UL
- Decrease energy dose
- Switch from BP to UBP

Identification of safe stimulation parameters in device labeling
Panel Question

Below are potential regulatory controls FDA could apply to ECT to mitigate risks of adverse cognitive and memory effects (especially with respect to anterograde and retrograde memory functioning):

a. Physician labeling recommendations for:
   i. Exclusive use of brief pulse (1-1.5 msec) waveform stimulus
   ii. Use of ultrabrief pulse (0.3 msec) stimulus
   iii. Exclusive use of unilateral nondominant electrode placement
   iv. Use of bifrontal electrode placement
   v. Limiting frequency of treatment to a maximum of twice weekly during a course of ECT
   vi. Monitoring cognitive status prior to ECT and throughout the course of treatment
Panel Question (continued)

b. Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment.

c. Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new IFU

Please discuss each of these potential controls and whether it, either alone or in combination with others, adequately mitigates the cognitive and memory risks of ECT.
Potential Mitigating Factors: Device Malfunction

- **General Controls (21 CFR §820)**
  - Good manufacturing practices (GMPs) Quality system regulations (QSRs)
- **International Safety Standards**
  - International Electrotechnical Commission (IEC) 60601-1-1: Safety Requirements for Medical Electrical Systems
  - International Electrotechnical Commission (IEC) 60601-1-2: Electromagnetic Compatibility

FDA recognized standards:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
Panel Classification Recommendation for ECT

- **Class II**
  - Reasonable assurance of safety and effectiveness provided by general and special controls

- **Class III**
  - High risk devices for which general and special controls are inadequate to assure safety and effectiveness
  - PMA required
Panel Question

Currently cleared indications for use (IFUs) for ECT devices include the following:

a. Depression (unipolar and bipolar)
b. Schizophrenia
c. Bipolar manic (and mixed) states
d. Schizoaffective disorder
e. Schizophreniform disorder
f. Catatonia

Please provide your overall recommendation for the classification (Class II or III) of the ECT device for each of the above indications.