Electroconvulsive Therapy (ECT): Relevant in the Twenty First Century

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ECT, ETC

What comes to mind when someone says:

‘Electroconvulsive Therapy?’
Stigma
ECT History

• Convulsive therapy
  – Insulin coma therapy 1933 Manfred Sakel (not always accompanied by seizures)
  – First with subcutaneous camphor, then IV metrazol
  – Based upon mistaken theory that seizures protected people from schizophrenia
  – 1937 First International Meeting on Convulsive Therapy in Switzerland
  – Not yet with electricity as a means of inducing seizure
ECT History

• Italians Cerletti and Bini found electricity to be an effective substitute for camphor or metrazol in inducing seizures.
• Treated the first human in 1937
• They were nominated for a Nobel Prize in 1940
ECT History

• By 1940, ECT introduced in England and the United States
  – Almansi and Impasto at Columbus Hospital in NYC
  – Lothar Kolinowsky at Psychiatric Institute
• Used widely in the 1940’s and 1950’s
• The only form of convulsive therapy that is still used today
• BUT, there have been changes in technique
Modifications in ECT

• Attempt to reduce confusion and memory disturbance as side effects
  – Use of Unilateral electrode placement
  – Use of brief pulse and ultra brief pulse instead of sine wave ECT
Modifications in ECT

• In the 1940’s and early 1950’s, ECT given WITHOUT muscle relaxants
  – Anterograde and retrograde amnesia
  – Seizures resulted in full scale convulsions
  – Rare but significant side effect was dislocation and fracture of long bones
Modifications in ECT

• Curare
  – South American poison that paralyzes muscles
  – Was used with Metrazol convulsive therapy 1940

• Succinylcholine
  – Synthetic muscle relaxant (1952, Holmberg with ECT)
  – Led to widespread use of “Modified ECT”
  – In combination with a short acting anesthetic
  – SAFER
ECT Modifications

• Anesthesia prevents the “locked in” feeling of muscle relaxant alone

• OXYGEN

• Monitoring Vitals, EKG

• Done in Recovery Room, OR or other area of a hospital
ECT History

• Decline of ECT use in 1950’s to 1970’s
  – Medications became available for depression, bipolar disorder, schizophrenia, schizoaffective disorder, psychosis
  – ECT was getting bad press
    • Came from negative perceptions in the media about ECT BEFORE anesthesia was routinely given
    • One Flew Over the Cuckoo’s Nest by Ken Kesey
      – ECT dangerous, inhumane, and overused
ECT History

• Brief Pulse and Constant Current ECT
  – 1976
  – Began replacing earlier ECT devices
  – Significantly less cognitive side effects
• The 1970’s saw criticism of ECT based upon uneven application of the treatment
ECT History

• 1980’s
  – Increased awareness of the cost effectiveness in treating depression

• NIH and NIMH
  – 1985 Consensus Statement about ECT
  – Supported ECT for narrow range of conditions - Depression
ECT History

• American Psychiatric Association
  – 1978 Task Force report on ECT
  – New Consent Standards
  – Recommended Use of Unilateral Electrode Placement
  – 1990 then 2001 further Task Force reports on ECT
  – Expanded role of ECT in modern medicine
Who should get ECT?

- Major Depression
- Acute Mania
- Schizophrenia
- Mental Disorders due to Medical Conditions
  - Malignant catatonia
  - Delirium
- Medical Disorders
  - NMS, parkinsonism, intractable seizures
“Famous” People who had ECT

- Kitty Dukakis
- Thomas Eagleton, senator and VP candidate
- Sherwin Nuland, surgeon and writer
- Sylvia Plath, writer and poet
- Yves Saint-Laurent
- Vivien Leigh
- Many others
What do these illnesses have in common?

Untreated, they can be deadly. Depression is a disease, not a weakness, and can lead to suicide.

Fortunately, depression can be treated and lives saved when symptoms are recognized and medical help is sought.

He is the best physician who is the most ingenious inspirer of hope.

– Samuel Taylor Coleridge, poet, critic, and philosopher (1772-1834)
Benefits of ECT

• Safe and effective treatment
• Beneficial for elderly depressed
• More rapid response than antidepressant medication
Risks of ECT

- Cardiovascular
- Cognitive
- Dental
ECT: How does it work?

• Theories
• We don’t know how it works
• We do know that it works
  – Clinical trials
  – Testimonials
Treatment Course

- Index treatment

- Continuation treatment (first 6 months after the initial treatment)

- Maintenance treatment
ECT-Mechanisms

- ECT as anticonvulsant
- Psychological theories
- Neurophysiology
- Biochemistry
- Gene expression
- Rndocrine
- Cognitive effects
Anticonvulsant effect

- Inhibitory inter-neurons
- Not the seizure, but an attempt to shut the seizure down
- Anticonvulsant medications are mood stabilizers
- ECT effective in depression, mania, and mixed states
- Used in status epilepticus
Psychological Theories

- Psychodynamic
  - Punitive

- High expectation of recovery
  - Placebo

- Adverse cognitive effects
  - Amnesia
Psychodynamic and Placebo Problems

- Sham vs. real ECT
  - Double blind
  - Random assignment

- Technical factors of administration matter
  - Anatomical positioning of electrodes
  - Intensity of electrical dosage
Problem with amnesia as therapeutic mechanism

• Cognitive change and therapeutic efficacy
  – Better cognitive functioning in those with greater symptomatic improvement.
  – Not one size fits all
Interpretation of Neurophysiological Effects

• Recruitment of endogenous inhibitory processes to terminate the seizure
  – Anticonvulsivse effects are progressive during ECT course
    • Increase in seizure threshold
    • Decrease in seizure duration
Interpretation of Neurophysiological Effects (con’t)

• Seizure threshold change
  – May be related to efficacy in major depression and mania

• Seizure duration change
  – Not related to efficacy
Brain imaging and ECT

• Need for high resolution studies (PET, fMRI) of cortical-subcortical functional systems.
Protein Synthesis

• Electrical induced generalized seizures result in short lasting reversible protein synthesis inhibition.
• No theory relating to efficacy
• Medication that inhibits protein synthesis interferes with long-term memory
Synapse formation may be altered

- ECS in rodents activates astrocytes
  - Increased staining for glial fibrillary acid protein
  - Increase in a marker for newly formed synapses relative to mature synapses
Blood-Brain Barrier Disruption

• Electrically induced seizures result in disruption of the blood-brain barrier
• Dependent on transient systemic hypertension and cerebral vasodilatation
• Increased vesicular transport by pinocytosis
• Transient increases in T-1 relaxation times
  – MRI measure of increased water content in the brain.
Blood-Brain Barrier Disruption (con’t)

• Acute, transient increase in the plasma of neurotransmitters and peptides
  – Epinephrine, norepinephrine, prolactin, beta-endorphin immunoreactivity, vasopressin, oxytocin, ACTH, cortisol, insulin FSH, LH
Blood-Brain Barrier Disruption (cont’t)

• Theory of increased permeability to an endogenous substance with antidepressant effects

• Schizophrenia patients respond better to ECT and antipsychotic than to either treatment alone
  – ? Increased levels of antipsychotic
Blood-Brain Barrier Disruption (con’t)

• Surges of endogenous substances in the plasma are not related to antidepressant effects
  – Exception is oxytocin-related neurophysin

• Magnitude of systemic hypertension is not related to clinical outcome
Biochemical Effects

• ECS alters receptor and peptide concentrations, receptor density, and signal transduction mechanisms

• Rodent studies
  – Limited generalizability to humans
  – Different timing, anesthetic, placement
  – Need for behavioral endpoints
Biochemical Effects (con’t)

- Peripheral body fluids and tissue samples
  - Relation to brain neurochemistry is unclear
  - Limited specificity of neuroendocrine probes
  - Limited strength of association to central measures of transmitters or peptide function
- Need for *in vivo* brain imaging techniques to probe neurochemical systems
Neurotransmitters

• Up-regulation of 5HT2 receptors
• Down regulation of beta receptors
  – Serotonin
  – Norepinephrine
  – Dopamine
Acetylcholine

- Reduction in central cholinergic function
  - Inc CSF Ach levels after spontaneous seizures
  - Chronic ECS results in reduction of muscarinic cholinergic receptor density in cortex and hippocampus
  - Functional decrease in 2nd messenger response in hippocampus
  - Acute decrease in brain Ach, ChAT, Acheterase
Acetylcholine (con’t)

- Chronic ECS decrease behavioral response to muscarinic agonists
- Antidepressant effects through reduced cholinergic supersensitivity
- Decreased cholinergic tone would be counterproductive in treatment of mania
- Relevance to cognitive side effects
Gamma Aminobutyric Acid

- ECS: functional inc in GABAergic activity
- Inc density of GABA B receptor
- GABA B receptor modulates release of other neurotransmitters
- Some GABA mimetics may have antidepressant properties
- Acute decrease in GABA synthesis/release
Endogenous Opioids

- Marked acute increase in $\beta$-endorphin immunoreactivity
- Chronic ECS increases met-enkephalin and $\beta$-endorphin concentration and synthesis in several brain regions
- Large molecular weight opioid peptide (anticonvulsant) released to CSF
Adenosine

• Implicated in cerebral excitability
• Caffeine and theophylline are adenosine antagonists
  – Increase seizure duration
  – No change seizure threshold
    • Independence of these phenomena
• Chronic ECS inc A1 adenosine receptors
Gene Expression

- ECS induces protooncogene products
  - C-fos, c-jun, jun-B, zif/268
  - Differ in time course and regional distribution from stress manipulation and caffeine induced seizure induction
  - Detection of commonalities between therapeutic seizure induction methods (ECT, florothyl, metrazol) may shed light on mechanisms
Gene Expression (con’t)

- The induced oncogenes are regulatory
- ECS alters mRNA, peptide, transmitter and enzymatic systems
- Differences have been elicited between ECS and antidepressant medication effects on the same transmitter system
Neuropeptides

• ECT modifies synthesis, release and metabolism of neuropeptides in the brain
• Series, not single treatment, has effect
• Changes persist at least one week
• Peptide specific (NPY, neurokinin A, STS)
• mRNA changes are region specific
Endocrine Hormones

- Endocrine hormones as neuromodulators
- ECT effective in treating neurovegetative depressive symptoms
  - Suggest hypothalamic dysregulation
- Generalized seizure from a centroencephalic pacemaker
- Variety of peptides are increased immediately following seizure
Endocrine Hormones (con’t)

• Complex effects on TRH and TRH-receptor function

• TSH in response to TRH
  – Decreased blunting (predictive of long-term remission)
  – More recent work: increased blunting

• L-triiodothyronine (T-3) supplementation
  – May improve clinical response
  – Reduce cognitive side effects
Endocrine Hormones (con’t)

• HPA axis
  – CRH is increased in CSF
  – DST response independent of clinical outcome
    • Decreased post dexamethasone cortisol
    • Abnormal DST responses
  – Plasma levels of exogenously administered dexamethasone increase during and after ECT
Mechanisms of Adverse Cognitive Effects

• Neuropathological effects
• No irreversible structural brain damage
  – Transient nature of most cognitive changes
  – Human postmortem studies have not linked neuronal cell loss to current ECT practice
  – Prospective structural imaging studies have failed to demonstrate change in cohorts of ECT patients
Mechanisms of Adverse Cognitive Effects (con’t)

• Neuropathological effects
  – Animal studies
    • Controlled perfusion fixation techniques fail to observe pathological change following ECS
    • Hippocampal cell counts do not change in animals receiving intensive and chronic ECS
      – Same technique does demonstrate cell loss in epileptic patients with frequent seizures
Mechanisms of Adverse Cognitive Effects (con’t)

• Neurophysiological theories
  – Deficits in retention of new information and recall or recognition of recent events
    • Consistent with effects on medial temporal structures long implicated in subserving long-term memory function
  • Consolidation dysfunction
    – Transient inhibition of protein synthesis may disrupt plasticity mechanisms
Mechanisms of Adverse Cognitive Effects (con’t)

– With oxygenation, seizures must be continuous for at least 25 to 30 min to result in cell death
  • Mismatch between metabolic demand and supply in vulnerable neurons
  • Agonist-receptor interactions that trigger dissipative fluxes of sodium and calcium ions across postsynaptic membranes
  • Agreement that minimum conditions for cellular necrosis do not apply to ECT
ECT Choices

• Bilateral versus Unilateral

• High versus low dose

• ECT versus pharmacotherapy (medication)
Mechanisms of Adverse Cognitive Effects (con’t)

• Neurophysiological correlates
  – Slow wave EEG activity may persist for weeks after ECT
  – Magnitude of slowing correlated with amnesia
• In conclusion, there is a reasonable evidence base for the use of ECT: it does not rest simply on anecdote, habit, and tradition. The trials that have been done reflect concerns that were uppermost at the time. In the 1970s, this concern was efficacy of electroshock per se, more recently it has been dose and site of shock administration. ECT remains an important treatment option for the management of severe depression.

In the depth of winter, I finally learned that within me there lay an invincible summer.

Albert Camus
Summary

1. Electroconvulsive therapy (ECT) is a safe and humane treatment for depression, bipolar disorder, schizophrenia and specific medical conditions.

2. Stigma is a barrier we can break down to allow for safe and effective treatment of mental disorders.

3. Mental health treatment greatly improves quality of life.
Thank you

• Discussion
• Questions
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