



DEPARTMENT OF
PSYCHIATRY

UNIVERSITY OF MICHIGAN
HEALTH SYSTEM

Electroconvulsive Therapy (ECT) in Youth with Treatment Resistant Mood disorders (TRM)

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Contents

1. History, mechanism of action
2. ECT in mood disorders; brief mention about catatonia
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6. Abbreviations:
 - Treatment (Tx)
 - TRD (treatment resistant depression)
 - TRM (treatment resistant mood disorders)
 - Interchangeably use minor, youth, children for < 18 years

Key points about ECT

- ECT is effective:
- 60 to 100 % response rates

ECT is under used:
Lack of familiarity
No absolute contraindications

Practical issues :
FDA approved
Moderate risk device
Consensus 1-3 psychiatrists
Informed consent

Indications:
Treatment resistant severe
disorders: mood, psychosis,
catatonia, NMS, emerging novel
indications

Side effects:
Physical discomfort
Reversible short term memory
impairment
Epilepsy is not a SE of ECT

Hippocrates to Ken Kesey (One that flew over the cuckoo's nest): A brief history of ECT

1940-1950's: Widespread ECT use
techniques improved, psychotropics discovered

400 BC



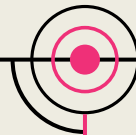
Hippocrates observed that convulsions appeared to cure “insanity psychosis”

1910 -
1930s



Medications used to induce convulsions to treat psychosis in Europe

1937



First ever ECT treatment conducted in Rome; Carletti & Bini

1941



First *pediatric* ECT 3 y/o with epilepsy

1947



Case series published on 98 ECT in youth (Bender)

Ghaziuddin and Walter, 2014

Hippocrates to Ken Kesey: A brief history of ECT

1960-1980s: ECT becomes less popular
Increased legal restrictions for ECT

1990-2000's: ECT image rehabilitation
Increased use of ECT

1962



Publication of
"One Flew Over
the Cuckoo's
Nest" by Ken
Kesey

1972



U.S. vice
presidential
candidate dropped
from ticket due to
ECT history

1983



26 states ban
pediatric ECT

1990



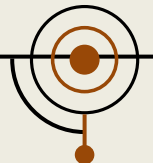
APA statement
endorses ECT for
<12 y/o in
specific situations

1997



Case series
published of
396 ECT in
youth (Rey)

2004



AACAP Practice
Parameters
published on
ECT in youth

Mode of Action

The “active ingredient”: a grand mal brain seizure without a generalized motor convulsion

Patient’s seizure threshold must be overcome (BL 1 to 1.5; UL 5-7)

Seizure threshold increases with age, therefore not an issue in the young

Seizures must be repeated until response

No “magic” number for total treatments needed

Benefits (and relapse if inadequate Tx) are rapid but not immediate

Mechanism of action (multi-modal)

Gene regulation & expression and distinct neurotrophic signaling Pathways

- Increased neurotransmitters, neuropeptides, synaptic remodeling, neuronal sprouting
- **Brain regions:** *prefrontal cortex, temporo-parietal cortex, neostriatum, hippocampus*
- fMRI study found increased R hippocampal connectivity and increased L hippocampal volume in CA2/3 subfield in a group treated with R UL (Abbott cc et al. 2014)
- **BDNF:** widely distributed in the brain, altered by stress and normalized with antidepressant or ECT (Haghighi et al. 2013)
- **TRN mRNA:** Animals studies find that repeated ECS resulted in a 20-fold increase in transational mRNA in hippocampal
- **Vascular endothelium:** Proliferation and neurogenesis
- **Gene expression:** rapid increase in a subset of gene expression.

Electroconvulsive Therapy (ECT): relevant clinical issues

- No evidence of brain damage, permanent loss of memory, inducing epilepsy; ECT has anticonvulsant properties (**Sackeim et al 1983**)
- Seizure disorder is not a contraindication; in presence of a psychiatric indication, management of seizures may improve (**Koong & Chen 2010, 2016**)
- ECT has been used to treat status refractory epilepticus (**Fink et al 1999**)
- Non-convulsive status epilepticus (NCSE) in 3 ECT patients (**Povlsen et al 2003**); however seizure like activity is routinely seen during ECT and possibly predict positive response (Fink 2004)- EEG abnormalities during ECT repeatedly shown and Povlsen's report likely a misinterpretation
- High association between seizures and DD-up to 46% (Autism, ID and genetic syndromes) (**Keller et al 2017**)

Why use ECT?

Benefit vs Risk

- **Clinical Benefits of ECT**

- Rapid response

- Highly regulated with stringent safeguards

- Efficacy well established and possibly exceeds many other treatments; 65 to 100%

- Estimated mortality/morbidity is 1 per 10,000 patients (0.01%- higher in severely ill).

- Overall risk may be < antidepressants (tricyclics)

- Risk similar to minor surgical procedure; possibly less risky than child birth

- **Risks of untreated or partially treated mood and other disorders**

- Chronicity

- School and social failure

- 10-15% suicide rate

- Substance abuse usually follows UP and BP

- Recurrence, relapse and disruption of life

- Continuation into adulthood

- Inter-generation impact of untreated disorders: poor maternal and infant outcomes

American Academy of Child and Adolescent psychiatry practice parameters about use of ECT in Children and Adolescents

- Published in 2004 by Ghaziuddin et al.
- Developed over 2 years in collaboration Committee for Quality Issues
- **Include:**
 - Literature review
 - Safe administration of ECT
 - Ethical and legal aspects
- **Main points:**
 - Indications: severe mood dis (UP, BP), schiz, schizoaffective, catatonia, NMS
 - Illness severity criteria: severe, persistent, impairing, may be life-threatening
 - Treatment resistance
 - Comorbid Axis I and II are not contraindication
 - No absolute medical contraindication

Severity of illness takes precedence over resistance

General Guidelines (setting up a service)

- Trained faculty, location of procedure, follow-up every case
- Second opinion: requirements vary by state and institution
- Consent and assent: informed, right to receive or refuse
- Hospitalization at start of treatment: safety, discharge criteria
- Evaluations by psychiatry, anesthesiology, general medical
- Collateral assessment; parents, previous treatment provider
- Standardized assessments: CDRS-R, YMRS, MMSE, MoCA, BFCRS
- Neuropsychological testing: pre and post; a thorough understanding of cognitive deficits

Psychiatric Indications and Contraindications

Indications:

- **Mood disorders:** severe/ treatment resistant mood disorder; both UP and BP; severity takes precedence over treatment resistance
- **Psychotic disorders:** severe/ treatment resistant
- **Neuropsychiatric syndromes:** Catatonia, NMS, malignant catatonia

Contraindications: None✓

Although, the following may be mistakenly considered as contraindications

- Personality disorders
- Anxiety disorders
- Eating disorders

Consent, Assent and rare use of court-ordered

- Written consent of a guardian, assent whenever possible
- Court order may be rarely necessary; combative minor, persistent refusal
- Two cases in 30 years with court ordered treatment
- **Case**
- 15 year, F, intact family, no trauma, realistic plan for suicide
- Severe mood symptoms from age 13 onwards
- Multiple treatment failures: AD, MS and AP + psychotherapy
- Poor social skills, isolative, suspicion for ASD
- Court order obtained from probate judge; parents fully supported
- Excellent response; remained euthymic 1.5 year later

Adolescent-Adult differences

Adolescents

- Rarely used (1% of all ECT cases); 100, 000 adults annually
- **At our center, 18% for the present academic year (2019 to 2020)**
- Greater number of past failed medication trials (9 in our sample)
- Higher suicidality
- Higher representation of psychotic disorders
- Longer hospital stay prior to ECT use
- Majority of psychiatrists do not have the necessary experience

Treatment Resistant and Severe Mood Disorders (TRM)



- **Severity:** Suicidality, impaired life sustaining function (food and water intake)
- **Treatment resistance:** No clear definition for any age (25%)
- **Indicated for unipolar and bipolar disorders**
- Definition in adults: failure to respond 2-3 AD + psychotherapy
- STAR*D: progressive decline in remission rates with more medication failures; only 13% remission by level 4
- One third of adolescents did not achieve remission at 72 weeks (18 months) (TORDIA; Vitiello et al. 2011)

Recent ECT studies involving adolescents with mood disorders

Zhand et al (2016):

n = 13, Tx 2008-2013, mean # of Txs = 14

Dx with depression, 77 % improvement rate, minor SEs

Puffer et al (2016):

n = 51, Mixed diagnostic group, Tx 1991-2013, 71% started with BL, 77% much improved at end of Tx

Karayagmurlu et al (2020):

n = 62, mean age = 17, 75% with BP or UP, ECT was more effective when no comorbidity but also effective with comorbid conditions

Ghaziuddin et al (2020): Details to follow

ECT in Adolescents with Mood Disorders; studies with a comparison group

| Variable name | n/ age | Affective dis/ other Dx | Electrode placement | Response or remission | Side-effects | Comments |
|-----------------------------|--------------|----------------------------|------------------------|--------------------------|---|--|
| Kutcher & Robertson 1995 | 16/ 19 | 16/16 | BL (87%) | Yes | 28% reported; HA commonest | Compared with ECT refusers |
| Stein et al. 2004 | 36/ 17.5 | 17/16 | Mixed | Yes | Manic switch =3; prolonged seizures = 2 | Compared with adults |
| Bloch et al. 2001 | 24/ 13 to 19 | 5/ mixed | BL | 58% remission | No serious SE | Compared with adults |
| Bloch et al.2008 | 13/ 13 to 20 | 33%/ 67% | BL | Yes | Not stated | Compared with adults |
| Taieb et al. 2002 | 11/19 | 11/0 | ? | Yes | Not stated | Compared with psychiatric controls |

Background: Use of ECT in psychosis

- ECT-use declined in psychosis with antipsychotic use starting in 1950's
- APA-TF: use ECT when safety concerns and/or lack of response to medications
- Resurgence of interest due to SEs associated with antipsychotics and a relatively large subgroup (20%) unresponsive to medications alone
- Meta-analysis (n = 392) found more rapid improvement, in comparison to sham ECT, when combined with antipsychotics (Tharyan & Adams, 2009)
- Lin & colleagues in a follow-up found fewer hospitalizations, reduced ER visits and lower cost in those who received ECT + meds versus those on meds alone

ECT in Psychotic disorders, Suicidality, Eating disorders

- **Psychosis:** Zhang et al (2012):
 - case controlled study of first break psychosis
 - age = 13-20 years; controls = 38, study group = 74
 - 74% response in study vs 50% in controls*
 - Improvement in PSG findings
- **Suicidality:** reduces completed suicidal behavior across diagnosis: rapid effect, however the attempt elevated attempt rates despite reduced completed rates
- **Eating disorders:** several case reports, can be life saving

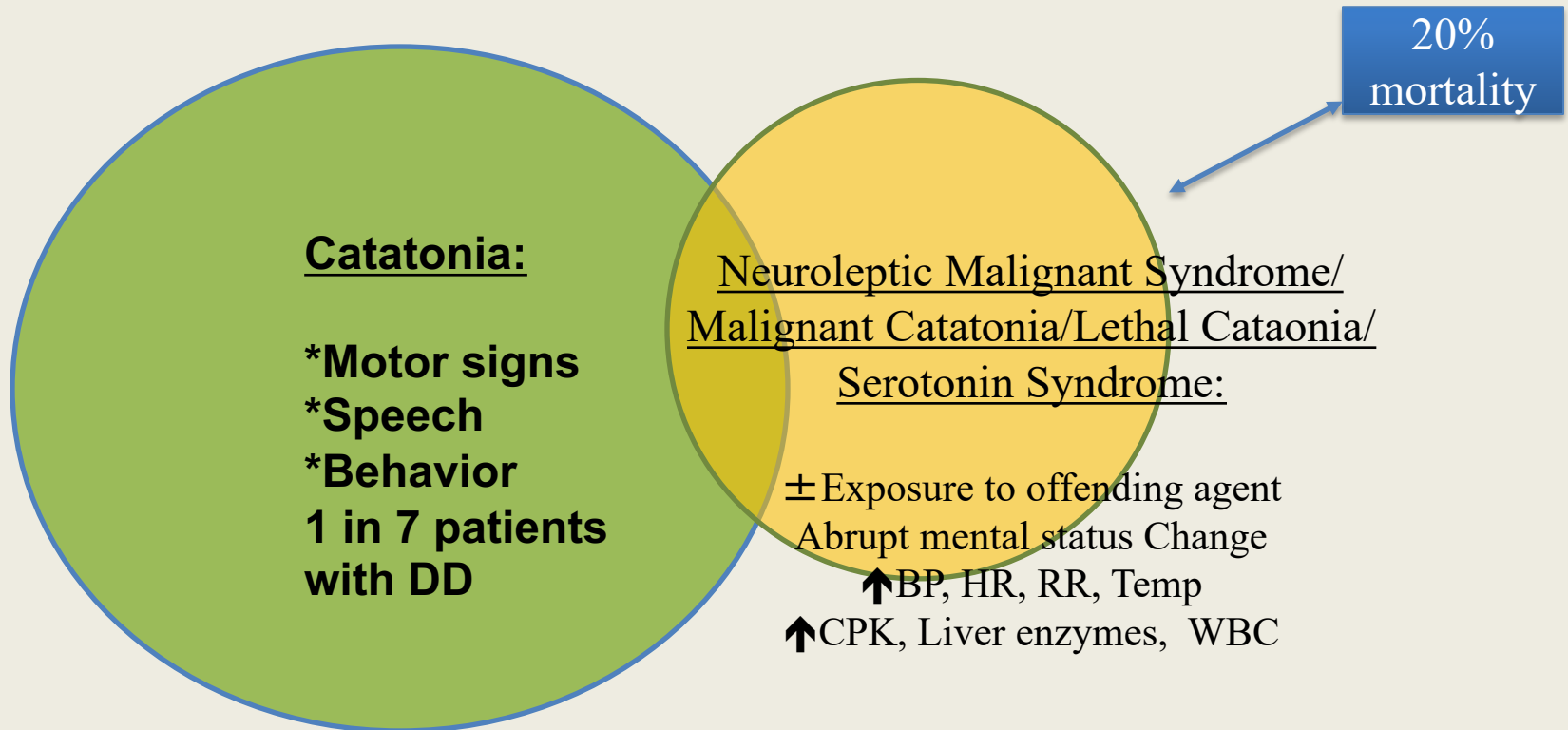
ECT in Psychosis contd

- ECT is useful in treatment refractory psychotic disorders (Petrides et al 2015)
- ECT has a role in first episode psychosis
- Lower recurrence rates in those who receive ECT (Ward et al 2018)
- Reduction noted in positive and negative symptoms (Grover et al 2017)
- Benefit of ECT appears to be durable (72% responders at 1 yr; Grover et al 2017)
- Higher response rate when ECT combined with antipsychotics (Petrides et al 2015)
- Better cognitive scores in those treated with ECT (Cusa et al. 2018)
- *Parents* whose child received ECT, compared to those who had only received medication, stated *that treatment was safe and adequate* information was provided about the procedure (Flamarique et al 2017)

ECT for Catatonia in autism spectrum disorders

- No difference in indications: mood disorders, psychosis, catatonia, NMS
- Catatonia is relatively more common in autism and other developmental delays; rates 12-17% (Wing & Shah; Ghaziuddin 2012)
- The most severe cases 2005 to 2017; ASD, ID, SIB (Wachtel 2019)
- N = 22, Age = 8 to 26 years, all Tx with BL ECT, followed by M-ECT
- 2 adults, 15 adolescents, 5 preadolescents, youngest case = 8 years
- Poor response to BNZ: dose range = 1- 27 mg/day, partial benefit to no benefit in majority, 2 worsened
- M-ECT (# = 16 TO 688) in all; intervals = 1 to q3 weeks; Hypothesis:
- Conclusion: ASD + catatonia often need ECT

Overlapping Conditions



2.5% of Catatonic patients develop Neuroleptic Malignant Syndrome/Malignant Catatonia/Serotonin Syndrome.

Electroconvulsive Therapy for the Treatment of Severe Mood Disorders during Adolescence (Ghaziuddin et al.2020)



- 54 patients, <18 years, Tx at UM for any mood dis
- 1996 to 2010
- Mood diagnoses:
 - MDD = 33 (61)
 - Mood Dis NOS = 4 (7)
 - BP (II or NOS) = 17 (32)
- AACAP guidelines were used
- MECTA device
- Brevital 1 mg/kg for sedation and succinylcholine 0.8 to 1 mg/KG for muscle relaxant; glycopyrrolate routinely given

Demographics

| Variable name | cases | Mean \pm SD | Frequency (%) |
|--|-------|----------------|---------------|
| Age | 54 | 15.8 \pm 1.5 | |
| Females★ | 30 | | 31(57) |
| Age of first psych contact | 52 | 11.2 \pm 3.6 | |
| Age of first MDD★ episode | 45 | 13 \pm 2.3 | |
| GAF | 54 | 22 \pm 9.5 | |
| HRSD★ | 25 | 22 \pm 6 | |
| Family history psych (1 st or 2 nd) | | | 35 (65) |
| FH of attempted or completed suicide | | | 22(41) |

Other Clinical Features

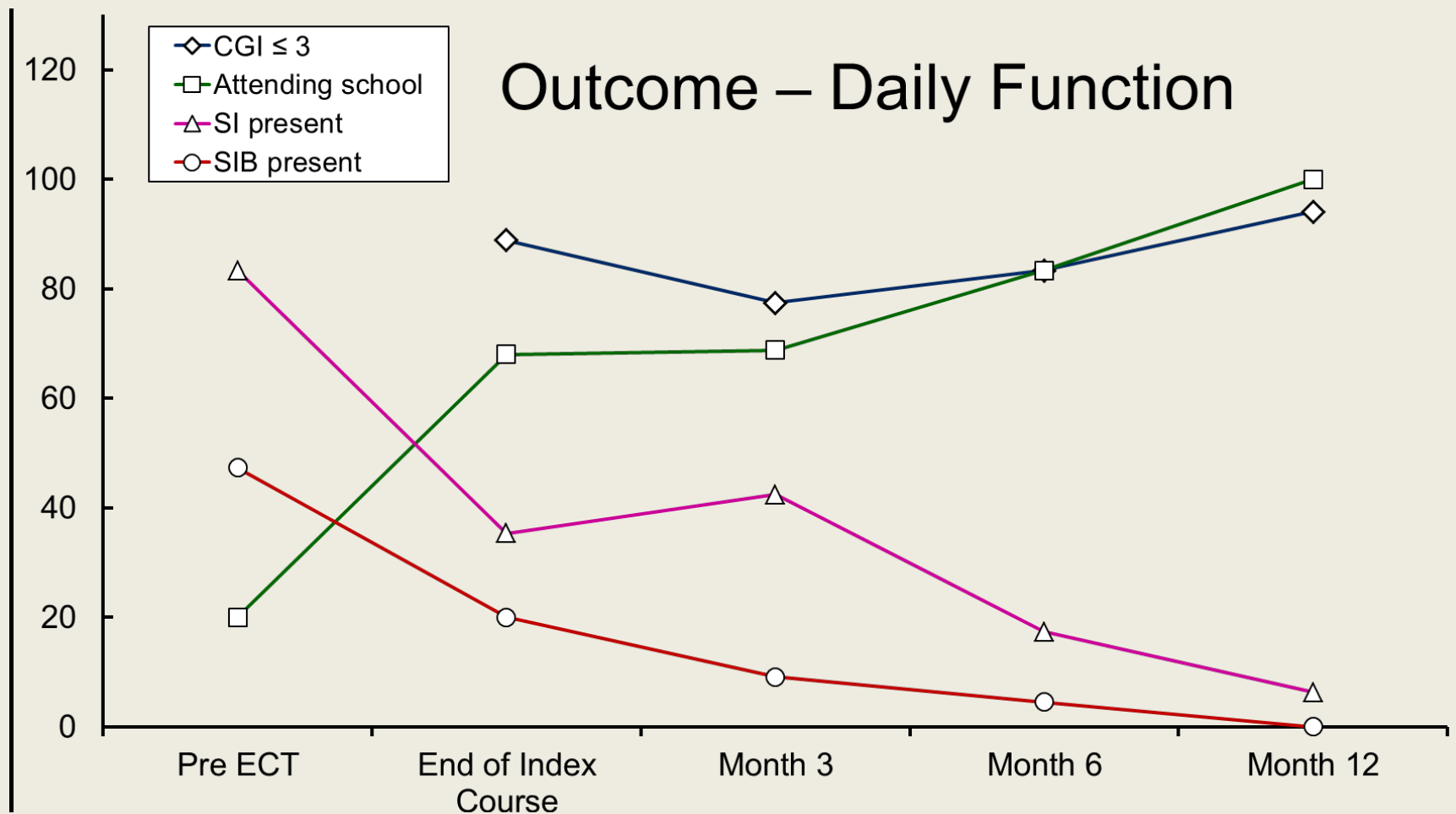
| Variable name | Cases | Mean + SD | Frequency (%) |
|----------------------|-------|----------------|---------------|
| Suicide attempt | 54 | | |
| Ever | | 2 ± 2 | |
| Past year | | 0.88 ± 1.3 | |
| Past month | | 0.4 ± 0.6 | |
| Medication Trials★ | | | |
| Any | 54 | 9 ± 4.7 | |
| SSRI | 53 | 2 ± 1 | |
| nSSRI | 53 | 2 ± 1.4 | |
| Antipsychotic | 53 | 2 ± 2 | |
| Mood stabilizer | 54 | $3 \pm$ | |
| Psychotherapy | | | 49 (91) |
| Past hospitalization | 53 | 3.8 ± 2.3 | |
| | 54 | 2.0 ± 2.2 | |

Comorbid Diagnoses

| Variable name | Number of Cases | Axis I frequency (%) | Axis II frequency (%) | Other symptoms |
|------------------------------|-----------------|----------------------|-----------------------|----------------|
| Dysthymia★ | 54 | 12 (22) | | |
| Anxiety Dis★ | 54 | 32 (59) | | |
| Psychotic Dis | 54 | 14 (26) | | |
| ASD | 54 | 10 (19) | | |
| Disruptive Dis | 54 | 13 (24) | | |
| Eating Dis | | 9 (17) | | |
| Substance, alcohol use/abuse | 54 | 8 (18) | | |
| Self injury | | | | 22 (41) |
| MR | | | 4 (7) | |
| Speech dis | | | 10 (19) | |
| Learning dis | | | 10 (19) | |

| ECT related variables | Mean \pm SD | Frequency (%) |
|--|-----------------------------|----------------------------|
| Mean Tx's in index course | 14 \pm 6 | |
| Number of index courses: 1 2 3 | | 40(76) 11(21) 2(4) |
| Electrode placement BL | | 49 (93) |
| Continuation Tx received in cases | | 13 (24)* |
| Seizure duration EEG Motor | 90 \pm 35 43 \pm 11 | |
| Prolonged seizures (>2) | 3 \pm 3 | |
| Primary reason for ECT refractory suicidality catatonia | | 39 (71) 9 (16) 4 (7) |
| BP (highest) systolic diastolic | 157 \pm 22 90 \pm 13 | |
| HR (highest) | 137 \pm 27 | |

One year Functional Outcome



Side-Effects

| Side Effect | Number of subjects | Mean \pm SD | Frequency (%) |
|---|--------------------|---------------|---------------|
| Prolonged seizure: Yes Mean number of prolonged seizures | 54 40 | 4.1 \pm 2.6 | 40(74) |
| Head ache | 52 | | 40 (77) |
| Fatigue | 52 | | 32 (62) |
| Subjective memory impairment | 50 | | 33 (60) |
| Confusion | 52 | | 21(40) |
| Nausea | 52 | | 19(37) |
| Muscle pain | 52 | | 14 (27) |
| Dizziness | 52 | | 11 (21) |
| Jaw pain | 52 | | 11 (21) |
| Vomiting | 52 | | 8 (15) |

Overall Improvement Rate (response + remission) and Side Effects

In a highly treatment resistant group,
53% response/ 15% remission after 4-5 weeks of
index course

82% response and 23.5% remission after 1 year

Headache was the main SE; other minor SE
noted on day of Tx

Follow up study of patients treated with ECT prior to age 18; Mitchell et al

- **OBJECTIVES:** examine current symptoms, attitudes, perception and functioning of patients treated with ECT when they were less than 18 years old from 1989 to 2015
- **RESULTS:** Based on self-rated scale, participants reported
 - 59.1% (n=13/22) participants indicated mild or no depression;
 - 65% (n=13/20) mild or no anxiety; the majority
 - 84.3% (n=16/19) perceived ECT as having improved overall illness
 - 27.3% (n= 6/22) reported no clinical impairment on a global functioning scale,
(83.3%, n=5/6) adequate academic performance
 - (78.3%, n=18/23) mild or no suicidality were endorsed by the majority reported.
- **CONCLUSIONS:** The majority reported mild or absent depression or anxiety. Most notably, a majority reported absence of suicidality and adequate academic performance.

UL vs. BL electrode placement

- Earlier studies found BL associated with more confusion and memory loss
- Current thinking is that UL treatment is only effective when suprathreshold electrical charge is used
- Suprathreshold implies 5 to 6 X of charge that would be necessary to induce a seizure
- At this dose, there is almost no difference in memory loss
- BL is also more predictable (less second guessing about optimum charge) and faster
- BL is highly recommended in serious/life-threatening conditions
- No current data in adolescents using ultra brief pulse UL

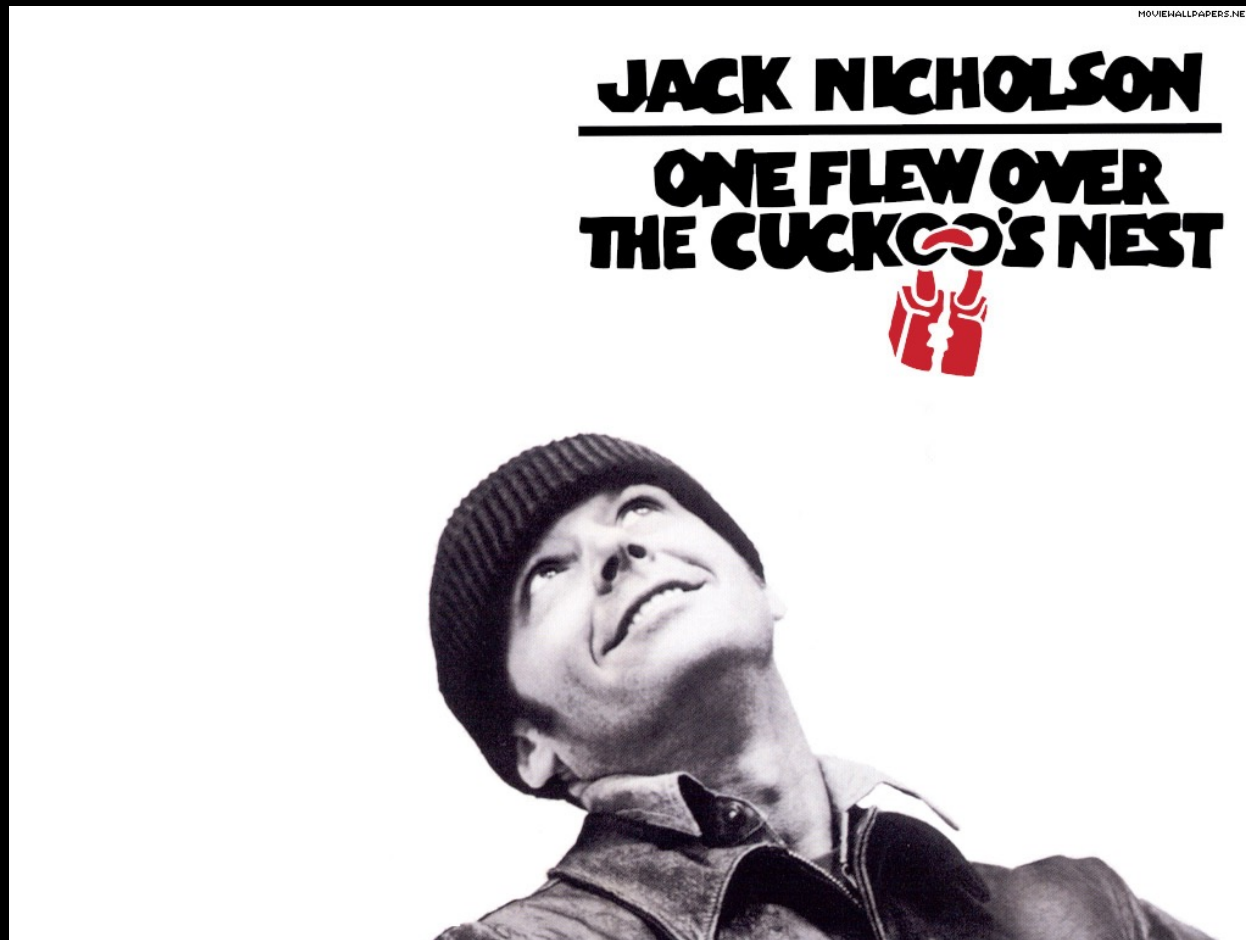
Fear of ECT

Fear of brain damage
Fear of loss of cognition
“cruel”, “inhumane”
Attitudes
Misinformation
Lack of training

Misinformation



Milos Forman's Vision of ECT;
negatively portrayal in most movies



Do repeated convulsions cause brain damage???

- No morphological deficit noted including imaging
- No neuronal changes on post-mortem examinations
- No evidence of glial damage or BBB dysfunction was observed
- No changes in serum neuron specific enolase (NSE; sensitive indicator of neuronal damage noted stroke, HI)

Cognitive Deficit and Amnesia

- Side-effects are common and mostly minor; individual variability
- Most patients experience almost full recovery
- Both anterograde amnesia (AA; new learning) and retrograde amnesia(RA).
- The AA is time limited to about 4 weeks. *Lisanby et al.*
- RA usually persists for months and some degree of RA is permanent
- RA involves mundane events, impersonal memories
- From a clinical perspective, the most significant cognitive side effect of ECT is RA for *autobiographical events*.
- **NMDA** receptor activation following seizures may be related to cognitive effects of ECT.
Theoretical benefit of Ketamine
- **Opioid** receptors and possible protective role of naloxone
- **Glutamate** system and possible protective effect of n-methyl-d-aspartate receptor agonists

Electroconvulsive Therapy In Adolescents: Experience, Knowledge, and Attitudes of recipients. *Walter et al 1999*

The results suggest that youth have a positive attitudes towards convulsive therapy.

Strikingly, vast majority of patients believed that illness was worse than its treatment. (ECT or pharmacotherapy).

3 expressed negative views.

Three quarters would recommended it to family members or friends.

88% of respondents regarded ECT as a legitimate treatment.

8% believed it should be outlawed.

Attitudes and Knowledge about ECT

- Overall inadequate knowledge of ECT among child and adolescent psychiatrists
- Germany: “urgent need” for education (Wilhelmy et al. 2018)
- Belgium: n= 151, 1% reported advanced knowledge of ECT among child and adolescent psychiatrists (De Meulenaere et al. 2018)
- USA: n = 625, 54 % stated minimal knowledge and 75% lack of confidence about providing second opinion among child psychiatrist and psychologists (Ghaziuddin et al. 2001)

Final points

- ***Safety***

- *Death in 1 of 10,000 patients or 1 per 80,000 treatments*
- *No fatalities reported among adolescents*
- *Can be used in patients with serious medical disorders*
- *Improved safety due to anesthesia*

Efficacy

- *Highly effective in 65 to 100%*
- *Our data found 82 % response rate in mood disorders*

Concern for brain damage

- *No scientific evidence*
- *Seizure must continue for hours before brain damage can occur*
- *Energy used is too small to cause electrical injury*
- *No evidence of lasting cognitive deficits in any age group*

Mechanism of action

- *Multiple underlying processes; most likely brain plasticity and gene expression*

Portrayal

- *Inaccurate portrayal as painful, for control or punishment*
- *Patient self reports are positive*

Lessons

- Treat conditions known to respond
- Use if recurrence especially in past responders
- Treat until sustained response; no value in a pre-determined number
- Use continuation ECT (< 6 months) and/or maintenance Tx (beyond 6 months)
- Individualize frequency, dosing and stimulus parameters
- Use BL-ECT
- ***“Not all ECT is equal” (electrode, seizure duration, point in Tx, medications)***



Drawbacks of ECT

- Anesthesia
- Repeated treatment is essential
- Inconvenience
- Side effects, although temporary

Future Directions

- Prospective trials
- Training all MH providers
- Hands on training for CAP
- **Counteract myths:**
 - “Painful/ inhumane”
 - “Tx of last resort”
 - “Brain damage”
 - “Irreversible memory loss”
 - “Psychological damage to adolescent”

Take home message

- Irrespective of age, ECT is an important, life-saving treatment
- Mental health providers have a responsibility to be knowledgeable and arrange referral when necessary

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