TEXAS SOCIETY OF CHILD AND ADOLESCENT PSYCHIATRY · JOINT PROVIDERSHIP CME

Clinical and Neurobiological Advances in Ketamine and ECT

Evidence, Guidelines, and Shared Decision-Making for Severe, Treatment-Resistant Psychiatric Disorders in Children and Adolescents

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DISCLOSURE · 2024–2025–2026

Conflict of Interest

João L. de Quevedo, MD, PhD · *Executive Director, Center for Interventional Psychiatry* · *John S. Dunn Behavioral Sciences Center at UTHealth Houston*

01

Paid to UTHealth Houston

Institutional support

CLINICAL RESEARCH SUPPORT · INDUSTRY

LivaNova · Neumora Therapeutics · Johnson & Johnson · Alto Neuroscience · Compass Pathways

CLINICAL RESEARCH SUPPORT · NON-INDUSTRY

Brigham and Women's Hospital · John S. Dunn Foundation · National Network of Depression Centers

02

Paid Directly to Dr. de Quevedo

Personal payments

CONSULTING

LivaNova · Libbs

SPEAKER / HONORARIA

Intra-Cellular Therapies · EMS · Libbs · Johnson & Johnson · Viatris

ROYALTIES

Grupo A/Artmed · Elsevier/Academic Press

All relationships have been reviewed and mitigated in accordance with ACCME guidelines. This presentation reflects independent clinical and scientific judgment.

WHAT YOU WILL TAKE AWAY

Learning Objectives

Apply the evidence

01

Use current evidence and consensus guidelines for ketamine and ECT in youth with severe, treatment-resistant psychiatric disorders.

Decide with families

02

Integrate developmental and family-centered considerations into shared decision-making for somatic treatments in pediatric populations.

Compare the options

03

Contrast ketamine and ECT on speed of response, durability, safety, and clinical appropriateness in pediatric practice.

Look ahead

04

Discuss emerging research, regulatory considerations, and future directions for somatic treatments in pediatric psychiatry.

WHERE WE ARE GOING

Roadmap

01

Neurobiological Advances

How ketamine and ECT converge on neuroplasticity

02

Ketamine C Esketamine in Youth

Trials, regulatory status, safety

03

ECT in Youth

Indications, efficacy, cognition

04

Comparison C Decision-Making

Matched care, family-centered choices

05

Regulation C Future Directions

Texas law, AACAP policy, what's next

WHY THIS MATTERS

The Clinical Problem in Youth

The unmet need

2nd–3rd

Leading cause of death among U.S. adolescents is suicide

≈ 40%

of adolescents with major depression do not remit with standard care (treatment-resistant)

2 drugs

Only fluoxetine (all ages) & escitalopram (≥12 y) are FDA-approved antidepressants in youth

Severe, refractory illness can't wait

Conventional antidepressants take 4–6 weeks to act and often fail. In acute suicidality, catatonia, refusal to eat or drink, and psychotic depression, the speed of response is itself a safety outcome — driving inpatient stays, morbidity, and risk.

Two rapid-acting, plasticity-based tools

Ketamine / esketamine and ECT both produce rapid antidepressant and anti-suicidal effects by engaging neuroplasticity — not the monoamine system. Both have a growing pediatric evidence base, and both raise distinct developmental, safety, and regulatory questions we will work through today.

CDC WISQARS youth mortality data; Pardossi et al., 2024; pediatric antidepressant labeling (FDA).

01

SECTION ONE

Neurobiological Advances

From the monoamine era to plasticity-based, rapid-acting treatment

A PARADIGM SHIFT

Beyond Monoamines: The Plasticity Hypothesis

The old model and its ceiling

Monoamine hypothesis: SSRIs/SNRIs raise serotonin and norepinephrine, but clinical benefit emerges over weeks.

Chronic stress and depression are associated with

synaptic loss and dendritic atrophy in the prefrontal cortex and hippocampus.

In severe, treatment-resistant youth, this slow ceiling is a clinical and safety problem.

The plasticity model

Rapid-acting treatments work by **restoring synaptic connectivity** — promoting synaptogenesis, dendritic spine growth, and neurotrophic signaling (BDNF–TrkB).

Ketamine and ECT both engage this final common pathway, which explains their speed and their distinct side-effect profiles.

This reframes them not as “last resort,” but as mechanism-driven interventions for the refractory, acutely ill patient.

Duman et al., 2016; Kadriu et al., 2019; Krystal et al., 2024 (review).

MECHANISM · PHARMACOLOGIC ROUTE

How Ketamine Works: The Glutamate Cascade

NMDA-R blockade

Blocks NMDA receptors on GABAergic interneurons (NR2B-rich)

→

Disinhibition

Pyramidal neurons released from inhibition → burst firing

→

Glutamate surge

Transient prefrontal glutamate release activates AMPA receptors

→

BDNF →TrkB →mTORC1

Neurotrophic & protein-synthesis signaling switched on

→

Synaptogenesis

New dendritic spines & restored connectivity → rapid antidepressant effect

Why it is fast — and what it means clinically

Antidepressant and **anti-suicidal** effects can appear within hours and persist for days after a single subanesthetic dose.

A parallel "at-rest" pathway (eEF2 kinase inhibition → BDNF translation) sustains plasticity beyond the acute glutamate surge.

Active metabolites and AMPA throughput — not simple NMDA blockade alone — carry the durable effect.

Hours, not weeks

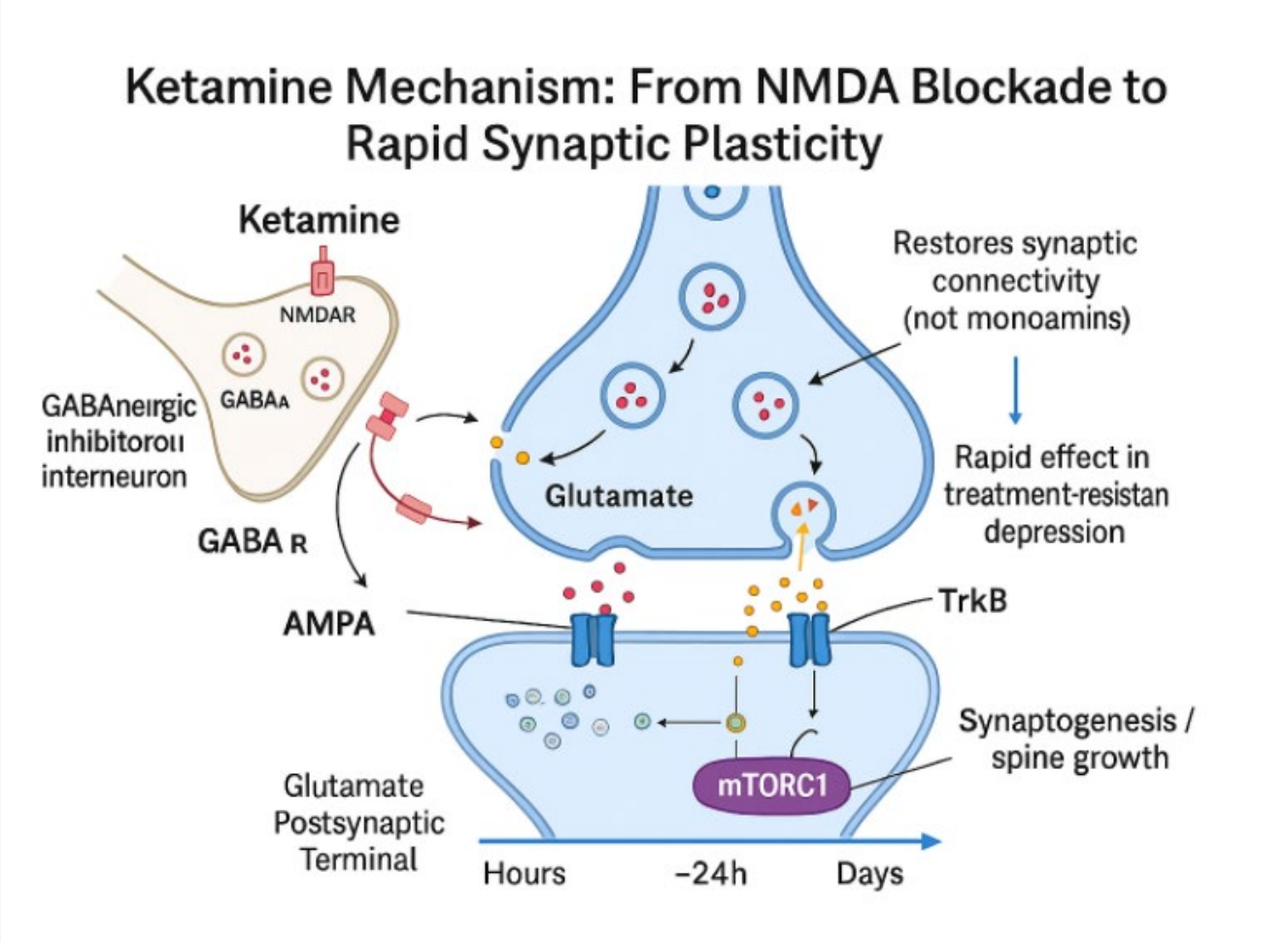
Onset: hours after one dose

Peak: ~24 hours

Single-dose effect: days → repeated dosing extends benefit

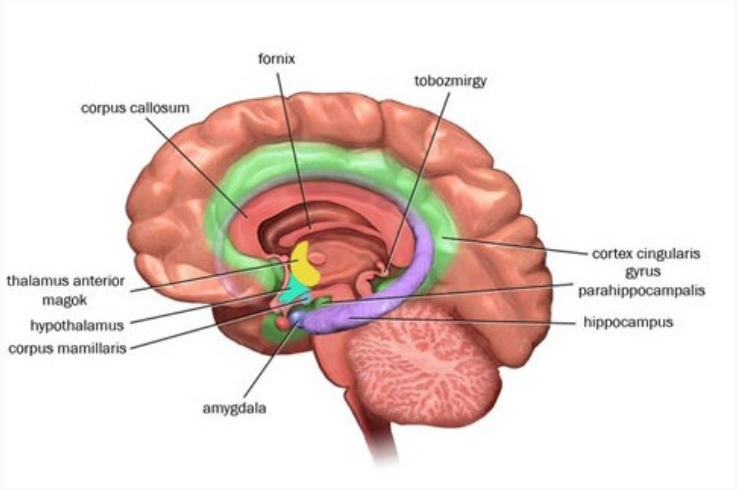
Kadriu et al., 2019; Duman et al., 2016; Beyond NMDA Receptors review, 2024.

From NMDA Blockade to New Synapses



Glutamatergic model of rapid antidepressant action (Kadriu et al., 2019; Duman et al., 2016). Schematic — not to scale. Duman RS, Aghajanian GK. *Synaptic dysfunction in depression: potential therapeutic targets.* Science. 2012;338(6103):68–72.

How ECT Works: Seizure-Driven Neuroplasticity



● Hippocampus ● Amygdala

Dose-dependent gray-matter increase, most pronounced in the dentate gyrus

Neurotrophic / neurogenesis

Seizures upregulate BDNF & VEGF and stimulate dentate-gyrus neurogenesis — synaptic remodeling and circuit reorganization.

Structural plasticity

MRI shows reversible, dose-dependent volume increases in hippocampus & amygdala (GEMRIC collaboration).

Anticonvulsant hypothesis

Rising seizure threshold across a course parallels clinical response — enhanced inhibitory (GABAergic) tone.

Connectivity normalization

Restores fronto-limbic network function disrupted in severe depression.

Abe et al., 2024; Oltedal et al., 2018 (GEMRIC); Frontiers Psychiatry review, 2025.

THE UNIFYING IDEA

Two Routes, One Destination: Neuroplasticity

Ketamine / Esketamine

NMDA antagonism → glutamate surge → AMPA
* BDNF/mTOR

Electroconvulsive Therapy

Generalized seizure → BDNF/VEGF → neurogenesis → remodeling

Enhanced Neuroplasticity

↑ BDNF–TrkB · synaptogenesis · fronto-limbic circuit remodeling

Rapid, robust response

Onset in hours–days, including anti-suicidal effects in severe illness

Developmental caveat. The adolescent brain is still myelinating and pruning. The same plasticity that drives benefit warrants careful attention to dose, frequency, and long-term neurocognitive follow-up — a recurring theme in the pediatric evidence.

02

SECTION TWO

Ketamine C Esketamine in Youth

Pharmacology, regulatory status, and the controlled-trial evidence

Forms, Pharmacology C Regulatory Status

Racemic ketamine (IV)

Subanesthetic 0.5 mg/kg over 40 min. Used off-label for depression; not FDA-approved for depression at any age.

Esketamine (intranasal)

S-enantiomer nasal spray. FDA-approved in adults for TRD and for MDD with acute suicidal ideation/behavior — not for patients under 18.

IV esketamine (investigational)

Studied in adolescent trials (0.25 mg/kg). Not a marketed pediatric product.

The regulatory reality in youth

No ketamine or esketamine product is FDA-approved to treat depression in anyone under 18.

All pediatric use is off-label, raising heightened responsibility to weigh available safety data and document informed consent/assent.

AACAP Psychopharmacology Committee

Advises extreme caution: controlled pediatric data remain limited. Esketamine is explicitly not indicated for pediatric patients, and IV ketamine for depression is unapproved at every age. Use within experienced, monitored settings.

FDA labeling (esketamine); AACAP Psychopharmacology Committee statement on ketamine.

Landmark Adolescent RCT (Dwyer et al., 2021)

Design

- Randomized, double-blind, midazolam-controlled crossover (active placebo)
- 17 adolescents, ages 13–17, with major depression
- Single IV ketamine 0.5 mg/kg vs midazolam, crossover at 2 weeks
- Highly refractory: ~3.2 prior failed treatments; mean episode ~21 months
- Primary outcome: MADRS at 24 hours

Results

Day 1

Significant MADRS reduction at 24 h vs midazolam

2 wks

Separation from placebo sustained across the full 2-week window

Rapid anti-depressant signal in a highly treatment-resistant adolescent sample.
Durability beyond a single adult dose — adult effects typically fade by 7–10 days; here separation held for 2 weeks.
Proof-of-concept: small sample, single dose — establishes a signal, not a protocol. Larger repeat-dose trials (e.g., for adolescent suicidality) are underway.

Dwyer JB et al. Am J Psychiatry, 2021; Lineham et al., 2024 (response predictors).

Esketamine in Adolescents: Two Controlled Trials

IV esketamine for MDD + suicidal ideation

Guangzhou randomized active-placebo trial (JAACAP, 2023)

- 54 adolescents (13–18), inpatient; 3 infusions of esketamine 0.25 mg/kg vs midazolam over 5 days
- Greater reduction in suicidal ideation (C-SSRS) and depressive symptoms vs placebo
- Well tolerated: nausea, transient dissociation, dry mouth, sedation, headache, dizziness
- Companion cognition study: no harm to cognition; processing speed improved

Esketamine nasal spray at imminent suicide risk

Phase 2b RCT (Kosik-Gonzalez et al., JAACAP, 2025)

- 147 adolescents (12–<18) at imminent suicide risk; nasal esketamine (28/56/84 mg) vs midazolam, twice weekly × 4 weeks, plus full standard of care
- Pooled 56 + 84 mg superior to placebo on depressive symptoms at 24 hours
- All groups improved on suicidality over 4 weeks (with hospitalization + therapy)
- AEs: dizziness, nausea, dissociation, headache, bitter taste, sleepiness

Guangzhou trial, JAACAP 2023; Kosik-Gonzalez et al., JAACAP 2025; MCCB cognition RCT, 2023.

Ketamine Safety C Tolerability in Youth

Acute, transient effects

Dissociation, transient blood-pressure & heart-rate rise, nausea, dizziness, sedation — typically resolve within the monitoring window.

Abuse C diversion potential

Schedule III; misuse risk warrants controlled administration, REMS-style monitoring for nasal spray, and no take-home dosing.

Unknowns to monitor

Long-term effects of repeated dosing on the developing brain, and urinary/bladder toxicity with chronic use, are not yet characterized in youth.

Risk mitigation

Cardiovascular & dissociation monitoring, trained staff, hemodynamic precautions; contraindicated with aneurysm/AVM or prior intracerebral hemorrhage.

FDA esketamine labeling & REMS; AACAP statement; pediatric trial safety data.

RESEARCH OPPORTUNITY

Now Enrolling: Adolescent Esketamine Study

About the study

A clinical research study evaluating intranasal esketamine for adolescents with treatment-resistant depression.

Study / NCT: *[add study name / NCT number]*

WHO MAY QUALIFY

- Adolescents [ages 12–17] with major depressive disorder
- Inadequate response to [≥ prior antidepressant treatment(s)]
- No active psychosis; additional study criteria apply
- Supervised visits, assessments & monitoring; compensation may be available

Scan to learn more or refer

[replace QR with study link]

Center for Interventional Psychiatry
Phone: [(713) 000-0000]
Email: [studyteam@uth.tmc.edu]

Investigational use in adolescents is research only. Replace bracketed fields with current study details before presenting.

03

SECTION THREE

ECT in Youth

An 80-year-old treatment with modern technique and a real pediatric evidence base

WHEN TO CONSIDER IT

ECT Indications C Eligibility in Youth

Evidence-based indications

Severe MDD / bipolar depression

Treatment-resistant or needing rapid, definitive response

Catatonia

Including malignant catatonia & neuroleptic malignant syndrome

Acute suicidality

Refusal to eat/drink; life-threatening deterioration

Psychotic C manic features

Severe affective episodes with psychosis; treatment-resistant mania

AACAP eligibility: three criteria

1. **Diagnosis** — A condition for which ECT is an accepted, evidence-based indication
2. **Severity** — Persistent, severe, and life-threatening or functionally disabling symptoms
3. **Treatment resistance** — Lack of response to adequate trials of appropriate pharmacotherapy and other modalities

Devices are labeled for catatonia or severe MDD/bipolar depression in patients aged ≥ 13.

AACAP Practice Parameter for ECT with Adolescents; FDA device labeling (≥ 13 y).

ECT Efficacy in Adolescents

78%

Response in a prospective bifrontal-ECT cohort of adolescents with MDD + suicidal ideation (Hu et al., 2025)

≈ 40–56%

Response rates in adolescents/young adults across multicenter chart-review series

85–100%

Remission in classic adolescent series for bipolar/psychotic depression & mania

What the evidence base looks like

Effectiveness in youth is **comparable to adults** despite higher rates of comorbidity (autism spectrum, anxiety, personality features).
Data are mostly retrospective / prospective cohorts — **no pediatric RCTs yet**; affective disorders and catatonia respond best.

Speed where it counts

In catatonia and severe affective states, meaningful stabilization often occurs within the first few sessions — a decisive advantage in emergencies.

Hu et al., 2025; multicenter chart review, J ECT 2024; Walter & Rey, 1997.

Catatonia C Psychiatric Emergencies

Treatment pathway for catatonia in youth

First line Benzodiazepine (lorazepam) challenge → **Definitive rescue** ECT for malignant or medication-resistant catatonia → **Often life-saving** Rapid stabilization when deterioration is imminent

Where ECT is first-line

- **Malignant catatonia**
- **Neuroleptic malignant syndrome (NMS)**
- Manic delirium / excited states unresponsive to medication
- Severe affective catatonia — recommended regardless of underlying etiology

Evidence note

Catatonia is infrequent but among the most severe syndromes in youth. ECT is well supported as effective and safe, though most data derive from case series and retrospective studies; standardized head-to-head benzodiazepine-vs-ECT protocols are lacking. In emergencies, delaying definitive treatment is itself a risk.

Armas-Neira et al., 2026; Rogers et al., 2023 (BAP catatonia guidelines).

EVIDENCE GAP · FROM OUR GROUP

Closing the Evidence Gap in Catatonia

The gap

Lorazepam (benzodiazepine) challenge is first-line and ECT is the definitive rescue for catatonia — yet this rests largely on **observational evidence**. There are
no randomized head-to-head trials comparing benzodiazepines and ECT, leaving sequencing and refractory care guided by experience.

The call

- Comparative, randomized trials of benzodiazepines vs ECT
- Evidence to guide first-line choice and optimal sequencing
- Clearer pathways for malignant / refractory catatonia
- Especially urgent in youth, where data are thinnest

Armas-Neira M, Scaini G, Shahani L, Quevedo J. *Closing the Evidence Gap in Catatonia: A Call for Comparative Trials of Benzodiazepines and ECT.* J ECT. 2026 (online ahead of print). PMID 41557581.

From the Center for Interventional Psychiatry, UTHealth Houston · doi:10.1097/YCT.0000000000001215

ECT Safety C Cognition in Youth

Transient memory effects

Mild, transient decline in verbal & spatial memory immediately post-treatment.

Rapid recovery

Typically full recovery within ~2 weeks; no prolonged impairment seen at 4-month follow-up.

Function can improve

Working memory, attention & executive function often improve from baseline as depression lifts.

Modern technique mitigates

Right-unilateral, ultra-brief pulse reduces cognitive effects without sacrificing efficacy.

Medical risk: comparable to brief general anesthesia; transient hypertension, arrhythmia, headache, muscle soreness are most common. Recent intracranial mass with edema is an absolute contraindication.

Hu et al., 2025 (adolescent cognition); Sackeim, 2021; Tørring et al., 2025.

04

SECTION FOUR

Comparison C Shared Decision-Making

Speed, durability, safety, appropriateness — and how families choose

Ketamine vs ECT: What the Trials Show

ELEKT-D (Anand et al., NEJM 2023)

Largest head-to-head trial: nonpsychotic treatment-resistant depression in adults (open-label, randomized, noninferiority).

55% vs 41%

Response: ketamine vs ECT (ketamine noninferior)

Memory

ECT showed greater short-term memory impact

Bottom line: in nonpsychotic adult TRD, ketamine was noninferior to ECT for response — but ECT may reduce severe symptoms faster and is preferred when psychosis is present.

Read with care

A corrected analysis clarified that ECT may be superior for acute-phase symptom severity, while response and remission did not differ significantly. ECT remains favored for psychotic depression, catatonia, and the most acutely ill.

Translating to pediatric practice

No head-to-head pediatric trial exists. Adult comparative data inform — but do not dictate — youth decisions, which must also weigh the developing brain, FDA/age restrictions, and family preference. Choice is individualized, not formulaic.

Anand et al., NEJM 2023; Jha et al., JAMA Netw Open 2024 (secondary analysis & correction).

AT A GLANCE

Ketamine vs ECT in Pediatric Practice

	KETAMINE / ESKETAMINE	ECT
Speed of response	Hours to days after dosing	Days; meaningful gains often within first sessions
Durability	Single dose fades in days; repeat/maintenance dosing needed	Robust acute course; maintenance ECT sustains remission
Best-fit indications	MDD + suicidal ideation; nonpsychotic TRD	Catatonia, NMS, psychotic/severe affective illness, emergencies
Safety / cognition	Dissociation, transient ↑BP; abuse potential; bladder/long-term unknowns	Transient memory effects, recover ~2 wks; anesthesia-level medical risk
Setting	Monitored clinic/infusion suite; nasal spray under REMS	Requires anesthesia & recovery; inpatient or specialized outpatient
Regulatory (youth)	**Off-label all ages; esketamine not approved < 18**	**FDA device labeling ≥ 13 y; restricted by some state laws**
Evidence base	Small RCTs + phase 2b in adolescents	Cohorts/case series; no pediatric RCT yet

Synthesis of cited adolescent and adult trials; FDA labeling; AACAP guidance.

Developmental C Family-Centered Decisions

Assent + consent

Pair developmentally appropriate assent from the young person with informed parental/guardian consent; revisit as the patient matures.

Family as partner

Engage caregivers in goals, expectations, and monitoring; address their fears directly and without judgment.

Counter stigma C myths

Replace media-driven fears of ECT and “drug” fears of ketamine with factual, balanced information.

Set realistic expectations

Be honest about response rates, the need for repeat/maintenance treatment, and side-effect profiles.

Weigh risks of NOT treating

Frame the real risks of ongoing severe illness — suicide, hospitalization, lost development — alongside treatment risks.

Document the conversation

Record alternatives discussed, benefits, risks, and the shared decision in the medical record.

AACAP shared decision-making principles; informed consent/assent standards.

Matched Care: Where Each Fits

Consider KETAMINE / esketamine when…

- Nonpsychotic MDD with acute suicidal ideation
- Rapid response needed and ECT not available/declined
- Family prefers to avoid anesthesia
- Adolescent in a monitored, experienced program

Consider ECT when…

- Catatonia, NMS, or psychotic depression
- Life-threatening urgency (refusal to eat/drink)
- Failure of or intolerance to other options
- Durable maintenance is the goal

Shared principles

- Confirm true treatment resistance first
- Offer earlier in course for severe illness
- Match intensity to severity & setting
- Re-assess and individualize continuously

05

SECTION FIVE

Regulatory Landscape C Future Directions

Policy, access, and the research agenda — with Texas in focus

The Regulatory Picture in Youth

Esketamine (nasal)

FDA-approved for adults only (TRD; MDD with acute suicidality). Not approved < 18 y; delivered under a REMS program.

IV / IM ketamine

Off-label at all ages. Use rests on clinician judgment, informed consent, and a monitored setting.

ECT device labeling

FDA labels devices for patients ≥ 13 y with catatonia or severe MDD / bipolar depression.

State laws vary

Some states restrict or ban pediatric ECT. Texas prohibits ECT under age 16 — stricter than FDA labeling.

AACAP Policy Statement

On ECT in youth · Feb 2025

1. **Ensure access** Adolescents who meet criteria should have access to ECT when clinically indicated.
2. **Oppose blanket bans** Strongly opposes legislative or legal restrictions that block appropriate care.
3. **Fund research** Supports dedicated funding to expand the pediatric evidence base.

FDA device labeling; AACAP Policy Statement on ECT (2025); Texas Health & Safety Code § 578.

CLOSE TO HOME

The Texas Access Gap — and Our Role

A stricter line than the FDA draws

Texas is one of a small number of states that **prohibit ECT for patients under age 16** — a threshold stricter than FDA device labeling (≥ 13 y) and at odds with AACAP guidance.

For a young child with malignant catatonia or life-threatening depression, this can mean

delayed care or out-of-state transfer at the worst possible moment.

Galveston and the Texas Gulf Coast sit within an academic corridor — UTMB here in Galveston and UTHealth Houston nearby — well positioned to deliver and study these treatments safely.

What clinicians can do

- Know your state statute and document medical necessity carefully
- Build referral pathways to experienced pediatric ECT and ketamine programs
- Educate families and colleagues to counter stigma with evidence
- Engage professional societies (AACAP, TSCAP) on policy and access
- Contribute cases to registries to strengthen the evidence base

Texas Health & Safety Code § 578.002; AACAP Policy Statement on ECT (2025).

Future Directions in Pediatric Somatic Treatment

Next-gen ketamine

Arketamine (R-ketamine) and oral/extended-release formulations aiming for efficacy with less dissociation and abuse potential.

Biomarkers of response

EEG, inflammatory, and neuroimaging markers to predict who responds and to personalize selection.

Maintenance protocols

Optimal dosing intervals and taper strategies to sustain remission while minimizing exposure.

Pediatric RCTs

Adequately powered, developmentally tailored trials — especially head-to-head ketamine vs ECT in youth.

Refined ECT technique

Ultra-brief pulse, electrode placement, and magnetic seizure therapy to preserve cognition.

Funding C registries

Dedicated research funding and multi-site registries to build evidence and inform policy.

Emerging-therapy reviews; ongoing trial registries; AACAP research-priority statements.

BRINGING IT TOGETHER

Key Takeaways

01

The evidence is real but uneven Adolescent ketamine RCTs and a phase 2b esketamine trial exist; ECT rests on consistent cohorts and decades of experience — but pediatric RCTs are still lacking.

02

Decisions are developmental and family-centered Pair assent with consent, partner with caregivers, counter stigma, and weigh the real risks of not treating severe illness.

03

Match the tool to the clinical picture Ketamine for rapid relief of nonpsychotic depression with suicidality; ECT for catatonia, psychosis, and the most severe, with durable maintenance.

04

Advocate, and advance the science Address the Texas access gap, support balanced policy, and push for the pediatric trials and biomarkers the field needs.

CONNECT WITH US

Refer a Patient to Our Center

Center for Interventional Psychiatry

WHAT WE OFFER

Electroconvulsive therapy (ECT) · ketamine / esketamine · TMS · clinical trials · interventional psychiatry consultation

WHO TO REFER

- Treatment-resistant depression (failed ≥ 2 adequate trials)
- Catatonia; severe or urgent mood episodes
- Patients who may be candidates for an interventional treatment or trial

Scan to refer

[replace QR with referral link]

How to refer

Phone: [(713) 000-0000]
Fax: [(713) 000-0000]
Epic referral: Center for Interventional Psychiatry

UTHealth Houston · Texas Medical Center. Replace bracketed contact fields with current referral details.

DISCUSSION

Thank You

Questions & discussion welcome

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