Brigham and Women's Hospital
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Innovations in Psychiatric Treatment - 2024

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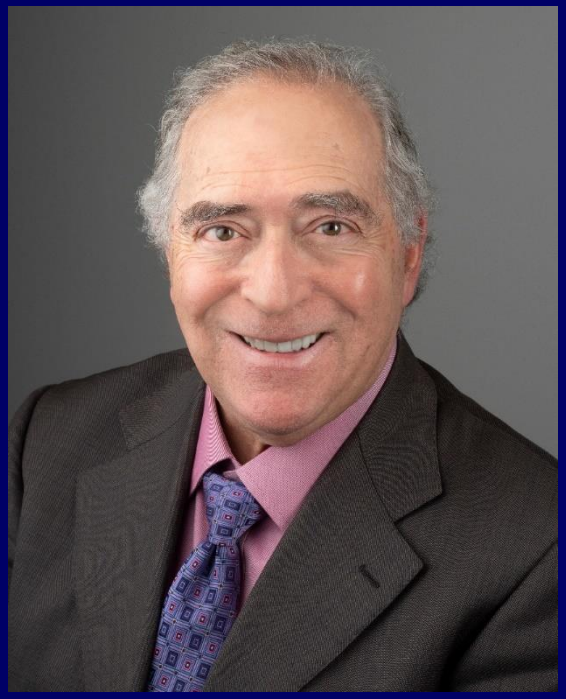

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Brexanolone in Postpartum Depression

- Minimum HRSD of 26
- Onset depression 3rd trimester or one month postpartum
- 60 hour infusion 90 or 60 ug/kg per hour
- Follow-up 30 days
- HRSD assessed at 60 hours
- Significant reduction compared to placebo
- Side-effects - headache, dizziness, sudden loss of consciousness. Continuous pulse oximetry is required
- No evidence for greater efficacy than SSRI or other antidepressant.
- REMS program required for treatment .
  - Meltzer-Brody et al. 2018 Lancet 392:1058-1070

Ketamine and Esketamine

- Single IV infusion of ketamine has antidepressant effect; may also have dissociative effects. Not FDA approved
- Abused for hallucinogenic effects for years.
- Esketamine- FDA approved for intranasal use in addition to oral antidepressants, has been more effective than placebo in inducing remission of depression.
- Administered under direct supervision, sedation and dissociation risks. Must monitor patients for 2 hours after administration. REMS program
- Schedule III controlled substance.

Ketamine – Antidepressant Efficacy

- Reduction in symptoms of depression 24 hours after single intravenous infusion in TRD.
- Supports glutamate receptor antagonists as rapid acting alternative in treatment of MDD.
- Safety and response durability are concerns.
- Therapeutic response not significant after 7 days.
- Safety concerns and abuse potential limit clinical application at present.

Ketamine –Clinical Issues

- Effects on blood pressure and heart rate
- Induction of dissociated states
- Psychotomimetic experiences
- Potential for abuse
- Majority of the literature focuses on treatment resistant depression (variably defined)
- Most trials exclude Bipolar Depression
  - Sanacora et al. JAMA Psychiatry 2017

Remaining Problems with Ketamine Infusion

- No universally established optimal dosing
- Routes of administration are being explored (intravenous, intranasal)
- No specific indication for major depression
- Outside of registered clinical trials, no mechanism to report outcomes and poorly regulated prescribing guidelines
- Potential for dependence and abuse
- Monitoring of medical issues a concern
  - Wilkinson et al AJP 2017

Intranasal Esketamine for TRD

- 28- 84 mg intranasal each nostril
- Twice weekly self-administered for first week; once weekly for first month, then q o wk for one month; flexible dosing thereafter
- Treatment through approved centers;REMS monitoring
- Side-effects; Sedation, dissociation, elevated BP, Suicidal ideation, Urinary symptoms; no driving for 24 hours

Intranasal Esketamine and newly initiated antidepressant in TRD

- 56 or 84 mg twice weekly intranasal for 4 weeks in combination with new SSRI or SNRI treatment
- MADRS scores demonstrate mildly positive results at 1 days and 28 days
- TRD patients with no psychiatric comorbidities or substance abuse, no acute suicide risk.
  - Popova et al. AJP 2019 176:428-438

Ketamine and treatment of suicidal ideation

- 80 adults on antidepressants treated adjunctively with ketamine infusion with midazolam as control.
- Ketamine demonstrated a reduction in suicidal ideation within 24 hours as compared to midazolam.
- The reduction in suicidal ideation lasted up to 6 weeks.
- Patients continued on their antidepressant medication.
- Meta-analysis suggests effect in most studies begins at day 1 and lasts up to 1 week.
- Effect on reduction in suicidal ideation appears to be present in non-depressed diagnoses as well as MDD.
  - Wilkinson et al. AJP 2017
  - Grunebaum et al AJP 2017

Studies on Long Term Efficacy of Ketamine and Novel modes of administration

- Intranasal ketamine as adjunctive to antidepressant treatment.
- Antidepressant effect persisted for up to two months after cessation of treatment.
- Antidepressant efficacy began at 1 week post-treatment.
- Studies of long-term treatment with iv ketamine are underway in TRD
- Study of subcutaneous ketamine in patients over age 60 (0.2-0.5 mg/kg improved remission rates and reduced relapse.
  - Daly et al. JAMA Psychiatry 2017
  - Kwon et al. J. Clin PharmTher 2018

Opioid Receptor Antagonism Blunts Antidepressant Effects of Ketamine

- Placebo or 50 mg of naltrexone preceding intravenous infusion of 0.5 mg/kg of ketamine
- Response defined by 17-item HRSD
- Naltrexone blocked the antidepressant effect of ketamine, but not the dissociative effect
- Could ketamine effect require both opioid and NMDA receptor activation?
  - Williams et al. Am J Psychiatry 2018;175:1205-1215

Remaining problems with Ketamine Treatment

- How long and how often to maintain infusion or intranasal treatment ?
- Risk of adverse effects including increase in suicidal ideation on withdrawal.
- High rates of relapse 3-4 months after off Ketamine
- Addictive potential and potential for serious adverse side effects
- How strong is efficacy data?
  - Schatzberg, AJP 176:6 June 2019

Recent studies of intranasal ketamine in treatment resistant depression

- Review of four phase three studies suggests efficacy of intranasal ketamine infusion with co-administered oral antidepressant. Three times as likely to induce remission than be discontinued due to side-effects.
- Another study of intranasal ketamine in elderly patients with TRD did not establish significant results; but positive trends seen in those 65-74 and with onset depression before 55 years.
  - Citrone et al. Journal Affective Disorders 27 (2020) 228-238. Ochs-Ross Am J Geriatric Pych 28:2 (2020)
  - 121-141

Ketamine -Consensus Statement -2021

- Rapid-onset action 1-2 days for intranasal and IV infusion
- Intranasal safety, efficacy, and tolerability for up to one year
- Evidence for long-term efficacy insufficient
- Safety concerns- dissociation, neuro/cognitive,genitourinary, hemodynamic
- No proven effect on reducing suicide completion
- Administer in multidisciplinary settings (REMS program)
  - McIntyre et al AJP 2021; 178:383-399

Dextromethorphan/Bupropion for Depression

- Dextromethorphan 45 mg/ Bupropion 105 mg
- Dextromethorphan is an NMDA receptor antagonist and sigma-1 receptor agonist; it also inhibits serotonin and norepinephrine reuptake.
- Bupropion increases serum concentration of dextromethorphan by inhibiting CYP2D6
- Bupropion inhibits norepinephrine and dopamine reuptake
- Intranasal esketamine is also an NMDA receptor antagonist
- Esketamine and the S-enantiomer of the IV anesthetic Ketamine are also NMDA receptor antagonists

Dextromethorphan/Bupropion for Depression

- Double blind phase 3 study, 80 patients with MDD randomized to 6 weeks of treatment with dextromethorphan 45 mg/bupropion 105 mg once daily, and then twice daily beginning day 3 compared to bupropion alone
- Mean change in MADRS depression rating scale over 1 to 6 weeks was significantly greater with the combination as compared to bupropion alone.
- The difference was observed at week 1 and statistically significant by week 2
- The remission rate at week 6 was significantly higher with the combination (46.5 % versus 16.2%)

Augmentation Medication Strategies for TRD

- Lithium – best established (7/9 controlled studies) Lower blood levels -0.4-0.6 meq/l effective
- T3 – 25-50 mcg. Efficacy established with TCAs
- Novel neuroleptics – Aripiprazole (Abilify), 5-10 mg (FDA approved)
- Olanzapine-Fluoxetine combination in bipolar depression

Cariprazine (Vraylar)

- Approved for treatment of manic or mixed episodes and schizophrenia, Bipolar Depression and adjunctive use in Unipolar Depression
- Indicated for Bipolar Depression
- 1.5 and 3 mg. dosage showed improvement in bipolar depression over six weeks compared to placebo
- Recent approval as a booster to antidepressants for unipolar depression in 1.5 -3.0 mg dosage
- Partial Agonist dopamine and serotonergic mediated effects.
  - Earley AJP 2019 176:439-448 June 2019

Lumateperone (Caplyta)

- Second generation antipsychotic approved in 2021 for Bipolar I and Bipolar II depression. Six week placebo controlled trial showed improvement in MADRS as early as one week.
- Dosage 42 mg per day with food.
- In patients with hepatic disease, the dosage is 21 mg per day.
- Valproic acid increases blood levels of lumateperone.
- Common side-effects include sedation/somnolence and dry mouth. Weight gain and EPS not common.

Neuromodulation Therapies

- ECT
- Transcranial magnetic stimulation
  - Better response in younger patients
- Deep Brain Stimulation
  - 40-75 % response up to 6 years
- Transcranial Direct Current Stimulation
  - Modulates excitability of cerebral cortex; investigational
- Magnetic Seizure Therapy
- Focal Electrically administered seizure therapy

Electroconvulsive Therapy

- Key indications – Psychotic Depression, Suicidal Press, Food Refusal, Treatment Refractory Depression, Parkinson's Disease, Refractory Manic Excitement.

- Medical Concerns – 4 deaths/100,000 treatments. Cardiac risks- recent myocardial infarction, unstable angina, hypertension, atrial fibrillation, post-cerebrovascular accident, intracranial aneurysm or space-occupying lesions or other causes of increased intracranial pressure.

- Post ECT maintenance – High rate of relapse particularly with psychotic depression; Post ECT medications - nortriptylene and lithium, MAO-I, Maintenance ECT.

Electroconvulsive Therapy

- After full course of 8-12 treatments, three times per week, treatment is not stopped abruptly (relapse rate 84% if no medication).
- Nortriptylene and lithium best studied post-ECT meds, significantly reduce relapse rate
- Maintenance ECT commonly employed in tapering manner with medications to support remission. F/U ECT treatments weekly for 1-2 months may be considered.
  - Espinoza and Keller NEJM 2022;386:667-72

Brain Stimulation in Treatment of Depression

- Vagal Nerve Stimulation (VNS)– recent FDA approval; utilized for a decade in treatment of epilepsy
- Transcranial Magnetic Stimulation (rTMS) – FDA approval; available clinically, valued in neurophysiologic research
- Deep Brain Stimulation
- Magnetic Seizure Therapy

Transcranial Magnetic Stimulation for Major Depression

- Left prefrontal rTMS, sham controlled 3 weeks of daily weekday treatment
- 195 antidepressant drug free patients with unipolar, non-psychotic depression
- Moderately treatment resistant
- Primary efficacy analysis, 14.1 % remitters with active rTMS and 5.1 % with sham
- “Statistically significant and clinically meaningful antidepressant effect”
  - George et al. Arch Gen Psych 2010;167:281-288

rTMS and Relapse Prevention

- Review of literature indicates potential benefit from maintenance treatment for relapse prevention
- Repeat course of rTMS also beneficial during relapse.
- Effective in unipolar and bipolar depression
- rTMS maintenance protocol may involve weekly reduction from 4 sessions to 1 session over one month;then alternate weekly treatment.
- Antidepressant treatment as usual
  - Rachid et al. Psychiatry Research 2017
  - Benadhira et al Psychiatry Research 2017

rTMS Mechanism of Action

- Stimulation of DLPFC revealed by rTMS combined with fMRI studies.
- Stimulation of DLPFC modulates anterior cingulate cortex. Modulates changes in the meso-cortico-limbic dopamine neurocircuit.
- Other rTMS studies including fMRI in PTSD suggest similar effects
- Studies underline importance of linking rTMS response with fMRi guided neuro-navigation
  - Tik et al.Neuroimage 2017
  - Philip et al.Biological Psychiatry 2018

rTMS Clinical Challenges

- What clinical factors predict response?
- What are the optimal stimulation parameters?
- How can the optimal site of stimulation be reliably found?
- The role of neuroimaging in guiding individualized rTMS treatment for depression.
- fMRI guided rTMS not clinically available
  - Luber et al Neuroimage 2017

Modifications of r-TMS

- Coil Design
- Site of Application Specific Region; L vs. R
- RX Frequency, pulse frequency, number
- Wave focus – e.g. theta
- Application of q EEG or f-MRI
- Accelerated intermittent theta burst stimulation treatment (aiTBS)

Accelerated intermittent theta burst Stimulation in rTMS

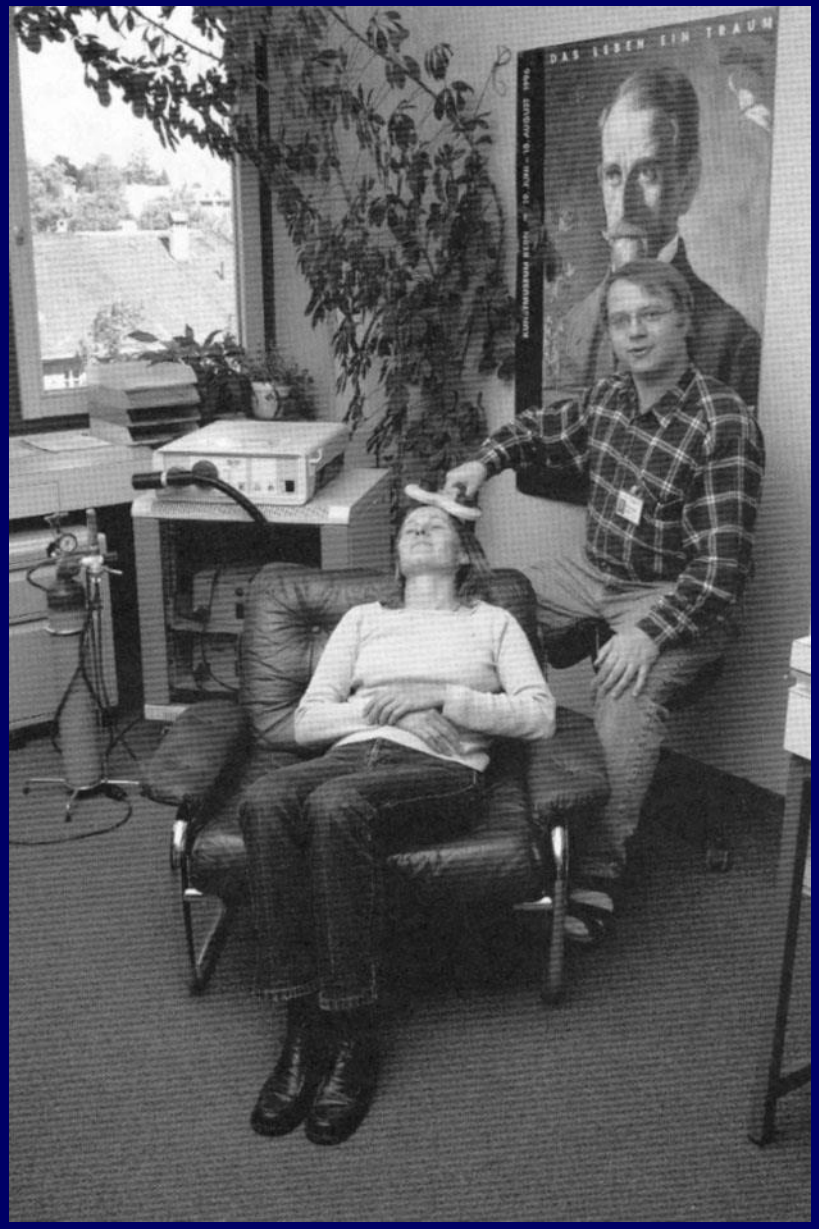
- 50 TRD pts. Received 20 aiTBS stimulation over four days to the left DLPFC.
- 38 % showed a 50% decrease in HRDS scores at two weeks (after one week of active and one week of sham controlled treatment)
- 30% of responders were in clinical remission.
  - J Affect Disord 2016 August 200:6-14

Accelerated rTMS

- 51 patients randomized to sham treatment, accelerated and conventional rTMS
- Accelerated 15 sessions/3 days; conventional 15 sessions/ 3 weeks
- Improvement in depressive symptoms at 3 weeks post-treatment for both active treatment groups; no difference in side-effects.
    - Kim et al. Clin Psychopharm and neuroscience, 2021;19 (1):73-83

Accelerated iTBS Protocol

- 5 days long
- 10 sessions per day; 50 minutes between each session
- 50 minutes interval shown to be optimal
- 90,000 pulses as this is the pulse dosage for a 6 week course of rTMS. FDA approved 18,000 pulses each day.
- Results equivalent to 6 week course rTMS
- Separation from sham at one week persisting for 5 weeks.
  - Cole et al AJP 2021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Psychedelics and Psychedelic Assisted Psychotherapy

- Randomized clinical trials support the efficacy of psilocybin in the treatment of depression and cancer-related anxiety
- Randomized clinical trials support the efficacy of MDMA for treatment of PTSD
- Both drugs designated as “breakthrough therapies by the FDA in 2017
- Research to support the use of LSD and micro-dosing psychedelic agents is observational and preliminary.

Psychedelics and Psychedelic assisted Psychotherapy

- More clinical trials needed using rigorous,validated methodology in controlled settings to address concerns regarding potential for abuse and psychiatric and medical sequelae in vulnerable populations
- Standardizing psychedelic assisted psychotherapy is necessary to facilitate research
- The expectations and personal experiences of the study subjects in response to psychedelic assisted psychotherapy is an important variable.
- The popularity in the general population of micro-dosing psychedelics every 3-5 days in the general non-psychiatric population raises other important questions
- No FDA approval for psychedelic treatment of depression or anxiety at this time.

MDMA-assisted therapy for severe PTSD

- Randomized double-blind placebo controlled study multi-site phase 3 study 18 week study, 3 experimental sessions weeks 1,5,9.
- After psychiatric medication washout, 90 participants randomized 1:1 to receive manualized therapy with MDMA or with placebo-three sessions - combined with three preparatory and nine integrative sessions.
- Primary endpoint - Symptoms measured by clinician administered PTSD symptom scale (CAPS-5); secondary endpoint, Sheehan disability scale (SDS)
- Assessed at baseline and two months after last experimental session
- MDMA treated group showed significant and robust decrease in CAPS score (p=0.0001) and SDS score (0.0116)
- No significant adverse events – no abuse, suicidality or QT prolongation.
  - Mitchell, Nature Science

MDMA for Treatment of PTSD

- 23 subjects, randomized, double blind cross over study
- Reduction in PTSD symptom rating of 53.7% two months after second treatment session,
- 53.7 % versus 20.5% for placebo.
- 26 subjects randomized double blind crossover, 1 month after second administration – 58.3% reduction in symptoms after 1 month in 75 mg group
- A follow-up study of 19 subjects in another study demonstrated sustained reduction in PTSD symptoms at 74 months post treatment

Mechanism of Action - MDMA

- Serotonin and Serotonin transporters important in the generation,consolidation, retrieval and reconsolidation of memories.
- Reduced serotonin transporter level (resulting in greater amounts of extracellular serotonin) predict propensity to develop PTSD, increase fear/anxiety and increase amygdala serotonin levels and induce greater blood oxygenation levels (BOLD) activity in response to fearful images
- MDMA exposure in humans has been shown to attenuate amygdalar BOLD activity during presentation of negative images
- MDMA enhances the extinction of negative memories through a mechanism of amygdalar serotonergic function and possibly enhanced oxytocin activity opening a “window of tolerance” to exploring negative memories

Psychedelics in the Treatment of Depression and Anxiety

- Phase 3 Trial of MDMA with Assisted Therapy For moderate to severe PTSD
- N = 53 with MDMA –AT; N= 51 Placebo AT
- Caps PTSD Score reduction -27.3 for MDMA – AT versus -14.8 for placebo with Therapy P=.001
- Sheehan Disability Scale Score -3.3 for MDMA – AT versus 2.1 for placebo with therapy P=.03
- No deaths or severe treatment related adverse events.
- Nature Med Vol 29 October 2023 2473-2480

Psilocybin for Depression

- A review of 8 studies indicates:
- Psychotherapy is important for optimal result
- Reduction in depressive symptoms occurs within 1 day to 1 week after 1 to 2 doses of Psilocybin
- Moderate to High Dose 10 mg to 30 mg/70 kg were more effective than 1 mg/70 kg dosage.
- Adverse effects mitigated by a controlled supportive environment.
- After each dosage, integration psychotherapy sessions occurred.
- Psilocybin was as effective as escitalopram in one study
- Behav Sciences 2023,13, 297

LSD for treatment of generalized anxiety disorder

- Phase 2b clinical trial of MM-120 lysergide d-tartrate or a placebo; No psychotherapy
- Four dosages of MM-120, 25,50, 100 or 200 micrograms
- Of participants receiving 100 or 200 micrograms, 78% had a clinically significant response rate, and 50% were in remission from GAD at week 4.
- LSD may have anxiogenic effects initially but anxiolytic effects after sustained or repeated administration.

LSD and generalized anxiety disorder

- One large clinical trial suggest lysergic acid diethylamide (LSD) combined with psychotherapy may be effective and well tolerated for anxiety disorders, but may have acute anxiogenic effects.
- Further studies are necessary to assess the role of adjunctive psychotherapy.
- LSD may be modified to reduce intensity and duration of action

CNS Drugs 2023 37; 733-754

Summary – Take Away Points

- New medications for postpartum depression and bipolar depression are reshaping clinical approaches to those conditions
- FDA approval of intranasal ketamine marks a key conceptual shift in the treatment of depression. But significant challenges regarding addictive concerns, adverse effects and long term efficacy remain
- Psychedelic agents such as MDMA for PTSD and Psilocybin for depression show promise in preliminary studies, and may be FDA approved within the next few years.

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