Bipolar Depression: How do we treat it?

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Disclosures

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Octapharma
Sage Therapeutics, Inc
Recordati
NIH R21"Modulating Inhibitory Contral Networks in Gambling Disorder with Theta Burst Stimulation
Bipolar Depression treatment
Out-line of the presentation

- Burden of the illness
- Bipolar depression clinical definition
- Bipolar and mixed: they are not the same
- Category vs specifier
- Back to clinic; comorbidities
- Focus on ADHD, OCD
- Approved treatment for bipolar depression and mixed
- Esketamine
- Post Partum Depression
- Circuitries
- Metabolic and Molecular target
- Neuromodulation: rTMS, tDCS
- Cognitive profile
- Medical comorbidities and inflammation
- Phase specific treatment and prevention
- Final remarks
Bipolar Depression:
burden of the illness

• US 2015: overall cost 202.1 billion dollars
• Due to the pervasiveness of depressive symptoms over time and higher indirect cost a greater proportion of the overall cost are attributed to depressive symptoms
• Manic and mixed symptoms account for direct cost because of higher inpatient treatment
• Suicide in both B1, B2 occurred in Dep phase, without significant difference in rates but more lethality in b2

(Clouter et al 2018)
Bipolar depression vs Mixed depression

- Bipolar depression is not always mixed
- Mixed depression is not always bipolar

McIntyer e Calabrese 2019
Beyond the DSM-5: overlapping symptoms relevance for mixed states

DSM-5 exclude “overlapping symptoms” of irritability, distractibility, insomnia, and psychomotor agitation as defining of the opposite polarity due to the presence of these symptoms in both mania and depression.

Alternative criteria for mixed features include the presence of:

- Irritability
- Anxiety
- Distractibility
- Psychomotor agitation
- Racing/crowded thoughts
- Initial and middle insomnia
- Indecisiveness
- Anger
- Increased talkativeness
- Emotional lability/tearfulness
- Inner tension
- Rumination
- Initial or middle insomnia
- Impulsivity
- Risky behaviors

Ask for:
- Family history of bipolar disorders
- Bipolar comorbidities (migraine, anxiety, SUD, obesity BED, ADHD, OCD)
ADHD Comorbid vs. Bipolar

- Frequent
- Hidden
- Confusing
- Comprehensive assessment
- To treat or not to treat
- Personality vs temperament
- Affect vs mood instability
Neurological soft signs
Bipolar vs unipolar

Sensorimotor Systems

• Neurological soft signs in bipolar and unipolar disorder: A case-control study. (Sagheer TA, 2018)

• Significant differences were found in the total NES score, motor coordination, sensory integration, sequence of complex motor act and other subscales among the three groups. Compared with healthy controls, patients with bipolar disorder showed significantly more total NSS signs, motor coordination signs and sensory-integration signs. When compared with patients with unipolar disorder, patients with bipolar disorder showed significantly more sensory integration signs and a trend of difference in the sequencing of complex motor acts and other subscales.

• bipolar I disorder performed significantly worse on two NES items from the sensory integration subscale, on one item from motor coordination and on four items from the 'others' subscale, the highest difference in performance being in items under the sequencing of complex motor acts subscale. (Negash et al 204)
Postural and regional cerebellar volume in adults with ADHD

- Affect instability
- And postural instability (Jansen et al 2019)

- We conclude that adult ADHD patients' major postural deficit consists of an impairment of a stable, long-term sensorimotor behavior, which fits very well to the concept of impulsivity and hyperactivity. (Hove et al 2019)
Placebo-controlled clinical trial of methylphenidate in the initial treatment of acute mania (MEMAP study)

• MTP WELL TOLLERATED futility was declared for methylphenidate and the RCT was stopped. In summary, although methylphenidate was well tolerated and safe in the full analysis set, it failed to show efficacy in the treatment of acute mania. (Hegery et al 2018)

• PREVENTION WITH MOOD STABILIZERS
  • The treatment with methylphenidate (10mg/kg, ip) increased locomotion in the open field test. The pretreatment with lithium (50mg/kg, ip) and valproate (400mg/kg, ip) significantly prevented the hyperlocomotion. (LS Souza, 2016)
Metilphenidate in bipolar disorder: what do we risk?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>%</th>
<th>N Rate</th>
<th>Period</th>
<th>Hazard Ratio</th>
<th>p</th>
<th>95% CI</th>
<th>Forest Plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study: methylphenidate (N=2,307)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mood-stabilizing medication</td>
<td>718</td>
<td>31.1</td>
<td>24</td>
<td>0–3 months</td>
<td>3.33</td>
<td>0.067</td>
<td>0.92–12.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3–6 months</td>
<td>1.00</td>
<td>1.000</td>
<td>0.20–4.95</td>
<td></td>
</tr>
<tr>
<td>Mood-stabilizing medication</td>
<td>1,103</td>
<td>47.8</td>
<td>144</td>
<td>0–3 months</td>
<td>0.48</td>
<td>0.002</td>
<td>0.30–0.77</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3–6 months</td>
<td>0.86</td>
<td>0.640</td>
<td>0.47–1.60</td>
<td></td>
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<tr>
<td>Previous study: antidepressants (N=3,240)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mood-stabilizing medication</td>
<td>1,117</td>
<td>34.5</td>
<td>42</td>
<td>0–3 months</td>
<td>2.83</td>
<td>0.028</td>
<td>1.12–7.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3–9 months</td>
<td>0.71</td>
<td>0.567</td>
<td>0.23–2.26</td>
<td></td>
</tr>
<tr>
<td>Mood-stabilizing medication</td>
<td>1,641</td>
<td>50.6</td>
<td>281</td>
<td>0–3 months</td>
<td>0.79</td>
<td>0.214</td>
<td>0.54–1.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3–9 months</td>
<td>0.63</td>
<td>0.020</td>
<td>0.42–0.93</td>
<td></td>
</tr>
</tbody>
</table>

MTP + mood stabilizers: no increased risk of mania
MTP alone: increased risk of mania
AD + mood stabilizers: no increased risk of mania
AD alone: increased risk of mania

Atomoxetina in ADHD with Bipolar

• Despite theoretically greater risk for induction of mania/hypomania with noradrenergic drugs in patients with bipolar disorder, open-label atomoxetine added to antimanic drugs significantly improved ADHD symptoms without worsening mania symptoms in comorbid youth.

• Findings from this pooled analysis indicated that augmentation of mood-stabilizer treatment with glutamate modulator agents (topiramate or memantine) may favor full response of obsessive-compulsive symptoms (risk ratio: 2.62, 95% confidence interval: 1.45-4.74) in patients with BD type I and OCD in the manic phase, and that it does not significantly induce adverse effects.

• Results of a narrative synthesis of observational studies indicated greater efficacy of mood-stabilizer treatment, with serotonin reuptake inhibitors less used. Findings from studies employing different designs were not compared, and our results should be interpreted cautiously.
Bipolar Depression treatment

- 4 : FDA approved

Table 5. Clinical Guideline to Treat Acute Bipolar Depressive Episodes

<table>
<thead>
<tr>
<th>Step</th>
<th>Medications</th>
</tr>
</thead>
</table>
| 1st   | - Start with quetiapine, lurasidone, or OTC  
       | - Consider add-on CBT. Never consider CBT as monotherapy |
| 2nd   | - Monotherapy with valproate or lithium  
       | - Combination of a mood stabilizer with lurasidone, modafnil, or pramipexole  
       | - Lithium plus pimozapirone  
       | - Carbamazepine plus FENP  
       | - Add escitalopram or fluoxetine on ongoing therapy  
       | - For the treatment of comorbid anxiety add paroxetine, quetiapine, valproate, or lurasidone, and consider mindfulness-based interventions as add-on ongoing therapy |
| 3rd   | - Aripiprazole, imipramine, or phenelzine monotherapy  
       | - Lithium or oxcarbazepine or L-sulpiride |
| 4th   | - Olanzapine, lamotrigine, or tranylcypromine, or carbamazepine monotherapy  
       | - Venlafaxine preferably in combination with an antidepressant  
       | - Armodafnil or ketamine on a mood stabilizer  
       | - Lithium plus fluoxetine or lamotrigine |
| 5th   | - ECT |
| Not recommended | Monotherapy with donepezil, paroxetine (except for comorbid anxiety), ziprasidone, gabapentin, lithium and rTMS, combination of any mood stabilizer with agomeline, paroxetine, ziprasidone, bupropion, celeprilb, levetiracetam, indexamfetamine or risperidone, Memantine plus lamotrigine and lithium plus aripiprazole, donepezil or imipramine. Not recommended also risperidone or ziprasidone for the treatment of concomitant anxiety |

Self-reported signs that treatment for depression is working (i.e., indication of treatment effectiveness). Respond

<table>
<thead>
<tr>
<th>How do you know that this treatment is working?</th>
<th>Answer options</th>
<th>Depression group N = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>I don't feel overly anxious, agitated, or irritable</td>
<td>62.7%</td>
<td></td>
</tr>
<tr>
<td>My negative self-talk goes down</td>
<td>54.1%</td>
<td></td>
</tr>
<tr>
<td>I don't dwell as much on negative experiences</td>
<td>52.4%</td>
<td></td>
</tr>
<tr>
<td>I get out of bed in the morning</td>
<td>51.4%</td>
<td></td>
</tr>
<tr>
<td>I feel hopeful about the future</td>
<td>44.6%</td>
<td></td>
</tr>
<tr>
<td>I am able to maintain concentration for activities, such as reading a book</td>
<td>51.4%</td>
<td></td>
</tr>
<tr>
<td>I feel happy</td>
<td>43.2%</td>
<td></td>
</tr>
<tr>
<td>I return to activities that I used to enjoy, such as cooking, gardening, or playing a sport</td>
<td>43.0%</td>
<td></td>
</tr>
<tr>
<td>I can make decisions</td>
<td>39.9%</td>
<td></td>
</tr>
<tr>
<td>I feel that I offer something to this world</td>
<td>38.9%</td>
<td></td>
</tr>
<tr>
<td>I go out with friends/family more</td>
<td>37.6%</td>
<td></td>
</tr>
<tr>
<td>I'm proactive about my life</td>
<td>34.6%</td>
<td></td>
</tr>
<tr>
<td>My family/friends comment on positive changes in mood/behavior</td>
<td>34.6%</td>
<td></td>
</tr>
<tr>
<td>My eating and/or sleep patterns go back to normal</td>
<td>34.1%</td>
<td></td>
</tr>
<tr>
<td>My physical symptoms disappear (headaches, nausea, etc.)</td>
<td>31.9%</td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>12.2%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive-behavioral treatment; OTC, over-the-counter; FENP, Free and Easy Wanderer Plan; IPSE, interpersonal and social rhythm therapy; Lam, lamotrigine; M3, mood stabilizer; OTC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.
Treatment of MDD with mixed features

No FDA- or EMA-approved medications

**What to avoid**

Avoid antidepressant monotherapy

TCSa and SNRIs: highest rates of emerging affective switch

ADs: no evidence of efficacy in BP depression

Even with mood stabilezers ADs could exacerbate irritability and insomnia

Bupropion and some SSRIs: lower risk of switch

IMAO for bipolar depression: some evidence of effectiveness

**What to consider**

Asenapine
Lurasidone
Olanzapine
Quetiapine
Ziprasidone

Cariprazine
Aripiprazole

Lithium
Valproate
Lamotrigine
# Recommendations for MDD with mixed features

## First line
**Monotherapy:** lurasidone, asenapine, quetiapine, quetiapine XR, aripiprazole, ziprasidone

## Second line
**Monotherapy:** lamotrigine, valproate, lithium, cariprazine, olanzapine

**Lithium, lamotrigine, or valproate + atypical Antipsychotic**

**Lithium + valproate**

**Lithium or valproate + lamotrigine**

**Olanzapine + fluoxetine**

## Third line
**Monotherapy:** carbamazepine

**Lithium + carbamazepine**

**Lithium + pramipexole**

**ECT**

**Lithium or lamotrigine or valproate or atypical antipsychotic + bupropion**

**Lithium or lamotrigine or valproate or atypical antipsychotic + SSRI**

**Lithium or lamotrigine or valproate or atypical antipsychotic + MAOI**

**Adjunctive modafinil, armodafinil, pramipexole**

**Adjunctive folic acid, inositol, ketamine, N-acetyl cysteine, omega-3 fatty acids, ramelteon, or celecoxib**

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Anger vs. Irritability

**Anger**

- Anger Attacks in Bipolar Depression: Predictors and Response to Citalopram Added to Mood Stabilizers
- Oommen K. Mammen, MD; Paul A. Pilkonis, PhD; Kadiamada N. R. Chengappa, MD; and David J. Kupfer, MD

**Irritability**

- Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study Fava et al 2016
- A placebo-controlled crossover study of iloperidone augmentation for residual anger and irritability in major depressive disorder.
- Ionescu DF, F 2016
Maintenance treatment
(and staging, and severity)

Continue with the effective acute treatment
Duration of maintenance treatment is indefinite

IF ANTIDEPRESSANTS ARE USED...
There is no substantial evidence in favor of long term use of antidepressant
Discontinuation is the usual policy when the patient recover from the mixed policy

• G.Fava and Kellner, (1993) focusing on mood and anxiety disorders, called staging the “neglected dimension in psychiatric classification”
• Early intervention strategies should aim to minimize disruption to normal developmental trajectories. It is likely that multifaceted strategies will be required, ones that integrate effective psychopharmacology with stage-specific and evidence-based psychosocial interventions
Dopaminergic agents for bipolar depression

Meta-analysis plot of RDC trials

Dopaminergic agents for bipolar depression increase both response and remission rates

No evidence of increased risk of mood switch

Tolerability (no increase vs placebo of restlessness, insomnia and suicidality). Only increased nausea

Dopamine agonists

- Pramipexole

Stimulants

- Methylphenidate
- Amphetamine salts
- Lisdexamphetamine

Stimulant-like agents

- Modafinil or armodafinil

Ketamine
Effective in bipolar depression and reduce suicidal ideation and anhedonia.

ZURALODONE (SAGE-217) is a positive allosteric modulator of the GABAA receptor.

Comparative Effectiveness of Esketamine in the Treatment of Anhedonia in Bipolar and Unipolar Depression

Anhedonia (item 8 MADRS) scores over 6 weekly esketamine infusions.

Rapid infusion of esketamine for unipolar and bipolar depression: a retrospective chart review


**Note:** Points represent means, and error bars show 95% confidence intervals estimated from standard errors.

**Abbreviation:** MADRS, Montgomery–Åsberg Depression Rating Scale.
Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression

Anti-anhedonic effect of ketamine and corresponding regression analyses with cerebral glucose metabolism. (a) Snaith–Hamilton Pleasure Scale (SHAPS) estimated scores from linear mixed model 1 (M1) indicating a significant reduction in anhedonia levels following ketamine (red) compared with placebo (blue). (b) Region of interest analysis with ventral striatum (VS) demonstrating a significant association between anti-anhedonic response to ketamine and increased glucose metabolism in the VS. Changes in anhedonia levels no longer significantly predicted VS change when change in overall depressive symptoms were controlled for. (d, e) Whole-brain corrected relationship between the anti-anhedonic effects of ketamine and (d) dorsal anterior cingulate cortex (dACC), cerebellum, (e) right putamen, VS and medial posterior orbitofrontal cortex increases in glucose metabolism. (f) Whole-brain corrected relationship between SHAPS score orthogonalized against MADRS score indicating that a significant increase in dACC metabolism was associated specifically with anti-anhedonic response to ketamine independent of overall change in depressive symptoms.

Episode focused treatment: Postpartum depression

- Until recently, there were no approved medications for the treatment of postpartum depression.
- Allopregnanolone is a naturally occurring neuroactive steroid whose serum levels decline precipitously following childbirth. This hormonal fluctuation has been postulated as playing a role in the pathophysiology of postpartum depression.
- Brexanolone is the first medication approved by the US Food and Drug Administration for the treatment of postpartum depression. Brexanolone is an intravenous proprietary formulation of allopregnanolone that can be administered to produce stable serum levels comparable with third-trimester concentrations in postpartum mothers.
- It is hypothesized to modulate neuronal excitability by functioning as an allosteric modulator of γ-aminobutyric acid-A receptors and is administered under monitoring as a 60h continuous infusion.
### Post Partum Depression

Allopregnanolone-based treatments for postpartum depression: Why/how do they work? Potential mechanisms implicated in the underlying neurobiology of PPD in relation to potential mechanisms of action mediating the antidepressant effects of allopregnanolone. 

+ indicates a strong relationship, - indicates no known interaction, ? Indicates the relationship is currently undetermined.

<table>
<thead>
<tr>
<th>Mechanisms of Action of Allopregnanolone</th>
<th>Implicated in the Underlying Neurobiology of PPD</th>
<th>Potential Mechanisms Mediating the Antidepressant effects of Allopregnanolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABAergic Dysfunction</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HPA Axis Dysfunction</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neurosteroid Deficits</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Altered Network Communication</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neuroinflammation</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Genetic Predisposition</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>
| Actions on pregnane X receptors/transcriptio
tal changes and gene regulation          | –                                             | ?                                              |
| Actions on membrane progesterone receptors/G-protein-coupled receptors | –                                             | ?                                              |
| Metabotropic Regulation of GABA receptors | –                                             | ?                                              |
Brexanolone in Postpartum Depression: *Post Hoc* Analyses to Help Inform Clinical Decision-Making

Gerbasi et al 2021
Toward precision medicine for bipolar disorder

- **Novel targets from classical neuropharmacology**
- Trace amine-associated receptors
- Lithium & GSK3
- **Phospho-CRMP2**

- **Inositol monophophatase**
- **Novel targets from human genetics**
- WNT / GSK3β / β-catenin signaling pathways
- Trace amine-associated receptors
- Peroxisome proliferator-activated receptors (PPARs)
- Psilocybin and psychedelics
- MT1 and MT2 receptors

- **B-Arrestin-2/AKT/PP2A-GSK3** signaling

Toward prevention of bipolar disorder in at risk children: Potential strategies ahead of the data

<table>
<thead>
<tr>
<th>Stage</th>
<th>Possible interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Vulnerability/at risk</td>
<td>Folate 2C, Vitamin D3 2C, Phosphatidylcholine 2C, Encourage good diet*, Careful and adequate treatment of mother's depression prepartum*, Adequate interventions targeting sleep/circadian rhythm stabilization across pregnancy and the postpartum period*</td>
</tr>
<tr>
<td>II: Well interval</td>
<td>Treatment of mothers’ postpartum and later depressions*, Added psychosocial support for the postpartum mother regardless of depression status*, For the newborn, infant, and young child: Good diet, consistent exercise, sleep hygiene, teach ability to delay gratification*, For older and school-age children: Team sports, vigorous exercise, and music lessons*, For adolescents with parents with BPI or II with experience of childhood adversity: greater emphasis on, and more intensive application of, the above generic recommendations, and in addition use of group psychoeducation and family focused therapy (FFT) or its equivalent: 2B, For children at high risk and are showing anger dyscontrol: facial emotion recognition training 2C, Acetyl-L-carnitine 2C</td>
</tr>
</tbody>
</table>

Possible interventions generally listed in the sequence of best-tolerated first.

UpToDate Grading 1 system: 1 = strong recommendation; 2 = weak recommendation;
Quality of evidence: A = high; B = moderate; C = low. (When evidence is limited to adults, quality of evidence is considered low for children.)

* = general universal recommendations
### Toward prevention of bipolar disorder in at risk children: Potential strategies ahead of the data

**III: Prodrome**

| A) Heterotypic prodrome (Anxiety, ADHD, ODD) | N-acetylcysteine 2B  
|                                           | Psychotherapy/FFT 1A  
|                                           | Stimulant (ADHD) 1B  
|                                           | Stimulant plus alpha 2 agonist 1B  
|                                           | Atomoxetine 2C  
|                                           | Modafinil 2C  
|                                           | EM Powerplus 2C  
|                                           | Lamotrigine (Anxiety) 2C  |

| B) Homotypic prodrome (Depression, Cyclothymia, BP-NOS) | Family-Focused Therapy or Psychoeducation 1A  
|                                                       | Omega-3-FA 2B  
|                                                       | N-acetylcysteine 2C  
|                                                       | Lurasidone 2C  
|                                                       | Other atypical antipsychotics 2C  
|                                                       | SSRIs 2C  
|                                                       | Lithium 2C  |

**IV: Onset**

| A) Stage II-IV with increased INFLAMMATION | Minocycline 2C  
|                                          | Acetylsalicylic acid 2C  
|                                          | Celecoxib 2C  |

| B) For more severe BP-NOS with: | Vitamin D3 2C  
| 1. Predominant MANIA | Folate 2C  
|                       | Lithium 2B  
|                       | Atypical antipsychotic (A.A.) 2B  
|                       | A.A. plus lithium 2C  
|                       | A.A. plus lithium plus an antimanic anticonvulsant 2C  
|                       | Valproate (VPA, but not in females of child bearing age 2C  |

Possible interventions generally listed in the sequence of best-tolerated first.

**UpToDate Grading 1 system:** 1 = strong recommendation; 2 = weak recommendation;

**Quality of evidence:** A = high; B = moderate; C = low. *(When evidence is limited to adults, quality of evidence is considered low for children.)*

* = general universal recommendations
Resting electroencephalographic correlates of the clinical response to repetitive transcranial magnetic stimulation: A preliminary comparison between unipolar and bipolar depression

Woźniak-Kwaśniewska, 2015

- EEG spectral power was partitioned using the common physiological frequency bands and was statistically analysed at the scalp level and after cortical source reconstruction.

- A significantly higher power in theta and beta bands in BP patients than in MDD patients, mainly localised in the prefrontal cortex. In addition, responders showed higher power in delta and theta bands in parietal regions and weaker frontal alpha power in the theta range. BP patients showed higher bilateral activity in the primary and supplementary motor regions, in dorsolateral prefrontal cortex and in the cingulate area. In the beta range, higher power in BP patients was observed bilaterally in the primary and supplementary motor regions and in the temporal pole, and only right-sided in the dorsolateral prefrontal cortex.

- BP patients demonstrated higher theta and beta band oscillations than MDD patients.

- In the theta range, BP patients showed higher bilateral activity in the primary and supplementary motor regions, in dorsolateral prefrontal cortex and in the cingulate area. In the beta range, higher power in BP patients was observed bilaterally in the primary and supplementary motor regions and in the temporal pole, and only right-sided in the dorsolateral prefrontal cortex.
Cognitive Profile in Bipolar Depression: treatment implications

- Features
- Relation with Emotional (Lima et al 2018)
- Target
- TMS ( )
- Lurasidone ( )
- Lamotrigine Shi et al 2018) Research concluded that lamotrigine may help alleviate the clinical symptoms and improve cognitive function in patients with depression of recurrent bipolar disorder
- Metabolic
- Antinflammatory
- Despite VPA and SB having a similar mechanism of action, both being histone deacetylase inhibitors, they showed different effects on the levels of cytokines. (Valvassori 2018)
- Microbiota?

- Prominent cognitive deficits have been documented in bipolar disorder, and multiple studies suggest that these deficits can be observed among non-affected first-degree relatives of those with bipolar disorder.
- Although there is variability in the degree of cognitive deficits, these deficits are robustly relevant for functional outcomes.
Neuroimaging Differences between Bipolar and Unipolar Depression

- There are differences in **Gray matter** volume in the **ACC, Hippocampus, Amygdala** and Dorsolateral Prefrontal Cortex (DLPFC)

BD showed a **thinner** DLPFC, also reduced integrity in the **anterior** part of the **Corpus Callosum** and **Posterior Cingulum**

Neuroimaging Differences between Bipolar and Unipolar Depression

- Different activation patterns in neural networks in the Amigdala, Anterior Cingulate Cortex (ACC), Prefrontal Cortex (PFC) and Striatum during Emotion/Reward/Cognition tasks.

- BD seems to have a **stronger** functionality connectivity pattern in ACC, PFC, Parietal and Temporal Regions and Thalamus

Mixed states: what about TMS?

40 mixed-state treatment-resistant patients

For the HAM-D there is a 35% of responders and a 10% of remitters.
For the YMRS there is a 15% of responders and a 32.5% of remitters.

Abstract
Introduction: Treatment options are limited for patients with bipolar depression. Antidepressants added to mood stabilizers even carry risks of precipitating mixed/manic episodes. Transcranial magnetic stimulation (TMS) may provide a safe and effective option for these patients.

Methods: Database analysis of the TMS Service at Sheppard Pratt Health System identified patients with bipolar disorder type I (BD1) or II (BD2) in a pure depressive phase at initiation of TMS. Records were reviewed for response and remission rates based on MADRS scores, time to effect, and adverse events, notably treatment-emergent affective switching. All had failed at least two prior treatments for depression, were currently on at least one mood stabilizer and off antidepressants. Stimulation parameters targeted left dorsolateral prefrontal cortex: 120% motor threshold, 10 pulses per second (pps) × 4s, intertrain interval (ITI) 26s, 75 trains (37.5 min/session) for 3,000 pps total, 5 sessions/week for 30 total treatments, or until remission criteria were met.

Results: A total of 44 patients with BD were identified, representing 15% of the total TMS population. 77% of those who completed a course of TMS met response criteria, and 41% of subjects who completed at least 25 treatments met remission criteria. Subjects with BD1 were more likely to respond, remit, or suffer an adverse event than those with BD2. No patient met clinical criteria for a manic/mixed episode, but four (10%) discontinued due to concerns of activation.

Conclusions: TMS is effective in the bipolar depressed population where episode focused intervention can be specifically offered. Risk of psychomotor agitation must be closely monitored.

Keywords
bipolar depression, bipolar disorder, neuromodulation, transcranial magnetic stimulation

FIGURE 1  (a) Percent of patients meeting remission by MADRS (MADRS ≤ 10). (b) Percent of patients meeting response by MADRS (50\% drop from baseline)
Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial

In this randomized clinical trial of 59 participants receiving a stable pharmacologic regimen, active transcranial direct current stimulation was associated with superior depression improvement and higher response rates than sham. Moreover, active transcranial direct current stimulation did not induce more manic/hypomaniac episodes compared with sham.

Discussion

In accordance with our primary hypothesis, active tDCS showed superior symptomatic improvement, based on HDRS-17 scores, compared with sham. This difference was associated with a medium effect size (NNT, 5.8; 95% CI, 3.3-25.8).

Those who received tDCS significantly more frequently developed skin redness. The results also suggest that the frequency of itching and burning was higher in the active group. These AEs are often reported after active tDCS and seem to be caused by the injected current in the skin. Nonetheless, there were no losses due to these AEs, which were short-lived. Also, these AEs did not affect blinding.

Transcranial DCS was tolerable and safe, with both groups presenting similar TEAS rates, which is a concern when treating depression with tDCS. Such a feature is advantageous compared with other pharmacologic interventions presenting higher rates of TEAS and other AEs. No patient receiving antidepressant monotherapy presented affective switches during the trial.

*JAMA Psychiatry. 2018 Feb; 75(2): 158–166.*
Medical, Comorbidities (or features) and treatment of bipolar depression

- Cardiovascular disorders, diabetes, and obesity are highly comorbid and arise earlier in the life course compared with the general population. Medical comorbidities are indicators of a worse outlook for patients with bipolar disorder. Mortality is also increased, with findings of a 30-year follow-up study showing that circulatory disorders and suicide are the main causes of death. (Grande et al Lancet 2016)

- Metabolomics of bipolar disorder (Hashimoto, 2018)
Inflammation as a target for bipolar depression

- Inflammation and reward circuitries (Jennifer C. Felger, 2018)
- Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis (Rosenblat et al 2016)
- N-acetylcysteine (NAC); aspirin; infliximab;
- minocycline;
- nonsteroidal anti-inflammatory drugs (NSAIDs);
- omega 3 polyunsaturated fatty acids;
- pioglitazone.
- Jess G Fiedorowicz, 2016 PT plus Quetiapine vs Quetiapine alone

Gut Microbiota Changes in Patients with Bipolar Depression (Hu, 2019)
Prevention of Bipolar progression
Toward prevention of bipolar disorder in at risk children: Potential strategies ahead of the data

2. Predominant DEPRESSION
   - Vitamin D3 2C
   - Folate 2C
   - N-acetylcysteine 2C
   - Acetyl-L-carnitine (if history positive for child abuse) 2C
   - Lurasidone (especially if CRP is elevated) 2B
   - Quetiapine 2C
   - Cariprazine 2C
   - Lamotrigine 2C
   - Lamotrigine plus lithium 2C

3. Prominent ULTRADIAN CYCLING
   - Nimodipine (especially if patient as the CACNA1C gene) 2C
   - Nimodipine plus lithium 2C
   - Nimodipine plus anticonvulsant 2C
   - Lithium plus valproate 2C

4. Comorbid SUBSTANCE USE
   - Adjunctive N-acetylcysteine (smoking, alcohol, cocaine, marijuana in adolescents) 2B
   - Adjunctive toipiramate (alcohol, cocaine) 2C

Possible interventions generally listed in the sequence of best-tolerated first.
UpToDate Grading 1 system: 1 = strong recommendation; 2 = weak recommendation;
Quality of evidence: A = high; B = moderate; C = low. (When evidence is limited to adults, quality of evidence is considered low for children.)
* = general universal recommendations
Childbirth and prevention of bipolar disorder: an opportunity for change


Childbirth and prevention of bipolar disorder: an opportunity for change. The Lancet Psychiatry.
Bipolar Depression: what we should do and what is often done

• Mood stabilizers are not widely used in Bipolar especially bip2
• Use of anti depressant as only is frequent
• Atypical Antipsychotic alone LAI are largely used
• Metabolic features are rarely monitored
• Prevention is missing
• Other then clinical and Neurotransmitter activity are neglected : immune , metabolic , neuroplasticity , etc...
Bipolar depression: a major unsolved challenge (R J. Baldessarini et al, 2020)

**Table 5 Current status of depression in bipolar disorder**

<table>
<thead>
<tr>
<th>Depression in bipolar disorder (BD) is the major residual psychiatric morbidity with available treatments, accounting for three-quarters of the 40–50% long-term time ill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresolved morbidity, and especially depression, is associated with excess medical morbidity, including metabolic syndrome and cardiovascular disease, with increased mortality</td>
</tr>
<tr>
<td>Suicide risk in BD is similar in types I and II BD, greater than in most other psychiatric disorders, ca. 20-times above general population rates, and strongly associated with depression, especially with agitation (mixed-dysphoric states), and in the days–weeks following hospital discharge</td>
</tr>
<tr>
<td>Predicting suicide in BD clinically is limited regarding individuals and timing</td>
</tr>
<tr>
<td>Treatments proposed to prevent suicidal behavior in BD include lithium, clozapine, and possibly ketamine and psychotherapies, which all require further study</td>
</tr>
<tr>
<td>Therapeutics of bipolar depression is far less well developed than for nonbipolar major depression, probably reflecting lack of recognition of differences between bipolar and unipolar depression</td>
</tr>
<tr>
<td>The short-term value and safety of antidepressant treatment for bipolar depression remains controversial, and long-term value remains virtually untested; it is best avoided with ongoing dysphoric agitation or mixed features</td>
</tr>
<tr>
<td>Some modern antipsychotics are effective in bipolar depression short-term; lithium and lamotrigine have modest prophylactic value long-term but are not adequately tested short-term; other anticonvulsant mood-stabilizers have very limited evidence of short- or long-term efficacy in bipolar depression</td>
</tr>
<tr>
<td>All available treatments for bipolar depression have risks of adverse metabolic or neurological effects; valproate and carbamazepine are also highly teratogenic</td>
</tr>
</tbody>
</table>
Summary:
- Clinical definition
- Comorbidities
- Individualized targets
- Circuitries oriented
- Stage and phase
- Cognitive
- Episode focused
- Prevention oriented

REDEFING DISORDER Or DIAGNOSTIC SYSTEM?

Staging

Cognitive

Metabolic – immune

Patient centered vs Category

Circuitries