MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Bipolar Depression: how do we treat it?

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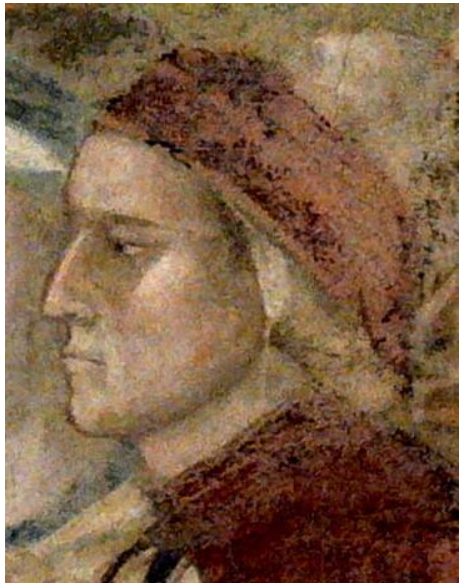
Bipolar Depression treatment Out-line of the presentation

- Burden of the illness
- Bipolar depression: clinical definition
- Bipolar and mixed they are not the same
- ATD for bipolar Depression: An Enduring controversy
- Back to clinic: comorbidities
- Approved treatment for bipolar depression
- Resistance and Esketamine
- Post Partum Depression
- The future and Metabolomic targets
- Neuromodulation: rTMS & tDCS
- Psychotherapy and psychoeducation
- Phase specific treatment and prevention
- Final remarks



- But leaving off subtle investigation, we can say say briefly that the purpose of the whole as well as the part is to remove those living in this life from the state of misery and to lead them to the state of bliss.

- **Dante Alighieri (1265-1321) Letter to Cangrande della Scala , 1316 .1320**

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).
- Delay of 6-8 years for the diagnosis (Post, 2010; Tondo, 2011; Clouter et al 2018)

What a Question!!

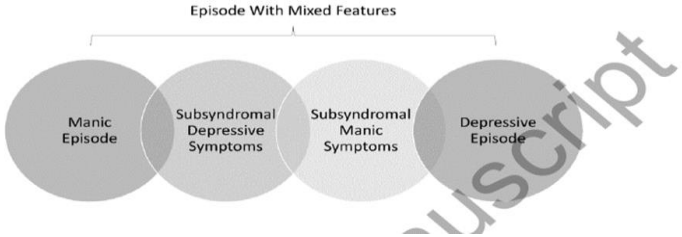
Searching terms……

- L'umore come va?
- What's up?

How to make (and share) a diagnosis of Bipolar Depression?

And the issue of the Spectrum vs category

- **DIRECT Factor for Diagnosis**
- Bipolar depression is not always mixed
- Decrease number of overlapping symptoms (to 2 or 1)(Kim et al 2016)



McIntyer e Calabrese 2019

MDQ screening cut off 7/13

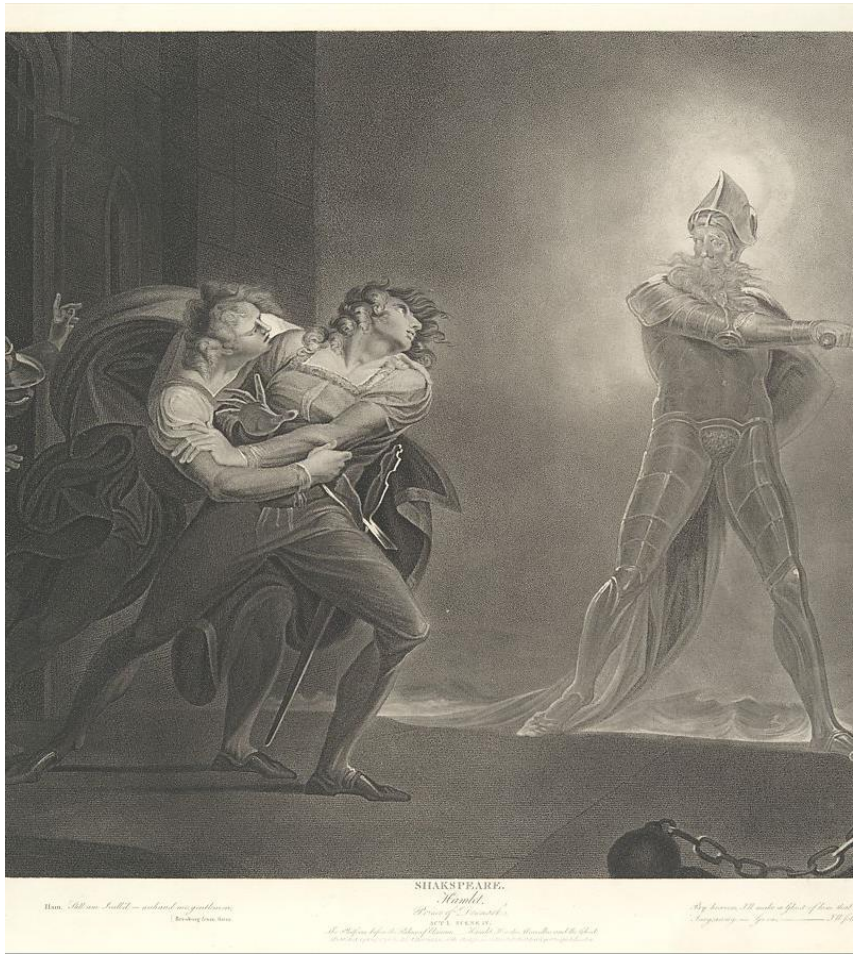
= sensitivity 0.62 ;specificity 0.85

False+ BLPD, SUD,PTSD False- History child abuse

(Paterniti –Bisserbe, 2018) (HCL-32) 32 item hypomania symptom checklist (Angst et al 2005)

- **IN-DIRECT Factor for Diagnosis**
- Mixed depression is not always bipolar
- Familal Mania
- Early onset dep
- Cyclotimic temperament
- Multiple, more then 4ep. in 10 y
- Dep with agit, irritab, insommia, talkative,psychotic
- Worsening with ATD
- Suicidal
- With SUD
- (Baldessarini, et. Al, 2020)
- Koukopoulos (K-DMX, 2013)
- Shahin Mixed Dep Scale (2020)
- Anhedonia and Psychomotor retardation vs agitation.

This entire story is meaningless without introducing the ghost…



The ghost appears and beckons Hamlet, who follows it. They all tell him not to go but he insists and threatens them with violence if they try and stop him. While he is away, one of the officers, Marcellus, commenting on what the ghost's appearance may mean, observes, "Something is rotten in the state of Denmark."

Antidepressant in Bipolar Depression: An Enduring Controversy (Micheal J Gitlin, 2019)

Antidepressants in Bipolar Depression: An Enduring Controversy

Michael J. Gitlin

The proper place and the optimal use of antidepressants in treating bipolar depression continues to be an area of great interest and greater controversy with passionate opinions more common than good studies. Even the handful of meta-analyses in the area disagree with each other. Overall, the evidence that antidepressants are effective in treating bipolar depression is weak. Additionally, many experts and clinicians worry greatly about the capacity of antidepressants to cause affective switching or mood destabilization. Yet, in short term controlled studies, with most patients also taking mood stabilizers, antidepressants are not associated with switches into mania/hypomania. Evidence of cycle acceleration with antidepressants primarily reflects treatment with older antidepressants, e.g., tricyclics. Similar evidence with modern antidepressants such as selective serotonin reuptake inhibitors (SSRIs) is lacking. The key questions should not be: are antidepressants effective in bipolar depression?; And: do antidepressants worsen the course of bipolar disorder? Rather, the question should be focused on subgroups: for which patients are antidepressants helpful and safe, and for which patients will they be harmful? Predictors of affective switching with antidepressants include: bipolar I disorder (vs. bipolar II), mixed features during depression, tricyclics vs. modern antidepressants, rapid cycling and possibly a history of drug abuse, especially stimulant abuse. Additionally, a number of recent studies have demonstrated both the safety and efficacy of antidepressant monotherapy in treating bipolar II depression. Finally, a subgroup of bipolar individuals need antidepressants in addition to mood stabilizers as part of an optimal maintenance treatment regimen.

Focus 2019; 17:278–283; doi: 10.1176/appi.focus.17306

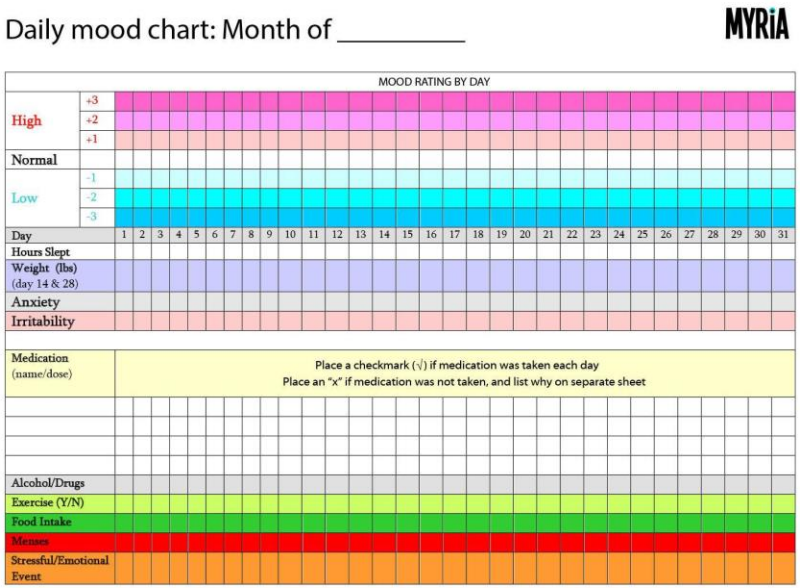
(Reprinted with permission from *Int J Bipolar Discord* (2018) 6:25)

The idea that the use of antidepressants in bipolar depression is not a yes or no question, but it depends on the characteristics of each individual patient.

"The proper place and the optimal use of antidepressants in treating bipolar depression continues to be an area of great interest and greater controversy with passionate opinions more common than good studies".

(Gotlin 2019; Elie Cheniaux & Antonio E Nardi, 2019)

Setting up a bipolar clinic and spreading the concept…



Daily mood chart: Month of _____

MYRiA

		MOOD RATING BY DAY																													
High	+3																														
	+2																														
	+1																														
Normal																															
Low	-1																														
	-2																														
	-3																														
Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Hours Slept																															
Weight (lbs) (day 14 & 28)																															
Anxiety																															
Irritability																															

Medication (name/dose)	Place a checkmark (√) if medication was taken each day Place an "x" if medication was not taken, and list why on separate sheet
Alcohol/Drugs	
Exercise (Y/N)	
Food Intake	
Menses	
Stressful/Emotional Event	

- Assessment tools beyond the SCID :
- The SCI MOODS http://www.spectrum-project.org/questionnaires/moods.html
- Self rating
- Severity
- Course
- Prodromal
- Crisis prevention

The most reliable and valid way to obtain a diagnosis of bipolar disorder is through a structured interview with a trained clinician (Akiskal, 2002).

The Mood Spectrum Interview

APPENDIX
Structure of the MOODS-SR: The "Mood-Manic" Subdomain

In the course of your life (including when you were a child), have you ever had periods of at least 3-5 days in which

29. . . .you felt persistently good or high?
30. . . .you (or others) found that your sense of humor and irony were very sharp
31. . . .even the smallest thing could make you enthusiastic?
32. . . .you liked to make puns or plays on words?
33. . . .you liked to make a lot of jokes (even ones that might have been inappropriate or out of place)?
34. . . .you were intrusive, insulting or tactless, or others thought that you were?
35. . . .you found it very pleasurable and easy to buy things, even things you didn't need?
36. . . .you gave lots of presents, even when you really couldn't afford them?
37. . . .you were warm, extroverted and sociable and it was very easy to introduce yourself to others or to make new friends?
38. . . .you were the kind of person to whom others were attacted because of your confidence, energy and ethusiasm?
39. . . .you did a lot of entertaining either at home or in restaurants?
40. . . .you enjoyed being the center of attention or were particularly seductive or flirtatious, as if you were playing a role?
41. . . .you had a particularly intense romantic life?
42. . . .Are you the kind of person who *always* had an intense romantic life?
43. . . .you wore clothing or a hairstyle that was dramatic, extravagant, very high fashion or very unusual?
44. . . .you were full of plans or got involved in many projects, jumping from one activity to another?
45. . . .you had difficulty saying NO to business or social opportunities, even when you knew you did not have time for them?
46. . . .you frequently (that is, more frequently than is common for your friends or acquaintances) changed . . .
    a) your job?
    b) your place of residence?
    c) your friends?
    d) your favorite sports or hobbies?
47. . . .you found it very pleasurable and exciting to get involved in dangerous, risky, challenging or emotionally intense activities?
48. . . .you tended to do the opposite of what people wanted you to do or to play the devil's advocate?
49. . . .your mood changed rapidly from happy to sad and back again?
50. . . .you felt like crying and laughing at the same time?
51. . . .you were very irritable, for example:
    a) even the smallest thing could make you very irritable?
    b) you found that you were particularly critical or sarcastic?
    c) you had great difficulty seeing other's points of view?
    d) you were unusually argumentative or showed unusual hostility?
52. . . .you had trouble controlling your temper, for example:
    a) you felt that you really needed to even the score?
    b) you found yourself shouting at people or starting arguments or fights even over minor matters?
53. . . .your mood became irritable or elevated when you had a medical problem such as the flu or a cold?
54. . . .your mood became irritable or elevated when you took medications (that were not prescribed to change one's mood), such as antibiotics, contraceptives, or steroids?
    I have never taken such medications.
55. . . .your mood became irritable or elevated when you were abusing (and clearly in relation to) alcohol, sedatives, hypnotics, anxiolytics, other substances, or within a month of withdrawal?
    I have never taken such substances.
56. . . .your mood became irritable or elevated when you increased your use of alcohol, sedatives, nicotine, caffeine, stimulants and similar substances when you were irritable or high?
    I have never taken such substances.
57. . . .If you answered YES to any of the questions from 29 to 56, were you seriously limited, preoccupied or troubled by what was happening to you?

- **Measuring Mood Spectrum: Comparison of Interview**
- **(SCI-MOODS) and Self-Report (MOODS-SR) Instruments**

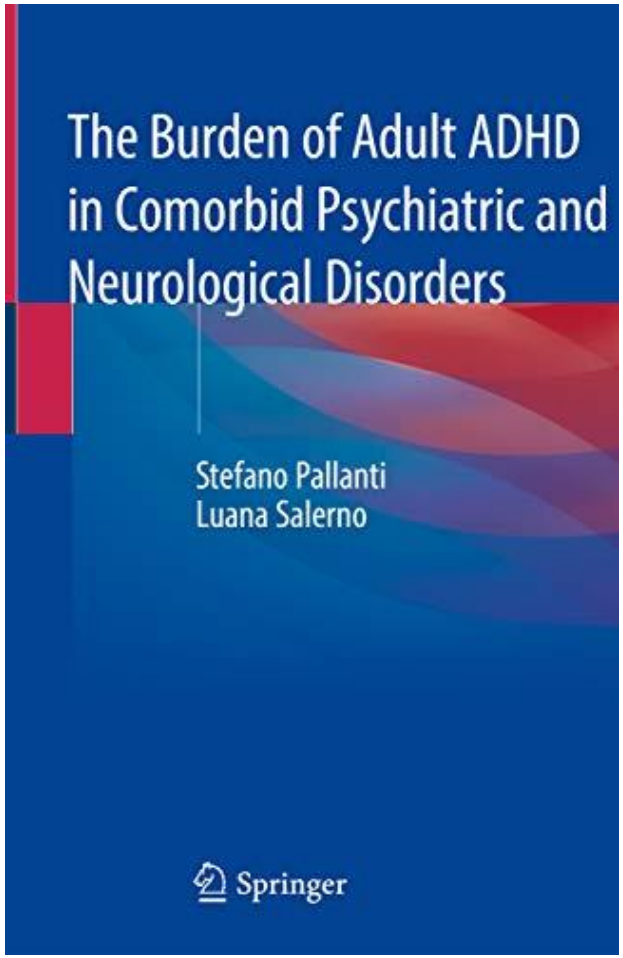
Table 2. Intraclass Correlation Coefficients and 95% Confidence Intervals for the Domains and Subdomains of the SCI-MOODS and MOODS-SR

	ICC	95% CI
Mood depressive	0.93	0.87-0.96
Mood manic	0.94	0.90-0.97
Energy depressive	0.91	0.84-0.95
Energy manic	0.88	0.79-0.93
Cognitive depressive	0.96	0.94-0.98
Cognitive manic	0.90	0.82-0.94
Rhythmicity	0.89	0.80-0.94
Total score	0.97	0.94-0.98

Basic concepts: Safety and Predominant polarity for decision making

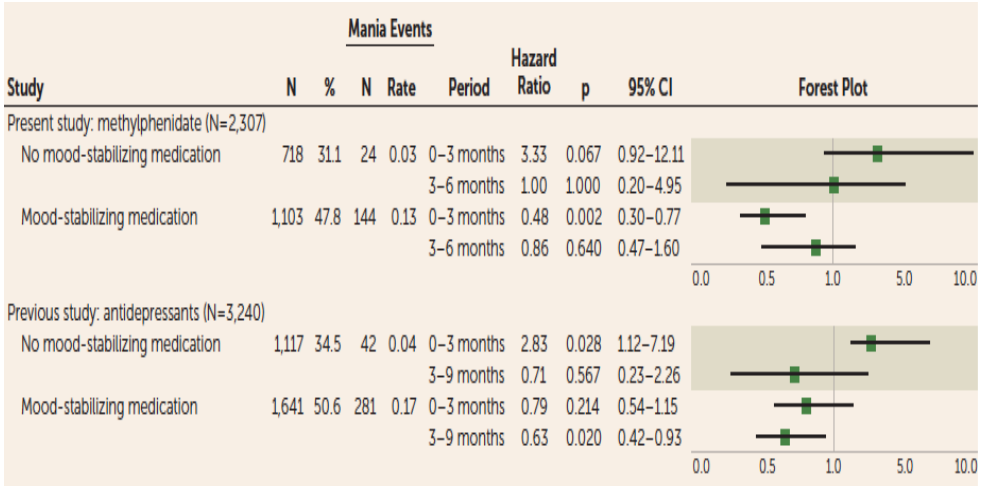
- The most important treatment modifiers are the presence of psychotic features and suicidal ideation. The importance of recognizing suicidality, cannot be emphasized enough given the outstanding excess mortality from suicide in untreated bipolar disorder patients (Angst F. et. A,l 2002)
- The issue of the mixed features (Angst 2007, Goodwin 2012)
- Consideration of the predominant polarity of the illness (Popovich, 2012) is a rather new concept in the optimization of long-term assessment and treatment that may already impact acute treatment decisions (Colom et. al, 2006)

Comorbid Mixed not Bipolar vs.Bipolar ADHD, PTSD, BLPD, ANXIETY, OCD



- Frequent
- Hidden
- Confusing
- Comprehensive assessment
- Neurological SNS
- Cognitive Assessment
- To treat or not to treat
- Personality vs temperament
- Affect vs mood instability

Metilphenidate in bipolar disorder: what do we risk?



Study	N	%	Mania Events N	Rate	Period	Hazard Ratio	p	95% CI
Present study: methylphenidate (N=2,307)								
No mood-stabilizing medication	718	31.1	24	0.03	0–3 months	3.33	0.067	0.92–12.11
					3–6 months	1.00	1.000	0.20–4.95
Mood-stabilizing medication	1,103	47.8	144	0.13	0–3 months	0.48	0.002	0.30–0.77
					3–6 months	0.86	0.640	0.47–1.60
Previous study: antidepressants (N=3,240)								
No mood-stabilizing medication	1,117	34.5	42	0.04	0–3 months	2.83	0.028	1.12–7.19
					3–9 months	0.71	0.567	0.23–2.26
Mood-stabilizing medication	1,641	50.6	281	0.17	0–3 months	0.79	0.214	0.54–1.15
					3–9 months	0.63	0.020	0.42–0.93

- 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. (L S Souza, 2016)
- 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.

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

Viktorin et al. The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder. Am J Psy, 2017.

Chang K, Nayar D, Howe M, et al. Atomoxetine as an adjunct therapy in the treatment of co-morbid attentiondeficit/hyperactivity disorder in children and adolescents with bipolar I or II disorder, J Child Adolesc Psycho - pharmacol 2009;19:547–51.

Dell'Osso B, Ketter TA. Use of adjunctive stimulants in adult bipolar depression. Int J Neuropsychopharmacol 2013;16:55–68.

Pharmacological Treatment for Comorbid Bipolar Disorder and Obsessive-Compulsive Disorder in Adults

Vitor de Mello Netto, Carolina A. Flores, Stefano Pallanti 2020

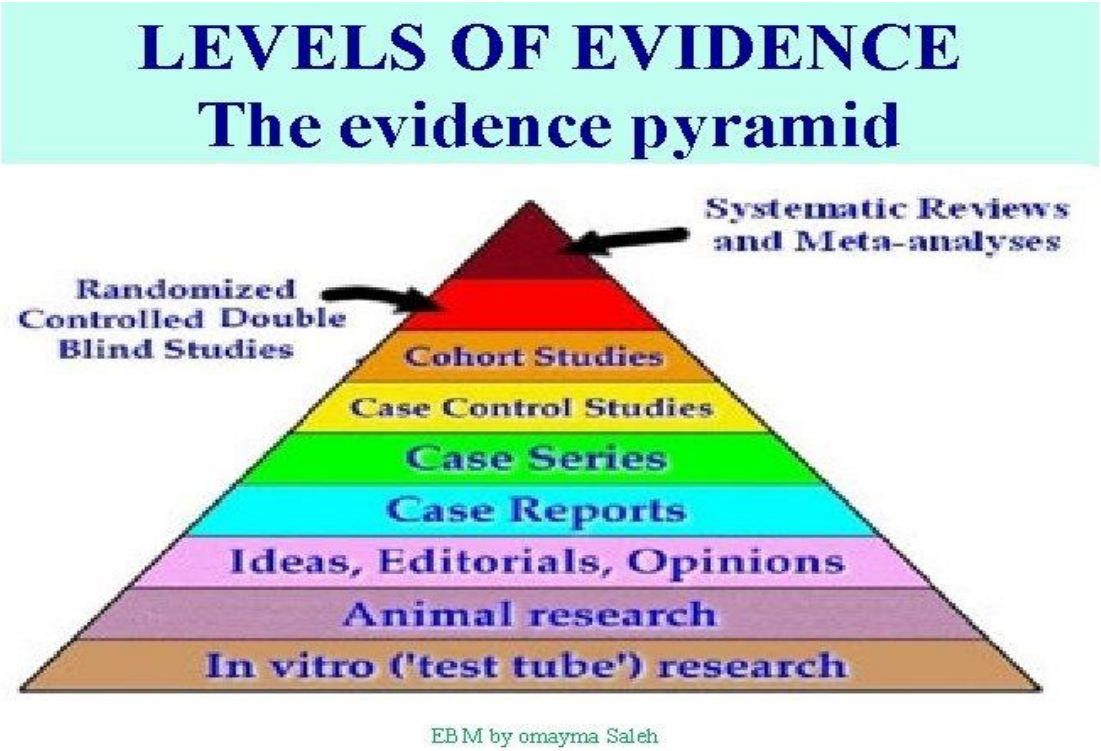
- Augmentation of mood-stabilizer treatment with glutamate modulator agents (topiramate or memantine) may favor full response of obsessive-compulsive symptoms in patients with BD type I and OCD in the manic phase, and that it does not significantly induce adverse effects.
- Results of a narrative synthesis of observational studies indicated greater efficacy of mood-stabilizer treatment, with serotonin reuptake inhibitors less used.
- When OCD is presenting with mixed mood symptoms give the priority to the treatment of mood

Lithium it's great but has low response for depressive episode

- Lithium, alone or in combination, appears to be effective in the treatment of bipolar depression and is considered a first-line treatment by Consensus specialists (Yatham L.N., et 2018). According to a meta-analysis of older studies lithium is superior to placebo in bipolar depression. But with a low response rate 36% (Zornberg G.L., Pope, 1993).
- Lithium's precise mechanisms of action remain to be established. However, lithium's possible neuroprotective effect may have a pleiotropic mechanism of action influencing several intracellular pathways namely, sodium/potassium ATPase pathways, GSK-3- related pathways as well as the expression of neurotrophic factors.
- Modifying the dopaminergic transmission by quetiapine's D2 receptor blocking activity results indirect mediating the cAMP-PKA and the arrestin-Akt-GSK-3 intracellular signal transduction pathways, which process may explain its long-term antimanic and mood stabilizing capability).

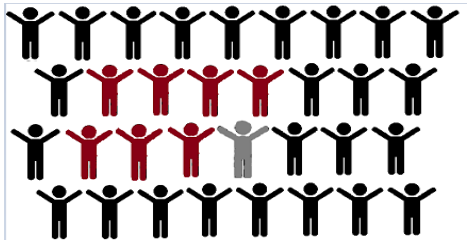
Drawing a line: Expert Opinion and EBM

- Some concepts to introduce before getting in the matter : expert opinion and EBM



Number Needed to Treat (NNT): the number of individuals who need to receive a treatment in order for just one person to receive benefit or to prevent an adverse outcome.

To be calculated one must find the **absolute risk reduction (ARR)**, meaning the amount that the risk is reduced by the treatment compared with people who didn't receive it.



ADVANTAGES	DISADVANTAGES
Immediate method of evaluating the efficacy of a treatment.	It may minimize the gravity and frequency of an adverce event.
Eases the confrontation between various treatments.	NNH derived from trials are generally higher (safer therapies) than real care settings.
Relatively easy to calculate and interpret. NNT and NNH are particularly useful when attempting to quantify categorical measures such as response, remission and safety Ideal is 1 : one treatment one therapeutic success	NNT does not account for an individual patient's baseline risk. If a patient's individual risk is higher or lower than that studied in a trial, his or her NNT will be lower or higher, respectively. (clinician treat individual not group)
	May not find significant differences between groups

Polarity Index of drugs

(Carvalho et al 2015)

Table 2. Number Needed to Treat for the Prevention of Manic and Depressive Episodes and Polarity Index of Drugs Used for Maintenance treatment of Bipolar Disorder.

Treatment	NNT mania	NNT depression	Polarity Index
Aripiprazole monotherapy (Keck et al., 2007)	7.0	73.0	10.4
Aripiprazole adjunctive to lithium/divalproex-pooled (Marcus et al., 2011; Woo et al., 2011)	9.0	38.0	4.2
Lamotrigine-pooled (Bowden et al., 2003; Calabrese et al., 2003)	50.4	20.2	0.4
Lithium-pooled (Prien et al., 1973; Bowden et al., 2000, 2003; Calabrese et al., 2003; Weisler et al., 2011)	4.4	6.1	1.4
Olanzapine monotherapy-pooled (Tohen et al., 2006; Vieta et al., 2012)	4.4	17.5	4.0
Olanzapine combined with lithium/divalproex (Tohen et al., 2004)	11.2	6.2	0.5
Oxcarbazepine combined with lithium (Vieta et al., 2008)	8.2	5.1	0.6
Quetiapine monotherapy (Weisler et al., 2011)	2.4	3.3	1.4
Quetiapine combined with lithium/divalproex-pooled (Vieta et al., 2008; Suppes et al., 2009)	7.1	5.9	0.8
Risperidone LAI monotherapy-pooled (Quiroz et al., 2010; Vieta et al., 2012)	4.0	36.3	9.1
Adjunctive risperidone LAI (Macfadden et al., 2009)	7.9	15.8	2.0
Divalproex (Bowden et al., 2000)	21.3	10.5	0.5
Ziprasidone Adjunctive to lithium/divalproex (Bowden et al., 2010)	14.1	55.1	3.9
Paliperidone ER (Berwaerts et al., 2012)	8.0	17.0	N/A

NNT values in italic are negative, indicating that placebo was more effective than active treatment, although results of original trials did not reach statistical significance. When more than one RCT was available for a given treatment, calculations represent pooled results. LAI, long-acting injection; N/A, could not be calculated accurately as the NNT for the prevention of depression is negative; NNT, number needed to treat; RCT, randomized controlled trials.

The «so called SGA» binding profiles
(and a Neurosciences based nomenclature , Zohar et al 2020)

Receptor Ki (nM)[1]	Clozapine (3)	Olanzapine (32)	Quetiapine (33)	Risperidone (4)	Paliperidone (34)	Sertindole (36)	Lurasidone[3] (38)
D_2	144	21	245	4.9	2.8	2.7	1.0
D_1	189	58	1277	147	41	12	262
D_3	270	49	240	3.6	6.9	2.5	15.7
D_4	39	14	2000	4.4	54	9.0	29.7
D_5	235	90	1738	563	29	NA[2]	NA
5-HT_{1A}	105	2063	431	427	638	280	6.4
5-HT_{2A}	5.2	2.65	135	0.17	1.2	0.28	0.47
5-HT_{2C}	10.7	14	1184	12	48	0.90	415
α_{1A} adrenergic	1.6	109	22	5.0	2.5	1.8	NA
α_{1B} adrenergic	7.0	263	39	9.0	0.70	NA	NA
H_1 histaminergic	2.0	4.9	7.5	15	5.6	130	>1000
M_1 muscarinic	14	24	120	>10,000	>10,000	NA	>1000

4 FDA approved at sub. antipsychotic dose; in a nutshell

- Superior to placebo in large randomized clinical trials (**OFC** Tohen et 2003, **Q** Calbrese et 2005,**L** Loebel et 2014 **C**, Durgam et 2016) **at a sub-antipsychotic dosage**
- Manic switch rates were not distinguished from placebo
- But…samples were highly selected, excluding the most severe patients, that is, the most agitated or aggressive patients, or those presenting suicidal ideation or substance abuse. Dropout rates were very high and, although the substance had outperformed placebo, response rates were not as high (Cheniaux E. et 2011)

- **OLANZANPINE** (Fluox) Antagonist D1D2D3
- 5HT2 NE alfa1 alfa2 H1
- **QUETIAPINE** Antagonist D1D2D3 5HT2 Ne alfa 1 alfa2 H1
- Norquetiapine Antagonist of NE transporter (NET), partial agonist activity at 5-HT_{1A} receptor
- **LURASIDONE** Antagonist D2 D3 5HT2 5HT7 alaf 2c partial agonist 5HT1
- **CARIPRAZINE** Antagonist 5HT2b
- partial Agonist D2 D3 5Ht1A
- desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR).

Cariprazine Bip. I the last comer

The dose recommended by the FDA for bipolar I depression ranges from 1.5 mg to 3mg per day (May 2019)

Table 2

Binding affinities of cariprazine

Receptor	Binding affinity (nM Ki)	Binding profile
D3	0.085	Partial agonist
D2L	0.49	Partial agonist
5-HT2B	0.58	Antagonist
D2S	0.69	Partial agonist
5-HT1A	2.6	Partial agonist
5-HT2A	18.8	Antagonist
H1	23.2	Antagonist
5-HT7	111.0	Antagonist
HT2C	134.0	Antagonist
α-1	155.0	Antagonist
Muscarinic	>1,000.0	Antagonist

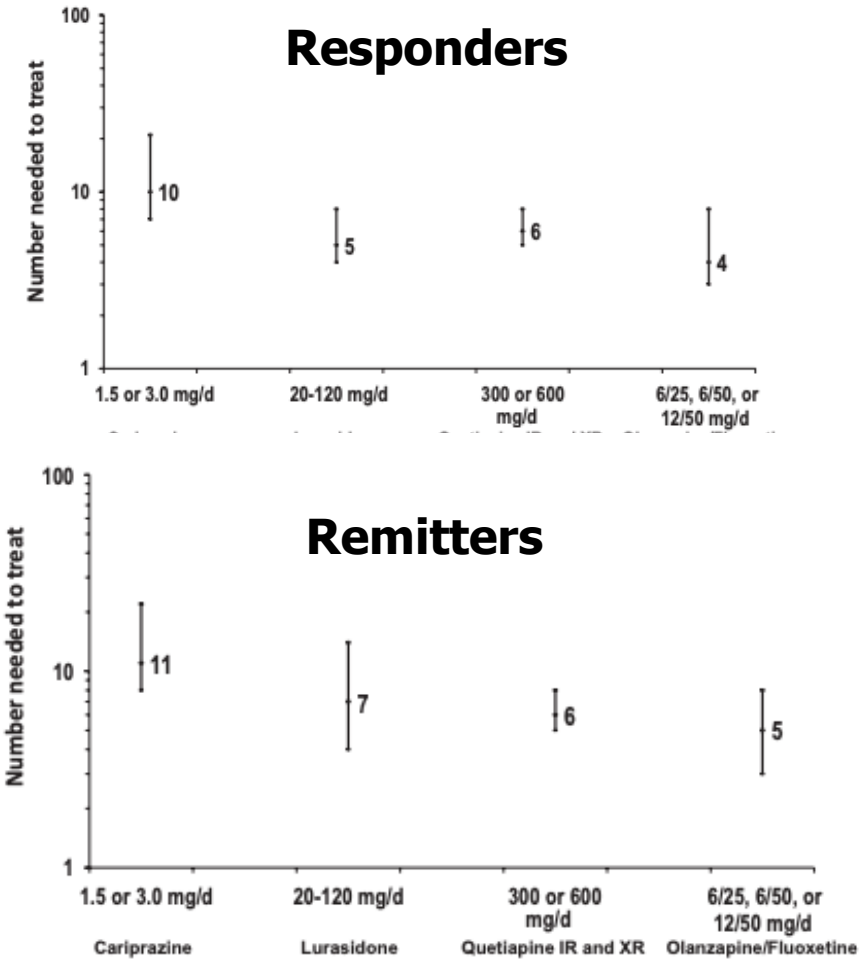
Study	Treatment	*n*	MADRS	
			Baseline	Change at week 6
Durgan[29]	Placebo	141	30.4	−11.1
	Cariprazine 1.5 mg/day	143	30.3	−15.1*
	Cariprazine 3.0 mg/day	145	30.6	−13.7
Earley[30]	Placebo	156	30.2	−12.6
	Cariprazine 1.5 mg/day	154	30.7	−15.1*
	Cariprazine 3.0 mg/day	164	31.0	−15.6*
MD-53[28]	Placebo	163	31.4	12.4
	Cariprazine 1.5 mg/day	162	31.5	14.8*
	Cariprazine 3.0 mg/day	153	31.5	14.1*

*$p < 0.05$ *versus* placebo.
MADRS, Montgomery Asberg Depression Rating Scale.

Mc Intyre, 2019

Number needed to treat: Cariprazine

(Citrome L., 2019; Pinto et al 2020)

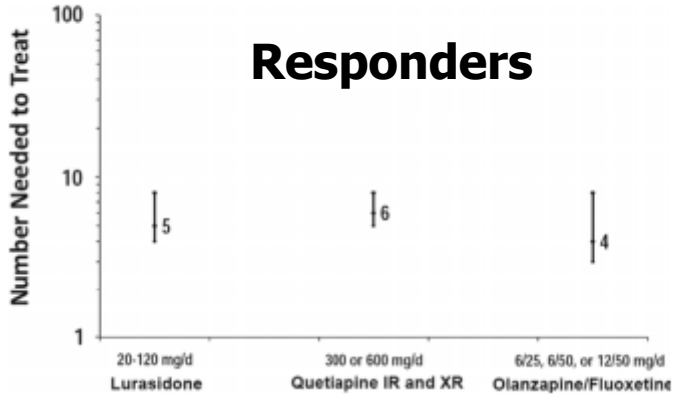


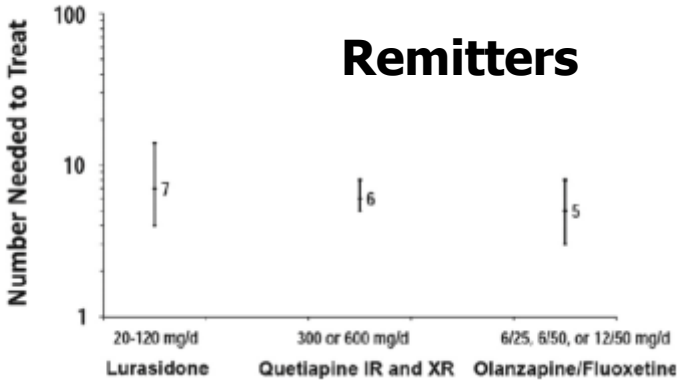
- The NNT based on MADRS remission for Cariprazine (NNT=10) is higher than the NNT for established first-line treatments such as olanzapine-fluoxetine combination (NNT=1.8), lurasidone(NNT: 4.6), and quetiapine (NNT=6) but is comparable to pooled antipsychotics (NNT=8.2), third-line treatments such as olanzapine (NNT=11), and better than monotherapies not recommended by CANMAT and ISBD guidelines.
- Benign weight and metabolic profile
- Not excessively sedating.

Number needed to treat: Lurasidone (Citrome L., et. al 2014) Lurasidone (Latuda) used alone or with lithium or valproate (Depakote)

Table 2
Response, remission, and number needed to treat vs. placebo (ITT population).

	Adjunctive lurasidone 20–120 mg/d vs. adjunctive Placebo		Lurasidone monotherapy 20–60 mg/d or 80–120 mg/d vs. placebo		
	Lurasidone	Placebo	Lurasidone 20–60 mg/d	Lurasidone 80–120 mg/d	Placebo
ITT population, *N*[a]	179	161	161	162	162
Responders, *n* (%)[b]	102 (57.0%)	68 (42.2%)	86 (53.4%)	82 (50.6%)	49 (30.2%)
NNT, response vs. placebo (95% CI)	7 (4–24)	NA	5 (3–8)	5 (4–11)	NA
Remitters, *n* (%)[c]	90 (50.3%)	57 (35.4%)	68 (42.2%)	64 (39.5%)	40 (24.7%)
NNT, remission vs. placebo (95% CI)	7 (4–23)	NA	6 (4–14)	7 (4–21)	NA





- Approved for the treatment of bipolar I depression as monotherapy and as adjunctive therapy
- Comparable benefits to other approved bipolar depression treatments
- less risk of harm
- more favorable ratio of benefit to harm likelihood

Olanzapine|fluoxetine (Symbyax)

- First FDA approved for TRD (2003) then Bipolar I (2009
- **Tohen M, Vieta E, Calabrese (2003)**
- The starting dose of SYMBYAX 3 mg/25 mg – 6 mg/25 mg
- A review of three controlled trials of OFC in bipolar depression found that the number needed to treat (NNT) for response compared with placebo was **4**, the NNT for remission was **5,** and the number needed to harm (i.e., to produce adverse effects) was 6 for clinically significant weight gain (i.e., at least 7% of baseline weight) (Citrome, 2011).
- A 25-week, randomized, double-blind comparison of OFC in various doses with 200 mg of lamotrigine for bipolar depression reported that OFC was significantly better for reduction of depression and mania rating scale scores and global improvement after a 7-week acute phase and at the end of the study 8Brown et al 20007,2009)
- FC trades simplicity of administration for loss of flexibility of dosing and lack of a generic preparation
- olanzapine for bipolar depression when combined with fluoxetine suggests that not only are serotonin reuptake
- blocking properties, a component of the antidepressant
- effect of olanzapine–fluoxetine combination therapy, but also 5HT2C antagonist actions Both olanzapine and fluoxetine are 5HT2C antagonists, and, in combination, the net 5HT2C antagonism is greater than with either drug alone. So, this olanzapine–fluoxetine combination for depression could be considered a potent SERT/5HT2C inhibitor.
- Special population
- Pregnancy???
- Children adolescent
- Mixed features (Benazzi, 2009)
- Non-steroid inflammatory agents (e.g., ibuprofen) may impair the effectiveness of fluoxetine.
- CYP1A2, including tobacco **smoke** and carbamazepine, decrease **olanzapine** concentration as well as **heavy coffee consumption** (Djordjevic N. et al. 2008), 2018)
- cognitive slowing or apathy seen with fluoxetine

Number needed to treat: Quetiapina

(Citrome L., 2014)

TABLE 8. Polarity index for commonly used maintenance treatments for bipolar disorder

Agent	Polarity index
Lithium	1.39
Lamotrigine	0.40
Valproate	0.49
Olanzapine	3.90
Aripiprazole	8.06
Risperidone long-acting injectable	12.09
Quetiapine with lithium/valproate	0.83

Data from reference 40; the polarity index may differ depending on which studies have been included when calculating the respective NNT values.[39,40]

- D2 Mean occupancy of 36+/-16% and in the thalamus. In the caudate nucleus there was an occupancy of 29+/-16% (p=0.0072). Individual occupancy levels did not exceed 59% in any of the striatal volumes of interest (Vernakelen et al 2010).
- Enhances the transmission of the central serotonergic networks, by its high antagonistic affinity for 5-HT(2A) and partial agonistic activity for the 5-HT(1A) receptors.
- The 5HT(1A) partial agonism causes an increase in the dopaminergic neurotransmission of the prefrontal cortex, and also, the affinity for the alpha 2-adrenoceptor brings a relative increase in extracellular noradrenergic release a tone in the prefrontal cortex.
- Very fast dissociation from the D2 receptor (Sumegi, 200)

The strage case of quetiapine lamotrigine anf folic acid: the third intruder

(Geddes et. Al, 2016)

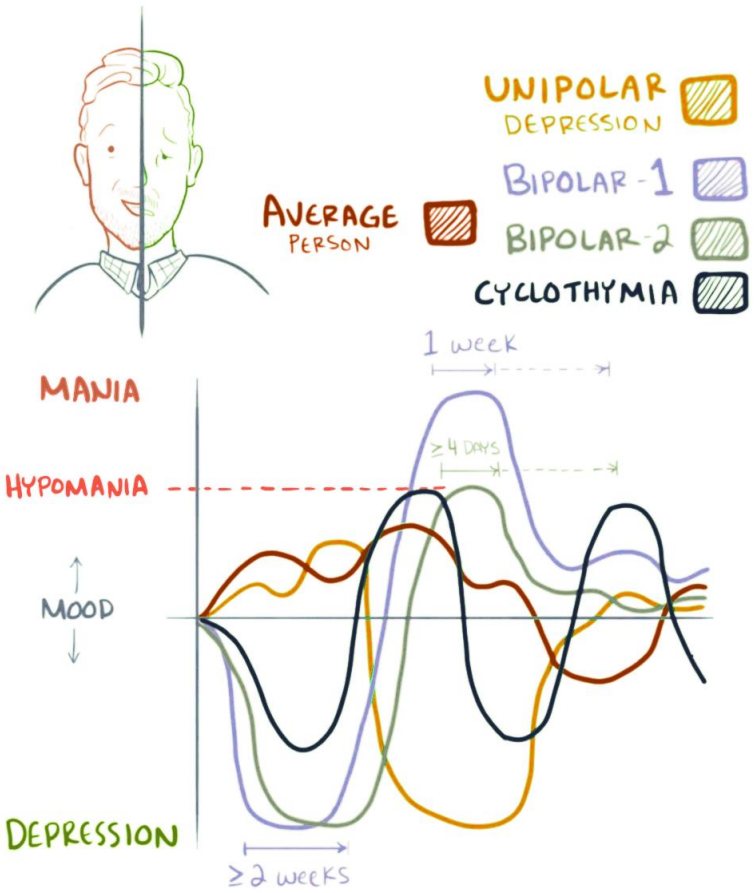
- 202 participants were randomly assigned; 101 to lamotrigine and 101 to placebo. The mean difference in QIDS-SR16 total score between the group receiving lamotrigine versus the placebo group at 12 weeks was -1·73 ([95% CI -3·57 to 0·11]; p=0·066) and at 52 weeks was -2·69 ([-4·89 to -0·49]; p=0·017).
- Folic acid was not superior to placebo.
- There was a significant interaction (p=0·028), with folic acid reducing the effectiveness of lamotrigine at 12 weeks.
- The mean difference on QIDS-SR16 was -4·14 ([95% CI -6·90 to -1·37]; p=0·004) for patients receiving lamotrigine without folic acid compared with 0·12 ([-2·58 to 2·82]; p=0·931) for those receiving lamotrigine and folic acid.

- Addition of lamotrigine to quetiapine treatment improved outcomes. Folic acid seems to nullify the effect of lamotrigine.

CEQUEL should encourage clinicians and patients to consider lamotrigine for bipolar depression, but also to be aware that concurrent folic acid might reduce its effectiveness.

Depressive or Manic predominance for guideline driven decision making?

The concept of predominant polarity (PP) is defined as presenting more symptoms of one polarity. Previous studies have defined PP as one polarity (either a depression or mania episode) occurring during at least two-thirds of the lifetime. Patients with DPP were more often medicated with lamotrigine and antidepressants, patients with MPP were more often treated with lithium, valproate, carbamazepine and first-generation antipsychotics. However, patients with DPP and MPP did not differ significantly with respect to the PI, although they received evidence-based and guideline-driven treatment (Sentissi et. al, 2019).



Clinical guideline to treat Acute Bipolar Depressive Episodes

1st step	• Start with quetiapine, lurasidone, or OFC • Consider add-on CBT. Never consider CBT as monotherapy
2nd step	• Monotherapy with valproate or lithium • Combination of a mood stabilizer with lurasidone, modafinil, or pramipexole • Lithium plus pioglitazone • Carbamazepine plus FEWP • 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 step	• Aripiprazole, imipramine, or phenelzine monotherapy • Lithium plus oxcarbazepine or L-sulpiride
4th step	• Olanzapine, lamotrigine, tranylcypromine, or carbamazepine monotherapy • Venlafaxine preferably in combination with an antimanic agent • Armodafinil or ketamine on a mood stabilizer • Lithium plus fluoxetine or lamotrigine
5th step	• ECT • Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
Not recommended	Monotherapy with donepezil, paroxetine (except for comorbid anxiety), ziprasidone, gabapentin, lithium and rTMS, combination of any mood stabilizer with agomelatine, paroxetine, ziprasidone, bupropion, celecoxib, levetiracetam, lisdexamfetamine or risperidone, Memantine plus lamotrigine and lithium plus aripiprazole, donepezil or imipramine. Not recommended also risperidone or ziprasidone for the treatment of concomitant anxiety

Fountoulakis K. N. et al., The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 3: The Clinical Guidelines. *International Journal of Neuropsychopharmacology* (2017) 20(2): 180–195

Level of Recommendation Concerning Monotherapy and Combination Treatment in Acute Bipolar Depression and also for Comorbid Anxiety

	Monotherapy				Combination					
Agent/modality	Overall	BD-I	BD-II	Comorbid anxiety	MS	Cbz	Lam	Li	Val	Recommended Dosage (mg/d)
Quetiapine	1	3	3	3	-	-	-	-	-	300–600
OFC	2	3	-	-	2	-	-	-	-	6 + 25; 6 + 50; 12 + 50
Lurasidone	2	-	-	3	2	-	-	-	-	20–120
Escitalopram	2	-	3	-	-	-	-	-	-	10
Fluoxetine	2	-	3	-	-	-	-	4	-	20–80
Valproate	3	3	5	3	-	-	-	-	-	500–2500 (50–100 mcg/mL)
Aripiprazole	3	3	-	-	-	-	-	5	-	5–30
Imipramine	3	-	-	-	-	-	-	5	-	75–300
Phenelzine	3	-	-	-	-	-	-	-	-	15–90
Olanzapine	4	4	-	-	-	-	-	-	-	5–20
Lamotrigine	4	4	4	-	-	-	-	4	-	50–200
Tranylcypromine	4	4	4	-	-	-	-	-	-	20–30
Venlafaxine	4	4	4	-	-	-	-	-	-	75–225
Carbamazepine	4	-	-	-	-	-	-	-	-	300–800
Lithium	5	-	4	5	-	-	2	-	-	600–1800
Paroxetine	5	5	5	3	5	5	-	5	5	20
Gabapentin	5	-	-	-	-	-	-	-	-	
rTMS	5	-	4	5	-	-	-	-	-	
Ziprasidone	5	5	-	5	5	-	5	5	5	
FEWP	-	-	-	-	-	1	-	-	-	36 g/d
Levothyroxine (L-T4)	-	-	-	-	2	-	-	-	-	300 mcg/d
Modafinil	-	-	-	-	2	-	-	-	-	100–200
Pioglitazone	-	-	-	-	-	-	-	2	-	30
Pramipexole	-	-	-	-	2	-	-	-	-	1–3
Armodafinil	-	-	-	-	4	-	-	-	-	150
Ketamine	-	-	-	-	4	-	-	-	-	0.5 mg/kg i.v. (single dosage)
L-sulpiride	-	-	-	5	-	-	-	3	-	50–75
Oxcarbazepine	-	-	-	3	-	-	-	2	-	600–1200
Agomelatine	-	-	-	-	5	-	-	5	5	
Imipramine	-	-	-	-	-	-	-	5	-	
Memantine	-	-	-	-	-	-	5	-	-	
Levetiracetam	-	-	-	-	5	-	-	-	-	
Bupropion	-	-	-	-	5	-	-	-	-	
Celecoxib	-	-	-	-	5	-	-	-	-	
Risperidone	-	-	-	5	5	-	-	-	-	

Level of Recommendation during the Maintenance Phase, Efficacy in the Prevention of Manic, Mixed, or Depressive Episodes and Recommended Dosages

	Monotherapy			Combination					
Agent/modality	Manic	depressive	Mixed	MS	Cbz	Lam	Li	Val	Recommended dosage
Quetiapine	2	2	-	1	-	-	-	-	300–800 mg/d
Olanzapine	2	2	2	4	-	-	-	-	5–20 mg/d
Lithium	2	3	-	-	-	-	-	-	0.6–1.2 mEq/L
Lamotrigine	4	4	-	-	-	-	-	-	50–400 mg/d
Psychoeducation	-	-	--	3	-	-	-	-	
Aripiprazole	1	5	-	2	-	5	-	5	10–30 mg/d
RLAI	1	5	-	2	-	-	-	-	25–50 mg/biweekly
Paliperidone	2	5	-	-	-	-	-	-	3–12 mg/d
Valproate	4	3	-	-	-	-	-	-	45–100 mg/L
Carbamazepine	4	4	-	-	-	-	-	-	4–12 mg/L
Ziprasidone	-	-	-	4	-	-	-	-	80–160 mg/d
Fluoxetine	-	2	-	-	-	-	-	-	10–40 mg/d
CBT	-	-	-	2	-	-	-	-	
Phenytoin	-	-	-	2	-	-	-	-	Mean studied 380 mg/d (blood levels 10 microgram/mL)
Paroxetine	-	-	-	3	-	-	-	-	20 mg/d
N-acetyl cysteine	-	-	-	4	-	-	-	-	2 g/d
Imipramine	5	5	-	-	-	-	5	-	
Memantine	-	-	-	5	-	-	-	-	
Oxcarbazepine	-	-	-	-	-	-	5	-	
Perphenazine	-	-	-	5	-	-	-	-	

Fountoulakis K. N. et al., The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 3: The Clinical Guidelines. *International Journal of Neuropsychopharmacology* (2017) 20(2): 180–195

Clinical Guideline to Treatment during the Maintenance Phase for Bipolar Disorder

1st step	• Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine, or risperidone (including RLAI) monotherapy • Consider CBT or psychoeducation as add-on to medication. Never consider CBT or psychoeducation as monotherapy • Take predominant polarity (if present) into consideration
2nd step	• Add fluoxetine or lithium on the first-step option • Lithium plus carbamazepine • Quetiapine plus lithium or valproate • Olanzapine or aripiprazole plus a mood stabilizer
3rd step	Add RLAI, valproate, carbamazepine, lamotrigine, or N-acetylcysteine on second-step treatment
4th step	Take into consideration the predominant polarity and add an agent with proven efficacy against the acute phase no matter whether it has proven maintenance efficacy. Consider adding venlafaxine or haloperidol
5th step	Consider any combinations from steps 1–4 that have not been tried Consider maintenance ECT Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
Not recommended	Adding memantine or perphenazine on a mood stabilizer, aripiprazole plus lamotrigine or valproate, lamotrigine plus valproate, lithium plus lamotrigine, imipramine, or oxcarbazepine.

Fountoulakis K. N. et al., The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 3: The Clinical Guidelines. *International Journal of Neuropsychopharmacology* (2017) 20(2): 180–195

Recomendations 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

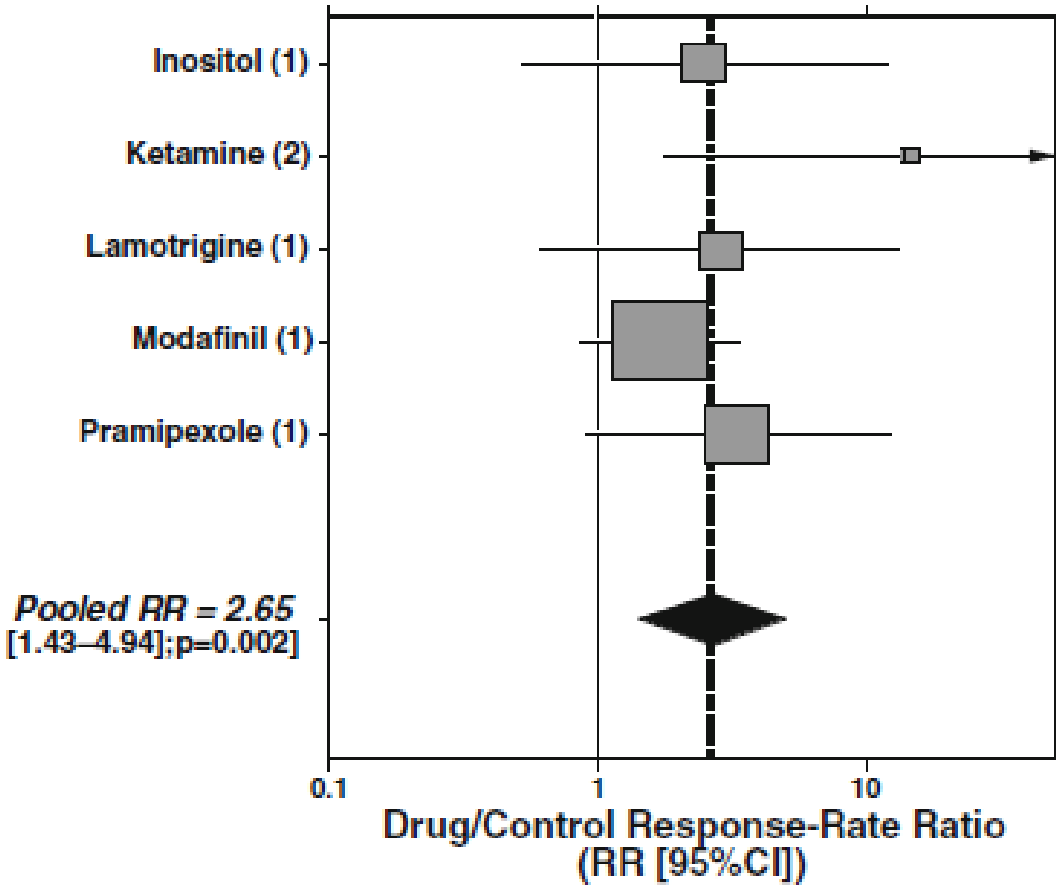
Stahl et al. Guidelines for the recogntion and managment of mixed depression. CNS spectrum 2017.

Criteria for treatment-resistant bipolar depression in adults

Criteria	
	A patient diagnosed with bipolar I or bipolar II disorder according to DSM-5 criteria who currently fulfil criteria for a current moderate or severe major depressive episode AND who failed to reach sustained symptomatic remission at least for 8 consecutive weeks or did not tolerate two different trials at adequate therapeutic doses for 8 weeks either with: 1. At least two treatments in monotherapy listed in box A **OR** 2. At least one treatment in monotherapy listed in Box A **AND** one treatment in Box A in combination with one different treatment in Box B
A	– Olanzapine (10–20 mg/day) and fluoxetine (20–60 mg/day)a – Quetiapine (300–600 mg/day) – Lurasidone (37–148 mg/day) – Lamotrigine (200–400 mg/day)b
B	– Lamotrigine (200–400 mg/day) – Valproate (1000–2000 mg/day)c – Lithium (reaching 0.8 mEq/L in plasma)
a. Combination of olanzapine and fluoxetine (OFC) and medications listed in Box B not supported by National Institute for Health and Care Excellence (NICE) and British Association for Psychopharmacology (BAP) treatment guidelines for bipolar Disorder. b. Combination of lamotrigine and valproate not supported by NICE and BAP treatment guidelines for bipolar disorder. If used, monitor side-effects and/or levels closely. c. Contraindicated in female patients of childbearing potential unless conditions of pregnancy prevention program are met.	

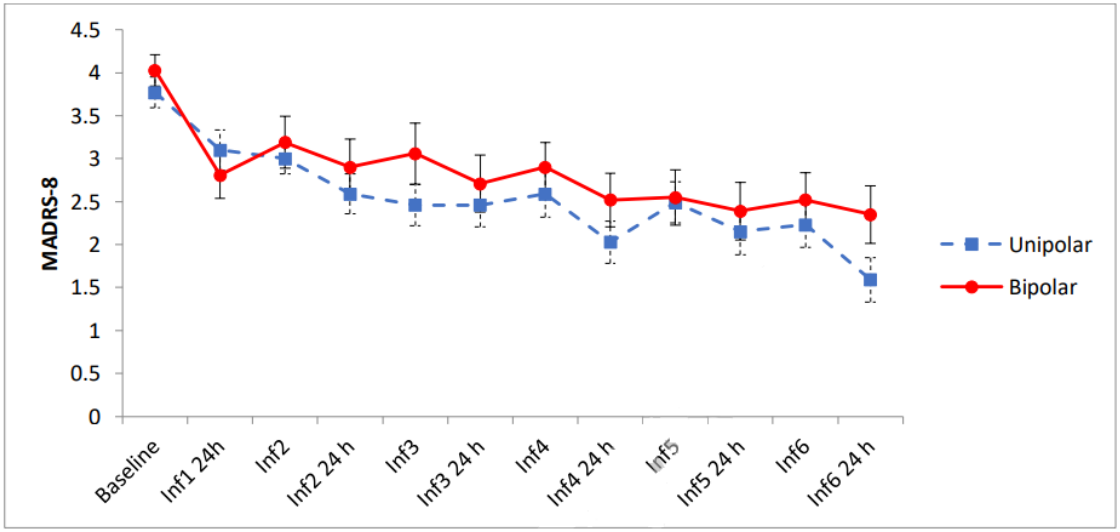
Hidalgo-Mazzei D. et al., Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition. The British Journal of Psychiatry (2019). 214, 27–35.

Treatment of resistant and refractory bipolar depression



Tondo L. et al., Options for Pharmacological Treatment of Refractory Bipolar Depression. Curr Psychiatry Rep (2014). 16:431

Subcutaneous Esketamine in the Treatment of Anhedonia in Bipolar and Unipolar Depression



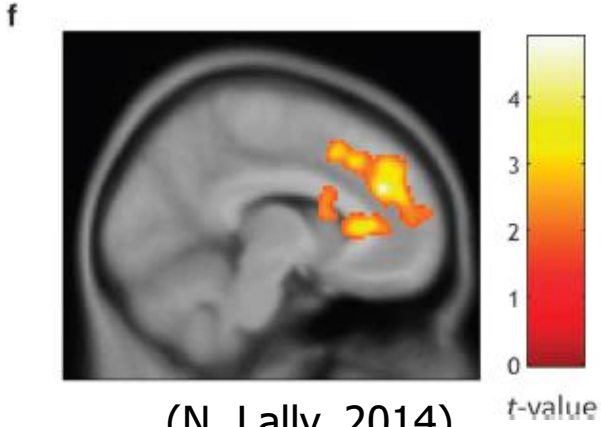
Anhedonia (item 8 MADRS) scores over 6 weekly esketamine infusions. Whole-brain corrected relationship between the anti-anhedonic effects of ketamine and (**d**) dorsal anterior cingulate cortex (dACC), cerebellum, (**e**) right putamen, VS and medial posterior orbitofrontal cortex increases in glucose metabolism. (N Lally Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression)

Esketamine was administered as an add-on treatment, in combination with current treatment. The initial esketamine dose was 0.5mg/kg, delivered by subcutaneous injection once a week for 6 consecutive weeks. Dose escalation (0.75-1.0 mg/kg) was performed throughout the infusion series for patients who had not achieved reduction ≥ 50% on MADRS scores at the 24-hour evaluation post-infusion.

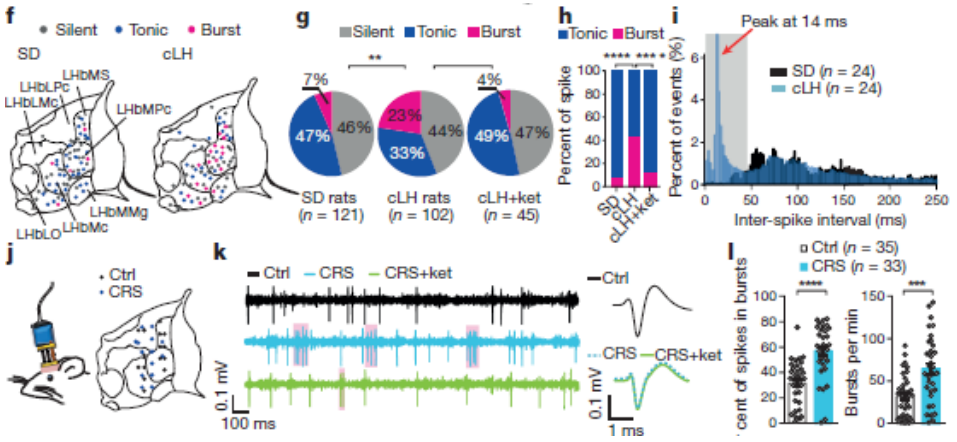
Delfino, Rodrigo Simonini, et al. "Comparative effectiveness of esketamine in the treatment of anhedonia in bipolar and unipolar depression.» *Journal of Affective Disorders* 278 (2021): 515-518.

Ketamine blocks bursting in the lateral habenula: the NMDAR pathway to rapid acting antidepressant (Yang et al 2018)

- K blockade of NMDAR-dependent bursting activity in the 'anti-reward center', the lateral habenula (LHb), mediates the rapid antidepressant actions of ketamine in rat and mouse models of depression
- ketamine quickly elevates mood by blocking NMDAR-dependent bursting activity of LHb neurons to disinhibit downstream monoaminergic reward centers and provide a framework for developing new rapid-acting antidepressants.



(N. Lally, 2014)



Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial

Stephen Kanes, Helen Colquhoun, Handan Gunduz-Bruce, Shane Raines, Ryan Arnold, Amy Schacterle, James Doherty, C Neill Epperson, Kristina M Deligiannidis, Robert Riesenberg, Ethan Hoffmann, David Rubinow, Jeffrey Jonas, Steven Paul, Samantha Meltzer-Brody

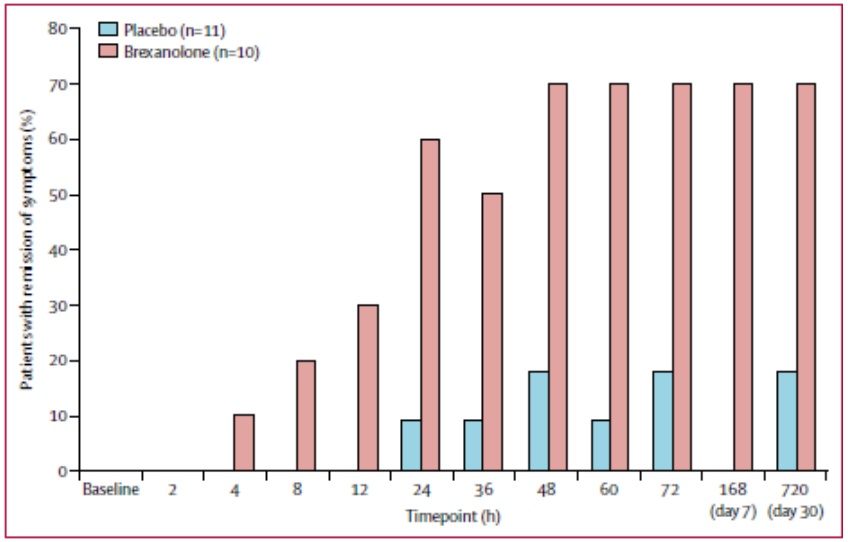


Figure 3: Patients with remission of symptoms

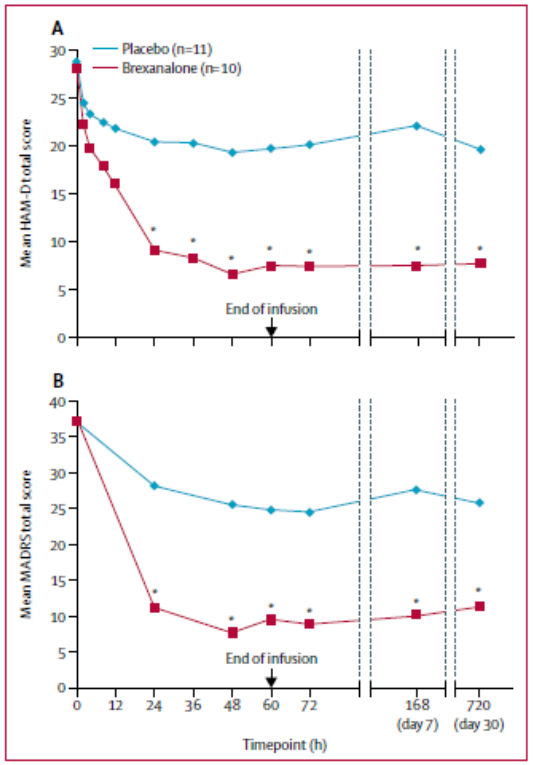
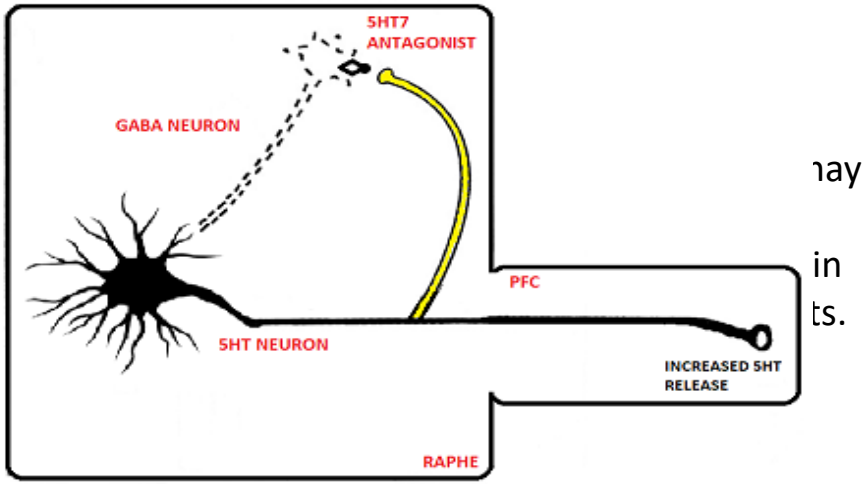


Figure 2: Mean HAM-D and MADRS total scores

Interpretation In women with severe post-partum depression, infusion of brexanolone resulted in a significant and clinically meaningful reduction in HAM-D total score, compared with placebo. Our results support the rationale for targeting synaptic and extrasynaptic $GABA_A$ receptors in the development of therapies for patients with post-partum depression. A pivotal clinical programme for the investigation of brexanolone in patients with post-partum depression is in progress.

Neuroactive steroids target both benzodiazapine-sensitive and insensitive GABA(a) receptors

Neuroactive steroids bind to GABA(a) receptors at a specific allosteric site (neuroactive steroid site), which enhances the inhibitory action of GABA at GABA(a).



Neuroactive steroids target both **benzodiazepine-sensitive** and **insensitive GABA(a) receptors**, which differs from the action of benzodiazepines which only bind to sensitive receptors. The binding to the benzodiazepine incentive GABA(a) receptors is considered the **primary mechanism** of the antidepressive action of neuroactive steroids.

Also, the use of **SAGE-17**, a synthetic orally active allopregnanolone analogue, has shown promising results as an antidepressant for early onset major depressive disorder

Cognitive Profile in Bipolar Depression: treatment implications

- Clinical Assessment: Speed-Processing Attention, ExFunc, Memory.
- Relation with Emotional (Lima et. al, 2018)
- Target for specific treatment:
- TMS (Pallanti et. al, 2014)
- Lurasidone (Lakshmi Nyatham, 2017)
- Lamotrigine (Shi et al 2018) may help alleviate the clinical symptoms and improve cognitive function in patients with depression of recurrent bipolar disorder
- Metabolic obesity worse performance in verbal memory, psychomotor processing speed, and sustained attention. Hypertriglyceridemia associated with a lower score in executive function tasks; hypertension associated with impairment in overall cognitive function (Restrepo Moreno, 2019)
- 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)
- 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.

Cognition improved independently from Clinical
Response with low /1Hz) rTMs Right DLPFC

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Neuropsychobiology

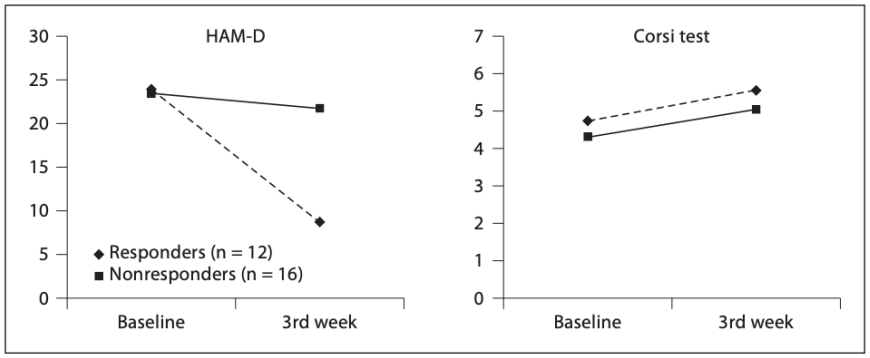
Original Paper

Neuropsychobiology 2012;65:227–235
DOI: 10.1159/000336999

Received: Augsut 30, 2011
Accepted after revision: January 30, 2012
Published online: May 25, 2012

Low-Frequency rTMS over Right Dorsolateral Prefrontal Cortex in the Treatment of Resistant Depression: Cognitive Improvement Is Independent from Clinical Response, Resting Motor Threshold Is Related to Clinical Response

S. Pallanti[a, c, d] A. Di Rollo[d] S. Antonini[d] G. Cauli[e] E. Hollander[b] L. Quercioli[d]



3 weeks LF rTMS over rDLPFC in 28 TRD patients

- **42.9%** responders (significant reduction HAMD, HAMA)
- Improve in **Corsi** block-tapping test and **verbal fluency** independent from depressive symptoms variation
- Significant decrease in **left hemisphere RMT** only in responders.

TMS for bipolar depression

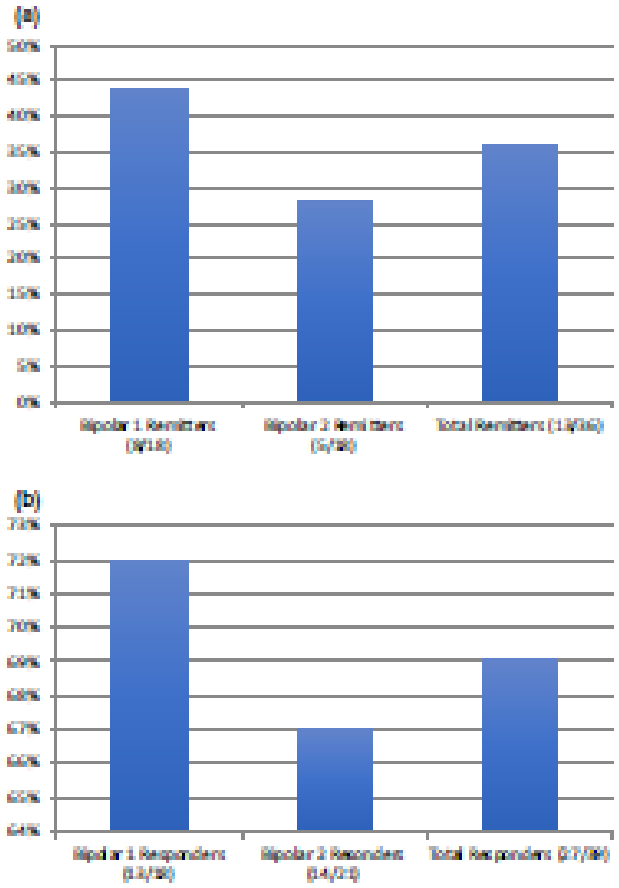
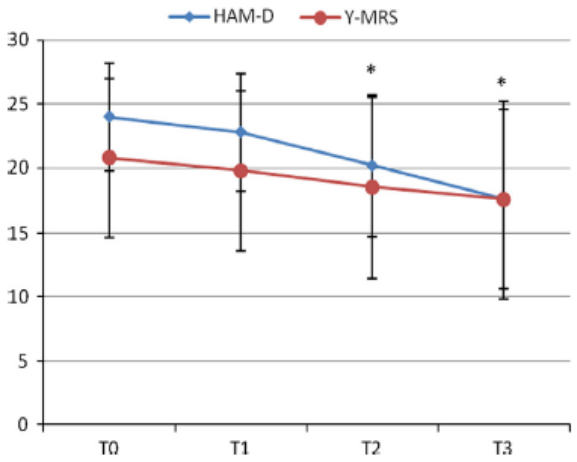


FIGURE 1 (a) Percent of patients meeting remission by MADRS (MADRS ≤ 10). (b) Percent of patients meeting response by MADRS (50% drop from baseline)

- 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,
- 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 (Goldwaser et. al, 2020).

Mixed states: what about TMS?



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Research report

rTMS in resistant mixed states: An exploratory study

Stefano Pallanti [a,b,c,d,*], Giacomo Grassi [b], Sarah Antonini [c], Leonardo Quercioli [c], Emilia Salvadori [b], Eric Hollander [e]

- 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.

Pallanti S, Grassi G,, Antonini A,, Quercioli L, Salvadori E., Hollander E. rTMS in resistant mixed states: an exploratory study. Psychiatry research. Journal of Affective Disorders, 2014.

Theta burst TMS multiple session is even better…

- Theta burst repetitive transcranial magnetic stimulation (r-TMS) had positive results for mood disorders, including Bipolar Dep.
- R-TMS treatment works by stimulating the left dorsolateral prefrontal cortex (DLPFC). In MDD, the DLPFC may be failing to inhibit the subgenual cingulate, and the result of this network failure is cognitive impairment and inwardly directed negative thoughts.
- Stimulating DLPFC, r-TMS corrects the mood imbalance and restores mood regulation.
- In initial numbers from his study of patients with a treatment-resistant mood disorder (TRD), Nolan found that after 5 days of sessions (10 hourly sessions at 1800 theta-burst pulses per hour), participants improved. On the Montgomery Asberg Depression Rating Scale (MADRS), he found an 80% average reduction of participants MADRS scores.

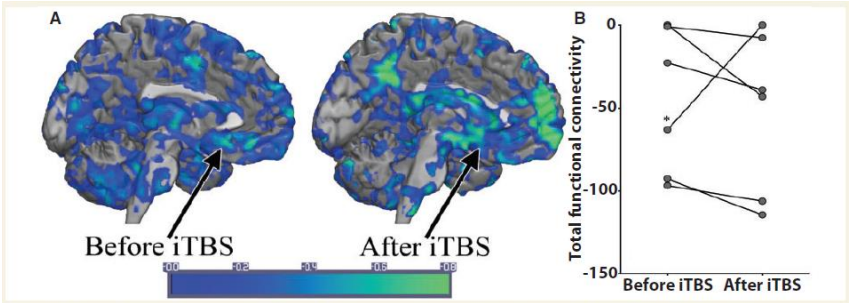


Figure 1 Personalized and targeted iTBS establishes new anti-correlations between L-DLPFC and SCC. (**A**) A representative participant's Fisher's R-Z transform map of anti-correlations between the L-DLPFC before and after iTBS. The arrow indicates the approximate location of SCC. (**B**) Total anti-correlation functional connectivity between L-DLPFC and SCC increases in magnitude after iTBS in five of six participants. Negative numbers on the vertical axis indicate the magnitude of anti-correlation. *The one participant in which the anticorrelation was reduced in magnitude had a diagnosis of Parkinson's disease and was taking levodopa.

Indications: FDA cleared a BDD

- High frequency left DLPFC for MDD – 2008

  "Indicated for the treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode".

- High frequency Deep TMS for MDD– 2013

  "Indicated for the treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode".

- High frequency Deep TMS for OCD – 2018

  "The Brainsway Deep Transcranial Magnetic Stimulation System is intended to be used as an adjunct for the treatment of adult patients suffering from Obsessive-Compulsive Disorder".

- iTBS for MDD– 2018

  "The MagVita TMS Therapy System w/ Theta Burst Stimulation is indicated for the treatment of MDD in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode".

- High frequency Deep TMS for smoking cessation – 2020

  "The Brainsway Deep Transcranial Magnetic Stimulation System is indicated to be used as an aid in short-term smoking cessation for adults".

- iTBS Deep TMS for MDD – 2021

  "The Brainsway Deep Transcranial Magnetic Stimulation System is indicated for the treatment of MDD in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode".

- **BIPOLAR DISORDER** – 2020

  FDA has granted breakthrough device designation for NeuroStar Advanced Therapy (Neuronetics Inc) TMS system for the treatment of bipolar depression.

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/hypomanic 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.

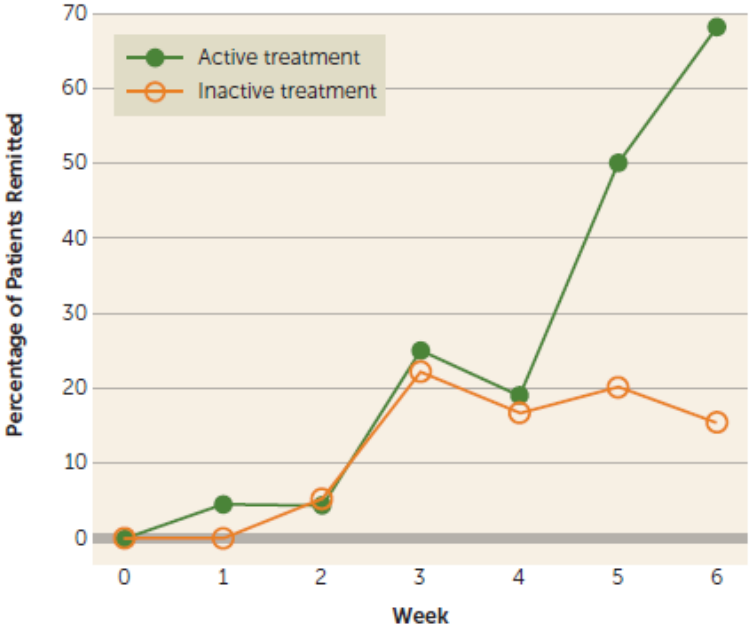
JAMA Psychiatry. 2018 Feb; 75(2): 158–166.

Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial

(Sit et al AJP 2018)

ADJUNCTIVE BRIGHT LIGHT THERAPY FOR BIPOLAR DEPRESSION

FIGURE 1. Remission Rates Across Study Weeks for Patients With Bipolar Depression Treated with Active (Bright White Light) or Inactive (Dim Red Light) Light Therapy[a]



[a] Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio=7.50, 95% CI=1.80, 31.28, p=0.003; adjusted odds ratio=12.64, 95% CI=2.16, 74.08, p=0.004).

- The study enrolled depressed adults with bipolar I or II disorder who were receiving stable dosages of antimanic medication (excluding patients with hypomania or mania, mixed symptoms, or rapid cycling). Patients were randomly assigned to treatment with either 7,000-lux bright white light or 50-lux dim red placebo light (N=23 for each group).
- At baseline, both groups had moderate depression and no hypomanic or manic symptoms. Compared with the placebo light group, the group treated with bright white light experienced a significantly higher remission rate (68.2% compared with 22.2%; adjusted odds ratio=12.6) at weeks 4-6 and significantly lower depression scores (9.2 [SD=6.6] compared with 14.9 [SD=9.2]; adjusted β=-5.91) at the endpoint visit. No mood polarity switches were observed. Sleep quality improved in both groups and did not differ significantly between them.

The data from this study provide robust evidence that supports the efficacy of midday bright light therapy for bipolar depression.

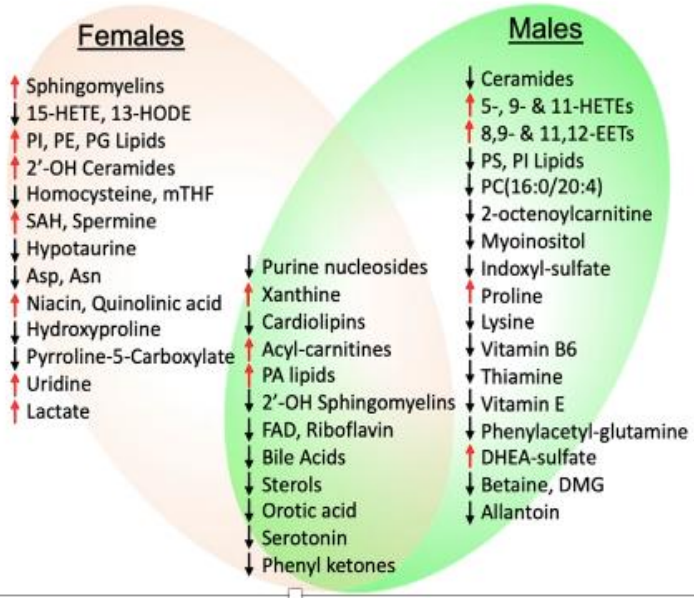
Psychoeducation, yes! Psychotherapy for Bipolar: sounds good

- Adjuvant psychotherapy in early-stage bipolar disorder: A protocol for systematic review and meta-analysis (Chen et al 2021).
- Psychotherapy for bipolar depression:
- a phase-specific treatment strategy?Swartz Frank 2001).
- Psychotherapy as monotherapy for the treatment of bipolar II depression: a proof-of-concept study (Swartz et.al, 2009).
- IPSRT plus quetiapine resulted in greater symptomatic improvement but also more side effects than IPSRT alone. A subset of participants improved with IPSRT alone, although absence of an inactive comparator limits interpretation of this finding. Receipt of preferred treatment was associated with better outcomes. (2018)
- Psychoeducation improved medication adherence and short-term knowledge about medication. No consistent effects on mood symptoms, quality of life, or functioning were found (Bnd and Anderson, 2015).
- To be economically viable, existing psychotherapy protocols need to be made briefer and more efficient for improved scalability and sustainability in widespread implementation. (Geddes , Miklowitz, 2013 LANCET)

Medical, Comorbidities (or features) and treatment of bipolar depression: toward "precision medicine" ?

- Metabolic pathways that may be important in the pathophysiology of MDD and BD were identified and predominantly center on glutamatergic metabolism, energy metabolism, and neurotransmission. Using online drug registries, we also illustrate how metabolomics can facilitate the discovery of novel candidate drug targets (Mc Donald et al 2019)

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)

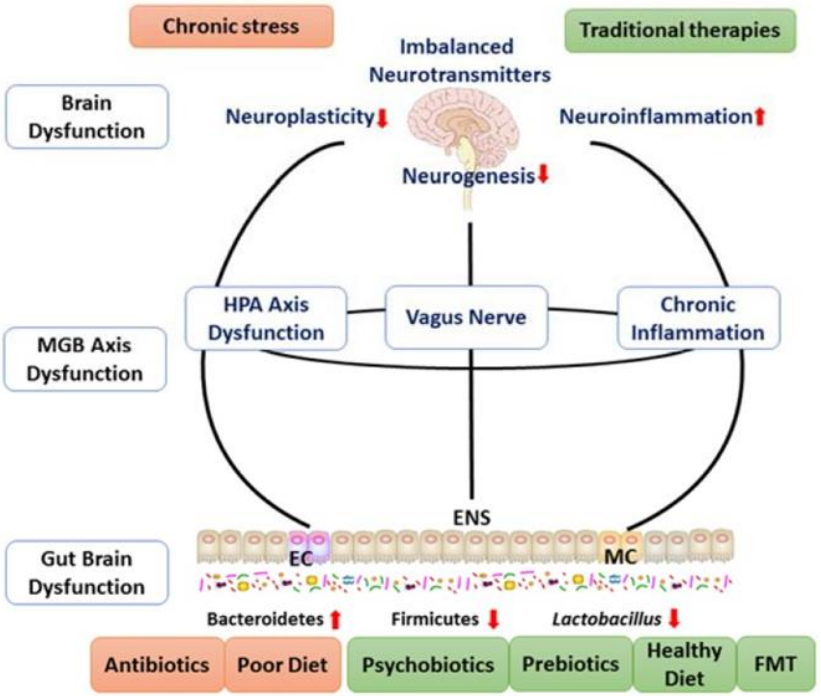


Metabolomics of bipolar disorder

(Hashimoto, 2018)

Inflammation as a target for bipolar depression: sparce evidences

- 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.



Gut Microbiota Changes in Patients with Bipolar Depression (Hu, 2019)

Prescription patterns in Bipolar: are we going in the right direction?

- Major changes took place in drug prescriptions during the study period. The decrease in the use of lithium and the constant high use of antidepressants do not align with recommendations from international guidelines.
- **Nationwide and population-based prescription patterns in bipolar disorder (Lars Vedel Kessing et al ,2016)**

- Approximately 40% of patients in Japan with a diagnosis of bipolar disorder have received antidepressants. Antidepressants were most often prescribed in combination with mood stabilizers, antipsychotics or both. Patients who were prescribed antidepressants received fewer mood stabilizers, more anxiolytics, and more hypnotics than those who did not receive antidepressant prescriptions)

- **Real-world clinical features of and antidepressant prescribing patterns for outpatients with bipolar disorder** (Tokimustu et al ,2020)
- Antidepressants were the first-choice agent twice as often as mood stabilizers. Lithium was sustained longer than monotherapy with other mood stabilizers. Time to augmentation was much shorter than time to change or discontinuation. (Baldessarini et al 2009)

Future of Bipolar Depression

Carvalho AF, Firth J, Vieta E.N Engl J Med. 2020 Jul 2;383(1):58-66

- Early clinical diagnosis
- Comorbidities
- The Fabulous 4….
- Person centered (not Guideline driven)
- Stage and phase
- Dimension oriented
- Cognitive
- Episode focused
- Prevention oriented

Anticipating Clinical while searching for bio-marker	Staging Continuation maintenance
Cognitive	Metabolic – immune low-grade inflammation
Patient centered vs Category	Circuitries focused and neuromdulation