Footnotes and commentary for the Blog post

The Good, the Bad, and the Ugly: an infographic on bipolar drugs

from Onward Mental Health

See the blog posts at: https://www.onwardmentalhealth.com/blog-1

[1] **Read this.** We have definitions for certain phrases used in this blog post. These phrases are short-hand for statistical concepts that help ensure statistical rigor and make the post more readable. Drug efficacy is presented as attributable benefit. Drug harms are presented as side effect frequency in treatment groups (insufficient data is available to present as attributable harm). See our **Definitions.**

[2] **Bipolar drugs work, but 75-85%+ of people don't see substantial symptom improvement attributable to them.** See our **Definitions.** This statement is equivalent to saying that ARRs for bipolar drugs vary between 15%-25% or NNTs vary between 4 and 6.7, when considering clinical response (>50% symptom reduction). **Antipsychotic** NNTs average 5.5-6. For **Lithium** ARR is about 16%. **Antidepressants** have weak evidence for bipolar and provide no value when added to mood stabilizers. Although individual studies sometimes arrive at NNTs less than 4 meta-analyses usually do not. Although combining these disparate NNT numbers into "75-85%" lacks strong mathematical rigor given their varying sources, quality, purposes, etc., it provides a reasonable (perhaps conservative) number, and offers simplification that aids understanding an important point: an individual is far more likely NOT to gain substantial benefit attributable to bipolar drugs than they are to gain it.

[3] **Mania placebo response rate.** Vieta (2005), Nierenberg (2015) and others note, *there are a number of clinical and methodological variables that are associated with placebo response*. Placebo response rates are highly variable, and we reduce them to a single number, making assumptions on influencing factors. In addition, drug response rates are often higher in comparator trials as compared to placebo-controlled trials.

In spite of this, it is important to arrive at a reasonable estimate since it helps inform simple binary and comparative therapy choices and understand the concept of attributable risk.

We have chosen average mania response rate from the following. Ketter (2011) asserts 30% from 35 study review. Sysko (2007) reviewed 20 studies to specifically capture placebo response rate for mania with result of 31%. Although having fewer studies than Ketter, Sysko's study goal was to specifically determine placebo response rate for mania and still has robust set of studies, so we select 31%

(a) **Vieta E, The use of placebo in clinical trials on bipolar disorder: a new approach for an old debate, Psychother Psychosom. 2005, PMID: 15627851.** *"…Placebo response in bipolar disorder trials is more likely to occur in patients who are mildly ill, bipolar II, mixed-episode, first-episode, rapid cycling, atypical, non-psychotic, substance abusers and medically ill. The use of concomitant medication such as benzodiazepines, a high frequency of visits, a high number of treatment groups and sites, fixed-dose designs, and the concomitant use of psychotherapy are likely to increase placebo response… Many reasons support the use of placebo in acute bipolar studies, whereas in maintenance the length of the treatment with placebo makes the decision more difficult… There are a number of clinical and methodological variables that are associated with placebo response."*

(b) **Nierenberg AA et al, Predictors of placebo response in bipolar depression, Int Clin Psychopharmacol. 2015, PMID: 25438027.** *"…The aim of this work is to investigate placebo response rates in placebo-controlled randomized clinical trials (RCTs) of pharmacological therapy in bipolar depression (BPD) and to identify predictors of placebo response and clinical trial outcome in BPD… Data extracted from 12 manuscripts and one*

poster, representing a total of 17 clinical trials, were pooled. A meta-regression showed that trial duration and baseline severity correlated with the risk ratio of responding to drug versus placebo. There was a trend toward statistical significance for a greater probability of receiving placebo to predict greater drug-placebo 'separation'. In conclusion, several modifiable factors, specifically the probability of receiving placebo, baseline illness severity, and trial duration, correlate with placebo response rates and/or clinical trial outcome in RCTs of pharmacotherapy for BPD, and should be taken into account when designing studies for BPD."

(c) **Ketter T et al, Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions?, Acta Psychiatr Scand. 2011, PMID: 21133854, https://goo.gl/J6j5oq, https://goo.gl/B6fMjB.**

(d) **Sysko R et al, A systematic review of placebo response in studies of bipolar mania, J Clin Psychiatry. 2007, PMID: 17854245.** *"…The purpose of this study was to examine placebo response rates in trials of acute bipolar mania… Twenty studies used a response criterion of a 50% or greater decrease on the Young Mania Rating Scale (YMRS) or Mania Rating Scale (MRS), or a designation of much or very much improved on the Clinical Global Impressions-Improvement scale (CGI, score of 1 or 2)… The response rate to placebo in studies of bipolar mania (31.2%) was similar to the rate observed in major depression (29.7%). Over a limited number of years, there was some indication of a change in placebo response on the YMRS in studies of bipolar mania; however, the small number of studies available for analysis limits our ability to draw definitive conclusions."*

[4] **Lithium attributable response. We choose 16% based on the following. Yildiz** (2011) = 16% (38 studies, N=1199 lithium patients, 8-weeks, overall NNT = 6.3, ARR = 1/6.3=15.9%); **Storosum** (2007) = 17%, N=470 in lithium group, NNT = 6, ARR = 1/6 = 17%; **Ketter** (2011) = 25% [35 studies but only N=134, **Combined Review**: The two largest studies (Yildiz and Sotorosum) are very close (16%, 17%), we go with larger size, Yildiz = 16%.

(a) **Yildiz A et al, Efficacy of Antimanic Treatments: Meta-analysis of Randomized, Controlled Trials, Neuropsychopharmacology. 2011, PMC3055677.** *"…We conducted meta-analyses of findings from randomized, placebo-controlled, short-term trials for acute mania in manic or mixed states of DSM (III–IV) bipolar I disorder in 56 drug–placebo comparisons of 17 agents from **38 studies** involving 10 800 patients... In several direct comparisons, responses to various antipsychotics were somewhat greater or more rapid than lithium, valproate, or carbamazepine; lithium did not differ from valproate, nor did second generation antipsychotics differ from haloperidol. ". Note: Table 3 indicates NNTs for mania = Carbamazepine N=427 (3.9) with ARR=26%, Valproate N=824 (4.9) with ARR = 17%. Combining these two with the lithium NNT of 6.3 yields a mood stabilizer overall N=2450, NNT = 5.6 with ARR=18%. By comparison SGA saw a combined NNT of 6.3 on N=7094.*

(b) **Storosum J et al, Magnitude of effect of lithium in short-term efficacy studies of moderate to severe manic episode, Bipolar Disord. 2007, PMID: 18076528.** *"…Six studies were identified. They involved a combined total of 470 patients in the lithium groups and 562 in the placebo groups. The overall standardized effect size was 0.40 [95% confidence interval (CI): 0.28, 0.53] and the overall NNT for response was 6 (95% CI: 4, 13). In the placebo groups response rates varied from 21% to 47%..."*

(c) **Ketter T et al, Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions?, Acta Psychiatr Scand. 2011, PMID: 21133854, https://goo.gl/J6j5oq, https://goo.gl/B6fMjB.**

[5] Acute bipolar depression placebo response. See notes in footnote #3. Nierenberg (2015) indicates a pooled placebo response for bipolar depression from 17 trials of 39.1%. Ketter (2011) reviewing 35 studies asserts 34%. This is similar to that of major depression found in other studies. We select 39% based on Nierenberg's specific focus on answering this question.

(a) **Nierenberg AA et al, Predictors of placebo response in bipolar depression, Int Clin Psychopharmacol. 2015, PMID: 25438027.** *"…**Pooled response rates for drug and placebo were 55.1 and 39.2%**, corresponding to a risk*

ratio for responding to active treatment versus placebo of 1.29 (P<0.001). A meta-regression showed that trial duration and baseline severity correlated with the risk ratio of responding to drug versus placebo."

(b) **Ketter T et al, Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions?, Acta Psychiatr Scand. 2011, PMID: 21133854, https://goo.gl/J6j5oq, https://goo.gl/B6fMjB.**

[6] **Lurasidone depressive response**. Ketter (2014) NNT=5, ARR = 20%. Figure 4. **Citrome (2014)** NNT = 5.

(a) **Ketter T et al, Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions?, Acta Psychiatr Scand. 2011, PMID: 21133854, https://goo.gl/J6j5oq, https://goo.gl/B6fMjB.**

(b) **Citrome L et al, Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed, J Affect Disord. 2014, PMID: 24246116**. *"…The NNT or NNH was calculated for lurasidone vs. placebo for … response (≥50% reduction from baseline on Montgomery Asberg Depression Rating Scale (MADRS) total score);* ***NNT vs. placebo for response was 5 for lurasidone monotherapy (both dose ranges) and 7 for adjunctive therapy****.*

[7] **Side effects prevalence.**

See footnote #1 for detail on definitions.

Available data on harms is of much lower quality than benefits, with especially sparse information on attributable harm. We therefore express harms as prevalence/frequency within the treatment group.

Harms data is highly variable. In nearly all cases, we seek to distill a potentially wide-range of frequency data to a single frequency percentage to simplify communication. Trying to do this with robust mathematical precision is difficult given the varying sources, quality of data, methods of quantifying, etc. Nonetheless, we will assert it when the data appears to support it and will not assert a value when the data is too sparse or questionable.

We use the following high-level logic and conventions in determining drug harms.

- We choose risk quantification associated with longer time frames, over those reflecting shorter timeframes. It may take time for the full side effects profile to manifest.
- We favor independent trials (over trials that appear to have potential for bias); trials with larger number of participants; trials that put specific emphasis in trial design and execution on quantifying harms; and trials that include direct participant feedback and self-reporting to assess harms data (though this is sometimes considered "liberal", we assert that participant experience of harms is vital and often the most important consideration).
- We seek harms data from trials on drugs for the treatment of bipolar. In some cases, there is more robust information on drug harms from studies examining the use of the drug for other diagnoses (e.g. antipsychotics and schizophrenia). Although harms data may be different for the same drug when applied to different diagnoses, if the only quality data is from other diagnoses, we may use it, since side effects are similar when applying the same drug to different diagnoses.

The following rationale was used to arrive at harms frequency:

- **Lithium**.
    - Weight gain (75%) from average of 77% and 73% in Gitlin (2016)
    - tremors (42%), midpoint of the 20-65% frequency range of Serretti (2013)
    - sexual dysfunction (37%) from Gitlin (2016)
    - chronic kidney disease (33%), from Aiff (2015)

    - hypothyroidism (14%) midpoint of Gitlin (2016) 8-19%.
- **Anticonvulsants**.
    - Elevated liver enzymes (11%) Leo (1999) midpoint of 5-15%.
    - tremors (10%) from Leo (1999).
    - rash (10%) for lamotrigine from Leo (1999).
- **Antipsychotics**.
    - Weight gain (90%+) from Bak and Nihalani.
    - sexual dysfunction (66%) from Kumar.
    - fatigue (35%) from Serretti.
    - tremors (17%) from Brooks (2011).
- **Antidepressants**.
    - Sexual dysfunction (58%) from Kelly (2008).
    - withdrawal difficulties (56%) from Davies (2018).
    - fatigue (21%) from Aston (2005).
    - weight gain (15%) from midpoint of 10-25% from Nihalani.
- **Benzodiazepines**.
    - Fatigue (50%) from Arbanas (2009).
    - sexual dysfunction (33%) from Arbanas (2009).
    - withdrawal syndrome (30%) midpoint of Higgit 15-44%.

(a) Aiff H et al, Effects of 10 to 30 years of lithium treatment on kidney function, J Psychopharmacol. 2015, PMID: 25735990. *"… About one-third of the patients who had taken lithium for 10-29 years had evidence of chronic renal failure but only 5% were in the severe or very severe category…"*

(b) Arbanas G et al, Adverse effects of benzodiazepines in psychiatric outpatients, Psychiatr Danub. 2009, PMID: 19270632. *"…One third of women and one quarter of men stopped taking benzodiazepines due to adverse effects. The mean number of adverse effects was 4.8 both in men and women. Those who stopped taking benzodiazepines didn't have more adverse effects in comparison to those who continued to use them.* ***More than half of the participants suffered from sleepiness, slowness and fatigue. One third of the participants said they noticed the change in sexual drive.*** *More then 30% of women noticed dizziness and only 6% of men. None of the participants said to have jaundice after using benzodiazepines. The same adverse effects were present in those who stopped taking the drugs and in those who continued to use them."*

(c) Ashton A et al, Antidepressant-related adverse effects impacting treatment compliance: Results of a patient survey, Curr Ther Res Clin Exp. 2005, PMC3964563. *"…The 4 AEs patients expressed as "extremely difficult to live with" were "weight gain" (104 patients [31%]), "unable to have erection" (83 [25%]), "difficulty reaching orgasm" (80 [24%]),* ***and "tired during the day/no energy" (69 patients [21%]).*** *The 3 most frequently cited improvements patients (n = 327) would make to their medications were better efficacy (176 patients [54%]) and eliminating AEs related to sexual desire and weight gain (112 [34%] and 105 [32%] patients, respectively)."*

(d) Bak M et al, Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis, PLoS One. 2014, PMCID: PMC3998960. *"…A meta-analysis was conducted of clinical trials of AP that reported weight change…Almost all AP showed a degree of weight gain after prolonged use, except for amisulpride, aripiprazole and ziprasidone, for which prolonged exposure resulted in negligible weight change…The level of weight gain per AP varied from discrete to severe…Given prolonged exposure, virtually all AP are associated with weight gain."*

(e) **Brooks JO et al, Safety and tolerability associated with second-generation antipsychotic polytherapy in bipolar disorder: findings from the Systematic Treatment Enhancement Program for Bipolar Disorder, J Clin Psychiatry. 2011, PMID: 20868629.** *"…This study sought to evaluate the safety and tolerability of SGA polytherapy compared to SGA monotherapy in bipolar disorder patients receiving open naturalistic treatment in the 22-site Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)… Almost 10% of*

patients taking SGAs were prescribed SGA polytherapy. After controlling for illness onset, age, baseline illness severity, and medication load, patients prescribed SGA polytherapy, compared to monotherapy, exhibited more dry mouth (number needed to harm [NNH] = 4), tremor (NNH = 6), sedation (NNH = 8), sexual dysfunction (NNH = 8), and constipation (NNH = 11) and were almost 3 times as likely to incur more psychiatric and medical care; there was no association with greater global functioning scores or percentage of days spent well."

(f) **Davies J et al, A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based?, Addictive Behaviors, 2018, https://goo.gl/8BbdgZ.** *"…More than half (56%) of people who attempt to come off antidepressants experience withdrawal effects. Nearly half (46%) of people experiencing withdrawal effects describe them as severe… 34% of the 430 people who had had a withdrawal reaction when stopping paroxetine had reactions that were so severe and/or long-lasting that they had to be treated with a reintroduction of the drug… Furthermore, two of the studies reviewed indicate that for 40% of people who withdraw the effects last at least 6 weeks (Zajecka et al., 1998) and for 25% they last 12 weeks or more (RCPsych, 2012)."* Note: 46% * 56% ~= 26% of people experience severe withdrawal effects.

(g) **Gitlin M, Lithium side effects and toxicity: prevalence and management strategies, Int J Bipolar Disord. 2016, PMCID: PMC5164879.** *"…Thirst and excessive urination, nausea and diarrhea and tremor are rather common side effects that are typically no more than annoying even though they are rather prevalent… weight gain and cognitive impairment from lithium tend to be more distressing to patients, more difficult to manage and more likely to be associated with lithium nonadherence… Lithium has adverse effects on the kidneys, thyroid gland and parathyroid glands, necessitating monitoring of these organ functions through periodic blood tests… Lithium-induced hypothyroidism is relatively common… In older studies, with data collected during a time when more (but certainly not all) patients were seemingly treated with lithium monotherapy, the majority of lithium-treated patients report at least one side effect with estimates ranging between 67 and 90%... **Nausea**, seen in 10–20% of lithium-treated patients, tends to be more prominent early in treatment… **Diarrhea** increases in prevalence in patients through the first 6 months of treatment and is seen in up to 10% of lithium-treated patients… **Excessive urination and thirst** (polyuria and polydipsia) are consistently found to be among the most common side effects associated with lithium with rates up to 70% in long-term patients… **Tremor**, primarily of the hands, is among the most common lithium side effects, seen in approximately one quarter of treated patients… Tremor is exceedingly common in the context of lithium toxicity… **Weight gain** is among the prevalent and distressing of lithium-associated side effects… Typical results include those of Vestergaard et al. (1980) who found that 20% of patients gained 10 kg or more. In another study, 77% of lithium-treated patients gained weight with an average increase of 6.3 kg (8% baseline body weight) (Chengappa et al. 2002). These results are remarkably similar to the 73% rate of weight gain in the Aarhus clinic (Vestergaard et al. 1988). Among more recent studies, mean weight change over one year in one double-blind study of lithium-treated patients was 4.2 kg (Calabrese et al. 2003)… The **decrease in creativity**, best demonstrated by an on/off study of idiosyncratic associations, may be particularly troublesome to the subset of bipolar patients involved in creative professions… An even smaller subgroup of lithium-treated patients progresses towards **end-stage renal disease (ESRD)** and ultimately dialysis and/or renal transportation. The prevalence of ESRD associated with lithium is difficult to estimate. One study found the risk to be almost eightfold compared to the general population… **Thyroid**. Overt hypothyroidism is estimated as having a prevalence of 8–19% with subclinical hypothyroidism showing rates up to 23% (Kleiner et al. 1999)… In the most recent study, 37% of euthymic bipolar patients on lithium acknowledged sexual dysfunction across multiple sexual domains (Grover et al. 2014)."*

(h) **Higgitt AC et al, Clinical management of benzodiazepine dependence, Br Med J (Clin Res Ed), 1985, PMCID: PMC1416639, https://goo.gl/LLdcra.** *"…The development of dependence after the long term use of benzodiazepines is now supported both by clinical evidence and by the results of double blind studies. Withdrawal symptoms have been reported after treatment for as little as four to six weeks... **The proportion of long term users of benzodiazepines in whom withdrawal symptoms may be expected to emerge has been variably estimated to be between 15% and 44%.**..Yet no one doubts that most patients currently taking*

benzodiazepines should stop them… data supporting their continued effectiveness over such a period [one year] are sparse-to say the least… Though drop out rates from withdrawal programmes are high when withdrawal is relatively abrupt,' on gradual withdrawal regimens almost all (88-100%) volunteers are successful in stopping their benzodiazepine intake…Roughly one third of these patients are free of problems after withdrawal. Of the remaining patients, about half tend to respond to antidepressants, but many may return to using benzodiazepines. Complete recovery is slow, and patients are likely to have symptoms for a year or more.' Thus, though on the whole gradual withdrawal programmes are successful, most participants are left with psychiatric problems and the long term effectiveness of withdrawal is unknown." **Kelly K et al, Toward achieving optimal response: understanding and managing antidepressant side effects, Dialogues Clin Neurosci. 2008, PMCID: PMC3181894.** *"…In a study by Demyttenaere et al of 272 outpatients receiving antidepressant therapy, 53% had discontinued treatment by the end of the 6-month study. Of these patients, 23% cited "adverse events" as the reason for their discontinuation… In a similar study, Hu et al found that 33% of patients had discontinued their treatment by the end of a 105-day period, with the most, often-cited reason being adverse effects (36%)… In both research and clinical contexts, an important challenge is presented by the phenomenological overlap between side effects and residual symptoms of depression… An additional, frequently overlooked factor that may confound interpretation of apparent adverse events has to do with discontinuation-emergent effects of antidepressants, which can resemble antidepressant side effects and/or residual symptoms…* ***In a study of 344 patients by Montejo-Gonzalez et al, 58% of patients reported sexual dysfunction when physicians directly inquired, compared with only 14% of those who spontaneously reported sexual dysfunction****. In a naturalistic study that directly inquired about, side effects through closed-ended questions, 34% of patients reported sexual dysfunction, with half of these patients (17% of the overall group) deeming it bothersome…* ***physicians underestimated the overall rate of side effects as well as the frequency of specific side effects*** *such as dry mouth, dizziness, drowsiness, headache, insomnia, rash or itching, blurred vision, diarrhea, and weight loss when compared with the actual rate reported by their patients. That clinicians underestimate the prevalence of side effects likely contributes to inadequate communication before and during prescription of antidepressants".*

(i) **Kumar A et al, A Comparative Study of Sexual Dysfunction due to Typical and Atypical Antipsychotics in Remitted Bipolar-I Disorder, Indian Journal of Psychiatry, 2004, PMCID: PMC2951652, https://goo.gl/QX99dw.** "…this study was done to determine the sexual dysfunction due to antipsychotics and to compare the same among typical and atypical antipsychotics… Results showed dysfunction in at least one phase of the sexual response cycle, comprising of desire, arousal and orgasm, was present in 66% of the sample population… there was no significant difference across the two groups [typical vs atypical] in the other aspects of sexual dysfunction as shown in the table 5."

(j) **Leo R et al, Anticonvulsant Use in the Treatment of Bipolar Disorder: A Primer for Primary Care Physicians, Prim Care Companion J Clin Psychiatry. 1999, PMCID: PMC181066.** *"…**Valproate**: Gastrointestinal disturbances are most common [side effect]…* ***Tremor develops in approximately 10% of valproate-treated patients…*** *" "…Valproate use is also associated with the possibility of elevation of liver enzymes…* ***Transient elevations have been reported in as many as 11% of valproate-treated patients****… Rare cases of fatal hepatotoxicity have been reported…" "…Because the risk of hepatotoxicity is highest early in the course of treatment, liver function tests should be conducted at monthly intervals during the first 6 months of treatment … Carbamazepine: Less common untoward effects associated with carbamazepine use include elevations in the liver enzymes (5%–15% of patients), hyponatremia (6%–31%), and* ***rash (10%–12%)…*** *Multiple drug interactions are possible with carbamazepine…**Lamotrigine**: A macular-papular or* ***erythematous rash developed in approximately 10% of 3501 i****ndividuals receiving lamotrigine in epilepsy trials"*

(k) **Nihalani N et al, Weight Gain, Obesity, and Psychotropic Prescribing, J of Obesity, 2011, PMC3034985.** *"…* ***Nearly every antipsychotic has been reported to cause weight gain****. Although comparison is limited by the different designs and recruitment procedures of reviewed studies, a MEDLINE search from 1966 to 2009 showed that the amount of* ***body weight gain was highest in patients treated with olanzapine (average body weight gain 2.3 kg/month), quetiapine (1.8 kg/month), and clozapine (1.7 kg/month). Treatment with***

risperidone showed moderate changes in body weight (average body weight gain 1.0 kg/month), where ziprasidone seemed to induce only slight body weight changes (0.8 kg/month). Asenapine causes up to 0.9 kg weight gain in the first three weeks of treatment *and its FDA Package Insert discusses a 52-week regulatory trial causing negligible weight gain over time, suggesting it may also be less metabolically problematic…* ***There is a 1–3 kg average weight gain on antidepressants in 10–20% of the population treated with them****."*

(l) **Serretti A et al, Side effects associated with psychotropic medications in patients with bipolar disorder: evidence from two independent samples, J Psychopharmacol. 2013, PMID: 23616438, https://goo.gl/8GX2H1***"… Our findings are consistent with available evidence suggesting that rates of lithium-induced tremors could be as high as 20-65%, being more common in patients treated with two or more drugs…". Note: From step-BD, those taking antipsychotics 35% felt sedated as compared to 18% not on antipsychotics [1/(35%-18%) = NNH = 6]; concentration difficulties from COPE-BD, NNH = 1/(.29-.13) = 6; fatigue from Cope-BD, NNH = 1/(.35-.19) = 6, tremors from Step-BD, NNH = 1/(.21-.06) = 7.*

[8] **Bipolar drug adherence.**

(a) **Gaudiano B et al, Improving Treatment Adherence in Bipolar Disorder: A Review of Current Psychosocial Treatment Efficacy and Recommendations for Future Treatment Development, Behav Modif. 2008, PMC3691269.** *"…Treatment adherence is a frequent problem in bipolar disorder, with research showing that upwards of 60% of bipolar patients are at least partially nonadherent to medications."*

(b) Garcia S et al, Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients A Systematic Review, J Clin Psychopharmacol 2016, *"…mean rates of treatment adherence are approximately 42% in schizophrenia and* ***41% in bipolar disorder****, with considerable variation between studies. Furthermore, medication adherence is a dynamic dichotomous behavior,* ***influenced by multiple factors that may be related to patients (adverse effects of medication),*** *their social relationships (family support and therapeutic alliance), cognitive problems such as impaired memory or attention, and the system for providing health services… Among the adverse effects of antipsychotics,* ***weight gain is probably the health problem that is most likely to result in non- adherence****. In fact, there is an association between adherence and patient BMI, adherence being lower among those with higher BMIs, and more subjective distress was related to weight gain.* ***Extrapyramidal adverse effects such as pseudoparkinsonism, akathisia, dyskinesia, and sexual dysfunction were also found to be of great importance in nonadherence****."*

(c) Johnson F et al, Factors That Affect Adherence to Bipolar Disorder Treatments: A Stated- Preference Approach, Medical Care, 2007, https://goo.gl/Nv1Wy4. *"…Subjects: Patients (N = 469) with self-reported bipolar disorder completed the survey which was programmed and administered to members of a chronic-illness Web panel... Self-reported current adherence is a strong factor in predicting adherence for better medications.. Conclusions****: Patients are the final health care decision makers; their satisfaction with a medication is likely to affect whether or not they adhere to the medication prescribed by their physician. In the case of bipolar disorder, this study suggests patients are likely to be more adherent to medications that reduce the severity of depressive episodes and do not cause weight gain or cognitive side effects.*** *By understanding the factors that improve adherence, health care providers can optimize prescribing patterns, which may ultimately lead to more effective management and improvement in the patient's condition."*

[9] **Weintock LM et al, Medication burden in bipolar disorder: A chart review of patients at psychiatric hospital admission, Psychiatry Res. 2014, PMC3968952.** *"…This retrospective chart review study examined rates of complex polypharmacy (i.e., ≥ 4 psychotropic medications), patterns of psychotropic medication use, and their demographic*

and clinical correlates in a naturalistic sample of adults with bipolar I disorder (BDI; N=230) presenting for psychiatric hospital admission… ***Patients reported taking an average of 3.31****(SD=1.46) psychotropic medications, and 5.94(SD=3.78) total medications at intake. Overall, 82 (36%) met criteria for complex polypharmacy."*

[10] **Alda M et al, Is Monotherapy as Good as Polypharmacy in Long-Term Treatment of Bipolar Disorder?, Can J Psychiatry. 2009, PMID: 19961659, https://goo.gl/ZqpHbq,** *"… A large proportion of patients with BD are being treated off label… with combinations of not only 2, but frequently 3 or more medications... The evidence to support such management is practically nonexistent…"*

[11] **Kingsbury S, Psychiatric Polypharmacy: The Good, the Bad, and the Ugly, Psychiatric Times, 1007, http://goo.gl/KIIsId.** *"...Although double-blind, placebo-controlled trials are considered the standard, relatively few such studies of polypharmacy exist. Therefore, clinicians must venture beyond this evidentiary base."*

[12] **Polypharmacy risk**.

(a) **Kingsbury S, Psychiatric Polypharmacy: The Good, the Bad, and the Ugly, Psychiatric Times, 1007, http://goo.gl/KIIsId.** *"…Persons with psychiatric disorders experience* ***increased risk for adverse drug interactions*** *because of the great frequency with which multiple medications are used. Using multiple antipsychotics concomitantly has been associated with* ***increased mortality*** *in patients with schizophrenia. Reports of adverse psychiatric polypharmacy effects are abundant, including* ***increased duration of hospital stay****…"*

(b) **Kingsbury S, Psychopharmacology: Rational and Irrational Polypharmacy, Psychiatric Services, Aug 2001, PMID: 11474046, http://goo.gl/PFE3Rk;** *"… most would agree that any use of multiple medications may increase the risk of adverse effects, drug interactions, … and medication errors…"*

(c) **Akici A, Rational pharmacotherapy and pharmacovigilance, Curr Drug Saf. 2007, PMID: 18690951.** *"… Prevalence of drug-related morbidity and mortality increase in correlation with the increase in drug use… Polypharmacy is among the major causes of drug-related morbidity and requires additional medication as treatment."*

[13] **Polypharmacy, bipolar drugs, and suicide.** Three of the five classes of bipolar drugs are associated with increased risk of suicide. These risks include ideation, attempts, or completion. Antidepressants are associated with increased suicidal ideation in people under 25 years of age and also associated with greater suicide in health adults.

(a) **Gazalle FK et al, Polypharmacy and suicide attempts in bipolar disorder, Rev Bras Psiquiat, 2007, PMID: 17435926, https://goo.gl/4nC2S1.** *"...****The number of suicide attempts was associated with the use of multiple drugs…*** *When... using three or more drugs… there is a paucity of systematic studies in this area…" "… There is evidence that patients who are submitted to multiple medications have an increased risk of side effects and early mortality…"*

(b) **Goldstein T et al, Predictors of Prospectively Examined Suicide Attempts Among Youth With Bipolar Disorder, Arch Gen Psychiatry, 2013, PMCID: PMC3600896.** *"…Among adults with bipolar disorder, 25% to 50% make at least 1 suicide attempt in their lifetime, and 8% to 19% will die of suicide…"*

(c) ***Anticonvulsants*****: Hitti M, WebMD, Epilepsy Drugs Get Suicide Risk Warning, https://goo.gl/WK8FqE.** *"...The FDA today announced that it will require makers of epilepsy drugs to add a warning about increased risk of suicidal thoughts and behaviors to the products' prescribing information or labeling…"*

(d) ***Antidepressants*****: NIMH, Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers , National Institute of Mental Health, https://goo.gl/G2wLPv.** *"…Following a thorough and comprehensive review of all the available published and unpublished controlled clinical trials of antidepressants in children and adolescents, the U.S. Food and Drug Administration (FDA) issued a public warning in October 2004 about an increased risk of suicidal thoughts or behavior (suicidality) in children and adolescents treated with SSRI antidepressant medications. In 2006, an advisory committee to the FDA recommended that the agency extend the warning to include young adults up to age 25. …"*

(e) ***Benzodiazepines*: Advisory Board, FDA requires 'black box' warnings for opioids, benzodiazepines, 2016, https://goo.gl/CM6CWG**. *"… FDA on Wednesday announced new label requirements for prescription opioids and drugs called benzodiazepines to include so-called "black box" warnings detailing that the drugs can be fatal if taken together.*

(f) ***Antidepressants*. Bielefeldt AØ et al, Precursors to suicidality and violence on antidepressants: systematic review of trials in adult healthy volunteersJ R Soc Med. 2016, PMC5066537.** *"…Eleven of the 130 published trials and two of 29 clinical study reports we received from the regulatory agencies presented data for our meta-analysis. Treatment of adult healthy volunteers with antidepressants doubled their risk of harms related to suicidality and violence, odds ratio 1.85 (95% confidence interval 1.11 to 3.08, p = 0.02, I2 = 18%). The number needed to treat to harm one healthy person was 16 (95% confidence interval 8 to 100; Mantel-Haenszel risk difference 0.06). There can be little doubt that we underestimated the harms of antidepressants, as we only had access to the published articles for 11 of our 13 trials... the 2003 practice guideline from the American Psychiatric Association states that 'clinical observations suggest that there may be an early increase in suicide risk as depressive symptoms begin to lift but before they are fully resolved…Because of this deeply ingrained idea, many psychiatrists believe that when patients become suicidal on an antidepressant drug, it is not an adverse effect of the drug but a positive sign that the drug starts working. However, a systematic review from 2009 showed that the research that has been carried out contradicts this belief, and our review also suggests that it is wrong. We found that antidepressants double the risk of suicidality and violence, and it is particularly interesting that the volunteers in the studies we reviewed were healthy adults with no signs of a mental disorder…While it is now generally accepted that antidepressants increase the risk of suicide and violence in children and adolescents(although many psychiatrists still deny this), most people believe that these drugs are not dangerous for adults. This is a potentially lethal misconception…As far as we know, our review is the first of the risk of suicide and violence in healthy volunteers."*

[14] **The American Psychiatric Association (APA) and overuse of antipsychotics**. The APA joined a broad campaign sponsored by the American Board of Internal Medicine (ABIM) Foundation to encourage practitioners and patients to consider the breadth of their treatment options and avoid unnecessary care. The APA focuses their effort on antipsychotics, commonly used as bipolar treatment. The importance of choosing wisely, however, goes beyond antipsychotics to all bipolar treatments, and indeed all medical disciplines, as evidenced by the fact that nine medical specialties joined the "Choosing Wisely" campaign. Leadership of the APA is clear (see below) that valid options should be considered, and the risks and side effects of drugs carefully weighed before choosing them. In addition, the growing APA Caucus on Complementary, Alterative, and Integrative Medicine is grounded in the use of nondrug alternatives (see www.IntPsychiatry.com)

(a) Sharfstein SS, Big Pharma and American Psychiatry: The Good, the Bad, and the Ugly, Psych News 2005, http://goo.gl/IzjQSW. Dr. Steven Sharfstein, past president of the APA, emphasizes: *"…There is widespread concern about the over-medicalization of mental disorders and the overuse of medications. Financial incentives and managed care have contributed to the notion of a 'quick fix' by taking a pill and reducing psychotherapy and psychosocial treatments…. despite the strong evidence base that many psychotherapies are effective…."*

(b) James Scully (MD, APA Medical Director and CEO), excerpt from a video of him speaking to the APA's participation in the Choosing Wisely® campaign, 2013, https://vimeo.com/74481474, copied 2015. Scully indicates: *"…Physicians and patients together should be thinking carefully, 'Are the medications really needed and are there downsides and negative consequences for overuse?'... Patients really need to be a part of the decision… of their own treatments…".*

(c) Watts V, APA Joins Campaign Urging Doctors, Patients to Choose 'Wisely', Psychiatric News, 2013, https://goo.gl/WQqbFF. *"…'the Choosing Wisely campaign [is]an initiative that encourages physicians, patients, and other health care stakeholders to engage in a dialogue concerning potentially unnecessary medical procedures that, in some instances, could result in harm… [Antipsychotics] carry risks including potentially harmful side*

effects. Unnecessary use or overuse of antipsychotics can contribute to chronic health problems, such as metabolic, neuromuscular, or cardiovascular problems, in people with serious mental illness,' said Joel Yager, M.D., chair of the APA Council on Quality Care (COQC)… The APA has recommended that antipsychotics should not be used routinely and should never be used without considerable thought, good clinical reasoning, and discussion with patients as to why under particular circumstances such a course would be preferable to alternative options…".

[15] **Bipolar antipsychotic polypharmacy. Brooks JO et al, Safety and tolerability associated with second-generation antipsychotic polytherapy in bipolar disorder: findings from the Systematic Treatment Enhancement Program for Bipolar Disorder, J Clin Psychiatry. 2011, PMID: 20868629.** *"…Almost 10% of patients taking SGAs were prescribed SGA polytherapy. After controlling for illness onset, age, baseline illness severity, and medication load, patients prescribed SGA polytherapy, compared to monotherapy, exhibited more dry mouth (number needed to harm [NNH] = 4), tremor (NNH = 6), sedation (NNH = 8), sexual dysfunction (NNH = 8), and constipation (NNH = 11) and were almost 3 times as likely to incur more psychiatric and medical care; there was no association with greater global functioning scores or percentage of days spent well…. Although* ***SGA polytherapy was fairly common in bipolar disorder, it was associated with increased side effects and health service use but not with improved clinical status or function.*** *Thus, SGA polytherapy in bipolar disorder may incur important disadvantages without clear benefit, warranting careful consideration before undertaking such interventions."*

[16] **Antipsychotic polypharmacy and early death.**

(a) **Waddington JL, Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study, Br J Psychiatry 1998, PMID: 9926037.** *"… Receiving more than one antipsychotic concurrently was associated with reduced survival, in the face of little or no systematic evidence to justify the widespread use of antipsychotic polypharmacy…"*

(b) **Joukamaa M et al, Schizophrenia, neuroleptic medication and mortality. Br J Psychiatry, 2006, PMID: 16449697.** *"…The number of neuroleptics used at the time of the baseline survey showed a graded relation to mortality. Adjusted for age, gender, somatic diseases and other potential risk factors for premature death, the relative risk was 2.50 (95% CI1.46-4.30) per increment of one neuroleptic…"*

[17] **National Institute of Mental Health (NIMH), Study Sheds Light on Medication Treatment Options for Bipolar Disorder, NIMH Archive**, https://goo.gl/q5YGxx. *"… For depressed people with bipolar disorder who are taking a mood stabilizer,* ***adding an antidepressant medication is no more effective than a placebo (sugar pill),*** *according to results published online on March 28, 2007 in the New England Journal of Medicine. The results are part of the large-scale, multi-site Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a $26.8 million clinical trial funded by the National Institutes of Health's National Institute of Mental Health (NIMH)…".*

[18] **Anticonvulsant prescribing trends.**

(a) **Greil W et al, Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009. J Affect Disord 2012, PMID: 22134044.** *"…Observational analysis of the pharmacotherapy of 2231 psychiatric inpatients with a current episode of bipolar depression… Overall 81.3% of patients received antidepressants (AD) (7.8% monotherapy), 57.9% antipsychotics (AP), 50.1% anticonvulsants (AC), 47.5% tranquilizers, and 34.6% lithium (Li)."*

(b) **Moreno C et al, National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth, Arch Gen Psychiatry. 2007, PMID: 17768268.** "…Youth and adults received a mood stabilizer in approximately two-thirds of the visits…"

(c) **Cascade M et al, Antidepressants in Bipolar Disorder, Psychiatry (Edgmont). 2007, PMC2922360.** *"…Although there are many products used to treat bipolar disorder, the most common categories included mood stabilizers (54%)(e.g., lithium and antiepileptics), antipsychotics (50%), and antidepressants (34%)…"*

(d) **Hayes J et al, Prescribing Trends in Bipolar Disorder: Cohort Study in the United Kingdom THIN Primary Care Database 1995–2009, PLoS One. 2011, PMC3233605**. *"… There were 5,224 patients diagnosed with bipolar disorder (2,017 men, 3207 women)… We carried out a retrospective cohort study of individuals in primary care with a diagnosis of bipolar disorder using The Health Improvement Network (THIN) primary care database… [There was a] 29.9% increase in the proportion of time spent on any mood stabiliser over the same time period (27.5% to 57.4%) (Figure 2)…"*

[19] **Kemp D et al, Bipolar depression: trial-based insights to guide patient care, Dialogues Clin Neurosci. 2008, PMC3181875.** *"… [for STEP-BD] In the end,* ***rates of durable recovery were similar between the antidepressant (23.5%) and placebo (27.3%) groups*** *…"*

[20] **Antidepressants for bipolar depression**. We use the definition of *treatments don't work* found in footnote #1. *The significant bulk of the evidence shows antidepressants provide symptom relief no better than placebo*. The first well-designed meta-analysis was in 2001 (Nemeroff) and it found that antidepressants didn't add benefit over placebo for those on lithium. The most impressive study was STEP-BD in 2007, the largest, federally funded treatment trial ever conducted for bipolar depression (NIMH). It made a stronger statement - it found that antidepressants were no more effective than placebo if people were taking a broader class of drugs – mood stabilizers. In fact, it led to less durable recovery than placebo (Kemp). A 2008 study (Ghaemi), confirmed the results of STEP-BD, focusing on the long-term. It, too, found that antidepressants weren't better than placebo if you were on mood stabilizers. In 2011, another meta-analysis (Sidor) found that antidepressants were not superior to placebo for bipolar depression. In 2012, a literature review (Amit) found that most well-controlled studies failed to show that antidepressants worked regardless of antidepressant class or bipolar subtype. A 2013 meta-analysis (Zhang) reached a more far reaching conclusion: that antidepressants were not of value in either the short-term or long-term. Given the controversy over antidepressant use for bipolar depression, an expert panel was convened in 2013 to make sense of it. (Pacchiarotti). They concluded there was insufficient information to make broad statements endorsing antidepressant use. A 2014 meta-analysis (McInerney) found that antidepressants were not effective as a monotherapy, consistent with the FDA's decision NOT to approve any antidepressant monotherapy for bipolar depression. A 2016 educational narrative (Mohammed) found insufficient evidence to support long-term use of antidepressants. While a 2016 system review and meta-analysis (McGirr) found clinical response and remission rates did not differ significantly between patients receiving adjunctive antidepressants and placebo. The above represents the preponderance of evidence regarding the efficacy of antidepressants for bipolar depression.

However, a smaller amount of evidence suggests antidepressant may provide some benefit. A 2004 meta-analysis (Gijsman) found antidepressant benefit in the short term, but this study has been highlighted by researchers for its methodological flaws. This includes Ghaemi 2011 who highlighted its reliance on one large study that classified an antipsychotic as a placebo and McInerney 2014 who cautioned using the study for the same reasons. A closer analysis of the cornerstone study in the meta-analysis (Tohen 2003) reveals a very large placebo group and relatively small treatment group, whose success was driven by only 40 people in the OFC group that responded. A 2017 meta-analysis (Liu) confirmed that antidepressant monotherapy was no better than mood stabilizer monotherapy for bipolar depression (and it has higher risk of switching) but found long-term benefit of antidepressants in avoiding new episodes of depression. Long-term reduction in rehospitalization rates were found in **Shvartzman (2018).** A 2013 meta-analysis (Valquez) found value in antidepressants over placebo but calls these conclusions "highly tentative" and notes that the "long-term prophylactic benefits [of antidepressants] against depressive recurrences… remain unproved**."**

The preponderance of evidence and the 2013 opinion of the expert task force that found no convincing data to support the broad efficacy of antidepressants for bipolar depression..

(a) **Amit B et al, Antidepressant Treatment for Acute Bipolar Depression: An Update, Depress Res Treat. 2012,** PMCID: PMC3272786; *"… We conducted a … search for papers published between 2005 and 2011 on the subject of antidepressant treatment of bipolar depression. Sixty-eight articles were included in the present*

*review… While a few studies did advocate the use of antidepressants, most well-controlled studies failed to show a robust effect of antidepressants in bipolar depression, regardless of antidepressant class or bipolar subtype…**There was no significant increase in the rate of manic/hypomanic switch**, especially with concurrent use of mood stabilizers… Antidepressants probably have no substantial role in acute bipolar depression…* ***Studies conducted in recent years have failed to demonstrate significant beneficial effects of antidepressants in the treatment of acute bipolar depression…*** *Although as a whole more studies concluded in favor of antidepressant treatment efficacy in both modalities, most of them suffered major methodological disadvantages, such as lack of a placebo arm small sample size or substantial industry involvement. However, although industry-sponsored, it is hard to dismiss the significant efficacy demonstrated for the first FDA-approved therapy for bipolar depression, olanzapine/fluoxetine combination (OFC), showing an effect size of 0.68 compared to 0.32 of olanzapine alone. On the other hand, the two studies showing lack of antidepressant efficacy were based on results of the STEP-BD and EMBOLDEN II trials, both of high methodological quality in terms of randomization, control, blinding, and sample size. Thus, a more recent meta-analysis, published in 2011 and incorporating the results of recent trials, showed no significant efficacy of antidepressants in the treatment of acute bipolar depression."*

(b) **Baldessarini RJ et al. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatr Serv 2007, PMID: 17215417.** *"…this study used the 2002-2003 U.S. national MarketScan research databases to identify 7,760 persons with ICD-9 bipolar disorder subtypes... The most commonly prescribed first drug class was antidepressants (50% of patients), followed by mood stabilizers (25%: anticonvulsants, 17%, and lithium, 8%), sedatives (15%), and antipsychotics (11%)…At study midpoint only 44% of patients were receiving monotherapy. Those receiving monotherapy were ranked by initial drug prescribed and percentage of patients (bipolar I and bipolar II): antidepressants (55% and 65%), lithium (51% and 41%), antipsychotics (32% and 31%), anticonvulsants (28% and 29%), and sedatives (28%, 25%)."*

(c) **Cascade EF et al, Antidepressants in Bipolar Disorder, Psychiatry (Edgmont). 2007, PMCID: PMC2922360.** *"… Although there are many products used to treat bipolar disorder, the most common categories included mood stabilizers (54%)(e.g., lithium and antiepileptics), antipsychotics (50%), and antidepressants (34%)…The use of antidepressants in bipolar disorder is perhaps the most controversial topic in the treatment of bipolar disorder… Until 2002, all bipolar treatment guidelines recommended antidepressant use as the first line treatment of bipolar depression. In that year, the APA treatment guidelines relegated them to second line use, after initial treatment with lithium or lamotrigine monotherapy…First, multiple, long-term, randomized studies have demonstrated lack of efficacy of antidepressants in prevention of depression in bipolar disorder, and no randomized data exist to the contrary; second, some observational data, including the only available randomized studies, indicate that antidepressants appear to be associated with long-term worsening of the course of illness (mainly rapid-cycling) in about one-third of bipolar subjects…Thus, our concern has been over long-term use in particular: If a drug is ineffective in most people and harmful in some, why use it?" "…Are antipsychotics mood stabilizers? I suggest not, though this is also a matter of controversy… the evidence is hard to ignore that this illness does not improve without mood stabilizers at the core of any treatment regimen." "… The FDA warns only of suicidal thoughts in its labeling; research does not indicate an increase in actual suicides…"*

(d) **Ghaemi SN et al, Antidepressants in bipolar disorder: the case for caution, Bipolar Disorders 2003, https://goo.gl/3USVHX.** "…, randomized data provide some evidence of increased risk of cycling with antidepressants. Further, the risk of suicide in bipolar depression can be taken as supportive of the use of lithium rather than antidepressants. In addition there appears to be little evidence of antidepressants being more effective than lithium or lamotrigine in the treatment of acute bipolar depression and even less evidence as to antidepressant efficacy in longer-term treatment in prevention of depressive relapse. Ultimately, the controversy over antidepressant use is not that antidepressants should never be used or that they should always be used; rather the issue is how frequently and for what duration should antidepressants be used in treating bipolar disorder. In practice, both in the US (despite North American guidelines) and in Europe, the majority of patients with bipolar disorder regularly receive antidepressants (50-80%), usually long-term. We

advocate a reversal of prescription patterns such that antidepressants would be used mostly short-term and in a minority of patients (perhaps 20-40%)…"

(e) Ghaemi S et al, Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks, Acta Psychiatr Scand. 2008, PMCID: PMC2718794. *"…In seven trials (350 BPD patients) involving 12 contrasts, long-term treatments that included ADs yielded* ***27% lower risk of new depression*** *vs. MS-only or no treatment [pooled relative risk, RR = 0.73; 95%CI 0.55–0.97;* ***number-needed-to-treat (NNT) = 11****], but* ***72% greater risk for new mania [RR = 1.72; 95% CI 1.23–2.41; number-needed-to-harm (NNH) = 7]. Compared with giving an MS-alone, adding an AD yielded neither major protection from depression (RR = 0.84; 95% CI 0.56–1.27; NNT = 16) nor substantial increase in risk of mania (RR = 1.37; 95% CI 0.81–2.33; NNH = 16)…*** *Available research on long-term use of ADs to treat patients diagnosed with BPD is not adequate to support their extraordinarily widespread, off-label, empirical use in clinical practice…* ***On balance, the research reviewed here suggests an unfavorable risk / benefit relationship for long-term AD treatment in BPD, especially BP-I disorder, in that adding an AD to an MS yielded little reduction in risk of BP depression beyond that achieved with MSs-alone****.... Particularly when given alone****, ADs were associated with considerable added risk of mania****… Long-term adjunctive AD treatment was not superior to Mood stabilizer-alone in BPD…****Compared with giving an MS-alone, adding an AD yielded neither major protection from depression (****RR = 0.84; 95% CI 0.56–1.27; NNT = 16)* ***nor substantial increase in risk of mania*** *(RR = 1.37; 95% CI 0.81–2.33; NNH = 16)… There were 74 new cases of mania and seven cases of hypomania. The pooled risk of new hypomanic or manic episodes was 72% greater in association with long-term use of ADs than without such treatment (RR = 1.72; 95% CI 1.23–2.41; z = 3.15, P = 0.002…****When AD was used with or without an MS in eight studies involving 364 participants, risk of new mania was significantly increased compared with use of MS-alone*** *(RR = 1.80; 95% CI 1.22–2.65)…* ***Particularly when given alone, ADs were associated with considerable added risk of mania (Fig. 2b; Table 3 and Table 4)." Note: Table #2 indicates that the rate of new depression while on antidepressants long term was 25.3% while the same rate for mood stabilizers or placebo was 35.5% for ARR = 10.2%, RR = .726… When AD was used alone in three other trials involving 118 patients, there was a significant 2.4-fold increase in risk of mania compared with use of MS-alone*** *(RR = 2.37; 95% CI 1.38–4.05)… When AD was combined with MS in five involving 246 patients, risk of mania was 37%, but non-significantly, greater than with MS-alone (RR = 1.37; 95% CI 0.81–2.33).* ***Long-term adjunctive AD treatment was not superior to MS-alone in BPD, further encouraging reliance on MSs as the cornerstone of prophylaxis…*** *Available research on long-term use of ADs to treat patients diagnosed with BPD is not adequate to support their extraordinarily widespread, off-label, empirical use in clinical practice…"*

(f) **Ghaemi S, Antidepressants in Bipolar Depression: A New Meta-Analysis for an Old Controversy, Psychiatric Times, 2011, https://goo.gl/naUf2E.** *"…One large study drove the whole meta-analysis (N = 433, accounting for 59% of the review sample), and it was an Eli Lilly–conducted study of olanzapine plus fluoxetine versus olanzapine plus placebo; in the meta-analysis, what was called "placebo" was actually olanzapine, whereas in most of the other studies, patients literally got placebo…"*

(g) **Gijsman HJ et al, Antidepressants for bipolar depression: a systematic review of randomized, controlled trials, Am J Psychiatry. 2004, PMID: 15337640**, https://goo.gl/rEJfK9. *"… Twelve randomized trials were included, with a total of 1,088 randomly assigned patients. Five trials compared one or more antidepressants with placebo: 75% of these patients were receiving a concurrent mood stabilizer or an atypical antipsychotic. Antidepressants were more effective than placebo. Antidepressants are effective in the short-term treatment of bipolar depression… Given the limited evidence, there is a compelling need for further studies with longer follow-up periods."*

(h) Gitlin M, Antidepressants in bipolar depression: an enduring controversy, International Journal of Bipolar Disorders 2018, PMC6269438. *"…Thus, the only reasonable conclusion would be that, with the relative paucity of data available, the effectiveness of antidepressants, whether prescribed as monotherapy or adjunctive to mood stabilizers for bipolar depression is still unproven… As one example, whereas when bipolar I patients switch, they do so almost equally into mania (45%) vs. hypomania (55%), bipolar II patients switch into*

hypomania 90% of the time (Bond et al. 2010). Additionally, whether all (mild) hypomanias need to be treated is debatable (Parker 2012). Finally, bipolar II patients demonstrate TEAS at approximately 50% the rate of bipolar I patients (Bond et al. 2010). Thus, ***switches with bipolar II patients are both less frequent and milder, diminishing the risk of antidepressant treatment considerably****… A corollary question is* ***whether bipolar II depression can be safely and effectively treated with antidepressant monotherapy. A handful of recent studies have*** *suggested both efficacy and safety of antidepressant monotherapy in short term studies in this population. (Amsterdam and Brunswick 2003; Amsterdam and Shults 2010; Amsterdam et al. 2010, 2015, 2016; Altshuler et al. 2017). In a recent study comparing venlafaxine to lithium, the SNRI showed greater efficacy with no differences in switch rates both in the acute study (12 weeks) and during a 6 month continuation study (Amsterdam et al. 2015, 2016). This is particularly noteworthy given that two prior studies (Vieta et al. 2002; Post et al. 2006) demonstrated higher switch rates with venlafaxine compared to an SSRI (in both studies) or bupropion (one study)… In a recent meta-analysis of the eleven studies examining the efficacy and safety* ***of longer term antidepressants (> 4 months), antidepressants were superior to placebo in preventing depressive episodes*** *(relative risk = 0.64, CI 0.49–0.83, p < 0.001), with or without mood stabilizers with no increase in manic/hypomanic episodes (Liu et al. 2017). Shorter studies (4–6 months) and longer term studies (6–24 months) showed similar findings.. Finally, a subtle and illustrative risk/benefit analysis was demonstrated in the Amsterdam and Shults study (2010). In this study, bipolar II patients who were short term responders to fluoxetine were randomly and blindly assigned to 1 year of treatment with either continued fluoxetine, lithium or placebo. Those subjects who continued on fluoxetine had fewer depressive relapses. There were no significant differences in a priori defined hypomanic episodes or mean mania rating scores across the three treatment groups.* ***However, examining Young Mania Rating Scales (YMRS) ratings, it is clear that there was more mood fluctuation/variability in those treated with fluoxetine compared to the other two groups. Thus, the "cost" of remaining undepressed (with antidepressant monotherapy) was an increase in affective lability****.. Bipolar II patients may be treated safely (at least in the short term) with antidepressant**s. Examine the quadrant bipolar ½ vs. short term/long term maintenance]… The key questions should not be simple dichotomous choices: are antidepressants effective for bipolar depression?, and are antidepressants harmful in bipolar patients? Rather,* ***the right questions should be: For which bipolar patients will antidepressants be helpful? and for which bipolar patients will antidepressants be harmful? All analyses agree that, in short-term studies, when antidepressants are added to mood stabilizers (in most of the patients), switch rates do not differ between antidepressants and placebo… Surprisingly, definitive evidence from large studies and meta-analyses that mood stabilizers diminish the risk of TEAS is lacking… A corollary question is whether bipolar II depression can be safely and effectively treated with antidepressant monotherapy. A handful of recent studies have suggested both efficacy and safety of antidepressant monotherapy in short term studies in this population. (Amsterdam and Brunswick 2003; Amsterdam and Shults 2010; Amsterdam et al. 2010, 2015, 2016; Altshuler et al. 2017)… In the largest double-blind, controlled study, no efficacy differences were seen in 142 bipolar II depressed patients randomized to sertraline [an SSRI], lithium, or lithium plus sertraline for 16 weeks (Altshuler et al. 2017)."***

(i) Kemp D et al, Bipolar depression: trial-based insights to guide patient care, Dialogues Clin Neurosci. 2008, PMC3181875. *"… [for STEP-BD] In the end,* ***rates of durable recovery were similar between the antidepressant (23.5%) and placebo (27.3%) groups*** *…"*

(j) **Liu B, Efficacy and safety of long-term antidepressant treatment for bipolar disorders – A meta-analysis of randomized controlled trials, J Affective Dis, 2017,** PMID: 28715727. *"…Efficacy and safety of long-term use of antidepressants (AD) in bipolar disorder (BD) patients remains highly controversial. Here we performed a meta-analysis of randomized controlled trials (RCTs) exploring the efficacy and safety of long-term AD use in BD patients…* ***Antidepressants were superior to placebo in reducing new depressive episodes in bipolar disorders without increasing risk of new manic/hypomanic episodes either used as monotherapy or in combination with MS****. Subgroup analyses revealed that greater benefit and lower risk may be achieved in BD II than in BD I. However,* ***compared with MS monotherapy, AD monotherapy significantly increased the risk of affective***

switch with no improvement in prophylaxis of new depressive episodes….[There is] elevated risk of affective switch of AD monotherapy compared with MS monotherapy…".

(k) **McElroy SL et al, A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II), J Clin Psychiatry. 2010, PMID: 20122366.** *"…740 patients (478 bipolar I, 262 bipolar II) with major depressive episodes (DSM-IV) were randomly assigned to quetiapine 300 mg/d (n = 245),* ***quetiapine 600 mg/d (n = 247),*** *paroxetine 20 mg/d (n = 122), or placebo (n = 126) for 8 weeks.* ***The primary end point was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score****… **Quetiapine-treated (both doses),** but not paroxetine-treated,* ***patients showed significantly greater improvements*** *(P < or = .05) in most secondary outcomes measures at week 8 versus the placebo group.* ***Paroxetine significantly improved Hamilton Anxiety Rating Scale scores versus placebo (P < . 05) but not MADRS or Hamilton Depression Rating Scale (HDRS) scores…"*** *Note: The Bipolar Book: History, Neurobiology, and Treatment (Yildiz) calls this "the best data of efficacy [of antidepressant monotherapy] so far…"*

(l) **McGirr A et al, Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials, Lancet Psychiatry. 2016, PMID: 28100425, https://goo.gl/TzYB1A. "…** *We identified six trials representing 1383 patients with bipolar depression. Second-generation antidepressants were associated with a small but significant improvement in clinician-rated depressive symptom score (standardised mean differences 0·165 [95% CI 0·051-0·278], p=0·004).* ***However, clinical response and remission rates did not differ significantly between patients receiving adjunctive antidepressants and those receiving placebo."***

(m) McInerney S et al, Review of Evidence for Use of Antidepressants in Bipolar Depression, Primary Care Companion CNS Disord. 2014, PMCID: PMC4321017. *"…The body of evidence on the use of antidepressant monotherapy to treat patients with bipolar depression is contentious, but the recommendations from evidence-based guidelines do not support antidepressant monotherapy for bipolar depression… Mood stabilizers should be used as first-line treatment for bipolar depression, and adjunctive antidepressant treatment should be considered only if this strategy fails…* ***Support for the efficacy and safety of antidepressants in the treatment of bipolar depression comes from a meta-analysis of 12 trials. [Gijsman 2004]*** *While there was a 1.86 risk ratio for response to antidepressants in the 5 placebo-controlled studies that compared 1 or more antidepressants with placebo,* ***this result should be treated with caution****, as 1 large study accounted for 69% (456/662) of the total number of patients in the comparison.* ***[Tohen 2003]*** *It should also be noted that, in 3 of the studies, patients received a concurrent mood stabilizer (lithium) or antipsychotic agent (olanzapine), so the comparison was not between antidepressant monotherapy and placebo…* ***Studies in this review have provided evidence that the risk of mood conversion may not actually occur in the current episode but rather lead to a lifetime risk of polarity change and mixed episodes [Strejilevich, Valentí, Pacchiarotti 2011, Sussman]"***

(n) Mohammed Z et al, Acute pharmacological treatment strategies for bipolar depression, Neuropsychiatry (2016), https://goo.gl/47Rgpv. *"…****This article is meant to be educational and narrative, and does not constitute a systematic review and grading of evidence*** *as there are several recent full reviews and meta-analyses available…the current evidence is not sufficient to inform clinical practice about the long term use of these medications [antidepressants]…* ***the efficacy of antidepressants as a group was neither statistically significant nor clinically meaningful (NNT of 50****)…."*

(o) **National Institute of Mental Health (NIMH), Study Sheds Light on Medication Treatment Options for Bipolar Disorder, 2007, NIMH Archive**, https://goo.gl/q5YGxx. *"… For depressed people with bipolar disorder who are taking a mood stabilizer, adding an antidepressant medication is no more effective than a placebo (sugar pill), according to results published online on March 28, 2007 in the New England Journal of Medicine. The results are part of the large-scale, multi-site Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a $26.8 million clinical trial funded by the National Institutes of Health's National Institute of Mental Health (NIMH)…".*

(p) Nemeroff CB et al, Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression, Am J Psychiatry. 2001, PMID: 11384898. https://goo.gl/z4r9ya. *"…For patients with high serum lithium levels, antidepressant response at endpoint also did not significantly differ from placebo… Antidepressants may not be useful adjunctive therapy for bipolar depressed patients with high serum lithium levels."*

(q) **Pacchiarotti I, Mazzarini L, Kotzalidis GD, et al. Mania and depression: mixed, not stirred. J Affect Disord. 2011.**

(r) **Pacchiarotti I et al, The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders, Am J Psych, 2013, PMCID: PMC4091043**. *"…The ISBD Task Force was made up of a panel of global experts on bipolar disorder, selected according to an objective procedure based on a Scopus search of citations on the specific topic of antidepressant use in bipolar disorder (number of citations per candidate during the past 3 years). The most cited authors (including several ISBD nonmembers) and some additional authors from key geographical areas were identified and invited by e-mail to participate; 76% agreed to participate…. The risk-benefit profile of antidepressant medications in bipolar disorder is controversial. When conclusive evidence is lacking, expert consensus can guide treatment decisions. The International Society for Bipolar Disorders (ISBD) convened a task force to seek consensus recommendations on the use of antidepressants in bipolar disorders…* ***There is striking incongruity between the wide use of and the weak evidence base for the efficacy and safety of antidepressant drugs in bipolar disorder****. Few well-designed, long-term trials of prophylactic benefits have been conducted, and there is insufficient evidence for treatment benefits with antidepressants combined with mood stabilizers…****Because of limited data, the task force could not make broad statements endorsing antidepressant use but acknowledged that individual bipolar patients may benefit from antidepressants… Short-term trials of adjunctive antidepressant treatment have reported mixed results, perhaps best exemplified by the contrasting findings in the two largest placebo-controlled trials carried out to date.*** *The first of these [Tohen 2003] compared the efficacy and safety of olanzapine monotherapy (5–20 mg/day, N=370) to placebo (N=377) in depressed bipolar I patients in an 8-week randomized double-blind trial with a small exploratory arm with several dosages of olanzapine-fluoxetine combinations. The olanzapine-fluoxetine combinations were more effective than olanzapine alone or placebo in improving MADRS depression scores at weeks 4–8. Limitations of the study included its lack of a fluoxetine monotherapy arm and a substantial dropout rate (38.5%)…* ***Limitations of the study included its lack of a fluoxetine monotherapy arm and a substantial dropout rate (38.5%)." Note: The Tohen study is the one of two studies they reference, the one supporting fluoxetine…*** *In the second trial* ***[Sachs 2007],*** *depressed bipolar I or II patients (N=366) [179 in treatment group] receiving treatment with a mood stabilizer (lithium, valproate, carbamazepine, or other antimanic agents approved by the U.S. Food and Drug Administration, alone or in combination) were randomly assigned to receive adjunctive antidepressants (bupropion or paroxetine) or placebo for up to 26 weeks.* ***Adjunctive antidepressants were no more effective than placebo*** *at any time, and overall,* ***23.5% of patients given an antidepressant and 27.3% given placebo met criteria for enduring recovery.***

(s) Sachs et al, Effectiveness of adjunctive antidepressant treatment for bipolar depression, N Engl J Med. 2007, PMID: 17392295. *"…****Forty-two of the 179 subjects (23.5%) receiving a mood stabilizer plus adjunctive antidepressant therapy*** *[over double the size of Tohen 2003] had a durable recovery, as did 51 of the 187 subjects (27.3%) receiving a mood stabilizer plus a matching placebo (P=0.40****). Modest nonsignificant trends*** *favoring the group receiving a mood stabilizer plus placebo were observed across the secondary outcomes. Rates of treatment-emergent affective switch were similar in the two groups…* ***The use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch.****"*

(t) Shvartzman Y et al, Adjunctive antidepressants in bipolar depression: A cohort study of six- and twelve-months rehospitalization rates, Eur Neuropsychopharmacol. 2018, PMID: 29449055. *"…there is a paucity of studies on the risk-benefit ratio of AD maintenance treatment in bipolar disorder (BD). We compared*

rehospitalization rates of patients with BD-I depressive episode who were discharged with mood stabilizers (MSs) and/or atypical antipsychotics (AAPs) with or without adjunctive AD. Ninety-eight patients with BD-I who were hospitalized with a depressive episode between 2005 and 2013 were retrospectively followed for 6-months and 1-year rehospitalization rates, as well as time to rehospitalization, according to treatment at discharge: MSs and/or AAPs with or without AD. Multivariable survival models adjusted for covariates known to influence rehospitalization were conducted. ***Six-months and 1-year rehospitalization rates were significantly lower in the adjunctive-AD treatment group compared to the no-AD group (9.2% vs. 36.4%, P = . 001, power = 0.87 and 12.3% vs. 42.4%, P = .001, power = 0.89, respectively).*** *Time to rehospitalization within 6-months and 1-year was significantly longer in the adjunctive-AD treatment group (169.9 vs 141 days, P = .001 and 335.6 vs 252.3 days, P = .001, respectively). Adjunctive-AD treatment at discharge reduced significantly the adjusted risk of rehospitalization within 6-months (HR = 0.081, 95% CI: 0.016-0.412, P = 0.002) and 1-year (HR = 0.149, 95% CI: 0.041-0.536, P = 0.004). In conclusion, adjunctive-AD therapy to MS/AAP at discharge from BD-I depressive episode hospitalization is associated with a lower rate of and a longer time to rehospitalization during a 1-year follow up period…* ***Moreover, adjunctive-AD treatment did not increase rehospitalization rates of manic episode****."*

(u) Sidor MM et al, Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis, J Clin Psychiatry. 2011, PMID: 21034686, https://goo.gl/XtwCya, *"…Double-blinded randomised controlled trials (RCTs) of up to 16 weeks' acute antidepressant treatment (included adjunctive or monotherapy and fixed- or flexible-dose) compared to an active drug or placebo for adults with bipolar I or II disorder (or a co-occurring mixed state) who were experiencing a current depressive state were eligible for inclusion…These studies were combined with earlier studies for a total of 15 studies containing 2,373 patients. The primary review outcomes were clinical response and remission… There was* ***no significant difference between antidepressants and placebo in rates of clinical response*** *(five RCTs, I^2=69%),* ***remission*** *(four RCTs, I^2=51%)* ***and affective switch*** *(six RCTs, I^2=0%). Antidepressants were not statistically superior to placebo or other current standard treatment for bipolar depression…"*

(v) Strejilevich SA, Martino DJ, Marengo E, et al. Long-term worsening of bipolar disorder related with frequency of antidepressant exposure. Ann Clin Psychiatry. 2011.

(w) Sussman M, Friedman M, Korn JR, et al. The relationship between use of antidepressants and resource utilization among patients with manic or mixed bipolar disorder episodes: findings from a managed care setting. J Affect Disord. 2012.

(x) Valentí M, Pacchiarotti I, Rosa AR, et al. Bipolar mixed episodes and antidepressants: a cohort study of bipolar I disorder patients. Bipolar Disord. 2011

(y) Vazquez G et al, Comparison of antidepressant responses in patients with bipolar vs. unipolar depression: a meta-analytic review, Pharmacopsychiatry. 2011, PMID: 21031345. "…Since there is considerable uncertainty about therapeutic responses to antidepressants among depressed patients diagnosed with bipolar (BP) vs. unipolar (UP) mood disorders, we have reviewed available studies that compared both types of depressed patients… We identified only 10 studies meeting even liberal inclusion criteria, and they varied greatly in size and design quality. The overall difference in antidepressant responses between BP (n=863) and UP (n=2 226) disorder patients was not significant (pooled RR=1.05; CI: 0.96-1.15; P=0.34). Based on meta-regression, we also found no difference in responses based on diagnosis or subtype, subjects/study, % women, average age, or length of treatment based on meta-regression. Risk of manic-switching averaged 2.50 vs. 0.275%/week among BP vs. UP disorder patients, including co-treatment with mood stabilizers in 70% of BP patients… "

(z) Vazquez G et al, Overview of antidepressant treatment of bipolar depression, Int J Neuropsychopharmacol. 2013, PMID: 23428003, https://goo.gl/K6gcKN. *"…We performed a comprehensive literature search for reports on treatments for bipolar depression, focusing on RCTs of antidepressants in acute major depressive episodes in patients diagnosed with type I or II BD… Well-designed, controlled trials of antidepressants for acute bipolar depression are rare, vary in size and quality and their findings have been notably inconsistent… Evidence of long-term, prophylactic benefit of antidepressants is even more limited… Of particular note, two of*

the largest, well-designed trials found no added benefit associated with treatment with a serotonin reuptake inhibitor (SRI) antidepressant or bupropion… 10 placebo-controlled antidepressant trials meeting inclusion... They involved a total of 1432 patients diagnosed with bipolar depression. These trials are few, heterogeneous in patient characteristics, duration and in additional treatments allowed, ***making conclusions highly tentative****. Nevertheless, the crude pooled response rate with antidepressant treatment was 44.8% (256/571) vs. 33.4% (288/861) with placebo (χ2 = 17.7, p < 0.0001)… The present primary meta-analysis indicated statistically significant overall efficacy of antidepressants vs. placebo in acute bipolar depression… Antidepressant treatment for BD patients is also encouraged by hoped-for, long-term prophylactic benefits against depressive recurrences, even though* ***such effects remain unproved****… These findings, and the paucity of compellingly effective alternatives, encourage continued study of antidepressants in bipolar depression."*

(aa) Zhang Y et al, Antidepressants for bipolar disorder: A meta-analysis of randomized, double-blind, controlled trials, Neural Regen Res. 2013, PMCID: PMC4146170*, (N=1244, "… Among 5 001 treatment studies published, 14 double-blind randomized controlled trials involving 1 244 patients were included in the meta-analysis… The primary outcome was the response and switching to mania. The secondary outcomes included remission, discontinuation rate, and suicidality… The current study showed that antidepressants were not associated with a significant increase in efficacy com-pared with placebo or other pharmacologic treatments in the acute and maintenance phase therapy of bipolar disorder… [the analysis]* ***does not support the short-term or long-term application of antidepressant therapy in patients with bipolar disorder****… The classes of antidepressants studied here, mostly SSRIs and TCAs,* ***did not increase the risk of switching****. This finding is consistent with another previous study. The rates of switching to mania did not support the belief that switching to mania is a common complication of treatment with antidepressants in bipolar disorder in the short-term spans of 4 to12 weeks or in long-term spans of 26 to 50 weeks.");*

[21] **Zhang Y et al, Antidepressants for bipolar disorder: A meta-analysis of randomized, double-blind, controlled trials, Neural Regen Res. 2013, PMCID: PMC4146170.** *"…Among 5 001 treatment studies published, 14 double-blind randomized controlled trials involving 1 244 patients were included in the meta-analysis. Eleven short-term studies and three maintenance studies were included.* ***Studies suggested that patients treated with antidepressants were not significantly more likely to achieve higher response and remission rates in the short-term or long-term treatment than patients treated with placebo and other medications… Existing evidence of efficacy does not support the short-term or long-term application of antidepressant therapy in patients with bipolar disorder…"***

[22] **Ghaemi S et al, Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks, Acta Psychiatr Scand. 2008,** PMCID: PMC2718794*. "…Available research on long-term use of ADs to treat patients diagnosed with BPD is not adequate to support their extraordinarily widespread, off-label, empirical use in clinical practice…* ***On balance, the research reviewed here suggests an unfavorable risk / benefit relationship for long-term AD [Antidepressant] treatment in BPD, especially BP-I disorder, in that adding an AD to an MS [mood stabilizer] yielded little reduction in risk of BP depression beyond that achieved with MSs-alone****.... Particularly when given alone****, ADs were associated with considerable added risk of mania****…When AD was used with or without an MS in eight studies involving 364 participants, risk of new mania was significantly increased compared with use of MS-alone** *(RR = 1.80; 95% CI 1.22–2.65)…* ***When AD was used alone in three other trials involving 118 patients, there was a significant 2.4-fold increase in risk of mania compared with use of MS-alone*** *(RR = 2.37; 95% CI 1.38–4.05)…."* 7 trials N=350.

[23] **Antidepressant prescribing rate for bipolar**.

(a) **Baldessarini RJ et al. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatr Serv 2007, PMID: 17215417**; *"…The most commonly prescribed first drug class was antidepressants (50% of patients)…"*

(b) **Greil W et al, Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009. J Affect Disord 2012, PMID: 22134044.** *"… Overall 81.3% of patients received antidepressants (AD) (7.8% monotherapy), 57.9% antipsychotics (AP), 50.1% anticonvulsants (AC), 47.5% tranquilizers, and 34.6% lithium (Li)…"*

(c) ***Ventimiglia J et al, Treatment of Bipolar Disorder, Psychiatry (Edgmont). 2009, PMC2790396****. "…Our analysis shows that, while a large portion of patients is treated by a single mechanism of action (44%), an equally sizable group of patients receives two or more drug classes (56%) to treat the disorder. From a therapeutic class perspective, 71 percent of patients with bipolar disorder receive an atypical antipsychotic, 53 percent receive a mood stabilizer, and 30 percent receive an antidepressant. While antipsychotics and mood stabilizers represent the vast majority of bipolar disorder monotherapy (90%), antidepressants are more commonly seen as part of a combination treatment."*

[24] **Pacchiarotti I et al, The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders, Am J Psych, 2013, PMCID: PMC4091043**. *"…The risk-benefit profile of antidepressant medications in bipolar disorder is controversial. When conclusive evidence is lacking, expert consensus can guide treatment decisions. The International Society for Bipolar Disorders (ISBD) convened a task force to seek consensus recommendations on the use of antidepressants in bipolar disorders…* ***There is striking incongruity between the wide use of and the weak evidence base for the efficacy and safety of antidepressant drugs in bipolar disorder.*** *Few well-designed, long-term trials of prophylactic benefits have been conducted, and there is insufficient evidence for treatment benefits with antidepressants combined with mood stabilizers…Because of limited data,* ***the task force could not make broad statements endorsing antidepressant use*** *but acknowledged that individual bipolar patients may benefit from antidepressants…"*

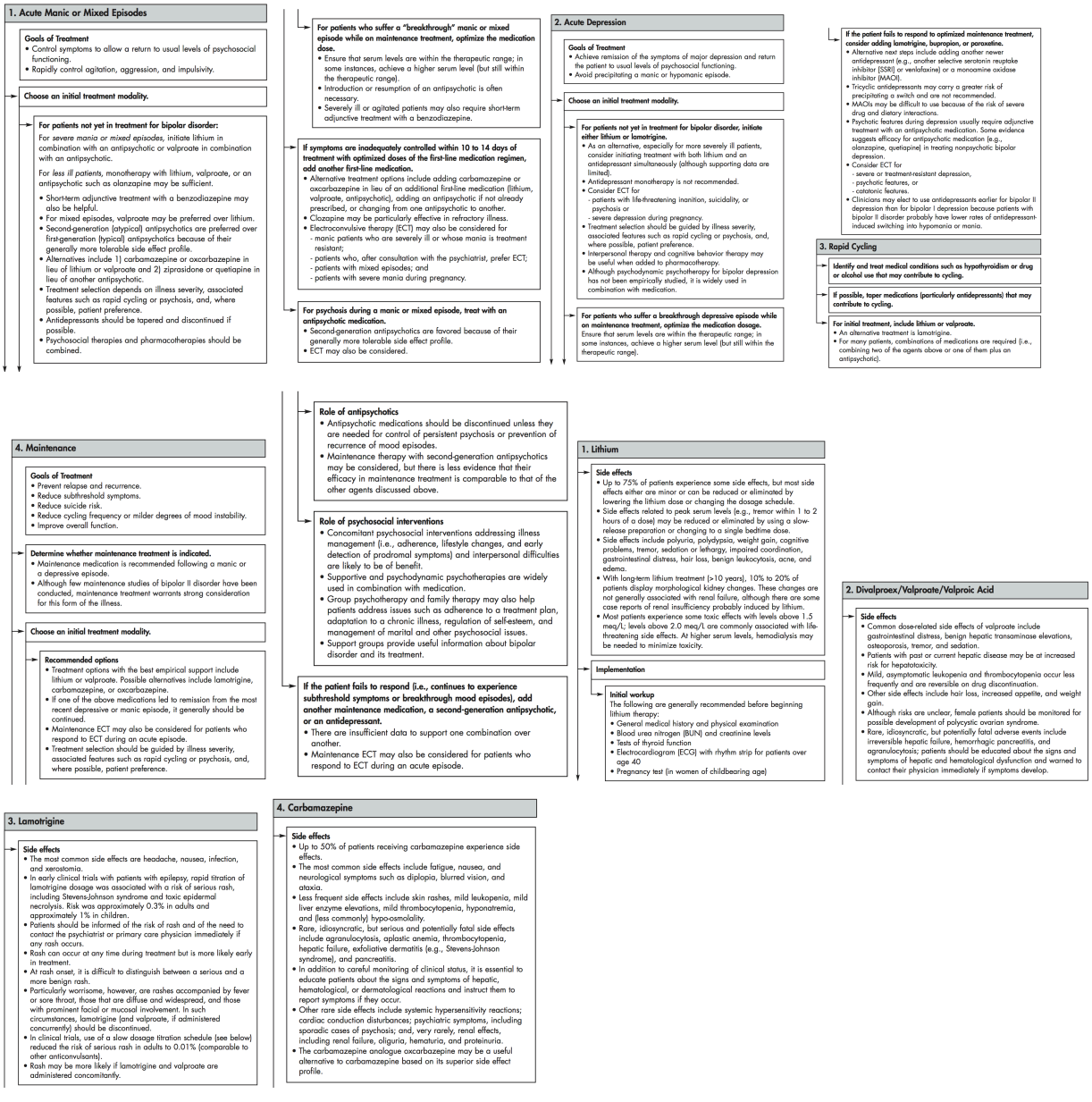
[25] **Prescribing guidelines for bipolar.**

(a) **Guzman F, Bipolar Disorder Treatment Guidelines: A 2018 Update, Pscyhopharmacology Institute, 2018, https://goo.gl/Xo82Ci.** "…You may notice that we have not included the guidelines published by the American Psychiatric Asssociation, this is because the document has not been updated since 2005…"

(b) **Hirschfeld R, GUIDELINE WATCH: PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH BIPOLAR DISORDER, 2ND EDITION, American Psychiatric Association, 2005 https://goo.gl/x3qBzc, copied from APA website 12/11/2018.** Note: these are not the APA guidelines, but a "Guideline Watch" which "reviews the most important studies" that are recent. With that said, there is a recommendation "prescription of antidepressants in the absence of a mood stabilizer is not recommended." *"…APA's Practice Guideline for the Treatment of Patients With Bipolar Disorder, 2nd Edition, was published in April 2002 (1). Since that time, a number of controlled treatment studies on aspects of bipolar disorder have been completed and published or are in press, including studies of second-generation (atypical) antipsychotics as monotherapy and as adjunctive treatment (with more traditional mood stabilizers) for the acute treatment of mania, studies of antiepileptic agents for the acute treatment of mania, trials for three medications for the acute treatment of bipolar depression, four monotherapy and one combination therapy relapse prevention studies, and studies of psychosocial interventions for maintenance. The evidence from these studies supports a substantially expanded set of options for clinicians who treat patients with bipolar disorder.* ***This guideline watch briefly reviews the most important of the studies****. The majority of the studies were industry supported…* ***Evidence for the efficacy of an antidepressant with adjunctive mood stabilizer is modest. Prescription of antidepressants in the absence of a mood stabilizer is not recommended for bipolar I patients****…. Maintenance treatment: Two large randomized, double-blind studies examined the utility of lamotrigine in the maintenance treatment of patients with bipolar I disorder…In the study of recently depressed patients both lamotrigine and lithium were superior to placebo in preventing any mood episode. Lamotrigine, but not lithium, was superior to placebo in preventing a depressive episode. Lithium, but not lamotrigine, was superior to placebo in preventing a manic, hypomanic,*

or mixed episode. With the exception of rash, there were no side effects of lamotrigine that exceeded placebo. There were no serious rashes. For the lithium group, the incidence of somnolence and tremor exceeded that of placebo…"

(c) **McIntyre J et al, TREATING BIPOLAR DISORDER A Quick Reference Guide, American Psychiatric Association, 2002, https://goo.gl/vYGtVQ, copied from APA website 12/11/20**

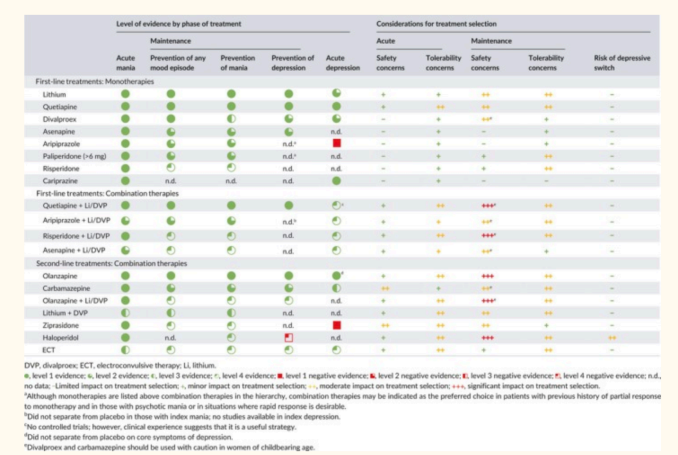


(d) **Grunze H et al, The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression, World J Biol Psychiatry. 2010, https://goo.gl/z1kxQU.** *"…We identified 10 pharmacological monotherapies or combination treatments with at least limited positive evidence for efficacy in bipolar depression, several of them still experimental and backed up only by a single study. Only one medication was considered to be sufficiently studied to merit full positive evidence...* ***The Canadian guidelines also recommend as a basic principle to discontinue antidepressants; however, the role of antidepressants in the treatment of bipolar depression remains controversial and will be discussed in more detail in the related chapter****… Clinically, the*

use of antidepressants especially in combination treatment remains common, perhaps reflecting this ongoing controversy… More recent, some doubts have been raised about the efficacy of antidepressants in milder forms of unipolar depression, as well as in adolescents. The issue of severity is important in establishing or clarifying the size of the effect of antidepressants… Overall, the controlled evidence for antidepressant efficacy of antidepressants as a group of medication in bipolar depression is inconclusive… Bipolarity has regrettably been an exclusion criterion in most antidepressant trials of the last two decades… The ***use of lithium rests on old unconvincing*** *trials of small scale and idiosyncratic design (Bhagwagar and Goodwin 2002). The latest controlled evidence in a large cohort study could not show separation of low-serum level lithium from placebo (Young et al. 2008)"*

(e) **Yatham L et al, Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder, Bipolar Disord. 2018, PMC5947163.** [See also b-Grunze for comments on Canada] *"…**Any patients presenting with mania who have been taking antidepressants should have these medications discontinued…"***

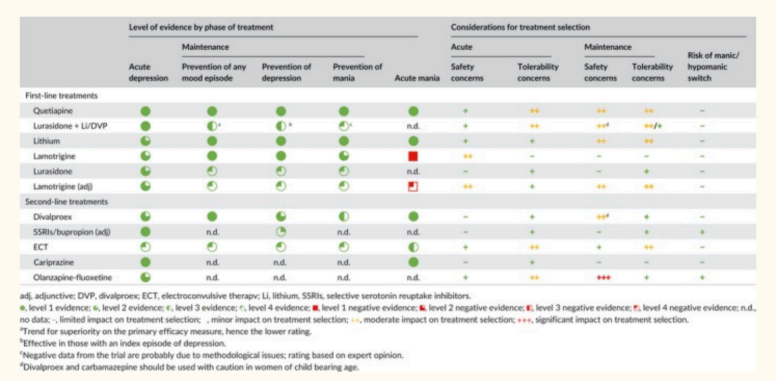
For acute mania



	Level of evidence by phase of treatment					Considerations for treatment selection				
	Maintenance					Acute		Maintenance		
	Acute mania	Prevention of any mood episode	Prevention of mania	Prevention of depression	Acute depression	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns	Risk of depressive switch
First-line treatments: Monotherapies										
Lithium	●	●	●	●	◔	+	+	++	++	–
Quetiapine	●	●	●	●	●	+	++	++	++	–
Divalproex	●	●	◐	◔	◔	–	+	++[a]	+	–
Asenapine	●	◔	◔	◔	n.d.	–	+	–	+	–
Aripiprazole	●	◔	◔	n.d.[c]	■	–	+	–	+	–
Paliperidone (>6 mg)	●	◔	◔	n.d.[c]	n.d.	–	+	+	++	–
Risperidone	●	◴	◴	n.d.	n.d.	–	+	+	++	–
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–	–
First-line treatments: Combination therapies										
Quetiapine + Li/DVP	●	●	●	●	◴[a]	+	++	+++[a]	++	–
Aripiprazole + Li/DVP	◔	◔	◔	n.d.[c]	◴	+	+	++[a]	++	–
Risperidone + Li/DVP	●	◴	◴	n.d.	◴	+	++	+++[a]	++	–
Asenapine + Li/DVP	◔	◴	◴	n.d.	◴	+	+	++[a]	+	–
Second-line treatments: Combination therapies										
Olanzapine	●	●	●	●	●[a]	+	++	+++	++	–
Carbamazepine	●	◔	◔	◔	◐	++	+	++[a]	++	–
Olanzapine + Li/DVP	●	◴	◴	◴	n.d.	+	++	+++[a]	++	–
Lithium + DVP	◐	◐	◐	n.d.	n.d.	+	++	++	++	–
Ziprasidone	●	◴	◴	n.d.	■	++	++	++	+	–
Haloperidol	●	n.d.	◴	■	n.d.	+	++	+++	++	++
ECT	◐	◴	◴	◴	◴	+	++	+	++	–

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.
●, level 1 evidence; ◔, level 2 evidence; ◴, level 3 evidence; ■, level 4 evidence; ◔, level 1 negative evidence; ◴, level 2 negative evidence; ■, level 3 negative evidence; ■, level 4 negative evidence; n.d., no data; –, limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.
[a]Although monotherapies are listed above combination therapies in the hierarchy, combination therapies may be indicated as the preferred choice in patients with previous history of partial response to monotherapy and in those with psychotic mania or in situations where rapid response is desirable.
[b]Did not separate from placebo in those with index mania; no studies available in index depression.
[c]No controlled trials; however, clinical experience suggests that it is a useful strategy.
[d]Did not separate from placebo on core symptoms of depression.
[e]Divalproex and carbamazepine should be used with caution in women of childbearing age.

For acute bipolar 1 depression:



	Level of evidence by phase of treatment					Considerations for treatment selection				
	Maintenance					Acute		Maintenance		
	Acute depression	Prevention of any mood episode	Prevention of depression	Prevention of mania	Acute mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns	Risk of manic/ hypomanic switch
First-line treatments										
Quetiapine	●	●	●	●	●	+	++	++	++	–
Lurasidone + Li/DVP	●	◐[a]	◐[b]	◔[a]	n.d.	+	++	++[d]	++/+[e]	–
Lithium	◔	●	●	●	●	+	+	++	++	–
Lamotrigine	◔	●	●	◔	■	++	–	–	–	–
Lurasidone	◔	◴	◴	◴	n.d.	–	+	–	+	–
Lamotrigine (adj)	◔	◴	◴	◴	■	++	+	++	++	–
Second-line treatments										
Divalproex	◔	●	◔	◐	●	–	+	++[d]	+	–
SSRIs/bupropion (adj)	●	n.d.	◔	n.d.	n.d.	–	+	–	+	+
ECT	◴	◴	◴	◴	◐	+	++	+	++	–
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–	–
Olanzapine-fluoxetine	◔	n.d.	n.d.	n.d.	n.d.	+	++	+++	+	+

adj, adjunctive; DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium, SSRIs, selective serotonin reuptake inhibitors.
●, level 1 evidence; ◔, level 2 evidence; ◴, level 3 evidence; ◴, level 4 evidence; ■, level 1 negative evidence; ◔, level 2 negative evidence; ■, level 3 negative evidence; ■, level 4 negative evidence; n.d., no data; –, limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.
[a]Trend for superiority on the primary efficacy measure, hence the lower rating.
[b]Effective in those with an index episode of depression.
[c]Negative data from the trial are probably due to methodological issues; rating based on expert opinion.
[d]Divalproex and carbamazepine should be used with caution in women of child bearing age.

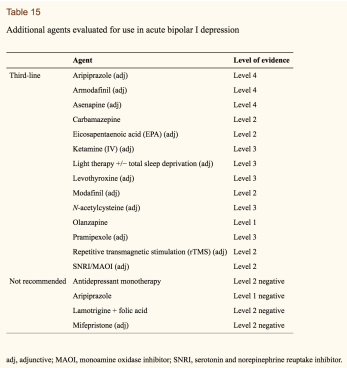


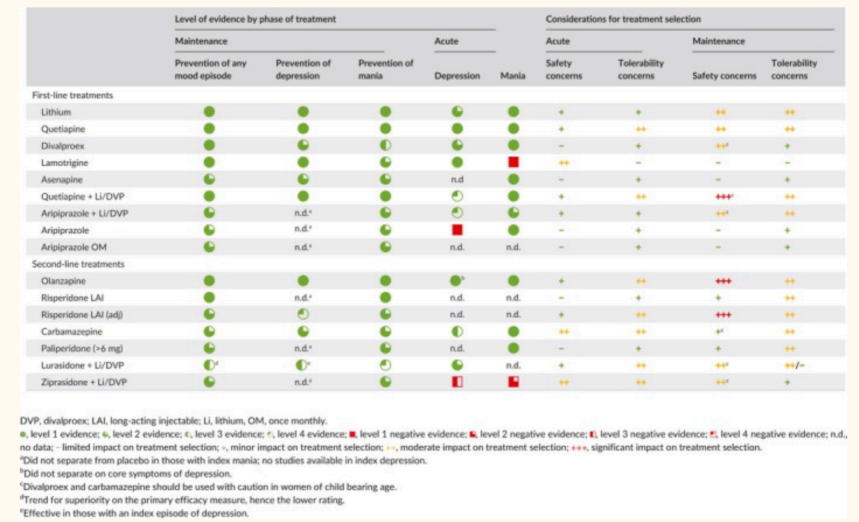
Table 15

Additional agents evaluated for use in acute bipolar I depression

	Agent	Level of evidence
Third-line	Aripiprazole (adj)	Level 4
	Armodafinil (adj)	Level 4
	Asenapine (adj)	Level 4
	Carbamazepine	Level 2
	Eicosapentaenoic acid (EPA) (adj)	Level 2
	Ketamine (IV) (adj)	Level 3
	Light therapy +/– total sleep deprivation (adj)	Level 3
	Levothyroxine (adj)	Level 3
	Modafinil (adj)	Level 2
	N-acetylcysteine (adj)	Level 3
	Olanzapine	Level 1
	Pramipexole (adj)	Level 3
	Repetitive transmagnetic stimulation (rTMS) (adj)	Level 2
	SNRI/MAOI (adj)	Level 2
Not recommended	Antidepressant monotherapy	Level 2 negative
	Aripiprazole	Level 1 negative
	Lamotrigine + folic acid	Level 2 negative
	Mifepristone (adj)	Level 2 negative

adj, adjunctive; MAOI, monoamine oxidase inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

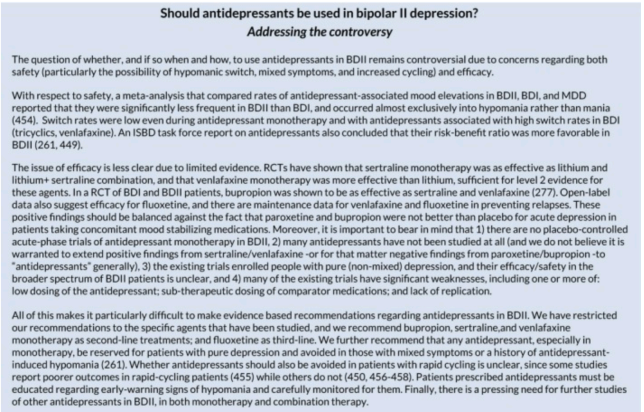
For bipolar 1 maintenance:



	Level of evidence by phase of treatment					Considerations for treatment selection			
	Maintenance			Acute		Acute		Maintenance	
	Prevention of any mood episode	Prevention of depression	Prevention of mania	Depression	Mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments									
Lithium	●	●	●	◔	●	+	+	++	++
Quetiapine	●	●	●	●	●	+	++	++	++
Divalproex	●	◔	◐	◔	●	−	+	++[c]	+
Lamotrigine	●	●	◔	●	■	++	−	−	−
Asenapine	◔	◔	◔	n.d.	●	−	+	−	+
Quetiapine + Li/DVP	●	●	●	◴	●	+	++	+++[f]	++
Aripiprazole + Li/DVP	◔	n.d.[a]	◔	◴	◔	+	+	++[a]	++
Aripiprazole	◔	n.d.[a]	◔	■	●	−	+	−	+
Aripiprazole OM	◔	n.d.[a]	◔	n.d.	n.d.	−	+	−	+
Second-line treatments									
Olanzapine	●	●	●	●[b]	●	+	++	+++	++
Risperidone LAI	●	n.d.[a]	●	n.d.	n.d.	−	+	+	++
Risperidone LAI (adj)	◔	◴	◔	n.d.	n.d.	+	++	+++	++
Carbamazepine	◔	◔	◔	◐	●	++	++	+[c]	++
Paliperidone (>6 mg)	◔	n.d.[a]	◔	n.d.	●	−	+	+	++
Lurasidone + Li/DVP	◐[d]	◐[e]	◴	◔	n.d.	+	++	++[a]	++/−
Ziprasidone + Li/DVP	◔	n.d.[a]	◔	■	■	++	++	++[a]	+

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.
●, level 1 evidence; ◕, level 2 evidence; ◔, level 3 evidence; ◴, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◩, level 4 negative evidence; n.d., no data; − limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.
[a]Did not separate from placebo in those with index mania; no studies available in index depression.
[b]Did not separate on core symptoms of depression.
[c]Divalproex and carbamazepine should be used with caution in women of child bearing age.
[d]Trend for superiority on the primary efficacy measure, hence the lower rating.
[e]Effective in those with an index episode of depression.

Bipolar 2 Depression



Should antidepressants be used in bipolar II depression?
Addressing the controversy

The question of whether, and if so when and how, to use antidepressants in BDII remains controversial due to concerns regarding both safety (particularly the possibility of hypomanic switch, mixed symptoms, and increased cycling) and efficacy.

With respect to safety, a meta-analysis that compared rates of antidepressant-associated mood elevations in BDII, BDI, and MDD reported that they were significantly less frequent in BDII than BDI, and occurred almost exclusively into hypomania rather than mania (454). Switch rates were low even during antidepressant monotherapy and with antidepressants associated with high switch rates in BDI (tricyclics, venlafaxine). An ISBD task force report on antidepressants also concluded that their risk-benefit ratio was more favorable in BDII (261, 449).

The issue of efficacy is less clear due to limited evidence. RCTs have shown that sertraline monotherapy was as effective as lithium and lithium+ sertraline combination, and that venlafaxine monotherapy was more effective than lithium, sufficient for level 2 evidence for these agents. In a RCT of BDI and BDII patients, bupropion was shown to be as effective as sertraline and venlafaxine (277). Open-label data also suggest efficacy for fluoxetine, and there are maintenance data for venlafaxine and fluoxetine in preventing relapses. These positive findings should be balanced against the fact that paroxetine and bupropion were not better than placebo for acute depression in patients taking concomitant mood stabilizing medications. Moreover, it is important to bear in mind that 1) there are no placebo-controlled acute-phase trials of antidepressant monotherapy in BDII, 2) many antidepressants have not been studied at all (and we do not believe it is warranted to extend positive findings from sertraline/venlafaxine -or for that matter negative findings from paroxetine/bupropion -to "antidepressants" generally), 3) the existing trials enrolled people with pure (non-mixed) depression, and their efficacy/safety in the broader spectrum of BDII patients is unclear, and 4) many of the existing trials have significant weaknesses, including one or more of: low dosing of the antidepressant; sub-therapeutic dosing of comparator medications; and lack of replication.

All of this makes it particularly difficult to make evidence based recommendations regarding antidepressants in BDII. We have restricted our recommendations to the specific agents that have been studied, and we recommend bupropion, sertraline,and venlafaxine monotherapy as second-line treatments; and fluoxetine as third-line. We further recommend that any antidepressant, especially in monotherapy, be reserved for patients with pure depression and avoided in those with mixed symptoms or a history of antidepressant-induced hypomania (261). Whether antidepressants should also be avoided in patients with rapid cycling is unclear, since some studies report poorer outcomes in rapid-cycling patients (455) while others do not (450, 456-458). Patients prescribed antidepressants must be educated regarding early-warning signs of hypomania and carefully monitored for them. Finally, there is a pressing need for further studies of other antidepressants in BDII, in both monotherapy and combination therapy.

Strength of evidence and recommendations for adjunctive psychological treatments for bipolar disorder[a]

	Maintenance: Recommendation (Level of Evidence)	Depression: Recommendation (Level of Evidence)
Psychoeducation (PE)	First-line (Level 2)	Insufficient evidence
Cognitive behavioural therapy (CBT)	Second-line (Level 2)	Second-line (Level 2)
Family-focused therapy (FFT)	Second-line (Level 2)	Second-line (Level 2)
Interpersonal and social rhythm therapy (IPSRT)	Third-line (Level 2)	Third-line (Level 2)
Peer support	Third-line (Level 2)	Insufficient evidence
Cognitive and functional remediation	Insufficient evidence	Insufficient evidence
Dialectical behavioural therapy (DBT)	Insufficient evidence	Insufficient evidence
Family/caregiver interventions	Insufficient evidence	Insufficient evidence
Mindfulness-based cognitive therapy (MBCT)	Insufficient evidence	Insufficient evidence
Online interventions	Insufficient evidence	Insufficient evidence

[a]See text for specific definitions of type of therapy and number of sessions needed ("dose of psychosocial intervention") corresponding to this recommendation and evidence.

f) **National Institute for Heath and Care Excellence, Bipolar disorder: assessment and management, Clinical guideline [CG185] Last updated: April 2018, https://goo.gl/8Y5d15.** *Note:* The following extracts from the guideline show that a) they do not recommend starting to take antidepressants for bipolar, b) they recommend stopping antidepressant use at certain times (mania), and 3) they do recommend Fluoxetine combined with olanzpine. For **mania and hypomania**, *"… If a person develops mania or hypomania and is taking an antidepressant (as defined by the British National Formulary [BNF]) as monotherapy: **consider stopping the antidepressant** and offer an antipsychotic as set out in recommendation 1.5.3, **regardless of whether the antidepressant is stopped**… If a person develops mania or hypomania and is taking an antidepressant (as defined by the BNF) in combination with a mood stabiliser, **consider stopping the antidepressant**…". For **depression**, "…If a person develops moderate or severe bipolar depression and is not taking a drug [which could include antidepressants] to treat their bipolar disorder, offer **fluoxetine combined with olanzapine**, [we consider this a combo drug and not strictly an antidepressant] or quetiapine on its own, depending on the person's preference and previous response to treatment… If a person develops moderate or severe bipolar depression and is already taking lithium, check their plasma lithium level. If it is inadequate, increase the dose of lithium; if it is at maximum level, add either **fluoxetine combined with olanzapine** or add quetiapine, depending on the person's preference and previous response to treatment… If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose within the therapeutic range. If the maximum tolerated dose, or the top of the therapeutic range, has been reached and there is a*

limited response to valproate, add fluoxetine combined with olanzapine or add quetiapine, depending on the person's preference and previous response to treatment."

g) **Goodwin G et al, Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology, Journal of Psychopharmacology, 2016, PMC4922419**. Bolding is my emphasis. The wording is highly nuanced. Tapered discontinuation "may be considered" [recommendation as an option] after remission (in cases of mania); "should usually be tapered and discontinued" [recommendation] in a manic episode of depression; "consider [recommendation as an option] tapering and discontinuing antidepressants that may contribute to cycling", and **not recommending but providing guidance if prescribed** "when considered [antidepressants] they should be co-prescribed with a drug for mania" and "if an antidepressant is prescribed as a monotherapy". *"… [In **acute depressive episodes],** Antidepressants (meaning drugs for a major depressive episode in a unipolar illness course) have not been adequately studied in bipolar disorder. Only the combination of fluoxetine with olanzapine has support as a specific treatment (***). The common use of other antidepressants in patients with bipolar disorder is an extrapolation from effects established in a unipolar illness course. **When considered [not a recommendation], they should be co-prescribed with a drug for mania (e.g. dopamine antagonists, lithium, valproate) in patients with a history of mania**… There is a risk of a switch to mania or mood instability during treatment for depression (I). While this will often reflect the natural history of the disorder, it may be increased by monotherapy with antidepressants… **In bipolar II disorder, if an antidepressant is prescribed [not a recommendation] as monotherapy, any increase in dose should be gradual** and there should be vigilance for and early management of any adverse reactions such as hypomania, mixed states or agitation In contrast to the common use of antidepressants, audit data suggest that **lamotrigine is too little** used outside specialist centres, given its efficacy in bipolar I, and suitability for bipolar II disorder… **Tapered discontinuation of antidepressant drugs may be considered** after full remission of symptoms (IV)… Depressive episodes that remit in bipolar disorder tend to be shorter than in unipolar disorder (I); in the absence of strong data for maintenance efficacy, **consider discontinuation of antidepressants** after as little as twelve weeks in remission… " For **long-term treatment**, "… The role of antidepressants in long-term treatment is not established by controlled trials; nevertheless **they appear to be used effectively in a minority of patients** in the long term… if rapid cycling poses particular long-term management problems Identify and treat conditions such as hypothyroidism or substance use that may contribute to cycling (**). Consider **tapering and discontinuing antidepressants** that may contribute to cycling…Rapid cycling obviously implies temporal severity and it may often be difficult to treat. In 30-40% of cases it may be preceded by exposure to antidepressants, and worsened by treatment with antidepressants (see below: treatment of depression), but there is no proof of a causal relationship…" Other material: "…Psychotropic drug prescribing for bipolar patients in the UK was fairly consistent over time. For patients taking lithium, around 20% took lithium alone, 45-50% took a second drug, about 30% a third, and 5% a fourth. This underlines current levels of polypharmacy. The added medicines are dopamine antagonists/partial agonists (55-60%), **antidepressants (35-40%),** valproate (13%), lamotrigine (5%), and depot or long acting drug (5%). For valproate, age/child-bearing potential did not seem to influence prescribing. Given these data, **antidepressants appear to be relatively over-prescribed** and lamotrigine relatively under-prescribed given the evidence of benefit…Unfortunately, there is a real **dearth of placebo controlled trials** [for antidepressants for bipolar depression] on which to make an evidence based recommendation…" Under **Long-term treatment**: "…**Antidepressants to which patients have shown an acute treatment response may, appropriately, be continued long term when the risk of a severe depressive relapse is high** (III)[not a recommendation to start by an OK to continue]. In bipolar I disorder, they should be used in combination with a medicine that has long-term antimanic efficacy (II)." Under Key Uncertainties, "…The **long-term value of antidepressants is not sufficiently established**."

h) **Medscape, Making Sense of Bipolar Treatment Guidelines: Example: Guidelines for the Treatment of Bipolar Depression, 2018, https://goo.gl/b3sfch. https://goo.gl/aofmGL.** *"… The APA guidelines favor beginning treatment for bipolar depression with lithium monotherapy, with lamotrigine considered an alternative first-*

line agent. While less evidence-based, the APA also acknowledges that combination therapy (with lithium and an antidepressant) is appropriate in some circumstances or preferred by some clinicians…"

i) **Nivoli AM et al, New treatment guidelines for acute bipolar depression: a systematic review, J Affect Disord. 2011, PMID: 20538341.** *"…The purpose of this work is to systematically review guidelines, consensus meetings and treatment algorithms on the acute treatment of bipolar depression updated or published since 2005, to critically underline common and critical points, highlight limits and strengths, and provide a starting point for future research… the results indicate a trend to the gradual acceptance of the use of the atypical antipsychotic quetiapine as monotherapy as first-line treatment.* ***Antidepressant monotherapy is discouraged in most of them****, although some support the use of antidepressants in combination with antimanic agents for a limited period of time.* ***Lamotrigine has become a highly controversial option****."*

j) **Malhi G, Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders, Australian and New Zealand Journal of Psychiatry 2015. https://goo.gl/qNZ8Re.** *"…The most recent meta-analyses provide conflicting evidence regarding the efficacy of antidepressants in bipolar depression compared with placebo (Sidor and MacQueen, 2011; Vázquez et al., 2011).* ***Inconsistent research findings do not allow for a final evaluation and recommendation of antidepressants in the treatment of bipolar depression****, therefore the ISBD task force concludes that 'clinical trials do not provide adequate support for the efficacy of antidepressant monotherapy in treating bipolar depression'….* **[For bipolar 2] antidepressants *may* [their italics] be used as monotherapy noting that the evidence is modest at best***, and that benefits are most likely early in the course of illness. While some patients appear to benefit from carefully monitored use of antidepressants, others suffer iatrogenic mood destabilization due to induced elevated states… Two recent studies provide contrary findings (Malhi, 2015a), with one suggesting that longterm continuation of antidepressants in patients with rapid-cycling bipolar disorder leads to a threefold increase in mood episodes during the first year of follow up (El-Mallakh et al., 2015) whereas continuation of antidepressant monotherapy in BD II provides prophylaxis with only minimal risk of switching…* ***In the treatment of bipolar depression, adjunctive antidepressants should be prescribed at usual dose ranges****… The clinical risk benefit ratio of antidepressants in bipolar depression needs to be determined on a case-by-case basis given considerable clinical heterogeneity in response patterns…*

ADMINISTRATION OF ANTIDEPRESSANTS IN BIPOLAR DISORDER	Grade
GENERAL CONSIDERATIONS	
8.1. The use of antidepressants in the treatment of bipolar disorder should be overseen by a psychiatrist where possible.	CBR
8.2. The clinical risks versus benefits of antidepressants in treating bipolar depression should be determined on an individual basis.	CBR
TREATMENT	
8.3. Antidepressant monotherapy should be avoided in the treatment of bipolar depression with two or more coterminous manic symptoms.	EBR III
8.4. Antidepressant monotherapy should be avoided for the treatment of an acute bipolar depressive episode that features psychomotor agitation or in the context of rapid cycling.	EBR III
8.5. Antidepressant monotherapy should be avoided in Bipolar I disorder.	EBR III
TREATMENT EMERGENT AFFECTIVE SWITCH (TEAS)	
8.6. Upon commencing antidepressants, patients with bipolar disorder should be closely monitored for symptoms of mania, and if these emerge antidepressant therapy should be discontinued.	CBR
8.7. Antidepressant therapy should be avoided in bipolar disorder patients with a history of rapid cycling and/or a high level of mood instability.	CBR
8.8. Antidepressant therapy should be avoided during 'mixed states' (mania with depressive features or depression with manic features).	CBR
8.9. The prescription of antidepressants should take into account any past history of a treatment emergent affective switch (TEAS).	CBR

"…a recent consensus statement from experts in the field recommends that, (a) patients should not use antidepressants if they have a history of past mania, hypomania or mixed episodes emerging during antidepressant treatment, and (b) antidepressants should be avoided in patients with high mood instability or with a history of rapid cycling (Pacchiarotti et al., 2013a, 2013b)…"

(l) **Kanba S et al, Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2012, Psychiatry Clin Neurosci. 2013, PMID: 23773266. https://goo.gl/eZouqv.** Note: the summary statement is clear that antidepressants are not recommended, and they are additionally explicit that they do not recommend it as a monotherapy. Their words "when an antidepressant is considered…" is not a recommendation to consider antidepressants. So it is appropriate to say these guidelines don't recommend antidepressants. *"…[bipolar disorders] **are resistant to antidepressants in the depressive episode**… Given the risk of manic switch, **an antidepressant alone (in particular, tricyclic antidepressants) is not recommended** for treating bipolar depression. For bipolar II disorder, small studies have reported that **fluoxetine and venlafaxine (not approved in Japan)** are effective… The use of antidepressants (particularly tricyclic antidepressants) is controversial, but **it is not currently recommended** as a treatment option considering the current data…. [For major depressive episode] "use of tricyclic antidepressants, single treatment [monotherapy, presumably] with antidepressants" are not recommended… Given the risk of manic switch, **an antidepressant alone (in particular, tricyclic antidepressants) is not recommended for treating bipolar depression**. " Therefore, when an antidepressant is considered an option for bipolar II depression, it should be done very carefully… for the efficacy of the combination therapy using mood stabilizers and antidepressants, there have been no reports with a high evidence level… Clinically, bipolar depression has frequently been treated using a combination of two mood stabilizers. However, there are no reports with a high evidence level in support of the efficacy of combination therapy with mood stabilizers as treatment for acute bipolar depression, except for a report of a placebo-controlled RCT showing that lithium (0.6–1.2 mEq/L) and lamotrigine (200 mg/day) was more effective than lithium and placebo (n = 124)… [From the overall summary of antidepressants] The use of antidepressants (particularly tricyclic antidepressants) is controversial, but it is not currently recommended as a treatment option considering the current data."*

(m) **Yatham LN et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord, 2006, PMID: 17156158**. *"…"*

(n) **Ghaemi SN et al, Antidepressants in bipolar disorder: the case for caution, Bipolar Disorders 2003, https://goo.gl/Gyjsvb.** *"…Over the last decade, reports generated in the US and Canada have pointed out the paucity of evidence on the efficacy of antidepressants in bipolar disorder. Further, recent North American-based treatment guidelines, including those of the American Psychiatric Association, have been conservative, recommending antidepressants only for severe bipolar depression… Moreover, if antidepressants are to be used, they should be withdrawn as early as possible. This shift away from antidepressant use has engendered criticism from some groups in Europe, particularly Germany… the research evidence appears to support US and Canadian-based treatment guidelines in which antidepressants use is restricted to cases of severe depression (or when the appropriate mood stabilizer combination has failed to prevent or reverse a depression); further the guidelines recommend antidepressant discontinuation after acute recovery… Eight of nine early randomized, double-blind placebo-controlled studies (n=163) for acute bipolar depression reported efficacy with lithium. [Zornberg 1993] .While many of these studies utilized a crossover design, it was possible to obtain 'unequivocal response,' defined as good response with lithium and relapse with placebo, from five studies.While some methodological limitations can reasonably be noted in individual studies, taken together*

***these older studies indicate at least a modest antidepressant effect of lithium in acute bipolar depression.*"**

Table 4. The case for caution with antidepressants in bipolar disorder

Con (Möller and Grunze, 2000)	Pro (Ghaemi et al., 2003)
1. The risk of antidepressant induced cycling is not high	1. The risk of antidepressant induced cycling is high
2. Antidepressants reduce the risk of suicidality	2. Antidepressants have not been shown to definitively prevent completed suicides and reduce mortality, whereas lithium has
3. Antidepressants are effective in treating bipolar depression	3. Antidepressants have not been shown to be more effective than mood stabilizers in acute bipolar depression and have been shown to be less effective than mood stabilizers in preventing depressive relapse in bipolar disorder
4. Mood stabilizers have not been shown to be effective in bipolar depression	4. Mood stabilizers, especially lithium and lamotrigine, have been shown to be effective in acute and prophylactic treatment of bipolar depressive episodes.
Conclusions and recommendations	Conclusions and recommendations
• Antidepressant associated risks are exaggerated	• There are significant risks of mania and long-term worsening of illness with antidepressants
• Antidepressants should be used frequently along with mood stabilizers	• Antidepressants should generally be reserved for severe cases of acute bipolar depression and not routinely used in mild to moderate cases
• Antidepressant treatment should be continued long-term (ideally 12 months) to avoid depressive relapse	• Antidepressants should be discontinued after recovery from the depressive episode and maintained only in those who repeatedly relapse soon after antidepressant discontinuation

[26] **Malhi G, Antidepressants in bipolar depression: yes, no, maybe?, BMJ 2015, https://goo.gl/RfXY7f.** ***"…****The use of antidepressants to treat bipolar depression is inevitable… the only pharmacotherapy alternatives are antipsychotics, anticonvulsants or lithium—none of which (like antidepressants) were developed specifically to treat bipolar depression."*

[27] **Nondrug options are crucial**. **Duckworth K, The Sensible Use of Psychiatric Medications, NAMI Advocate Magazine, Winter 2013, https://goo.gl/GMIuSU.** "... psychiatric medications... are rarely enough to promote recovery alone... Use of non-medication strategies is crucial for most clinical situations."

[28] **Davies J et al, A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based?, Addictive Behaviors, 2018, https://goo.gl/8BbdgZ.** *"…More than half (56%) of people who attempt to come off antidepressants experience withdrawal effects. Nearly half (46%) of people experiencing withdrawal effects describe them as severe…"* Note: 46% * 56% ~= 26% of people experience severe withdrawal effects.

[29] Liu B, Efficacy and safety of long-term antidepressant treatment for bipolar disorders – A meta-analysis of randomized controlled trials, J Affective Dis, 2017, PMID: 28715727. *"…Efficacy and safety of long-term use of antidepressants (AD) in bipolar disorder (BD) patients remains highly controversial. Here we performed a meta-analysis of randomized controlled trials (RCTs) exploring the efficacy and safety of long-term AD use in BD patients… Antidepressants were superior to placebo in reducing new depressive episodes in bipolar disorders without increasing risk of new manic/hypomanic episodes either used as monotherapy or in combination with MS. Subgroup analyses revealed that greater benefit and lower risk may be achieved in BD II than in BD I. However,* ***compared with MS monotherapy, AD monotherapy significantly increased the risk of affective switch with no improvement in prophylaxis of new depressive episodes….[There is] elevated risk of affective switch of AD monotherapy compared with MS monotherapy…".***

[30] See definitions. **National Institute of Mental Health (NIMH), Study Sheds Light on Medication Treatment Options for Bipolar Disorder, NIMH Archive**, https://goo.gl/q5YGxx. *"… For depressed people with bipolar disorder who are taking a mood stabilizer,* ***adding an antidepressant medication is no more effective than a placebo (sugar pill),*** *according to results published online on March 28, 2007 in the New England Journal of Medicine. The results are part of the large-scale, multi-site Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a*

$26.8 million clinical trial funded by the National Institutes of Health's National Institute of Mental Health (NIMH) …".

[31] Ketter TA et al, Balancing benefits and harms of treatments for acute bipolar depression, J Affect Disord. 2014, PMID: 25533911, https://goo.gl/YnCpz1. *"… Older approved treatments [olanzapine-fluoxetine combination (OFC) and quetiapine] were efficacious (response NNT=4 for OFC, NNT=6 for QTP), but **similarly likely to yield harms** (OFC weight gain NNH=6; QTP sedation/somnolence NNH=5)...".*

[32] **Ghaemi S et al, Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks, Acta Psychiatr Scand. 2008,** PMCID: PMC2718794. *"…In seven trials (350 BPD patients) involving 12 contrasts, long-term treatments that included ADs yielded **27% lower risk of new depression** vs. MS-only or no treatment [pooled relative risk, RR = 0.73; 95%CI 0.55–0.97; **number-needed-to-treat (NNT) = 11**], but **72% greater risk for new mania [RR = 1.72; 95% CI 1.23–2.41; number-needed-to-harm (NNH) = 7]**. Available research on long-term use of ADs to treat patients diagnosed with BPD is not adequate to support their extraordinarily widespread, off-label, empirical use in clinical practice… Particularly when given alone**, ADs were associated with considerable added risk of mania**… Long-term adjunctive AD treatment was not superior to Mood stabilizer-alone in BPD…"*

Gitlin M, Antidepressants in bipolar depression: an enduring controversy, International Journal of Bipolar Disorders 2018, PMC6269438. *"…Thus, the only reasonable conclusion would be that, with the relative paucity of data available, the effectiveness of antidepressants, whether prescribed as monotherapy or adjunctive to mood stabilizers for bipolar depression is still unproven… In a recent meta-analysis of the eleven studies examining the efficacy and safety **of longer term antidepressants (> 4 months), antidepressants were superior to placebo in preventing depressive episodes** (relative risk = 0.64, CI 0.49–0.83, p < 0.001), with or without mood stabilizers with no increase in manic/hypomanic episodes (Liu et al. 2017). Shorter studies (4–6 months) and longer term studies (6–24 months) showed similar findings.. Finally, a subtle and illustrative risk/benefit analysis was demonstrated in the Amsterdam and Shults study (2010). In this study, bipolar II patients who were short term responders to fluoxetine were randomly and blindly assigned to 1 year of treatment with either continued fluoxetine, lithium or placebo. Those subjects who continued on fluoxetine had fewer depressive relapses. There were no significant differences in a priori defined hypomanic episodes or mean mania rating scores across the three treatment groups. **However, examining Young Mania Rating Scales (YMRS) ratings, it is clear that there was more mood fluctuation/variability in those treated with fluoxetine compared to the other two groups. Thus, the "cost" of remaining undepressed (with antidepressant monotherapy) was an increase in affective lability."***

[33] **McInerney S et al, Review of Evidence for Use of Antidepressants in Bipolar Depression, Primary Care Companion CNS Disord. 2014,** PMCID: PMC4321017. *"…The body of evidence on the use of antidepressant monotherapy to treat patients with bipolar depression is contentious, but the recommendations from evidence-based guidelines do not support antidepressant monotherapy for bipolar depression… **Studies in this review have provided evidence that the risk of mood conversion may not actually occur in the current episode but rather lead to a lifetime risk of polarity change and mixed episodes [Strejilevich, Valentí, Pacchiarotti 2011, Sussman]"***

[34] **Omega 3 Fatty Acids**.

(a) Bozzatello P et al, Supplementation with Omega-3 Fatty Acids in Psychiatric Disorders: A Review of Literature Data, J Clin Med. 2016, PMC4999787. *"…some beneficial effects of omega-3 HUFAs in bipolar disorders were observed. The conclusions of systematic reviews and meta-analyses provided initial evidence that bipolar depressive symptoms, but not manic symptoms, may be improved by adjunctive administration of omega-3 fatty acids"*

(b) Shakeri J et al, Effects of Omega-3 Supplement in the Treatment of Patients with Bipolar I Disorder, Int J Prev Med. 2016, PMC4882968. *"…In this double-blind clinical trial, 100 patients suffering from BIDs were randomly divided into two, i.e. control (n = 50) and experimental (n = 50) groups. In addition to the other standard treatments, 1000 mg of omega-3 supplement was given to the experimental group on daily basis for 3 months and placebo was given to the control group... Before intervention, mean severity of mania in the experimental group (23.50 ± 7.02) and control group (23.70 ± 8.09) was not significant (P ≤ 0.89). The difference after the*

intervention in the experimental group (10.64 ± 3.3) and control group (20.12 ± 6.78) was significant (P < 0.01). The mean intensity of mania before (23.50 ± 7.02) and after (10.64 ± 3.3) intervention reported to be significant at P < 0.05."

[35] **Bright Light Therapy**.

(a) Yorguner Kupeli N et al, Efficacy of bright light therapy in bipolar depression, Psychiatry Res. 2018, PMID: 29268206. *"…this study evaluates the efficacy and safety of BLT [Bright Light Therapy] as an add-on treatment for BD. Thirty-two BD outpatients were randomly assigned to BLT (10000lx) or dim light (DL, < 500lx). During a two-week period, light was administered each morning for 30min.… Response rates for BLT and DL were 81% and 19%, and remission rates were 44% and 12.5%, respectively. Analyses showed statistically significant reductions in depression scores for the BLT group compared with the DL group on all scales. Side effects were similar in both groups, with headache as the most common side effect. The results suggest that BLT is an effective and safe add-on treatment for BD."*

(b) Sit DK et al. Adjunctive bright light therapy for bipolar depression: a randomized double-blind placebo-controlled trial, Am J Psychiatry. 2018, PMID: 28969438. *"…a 6-week randomized double-blind placebo-controlled trial to investigate the efficacy of adjunctive bright light therapy at midday for bipolar depression… 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."*

(c) Samuelson K, Bright light therapy at midday helped patients with bipolar disorder, 2017, https://goo.gl/exe4xC. *"…Previous studies found morning bright light therapy reduced symptoms of depression in patients with Seasonal Affective Disorder (SAD.). But patients with bipolar disorder can experience side effects such as mania or mixed symptoms from this type of depression treatment. This study implemented a novel midday light therapy intervention in an effort to provide relief for bipolar depression and avoid those side effects… Compared to dim placebo light, study participants assigned to bright white light between noon and 2:30 p.m. for six weeks experienced a significantly higher remission rate (minimal depression and return to normal functioning). More than 68 percent of patients who received midday bright light achieved a normal level of mood, compared to 22.2 percent of patients who received the placebo light…"*

[36] **Folic Acid. Coppen A et al,. Folic acid enhances lithium prophylaxis. J Affect Disord. 1986, PMID: 2939126.** *"… A double-blind trial was carried out to investigate the effect on affective morbidity of a daily supplement of 200 micrograms folic acid or a matched placebo in a group of 75 patients on lithium therapy. During the trial the patients with the highest plasma folate concentrations showed a significant reduction in their affective morbidity. Patients who had their plasma folate increased to 13 ng/ml or above had a 40% reduction in their affective morbidity. It is suggested that a daily supplement of 300-400 micrograms folic acid would be useful in long-term lithium prophylaxis.*

[37] **Amino Acids**. **Scarna A et al, Effects of a branched-chain amino acid drink in mania, Br J Psychiatry. 2003, PMID: 12611783.** *"…Relative to placebo, the BCAA drink lowered mania ratings acutely over the first 6 h of treatment. In protocol completers there was a persistent advantage to the BCAA group 1 week after the end of treatment…"*

[38] **Dickerson F et al, Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial, Bipolar Disord. 2018, PMID: 29693757.** *"…Patients hospitalized for mania (N = 66) were randomized after discharge to receive 24 weeks of adjunctive probiotics… During the 24-week*

observation period there were a total of 24 rehospitalizations in the 33 individuals who received placebo and eight rehospitalizations in the 33 individuals who received the probiotics (z = 2.63, P = .009). Hazard functions indicated that ***the administration of the probiotics was associated with a significant advantage in time to all psychiatric rehospitalizations*** *(hazard ratio [HR] = 0.26, 95% confidence interval [CI] 0.10, .69; P = .007). Probiotic treatment also resulted in fewer days rehospitalized (mean 8.3 vs 2.8 days for placebo and probiotic treatment, respectively; χ2 = 5.17, P = .017). The effect of the probiotic treatment on the prevention of rehospitalization was increased in individuals with elevated levels of systemic inflammation at baseline."*

[39] **Cognitive Behavioral Therapy. Chiang KJ et al, Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: A meta-analysis of randomized controlled trials, PLoS One, PMC5417606**. *"…A total of 19 RCTs comprising 1384 patients with type I or II BD were enrolled in our systematic review and meta-analysis. The main analysis revealed that CBT could lower the relapse rate (pooled OR = 0.506; 95% CI = 0.278 −0.921) and improve depressive symptoms (g = −0.494; 95% CI = −0.963 to −0.026), mania severity (g = −0.581; 95% CI = −1.127 to −0.035), and psychosocial functioning (g = 0.457; 95% CI = 0.106–0.809).* ***CBT is effective in decreasing the relapse rate and improving depressive symptoms, mania severity, and psychosocial functioning, with a mild-to-moderate effect size. Subgroup analyses indicated that improvements in depression or mania are more potent with a CBT treatment duration of ≥90 min per session, and the relapse rate is much lower among patients with type I BD****"*

[40] **Aspirin. Haarman B et al, Aspirin for recurrence prevention in bipolar disorder - promising, yet clinically understudied?, Bipolar Disord. 2018, PMID: 30472767, https://goo.gl/Zc9qWB.** *"… Savitz et al. tested the efficacy of aspirin and minocycline as augmentation therapy for bipolar depression. Ninety-nine depressed outpatients with BD were enrolled in a 6 week, double-blind, placebo-controlled trial… When all four arms were included in the analysis, there* ***was a main effect of aspirin on depressive symptoms*** *that was driven by both the M + A and the P + A groups (p(two-tailed) = 0.019, odds ratio = 3.7,* ***number needed to treat = 4.0****)… Saroukhani et al. assessed the effect of 240 mg aspirin on lithium-related sexual dysfunction in 32 men with stable bipolar affective disorder in a 6 week randomized, double-blind, placebo-controlled study. At the end of the study, patients in the aspirin group showed significantly greater improvement in total sexual function (63.9% improvement from baseline) and erectile function domain (85.4% improvement from baseline) scores than the placebo group (14.4% and 19.7% improvement respectively). The mood symptoms remained stable over the course of the study…"*

[41] **Frequency of biomedical issues causing or exacerbating mental distress**.

(a) Koranyi EK et al, Physical illnesses underlying psychiatric symptoms, Psycho Psychosom. 1992, PMID: 1488499, http://goo.gl/V9Wi23. *"…A substantial portion of the physical illnesses (27.1 %) produced symptoms showing direct relation to the psychopathology of the patient."*

(b) **Koran L, MEDICAL EVALUATION FIELD MANUAL, 1991, http://goo.gl/TPNL9t, copied 10/30/2013.** *"…It reveals that 39% of psychiatric patients studied were found to have active medical diseases, many of which caused or worsened their mental condition."*

[42] APA Caucus on Complementary and Integrative Medicine.

(a) American Psychiatric Association, Integrative Medicine, http://goo.gl/cPcHua. See www.intpsychiatry.com.

(b) Caucus members published *Complementary and Integrative Treatments in Psychiatric Practice*, 2017, by Patricia L. Gerbarg;M.D.; Philip R. Muskin; Richard P. Brown, from American Psychiatric Association Publishing.