Footnotes for the Infographic

Bipolar Drugs: Benefits, Risks and Limitations

from Onward Mental Health

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[1] **Read this.** We define certain phrases used in the infographic. These phrases are short-hand for statistical concepts that help ensure statistical rigor and make the infographic more readable. Drug benefits are expressed in terms of attributable benefit. Drug harms are expressed in terms of frequency within the treatment group (we would prefer to express them in terms of attributable harm but there is very little supporting data available). See our **Definitions**.

[2] **Weinstock LM et al, Medication burden in bipolar disorder: a chart review of patients at psychiatric hospital admission. Psychiatry Res. 2014, PMCID: PMC3968952**. *"… Individuals with bipolar disorder (BD) often receive complex polypharmacy [≥4 psychotropic medications] regimens as part of treatment… Patients reported taking an average of 3.31 (SD=1.46) psychotropic medications… Overall, 82 (36%) met criteria for complex polypharmacy."*

[3] **Polypharmacy risk**.

(a) **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…"*

(b) **Gazalle FK et al, Polypharmacy and suicide attempts in bipolar disorder, Rev Bras Psiquiat, 2007, PMID: 17435926, https://goo.gl/4nC2S1**. *"…The aim of this study was to assess the association between suicide attempts and the use of multiple drugs in patients with bipolar disorder… The number of suicide attempts was associated with the use of multiple drugs… Our findings support the notion that the use of combination therapy in bipolar disorder may be related to severity of the BD, such as number of suicide attempts… There is evidence that patients who are submitted to multiple medications have an increased risk of side effects and early mortality…""*

(c) **Jamison KR, Suicide and bipolar disorder, J Clin Psychiatry. 2000, PMID: 10826661.** *"…At least 25% to 50% of patients with bipolar disorder also attempt suicide at least once…"*

(d) **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…"*

[4] **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…"*

[5] **Glick I, Undiagnosed Bipolar Disorder: New Syndromes and New Treatments, Prim Care Companion J Clin Psychiatry. 2004, PMCID: PMC427610**, *"… Management [of bipolar] requires trial-and-error use of medications…"*

[6] **Duckworth K, The Sensible Use of Psychiatric Medications, NAMI Advocate, 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..."*

[7] **Bipolar symptom frequency**.

a) **Judd LL et al, The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002, PMID: 12044195** *Note: People with bipolar I diagnosis have symptoms 47.3% of the time*.

b) **Judd LL et al. Long-term symptomatic status of bipolar I vs. bipolar II disorders. Int J Neuropsychopharmacol. 2003, PMID: 12890306**. *Note: People with bipolar II diagnosis have symptoms 55.8% of the time.*

c) Judd L, A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder, Archives of General Psychiatry, 2003, PMID: 12622659, https://goo.gl/e1zB6g. *"…Patients with BP-II were symptomatic 53.9% of all follow-up weeks: depressive symptoms (50.3% of weeks) dominated the course over hypomanic (1.3% of weeks) and cycling/mixed (2.3% of weeks) symptoms. Subsyndromal, minor depressive, and hypomanic symptoms combined were 3 times more common than major depressive symptoms"*

[8] **Lithium bipolar efficacy**. We assert efficacy by merging varying data in the following manner:

- **Mania response**: **16%.** Severus (13.4%) N=753, Fountoulaks (49%-25% = 24%), Ketter 2011 NNT=4, N=134; Srivastava NNT=4, and Yildiz (1/6.3=15.9%). **Evaluation**: Yildiz (N=1199) is largest analysis. Severus is episodic and not symptom reduction so not used here. Go with Yildiz 15.9%.
- **Depression response**: **0%.** DeJong (0%), Ketter 0%, Won 0%.
- **Any mood relapse/event: 21%.** Severus (22%), Ketter 2011 14% (N=134), and Geddes (20%, N=770). **Evaluation**: Ketter much smaller sample. Choose midpoint of Severus and Geddes is 21%.
- **Mania relapse: 12%.** Geddes 10% N=565; Severus 13% N=652. **Evaluation**: choose midpoint, rounding to larger study. Not used in infographic.
- **Depression relapse: 7%.** Geddes 7% N=565, Severus 7%. Not used in infographic.

a) **Geddes JR et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004, PMID: 14754766, https://goo.gl/ZauzZE**. "…Outcomes investigated included risk of relapse (manic, depressive, and total) as well as risk of specific adverse effects and total withdrawal rates… five were randomized trials that compared lithium with placebo in bi-polar disorder patients (N=770) and were thus included in the analyses (Table 1)" Note: Lithium improves yearly manic relapse rate 24% → 14% = 10% for NNT=10, N=565. Lithium improves ANY mood relapse 60% → 40% = 20%, N=770. Lithium improves depressive relapse 7% (32%-25%), N=565.

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.** *"… Individual study and pooled study analyses of NNT and NNH were conducted using 35 retrieved studies of medication approved for the treatment of bipolar disorder by the US FDA." Figure 3 show Lithium mania response NNT = 4 (ARR=25%), depression response 0%, maintenance (assume any mood) NNT=7, ARR=14%.*

c) **Fountoulakis K et al, Treatment of bipolar disorder: a systematic review of available data and clinical Perspectives, Int J Neuropsychopharmacol. 2008, PMID: 18752718, https://goo.gl/FH1Fj3.** *"…There are two placebo-controlled studies (Bowden et al., 1994, 2005) suggesting that the percentage of acutely manic patients that responded (at least 50% reduction of symptoms) is around 49% for lithium vs. 25% for placebo."*

d) **Srivastava S et al, Clinical Relevance of Treatments for Acute Bipolar Disorder: Balancing Therapeutic and Adverse Effects, Clinical Therapeutics, 2011, PMID: 22177379**. *"… For acute mania, lithium compared with other FDA-approved agents yielded substantively less sedation (NNH, 27 vs 517) yet broadly similar efficacy (NNT, 4 vs 4 – 8), and thus a more favorable efficacy:sedation likelihood (LHH, 6.8 vs 0.7–3.4)"*

e) **Won E et al, An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms, Int J Mol Sci. 2017, PMC5751281.** *"…Although only a few RCTs have been conducted on the treatment effects of lithium in bipolar depression, several treatment guidelines recommend lithium as a first-line treatment agent for bipolar I disorder (BD-I) depression. Possibly considered a disadvantage, lithium has been shown to have less efficacy in treating bipolar depression compared to*

quetiapine and antidepressants such as venlafaxine by previous studies. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in the acute phase of BD-I or bipolar II disorder (BD-II) major depression reported quetiapine, but not lithium, to have significant treatment efficacy compared to placebo"

f) **Burgess SSA et al, Lithium for maintenance treatment of mood disorders, Cochrane Database Syst Rev. 2001, PMID: 11687035. "***…Nine studies were included in the review, reporting on 825 participants randomly allocated to lithium or placebo. Lithium was found to be more effective than placebo in preventing relapse in mood disorder overall, and in bipolar disorder. The most consistent effect was found in bipolar disorder (random effects OR 0.29; 95% CI 0.09 to 0.93). In unipolar disorder, the direction of effect was in favour of lithium, but the result (when heterogeneity between studies was allowed for) did not reach statistical significance… This systematic review indicates that lithium is an efficacious maintenance treatment for bipolar disorder."*

g) **DeJongh B et al, Lithium use in bipolar disorder: Summary of evidence for acute mania, acute depression, and maintenance treatment, Mental Health Clinician: July 2012, https://goo.gl/VAzCNg.** *"…A 1993 review identified eight studies that found lithium to be more effective than placebo for the treatment of bipolar depression. Many of these studies had design and methodological limitations, however… A more recent randomized, placebo-controlled study assessed the antidepressant effects of quetiapine and lithium for bipolar depression. This was an 8-week trial in which 136 subjects… no statistically significant differences were found between lithium and placebo in reducing depression severity (p=0.123)"*

h) **Severus E et al, Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis, Int J Bipolar Disord. 2014, PMC4272359.** *"…" Note: **For any episode,** Figure 2 indicates 258 events in the lithium group (N=753) as compared to 467 events in the placebo group (N=827). The frequency in the treatment group = 258/753 = 34.3% while the placebo group found 467/827 = 56.5%. The absolute risk reduction = 56.5%-34.3% = **22.2%** and the relative risk = 34.3%/56.5% = 60.7%. **For depression**, figure 3 shows 130 events in the lithium group (N=652) as compared to 196 events in the placebo group (N=723). The frequency in the treatment group = 130/652 = 19.9% while the placebo group found 196/723 = 27.1%. The absolute risk reduction = 27.1%-19.9% = **7.2%** and the relative risk = 19.9%/27.1% = 73.4%. **For mania**, figure 3 shows 85 events in the lithium group (N=652) as compared to 197 events in the placebo group (N=723). The frequency in the treatment group = 85/652 = 13.0% while the placebo group found 191/723 = 26.4%. The absolute risk reduction = 26.4%-13.0% = **13.4%** and the relative risk = 13%/26.4% = 49.2%.*

i) **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... "* Note: Table 3 indicates Lithium NNT = 6.3 for mania for N=1199.

j) **Ghaemi SN et al, Antidepressants in bipolar disorder: the case for caution, Bipolar Disorders 2003, https://goo.gl/Gyjsvb.** *"…**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**."*

[9] **Lithium withdrawal**.

a) **Cundall RL et al, A controlled evaluation of lithium prophylaxis in affective disorders. *PsycholMed*. 1972**. ↩

b) **Baldessarini RJ et al, Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. *BipolarDisord, 1999*.** ↩

c) **Suppes T et al, Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *ArchGenPsychiatry*. 1991.** ↩️

[10] **Lithium and suicide**. Suicide rate improvements vary. We seek % decreases instead of ratios to better capture the overall impact. The most reliable study seems to be **Song** which estimates suicide reduction at 12%.

a) **Aiken C, The Year in Bipolar: 7 Practice-Changing Papers From 2017, Psychiatric Times, 2017, https://goo.gl/Pi6qUp**. *"…epidemiologic studies suggest that lithium lowers that risk to a level comparable to that in the general population… What those studies have lacked is a controlled design, but controlled trials are usually underpowered to detect rare events like suicide. This new study [b-Song] bridges that gap by combining a large cohort (50,000 patients over an 8-year period) and a case-control design in which each patient served as his or her own control. The anti-suicide effects were unique to lithium and not seen with valproate… Concerns about overdose on lithium often limit its use in suicidal and impulsive patients… this study arrived at a unique finding: that family therapy is superior to individual psychotherapy at preventing relapses in bipolar disorder… Light therapy treats bipolar depression with a large effect size, according to 2 randomized controlled trials."*

b) **Song J et al, Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients With Bipolar Disorder, Am J Psych, 2017, https://goo.gl/VdEsJD.** *"...Through linkage of multiple Swedish national registers, 51,535 individuals with bipolar disorder were followed from 2005 to 2013 for treatment with lithium and valproate. Stratified Cox regression was used to estimate the hazard ratios of suicide-related events during treated periods compared with untreated periods. For significant associations between medication and suicide-related events, the population attributable fraction was estimated to assess the public health impact for patients with bipolar disorder… The main outcome was suicide-related events, defined as attempted or completed suicide... During follow-up, 10,648 suicide-related events occurred.* ***The incidence rate was significantly decreased by 14% during lithium*** *treatment (hazard ratio 0.86, 95% confidence interval [CI] 0.78–0.95) but not during valproate treatment (hazard ratio 1.02, 95% CI 0.89–1.15)… Estimates of the population attributable fraction suggested that 12% (95% CI 4%-20%) of suicide-related events could have been avoided if patients had taken lithium during the entire follow-up…"*

c) **Goodwin F et al, Suicide Risk in Bipolar Disorder During Treatment With Lithium and Divalproex, JAMA, 2003, PMID: 13129986, https://goo.gl/qvSjtq.** *"Population-based sample of 20 638 health plan members aged 14 years or older who had at least 1 outpatient diagnosis of bipolar…Main Outcome Measures Suicide attempt… risk of suicide attempt and suicide death is lower during treatment with lithium than during treatment with divalproex… risk of suicide death was 2.7 times higher (95% confidence interval [CI], 1.1-6.3; P = .03) during treatment with divalproex than during treatment with lithium. Corresponding hazard ratios for nonfatal attempts were 1.7 (95% CI, 1.2-2.3; P = .002) for attempts resulting in hospitalization and 1.8 (95% CI, 1.4-2.2; P<.001) for attempts diagnosed in the emergency department."I*

d) **Moncrieff J, Lithium and Suicide: What Does the Evidence Show?, Mad in America, 2015, https://goo.gl/Hruuej**. *"... most trials of lithium are not trials of starting lithium, but trials of stopping lithium. They consist of a comparison between people who have been taken off lithium (or other medication) and put on placebo and people who have continued to take it… comparing the effects of continuing on lithium with the effects of stopping it is clearly not the same as establishing the prophylactic effects of starting lithium in terms of suicide as well as relapse…"*

e) **Geddes JR et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004, PMID: 14754766. https://goo.gl/ZauzZE**. *"…Data from these randomized trials were insufficient to estimate the possible suicide prevention effect of lithium…"*

f) **Tondo L et al, Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis, Acta Psychiatr Scand. 2001, PMID: 11531653.** *"… Suicide risk was consistently lower during long-term treatment of major affective illnesses with lithium in all studies in the meta-analysis…"*

g) **Moncrieff J, NICE Guidelines for Bipolar Disorder- a Missed Opportunity, Mad in America, 2014, https://goo.gl/e5iC5d.** *"…It has been recognised for decades now, however, that the evidence for lithium is fatally flawed by the fact that you are more likely to have a relapse of your bipolar disorder after stopping lithium treatment than you were before you started it. Studies of long-term lithium treatment consist of taking some people off lithium (or other long-term sedative drugs) and putting them on to a placebo. The fact that most (although not all) of these studies find higher rates of relapse among those on placebo cannot be taken to indicate the effectiveness of lithium, however, since it may simply demonstrate the risks of coming off lithium. Whether going on lithium in the first place has any benefit has never been established."*

h) **Tondo L, Baldessarini RJ. Suicidal behavior in mood disorders: response to pharmacological treatment. Curr Psychiatry Rep. 2016, PMID: 27542851. https://goo.gl/SjWBFW.** *"…In bipolar disorder, and possibly also unipolar major depression, an underprescribed medical intervention with substantial evidence of preventive effects on suicidal behavior is long-term treatment with lithium… Antisuicidal effects of anticonvulsant mood stabilizers (carbamazepine, lamotrigine, valproate) appear to be less than with lithium… "*

i) **Tondo L et al, Effect of Lithium Maintenance on. Suicidal Behavior in Major Mood Disorders, NY Acad Sci, 1997, PMID: 9616808.** *"…We reviewed evidence of a possible antisuicide action of lithium maintenance treatment in mood disorders. Of 28 published studies involving over 17,000 patients with major affective illnesses, most yielded supportive evidence: risk of suicides and attempts averaged 3.2 versus 0.37 per 100 patient-years without versus with lithium (8.6-fold difference). In a new study of 284 bipolar I- and II-disordered patients, corresponding rates (2.2 vs. 0.39/100 patient-years) differed by 5.6-fold (p< 0.001); moreover, after discontinuing lithium rates of suicidal acts rose by 7-fold (16-fold within the first year), and fatalities increased by nearly 9-fold. Lithium maintenance treatment in recurring major mood disorders has strong evidence of antisuicide effects not demonstrated with any other mood stabilizer. Close association of suicide and depression in bipolar disorder emphasizes the need for improved identification and treatment of bipolar depression."*

j) **Ciprani, Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis, BMJ, 2013, https://goo.gl/gtA983.** *"…48 randomised controlled trials (6674 participants, 15 comparisons) were included. Lithium was more effective than placebo in reducing the number of suicides (odds ratio 0.13, 95% confidence interval 0.03 to 0.66) and deaths from any cause (0.38, 0.15 to 0.95). No clear benefits were observed for lithium compared with placebo in preventing deliberate self harm (0.60, 0.27 to 1.32). In unipolar depression, lithium was associated with a reduced risk of suicide (0.36, 0.13 to 0.98) and also the number of total deaths (0.13, 0.02 to 0.76) compared with placebo. When lithium was compared with each active individual treatment a statistically significant difference was found only with carbamazepine for deliberate self harm. Lithium tended to be generally better than the other active comparators, with small statistical variation between the results… The main limitation of the review is the quantity of the primary evidence. The sample size of most included studies (29 out of 48, 60%) was fewer than 100 participants, with overall few suicide and deliberate self harm events. The low event rate may reflect the fact that usually people judged to be at high risk of suicide are not normally recruited into randomised trials."*

[11] **Lithium and Dementia.**

(a) Forlenza OV et al, Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial, Br J Psychiatry. 2011, PMID: 21525519. "…Forty-five participants with aMCI were randomised to receive lithium (0.25-0.5 mmol/l) (n = 24) or placebo (n = 21) in a 12-month, double-blind trial. Primary outcome measures were the modification of cognitive and functional test scores, and concentrations of cerebrospinal fluid (CSF) biomarkers (amyloid-beta peptide (Aβ(42)), total tau (T-tau), phosphorylated-tau) (P-tau)… Lithium treatment was associated with a significant decrease in CSF concentrations of P-tau (P = 0.03) and better performance on the cognitive subscale of the Alzheimer's Disease Assessment Scale and in attention tasks. Overall tolerability of lithium was good and the adherence rate was 91%... The present data support the notion that lithium has disease-modifying properties with potential clinical implications in the prevention of Alzheimer's disease."

(b) Gerhard T et al, Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study, Br J Psychiatry. 2015, PMID: 25614530. *"…*To examine the association of lithium and dementia risk in a large claims-based US cohort of publicly insured older adults with bipolar disorder. The cohort included individuals ≥50 years diagnosed with bipolar disorder who did not receive dementia-related services during the prior year. Each follow-up day was classified by past-year cumulative duration of lithium use (0, 1-60, 61-300 and 301-365 days). Dementia diagnosis was the study outcome. Anticonvulsants commonly used as mood stabilisers served as a negative control. **Compared with non-use, 301-365 days of lithium exposure was associated with significantly reduced dementia risk (hazard ratio (HR) = 0.77,** 95% CI 0.60-0.99). No corresponding association was observed for shorter lithium exposures (HR = 1.04, 95% CI 0.83-1.31 for 61-300 days; HR = 1.07, 95% CI 0.67-1.71 for 1-60 days) or for any exposure to anticonvulsants. Continuous lithium treatment may reduce dementia risk in older adults with bipolar disorder."

(c) Nunes PV et al, Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder, , Br J Psychiatry. 2007, PMID: 17401045. *"…We compared the prevalence of Alzheimer's disease between 66 elderly euthymic patients with bipolar disorder who were on chronic lithium therapy and 48 similar patients without recent lithium therapy. The prevalence of dementia in the whole sample was 19% v. 7% in an age-comparable population. Alzheimer's disease was diagnosed in 3 patients (5%) on lithium and in 16 patients (33%) who were not on lithium (P<0.001). Our case-control data suggest that lithium treatment reduced the prevalence of Alzheimer's disease in patients with bipolar disorder to levels in the general elderly population. This is in accordance with reports that lithium inhibits crucial processes in the pathogenesis of Alzheimer's disease."*

(d) Nunes MA et al, Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease, Curr Alzheimer Res. 2013, PMID: 22746245. *"…a group just found that lithium has disease-modifying properties in amnestic mild cognitive impairment with potential clinical implications for the prevention of Alzheimer's Disease (AD) when a dose ranging from 150 to 600 mg is used. As lithium is highly toxic in regular doses, our group evaluated the effect of a microdose of 300 µg, administered once daily on AD patients for 15 months. In the evaluation phase, the treated group showed no decreased performance in the mini-mental state examination test, in opposition to the lower scores observed for the control group during the treatment, with significant differences starting three months after the beginning of the treatment, and increasing progressively. This data suggests the efficacy of a microdose lithium treatment in preventing cognitive loss, reinforcing its therapeutic potential to treat AD using very low doses."*

[12] **Lithium Toxicity and overall side effects.** See footnote #1 for. We choose **weight gain** 75% from average of 77% and 73% in Gitlin; **sexual dysfunction** 37% from Gitlin, **hypothyroidism** 14% midpoint of Gitlin 8-19%, **excess urination** 70% from Gitlin, **renal failure** 2.5X from Close, and **tremors** 42% midpoint of the 20-65% frequency range of Serretti.

a) **Close H et al, Renal Failure in Lithium-Treated Bipolar Disorder: A Retrospective Cohort Study, PLoS One. 2014, PMC3966731.** *"…Ever use of lithium was associated with a hazard ratio for renal failure of 2.5 (95% confidence interval 1.6 to 4.0) adjusted for known renal risk factors. Absolute risk was age dependent, with patients of 50 years or older at particular risk of renal failure: Number Needed to Harm (NNH) was 44 (21 to 150)." Note: NNH=44, ARI=2%.*

b) **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)."*

c) **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…".*

d) **Dolls A et al, The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: A review, Int Clin Psychopharmacol. 2013, PMID: 23873292. https://goo.gl/Q4Vwds.** *"…**Tremor has been reported in up to 65% of patients using lithium** (Gelenberg and Jefferson,1995) and in 1–6% of those using VPA**… Nausea, vomiting, and diarrhea are common**, although generally transient, side effects of lithium and VPA (Bowden etal., 1994, 2000), **occurring in up to 50% of patients**. **A 5–10% weight gain** is experienced by 25–50% of patients using lithium… The prevalence of **weight gain with VPA treatment is estimated to occur in 3–20%** of patients and ranges between 3–10 kg over a period of 3–12 months (Pijl and Meinders, 1996; Bowden, 2003 … **hypothyroidism, which occurred in 5% of patients on lithium** … A long-term lithium use of 10 years or more is probably associated with a risk of developing **chronic renal failure** although this could not be confirmed in a meta-analysis… **a benign rash occurred in 8.3% of lamotrigine patients** in controlled settings (n= 1198) and in 13.1% of patients (n= 257) in an open-label setting… Lithium appears to have minor effects on **sexual function**. In an earlier study, 14% of bipolar patients on lithium monotherapy reported a negative effect… The literature on sexual side effects of anticonvulsants is almost entirely restricted to their use in epilepsy… **Hepatological side effects** Asymptomatic elevation of transaminases during treatment with VPA is observed in about 40% of cases…"*

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[13] **Lithium and thyroid abnormalities**. Prevalence of enlarged thyroid is 55% from the cross sectional study mentioned by Kibrige.

a) **Kibirige D et al, Spectrum of lithium induced thyroid abnormalities: a current perspective, Thyroid Res, 2013, PMCID: PMC3568739,** *"…Goitre [an abnormal enlargement of the thyroid] is the most common clinical finding noted among patients on lithium therapy… [In a] survey by Bocchetta et al… the prevalence of a visible and / clinically palpable goitre was 51%... [Other] studies have reported similar findings of higher frequency of goitre of 50%-59% among lithium treated patients… In one cross sectional study to determine the thyroid size and*

prevalence of goitre among 96 treated patients with affective disorders in Germany, goitre was reported among 53 (55%) patients on lithium therapy and 19 (20%) controls (p = 0.003)…"

[14] **Lithium and kidney damage**. Although complete renal failure is the most severe example of kidney damage, chronic kidney disease, an intermediate presentation that can lead to complete renal failure. We use **Aiff** 33% figure in the infographic.

a) **American Kidney Fund, Kidney Failure (ESRD) Causes, Symptoms, & Treatments, https://goo.gl/Gyd7MJ,** "… *Kidney failure, also called end-stage renal disease, is the last stage of chronic kidney disease…*".

b) 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…"*

c) **(c) Close H et al, Renal Failure in Lithium-Treated Bipolar Disorder: A Retrospective Cohort Study, PLoS One. 2014, PMCID: PMC3966731**. *"…Ever use of lithium was associated with a hazard ratio for renal failure of 2.5 (95% confidence interval 1.6 to 4.0) adjusted for known renal risk factors. Absolute risk was age dependent, with patients of 50 years or older at particular risk of renal failure: Number Needed to Harm (NNH) was 44 (21 to 150)…"*

d) **(d) Gupta S et al, Drug information update. Lithium and chronic kidney disease: debates and dilemmas, BJPsych Bull. 2017, PMCID: PMC5537577.** *"…The association between CKD and lithium has been known for a long time, and monitoring renal function in patients receiving lithium therapy has been the norm for many decades. Despite this, there has been little research into the renal adverse effects of lithium so far... Despite significant progress over the past two decades, doubts still remain about the existence and magnitude of the risk…"*

[15] National Institute of Health, LABEL: LITHIUM CARBONATE- lithium carbonate tablet, extended release, https://goo.gl/oC3Apf, https://goo.gl/HkAHU8.

[16] **Anticonvulsant efficacy**. The following supports the logic in the anticonvulsant efficacy table.

Acute Depression – Lamotrigine. <blank>. %. Bowden (2009) notes it has lacked efficacy in acute bipolar depression in most randomized trials. **Zeid (2016)** indicates all five trials of lamotrigine in acute bipolar depression were negative and "not clinically significant". **Geddes (2009)** indicates NNT=11 for depression and of questionable efficacy. **Srivastava** shows NNT=12 for depression. **Popovic (2011)** NNT=7. **Ghaemi (2008)** examines the full evidence including a number of unpublished negative studies and finds no evidence of efficacy. In **Chou (2009),** another voice finds no convincing evidence for efficacy, and Chou indicates his ratings grounded to a large extent on clinical experience. **Calabrese (1999)** N=195 gives response rate for highest dose 51% less 26% placebo = ARR = 25% (NNT=4). **Evaluation**: Underlying studies for Geddes all failed to show benefit over placebo on primary measure, but secondary measures showed benefit overall of NNT=12, but much better for severely depressed (NNT=7). Geddes is by far the larger study. We choose to "---" since the most complete analysis seems to be Ghaemi who acknowledges benefit in relapse prevention but shows how benefit for acute depression is unconvincing in total.

Acute Depression – Valproate. <blank>%. Cochrane (2013) indicates that the data quality on valproate is "not good". This is echoes in **Smith (2010) and Bond (2010)** that appear to have done identical meta-analyses hampered by low # of participants and short duration (N=142). **Renaires (2013)** indicates it has value for BP depression but also offers caveat about small sample size. **Selle (2014)** indicates 2 of 4 trials failed to find benefit for depression, but in meta-analysis, NNT=4.4= 22.7% ARR. With paucity of evidence, we choose to leave it blank, meaning insufficient data. Smith (2010) is the strongest evidence of acute depressive value and could be the basis for asserting some value.

Acute Depression – Carbamazepine. <blank>%. Fountoulakis (2012) indicates scant evidence. **Selle (2014)** indicates that for acute depression, Carbamazepine NNT = 3.4=29.4% ARR, but small N.

Acute Mania-Valproate. 20%. Yildiz (2011) N=824, ARR = 20% (NNT=4.9). **Ketter (2011)** N=261, NNT=7, ARR = 1/7= 14%. **Bowden (1994)** (ARR = 23% = 48% Valproate – 25% placebo) N=68. Choose Yildiz since it is largest study. Cochrane indicates that the data quality on valproate is "not good".

Acute Mania-Lamotrigine. <blank>%. Bowden (2009) indicates ineffective for mania. **Ng (2007)** "the available randomized controlled trials of lamotrigine in the treatment of bipolar disorder have only demonstrated convincing efficacy in the prophylaxis of bipolar depression." **Ketter (2011)** gives no data for lamotrigine in table.

Acute Mania-Carbamazepine. 25%. Yildiz (2011) N=427, NNT=3.9, ARR=25.6%. **Ketter (2011)** NNT=4, N=223. **Weisler (2004)** indicates absolute risk reduction for mania and mixed episode = 41.5%-22.4% = 19%.

Mood Relapse – Lamotrigine. 17%. Popovic (2011) indicates Lamictal for any episode reduction NNT=5-7, ARR=20%-14% (midpoint 17%). **Goodwin (2004)** N=1315 indicates an ~18% absolute risk reduction from depressive and manic relapse. **Bowden (2009)** notes strong evidence for effectiveness in maintenance treatment, principally for depression. **Ketter (2011)** indicates lamotrigine monotherapy for relapse has NNT=9, ARR=11%. Go with Popovic since Goodwin is a visual estimate.

Mood Relapse – Valproate. 13%. Bowden (2000) no difference between divalproex and placebo, N=372, 12 months. **Ketter (2011)** NNT = 8, ARR=12.5% as monotherapy; Cochrane indicates that the data quality on valproate is "not good". **Fountoulakis (2012)** indicates valproate is equivalent to lithium in mood episodes, also confirmed by **Cochran**, and supported by **Ketter (2011)** which lists valproate NNT=8 and lithium=7 for maintenance therapy. Go with Ketter 12.5%, though this is a fair bit lower than for lithium.

Mood Relapse Carbamazepine. <blank>%. Ketter (2011) indicates no entry. Fountoulakis (2012) indicates scant evidence.

(a) Bond DJ et al, Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis, J Affect Disord. 2010, PMID: 20044142. "*…We identified four trials, with a total sample size of 142 patients. The relative risks of response (RR=2.10, p=0.02) and remission (RR=1.61, p=0.04) were significantly greater for divalproex than placebo. Mean response rates were 39.3% for divalproex and 17.5% for placebo, and mean remission rates were 40.6% and 24.3%, respectively."*

(b) **Bowden CL et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA. 1994, PMID: 8120960.** *"…Intent-to-treat analysis for efficacy was based on data from 68, 35, and 73 patients in the divalproex, lithium, and placebo groups, respectively. Groups were initially comparable except that all eight patients with four or more manic episodes in the previous year were in the divalproex group. In 30%, 33%, and 51% of the above groups, treatment was prematurely terminated due to lack of efficacy, with fewer premature terminations from divalproex than placebo (P = .017). The proportions of patients improving at least 50% were higher for divalproex and lithium groups than for the placebo group: 48% for divalproex (P = .004) and 49% for lithium (P = .025) vs 25% for placebo. Divalproex was as effective in rapid-cycling manic patients as in other patients."*

(c) **Bowden CL et al, (Divalproex Maintenance Study Group A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder):. Arch Gen Psychiatry 2000, PMID: 10807488**. https://goo.gl/2vLTZL. Fountoulakis indicates ***"…****A randomized, double-blind, parallel-group multicenter study of treatment outcomes was conducted over a 52-week maintenance period… The primary outcome measure was time to either a manic or depressive episode, subsequently referred to as any mood episode… Several factors may have contributed to the surprisinglygood outcomes in the placebo group. Patients with mild forms of bipolar disorder may have been selected for the study because of the enrollment requirement that 2 consecutive GAS scores had to be above 60… Patients who met the recovery criteria within 3 months of the onset of an index manic episode (n = 372) were randomized to maintenance treatment with divalproex, lithium, or placebo in a 2:1:1 ratio…* ***The divalproex group did not differ significantly from the placebo group in time to any mood episode… Tremor was significantly more common in the lithium group than in the placebo group. The divalproex group also had a significantly higher incidence of sedation, infection, and tinnitus than***

***the lithium group**… The divalproex group showed a trend for longer time to recurrence of any major affective episode than the lithium group... The effectiveness of lithium was less than that reported in other placebo-controlled studies, but consistent with the outcomes of naturalistic studies of lithium as maintenance therapy in bipolar disorder over the past decade… Our data indicated no greater efficacy for divalproex than for placebo or lithium in preventing the recurrence of mania sufficiently severe to require hospitalization and/or associated with an MRS score of 16 or more, the development of a depressive episode, or the development of the first mood episode of either type. However, divalproex was significantly more effective than either placebo or lithium on several other outcome measures, including the rates of recurrence of affective episodes severe enough to warrant patients' discontinuation from the study…"*

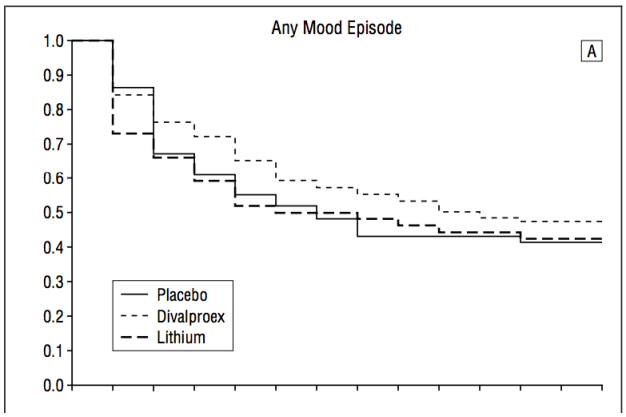


Table 6. Incidence of Adverse Effects With Significantly Greater Frequency by Treatment Group

Adverse Effect	Treatment Group, No. (%) Divalproex (n = 187)	Lithium (n = 94)	Placebo (n = 94)	Significant Differences (*P*)*
Nausea	79 (42)	41 (45)	29 (31)	Lithium > placebo (.05)
Diarrhea	65 (35)	42 (46)	28 (30)	Lithium > placebo (.02)
Tremor	77 (41)	38 (42)	12 (13)	Lithium > placebo (<.001) Divalproex > placebo (<.001)
Sedation	78 (42)	24 (26)	33 (35)	Divalproex > lithium (.02)
Weight gain	39 (21)	12 (13)	7 (7)	Divalproex > placebo (.004)
Polyuria	15 (8)	17 (19)	9 (10)	Lithium > divalproex (.01)
Thirst	11 (6)	14 (15)	7 (7)	Lithium > divalproex (.01)
Alopecia	30 (16)	7 (8)	6 (6)	Divalproex > placebo (.03)
Infection	51 (27)	12 (13)	18 (19)	Divalproex > lithium (.009)
Tinnitus	11 (6)	0 (0)	1 (1)	Divalproex > lithium (.01)
Tachycardia	1 (<1)	4 (4)	1 (1)	Lithium > divalproex (.04)
Akathisia	1 (<1)	4 (4)	1 (1)	Lithium > divalproex (.04)
Dry eyes	0 (0)	3 (3)	0 (0)	Lithium > divalproex (.03)

** By Fisher exact test.*

(d) **Bowden CL, Anticonvulsants in bipolar disorders: current research and practice and future directions, Bipolar Disord. 2009, PMID: 19538683**. *"…Valproate, principally as divalproex, has strong evidence for effectiveness in mania… Lamotrigine has strong evidence for evidence for effectiveness in maintenance treatment of bipolar disorder, principally for benefits in depressive states. Lamotrigine has been established as ineffective in mania and has lacked efficacy in acute bipolar depression in most randomized trials..."*

(e) **Calabrese JR et al, A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group, J Clin Psychiatry. 1999, PMID: 10084633.** *"… Outpatients with bipolar I disorder **experiencing a major depressive episode** (DSM-IV, N = 195) received lamotrigine (50 or 200 mg/day) or placebo as monotherapy for 7 weeks… Lamotrigine 200 mg/day demonstrated significant antidepressant efficacy on the 17-item HAM-D, HAM-D Item 1, MADRS, CGI-S, and CGI-I compared with placebo. Improvements were seen as early as week 3. Lamotrigine 50 mg/day also demonstrated efficacy compared with placebo on several measures. **The proportions of patients exhibiting a response on CGI-I were 51%, 41%, and 26% for lamotrigine 200 mg/day, lamotrigine 50 mg/day, and placebo groups, respectively.** Adverse events and other safety results were similar across treatment groups, except for a higher rate of headache in the lamotrigine groups…"*

(f) **Chou J, Lamotrigine in Acute Bipolar Depression: Two Thumbs Up—or One?, Psychiatric Times, 2009, https://goo.gl/tw8kiB.** *"…There are, of course, many areas of controversy in the literature, and one of those concerns the utility of lamotrigine in acute bipolar depression… I believe that Nassir Ghaemi, MD, MPH, has expressed considerable skepticism that the claim is supported by placebo-controlled studies**… My impression, too, is that there is no convincing randomized, placebo-controlled evidence for lamotrigine in the acute phase of bipolar depression (although it may be useful as a maintenance agent). Ronald Pies, MD, Editor in Chief Psychiatric Times…** Dr. Chou responds: Thank you for the input, which is much appreciated…. I understand the skepticism, especially given the single positive study and the several negative/failed studies. On the basis of only placebo-controlled studies, I would agree with changing the "++" to a single "+." If you want to consider the numerous recommendations from practice guidelines as well as clinical experience/ expert recommendations (including*

my own), I would keep the "++," but obviously, this is not the spirit of the remainder of the review." Note: Chou is relying on clinical experience and not gold standard evidence.

(g) **Cochrane, Valproate for keeping people with bipolar disorder well, after mood episodes, 2013, https://goo.gl/Z8J57h**. *"…We found six studies, including a total of 876 participants. The quality of the studies in terms of design was not good, which means that the effects of some drugs might have been overestimated. All of the trials taken together suggest that valproate might help to prevent relapse in bipolar disorder, especially depressive episodes. However, because of limited available evidence, conclusions on valproate compared with placebo and lithium (or other active drugs) cannot be made with any reliable degree of confidence… When we combined the findings of all studies comparing valproate with lithium,* ***the evidence did not favour valproate or lithium in terms of efficacy. People taking valproate over a long time were more likely than patients given lithium to keep taking their allocated medication****."*

(h) **Fountoulakis KN, Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry, Eur Arch Psychiatry Clin Neurosci. 2012, PMID: 22622948**. *"…Lamotrigine is efficacious in the prevention of depression, and it remains to be clarified whether it is also efficacious for mania…The data on the efficacy of antiepileptics against bipolar depression are poor and inadequate… For lamotrigine, five trials on acute depression were negative concerning the primary outcomes but showed some benefit on the basis of secondary outcomes (on the basis of these secondary outcomes, response rates were 50% for lamotrigine and double of those for placebo).."*

(i) Geddes JR et al, Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials, Br J Psychiatry. 2009, PMID: 19118318. https://goo.gl/SjDVj1. *"…Individual data from 1072 participants from five randomised controlled trials were obtained…* ***Lamotrigine was superior to placebo in people with HRSD score >24*** *(RR=1.47, 95% CI 1.16-1.87, P=0.001) but not in people with HRSD score < or =24 (RR=1.07, 95% CI 0.90-1.27, P=0.445)… Patients receiving lamotrigine were more likely to respond to treatment than those receiving placebo, using the HRSD (RR 1.27, 95% CI 1.09 to 1.47) and using the MADRS (RR 1.22, 95% CI 1.06 to 1.41)…* ***The NNT to achieve one more response than placebo was 11 (95% CI 7 to 25) using the HRSD and 13*** *(95% CI 7 to 33) using the MADRS… Lamotrigine was superior to placebo in patients with* ***severe depressive symptoms*** *(HRSD score more than 24) at randomisation (RR 1.47, 95% CI 1.16 to 1.87;* ***NNT 7****, 95% CI 4 to 17; SMD -0.24, 95% CI -0.42 to -0.06), and this interaction was also found using the continuous MADRS as the independent variable... "*

(j) Ghaemi N et al, Publication Bias and the Pharmaceutical Industry: The Case of Lamotrigine in Bipolar Disorder, Medscape J Med. 2008, PMC2580079. *"…In particular,* ***the drug [lamotrigine] has very limited, if any, efficacy in acute bipolar depression and rapid-cycling bipolar disorder, areas in which practicing clinicians, as well as some academic leaders, have supported its use.*** *The negative unpublished data now made available on lamotrigine provide an important context for clinical practice and research, and also raise important scientific and public policy concerns about having access to studies showing inefficacy with psychotropic medications... Of major US pharmaceutical companies, so far only GSK has provided data on unpublished negative studies with results that were unfavorable to their product lamotrigine (Lamictal)… This was not a voluntary act but rather due to legal judgment brought by the state of New York after a lawsuit about paroxetine use in children… Recently,* ***using meta-analysis, academic investigators have published the results of 5 negative studies with lamotrigine in acute bipolar depression in more detail, confirming lack of benefit for primary outcomes****. When pooling those 5 studies to produce a large sample of over 2000 subjects,* ***a small effect size of depressive symptom benefit was statistically significant****. However, more benefit was seen in a subgroup analysis of those with high severity of depressive symptoms… Two non-industry-funded studies found some benefit with lamotrigine in acute bipolar depression and another recent one not yet published). Yet the unpublished negative studies described here are needed to put such positive studies in context. Many clinicians and academics widely view lamotrigine as an effective treatment for, colloquially, "bipolar depression," even though the entire literature is less consistent on this point than many clinicians and academics appear to*

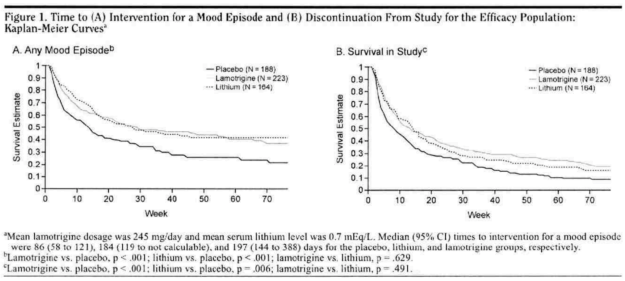
assume... Further, numerous review papers of lamotrigine in bipolar disorder cite the single published study as evidence of benefit in acute bipolar depression, but make no mention of the unpublished studies… ***This problem takes nothing away from the evidence of lamotrigine's benefit in prophylaxis of bipolar disorder****, particularly in prevention of depressive episodes, although it should be noted that the benefits seen in those prophylaxis studies are limited to patients who initially tolerated and appeared to respond to lamotrigine for acute mood episodes. But preventive benefit does not necessarily translate to acute efficacy, or vice versa…* ***narrative reviews of agents for bipolar disorder will provide the false impression that certain agents, such as lamotrigine****, have been consistently effective whenever they were studied, since positive studies are evidently more likely to be reported at Web sites or in published articles. The practice of burying negative data in infrequently read review papers seems to be one approach to "publishing" such data, as exemplified by the single GSK-sponsored review paper which briefly summarized 5 negative studies with limited detail..* ***The clinical relevance of the lamotrigine studies is notable: Taking the negative outcomes into account, as of now, one might say that this agent is reasonably effective in maintenance treatment of bipolar disorder, particularly in prevention of depression, among patients who initially tolerate and may benefit from acute lamotrigine treatment. It is proven ineffective in acute mania, rapid cycling, and acute bipolar depression.****"*

(k) Goodwin G, A Pooled Analysis of 2 Placebo-Controlled 18-Month Trials of Lamotrigine and Lithium Maintenance in Bipolar I Disorder, J Clin Psy 2004, PMID: 15096085. https://goo.gl/jAfumf. *"…[N=1315] Lamotrigine and lithium were superior to placebo for time to intervention for any mood episode (median survival: placebo, 86 days…; lithium, 184 days…lamotrigine, 197 days)… Lamotrigine and lithium stabilized mood by delaying the time to treatment for a mood episode. Lamotrigine was effective against depression and mania, with more robust activity against depression."* **Note:** Estimate from figure 1 is that in 50 weeks 25% in placebo group avoided relapse and 43% in lamotrigine group for ARR= 18%.

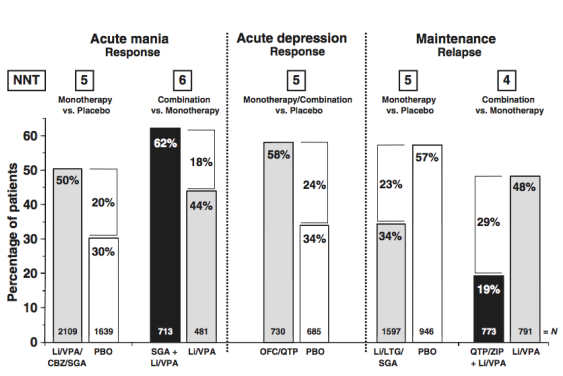
Table 5. Adverse Events Occurring in ≥ 10% of Patients in 2 Pooled Studies of Bipolar I Patients (%)

Adverse Event	Open-Label Phase (N = 1305)	Randomized Phase: Placebo (N = 190)	Lithium (N = 166)	Lamotrigine (N = 227)
Headache	25	19	15	19
Nausea	12	11	20[a]	14
Infection	11	13	13	13
Rash	11	5	5	7
Dizziness	10	9	8	7
Somnolence	9	7	13[a]	9
Diarrhea	8	8	19[a,b]	7
Insomnia	8	6	10	10
Tremor	4	5	15[a,b]	4

[a]p < .05 lithium vs. placebo.
[b]p < .05 lithium vs. lamotrigine.



(l) **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.** *"… Individual study and pooled study analyses of NNT and NNH were conducted using 35 retrieved studies of medication approved for the treatment of bipolar disorder by the US FDA." Figure 3 shows acute mania montherapies NNT and NNH. Overall 30% response rate from placebo with Lithium response = 52% for 22% absolute response rate. Lithium NNT = 1/(52%-30%) = 4.5 (though his graphic shows NNT=4).*



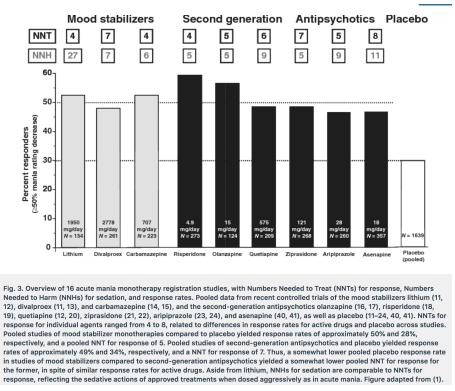


Fig. 3. Overview of 16 acute mania monotherapy registration studies, with Numbers Needed to Treat (NNTs) for response, Numbers Needed to Harm (NNHs) for sedation, and response rates. Pooled data from recent controlled trials of the mood stabilizers lithium (11, 12), divalproex (11, 13), and carbamazepine (14, 15), and the second-generation antipsychotics olanzapine (16, 17), risperidone (18, 19), quetiapine (12, 20), ziprasidone (21, 22), aripiprazole (23, 24), and asenapine (40, 41), as well as placebo (11–24, 40, 41). NNTs for response for individual agents ranged from 4 to 8, related to differences in response rates for active drugs and placebo across studies. Pooled studies of mood stabilizer monotherapies compared to placebo yielded response rates of approximately 50% and 28%, respectively, and a pooled NNT for response of 5. Pooled studies of second-generation antipsychotics and placebo yielded response rates of approximately 49% and 34%, respectively, and a NNT for response of 7. Thus, a somewhat lower pooled placebo response rate in studies of mood stabilizers compared to second-generation antipsychotics yielded a somewhat lower pooled NNT for response for the former, in spite of similar response rates for active drugs. Aside from lithium, NNHs for sedation are comparable to NNTs for response, reflecting the sedative actions of approved treatments when dosed aggressively as in acute mania. Figure adapted from (1).

Table 3. Selected NNTs in bipolar disorder: response or relapse/recurrence prevention compared to placebo (for monotherapy) or lithium/valproate (for adjunctive therapy)

	Acute Mania (monotherapy)	Acute Mania (adjunctive)	Acute Bipolar depression	Maintenance (monotherapy)	Maintenance (adjunctive)
Mood stabilizers					
Lithium	4			7	
Divalproex, ER	7			8*	
Carbamazepine ER	4				
Lamotrigine			12*	9	
Typical antipsychotics					
Chlorpromazine					
Haloperidol	5*	6*			
Atypical antipsychotics					
Olanzapine	5	5	12*	3	
Risperidone	4	6		4 (LAI)	? (LAI)
Quetiapine, XR	6	8	6	4*	4
Ziprasidone	7		−1980*		8
Aripiprazole	5	7	44*	6	
Asenapine	8	?			
Other					
Olanzapine + Fluoxetine			4		

NNTs are for rates of response (at least 50% decrease in acute mania or depression ratings) or relapse/recurrence (re-emergence/emergence of a syndromal mood episode) prevention compared to placebo (monotherapy) or compared to lithium/valproate (adjunctive therapy).
LAI, long-acting injectable formulation; ER, XR, Extended Release formulation; ?, data not published.
*Not US FDA-approved treatments.
See text for references to individual studies.
Adapted from (1).

Table 4. Bipolar maintenance and NNT for relapse/recurrence prevention compared to placebo (for monotherapy) or lithium/valproate (for adjunctive therapy)

	Episode prevention	Mania prevention	Depression prevention
Mood stabilizers			
Lithium (35)	7	8	49
Divalproex (34)*	8	22	11
Lamotrigine (35)	9	23	15
Atypical Antipsychotics			
Olanzapine (37)	3	5	12
Aripiprazole (36)	6	6	64
Risperidone LAI (42)	4	4	−26
Quetiapine (43)*	4	?	?
Quetiapine + Li/DVPX (38, 39)	4	8	6
Ziprasidone + Li/DVPX (44)	8	10	56
Risperidone LAI + Li/DVPX (45)	?	?	?

NNTs are for rates relapse/recurrence (re-emergence/emergence of a syndromal mood episode) prevention compared to placebo (monotherapy) or compared to lithium/valproate (adjunctive therapy).
?, data not published.
*Not US FDA-approved treatments. Data from (34–39, 42–45).
Adapted from (1).

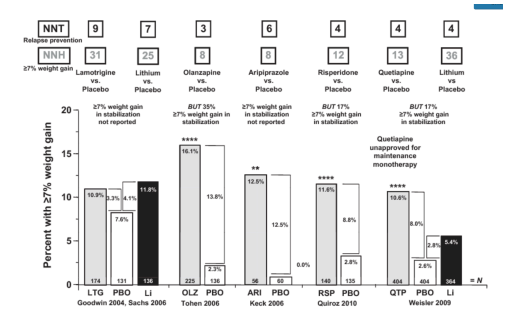


Fig. 7. Lamotrigine, lithium, olanzapine, aripiprazole, risperidone, and quetiapine: pivotal bipolar monotherapy maintenance studies – Numbers Needed to Treat (NNTs) for relapse/recurrence prevention, Numbers Needed to Harm (NNHs) for weight gain, rates. Mood stabilizers compared to placebo have mid- to high-single-digit NNTs, but even higher double-digit NNHs. Secondgeneration antipsychotics have lower single-digit NNTs, but also single-digit to low double-digit NNHs. LTG, lamotrigine; Li, lithium; OLZ, olanzapine; ARI, aripiprazole; RSP, risperidone long-acting injectable formulation; QTP, quetiapine; PBO, placebo. **P < 0.01, ****P < 0.0001 vs. placebo. Data from (35–37, 42, 43, 51). Figure adapted from (1).

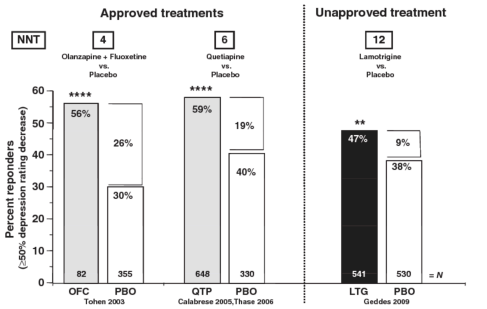
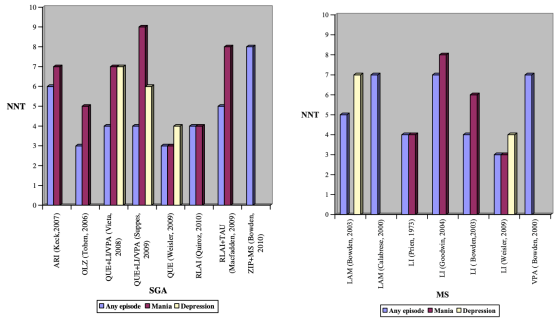


Fig. 4. Overview of Contemporary Acute Bipolar Depression Studies – Numbers Needed to Treat (NNTs) for Response, and Response Rates. The approved treatments have single-digit NNTs for response. OFC, olanzapine plus fluoxetine combination; QTP, quetiapine; LTG, lamotrigine; PBO, placebo. **P < 0.01, ****P < 0.0001 vs. placebo. Data from (29–33). Figure adapted from (1).

*(m)***Ng F et al, The role of lamotrigine in the management of bipolar disorder, Neuropsychiatr Dis Treat. 2007, PMC2655087.** *"…This review examines the published clinical trials of lamotrigine in bipolar treatment. While the data supports its tolerability and safety, the* ***strongest evidence for its efficacy lies in the prevention of bipolar depression****, with* ***weaker evidence for the treatment of acute bipolar depression****, refractory unipolar and bipolar depression, and rapid cycling bipolar disorder… the available randomized controlled trials of lamotrigine in the treatment of bipolar disorder have only demonstrated convincing efficacy in the prophylaxis of bipolar depression... **[For mania]** One was an 8-week study of 16 lithium-refractory manic and hypomanic patients, which found lamotrigine to be no more useful than placebo. Conclusions of efficacy are difficult to make considering the small sample size and refractory population. In the other two cited studies, neither found lamotrigine to be superior to placebo in the treatment of acute mania… Lamotrigine has emerged with a distinct place in the pharmacological treatment of bipolar disorder, with the potential to treat and prevent bipolar depression… **[For bipolar depression]…** Calabrese and colleagues reported the first double-blind placebo-controlled trial of lamotrigine monotherapy in the treatment of bipolar I depression. They recruited 195 subjects meeting the DSM-IV diagnostic criteria for bipolar I disorder who were in a major depressive episode. These patients were randomized into 3 monotherapy treatment arms of equal size (N = **66),** consisting of 50 mg/day lamotrigine, 200 mg/day lamotrigine and placebo, given over 7 weeks… Both lamotrigine groups showed moderately larger margins of improvement than placebo… In the second monotherapy study (Frye et al 2000) (Table 2), lamotrigine was compared with gabapentin and placebo in a double-blind, randomized, crossover trial on 31 patients with refractory unipolar and bipolar affective illness requiring hospitalization… Patients were randomized, with stratification by diagnostic classification, to receive sequential 6-week trials of each of the 3 treatment arms… 52% of the lamotrigine group had a rating of "much improved" or "very much improved", compared with 26% of the gabapentin and 23% of the placebo groups (p = 0.031). [ARR = 52%-23%=29%] When response rates were analysed by affective episode types, both mania (lamotrigine 44%, gabapentin 20%, placebo 32%) and depression (lamotrigine 45%, gabapentin 26%, placebo 19%) [ARR = 45%-19% = 26%]* ***showed similar non-significant trends****… In an extension to this study with a bigger sample size (N = 45), of which there were 35 bipolar and 10 unipolar treatment-refractory patients, response rates of 53% for lamotrigine, 28% for gabapentin and 22% for placebo [ARR = 53%-22% = 31%]…* ***These studies lend further support for the efficacy***

of lamotrigine in bipolar depression, but their generalizability is restricted by their highly-refractory and diagnostically heterogeneous populations… it would seem prudent to await greater evidence of efficacy before designating lamotrigine as first-line treatment for other bipolar indications…"

(n) **Popovic D et al, Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder, Psychopharmacology (Berl). 2011, PMID: 21052983, https://goo.gl/dpcJJo**. Note: this study is for maintenance treatment. *"…In 15 studies, aripiprazole, olanzapine, quetiapine, risperidone long-acting injection, lithium, lamotrigine, and divalproex proved effectiveness in terms of NNTs (≥10% advantage over placebo) for prevention of relapse into any mood episode… Due to the episodic and chronic nature of bipolar disorder (BD), maintenance therapy represents a critical part of treatment; however, there is a paucity of studies comparing effectiveness of available long-term treatments…The aim of this study is to determine and compare the efficacy of pharmacological treatments for maintenance treatment of BD "* Note: for antipsychotic mania NNTs = 3-9, depression NNTs = 4-7, and 3-8 any episode.



(o) Reinares M et al, A systematic review on the role of anticonvulsants in the treatment of acute bipolar depression, Int J Neuropsychopharmacol. 2013, PMID: 22575611 https://goo.gl/FC4yW9. *"…Studies supported the efficacy of divalproex as monotherapy in acute bipolar depression but small sample size was a common methodological limitation. Findings were inconclusive for lamotrigine and carbamazepine although overall lamotrigine may have a beneficial but modest effect…. available data for most other [beyond divalproex and lamotrigine] anticonvulsants are inconclusive… **Lamotrigine** has shown efficacy in the prophylaxis of bipolar disorder, especially in patients with depressive-predominant polarity (Bowden et al.2003; Calabrese et al.2003; van der Loos et al.2011). The efficacy of lamotrigine in reducing depressive relapses is considered its main strength (Popovic et al.2011; Vieta & Rosa, 2007). However, the efficacy of lamotrigine in acute bipolar depression is still debated… The tolerability of lamotrigine was comparable to placebo with the most common adverse events being headache, nausea and rash… Therefore, at the moment the antidepressant effect of lamotrigine in acute bipolar depression seems present but modest… **Valproate**: Divalproex as a maintenance treatment has been shown to improve depressive morbidity (Bowden et al.2000) and reduce the probability of depressive relapse in bipolar patients (Gyulai et al.2003). However, there are a few (n = 3) RCTs on the use of divalproex monotherapy for acute bipolar depression (Davis et al.2005; Ghaemi et al.2007; Muzina et al.2011). The trials duration range was between 6 and 8 wk… "*

(p) Selle V et al, Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics, Pharmacopsychiatry. 2014, PMID: 24549862, https://goo.gl/aUNedP. *"… Overall, pooled drug-over-placebo responder-rate superiority (RR) was moderate [with] NNT was 8.2… Notably, drugs were superior to placebo in only 11/24 trials (5/5 with quetiapine, 2/4 with valproate), and only lamotrigine, quetiapine and valproate had > 2 trials. Treatment-associated mania-like reactions were uncommon (drugs: 3.7%; placebo: 4.7%)."* Note: Table 3 shows anticonvulsant NNTs for depression (valproate 4.4, Carbamazepine 3.4. 23% = (1/4.4); 29% - (1/3.4, the carbamazepine study only had 70 participants).

Table 3 Summary of meta-analyses: Effects of specific agents in placebo-controlled trials for acute bipolar depression.

Treatment	Trials (n)	Subjects (N)	RR [95% CI]	RR z-score (p-value)	NNT [95% CI]	NNT z-score (p-value)	SMD [95%CI]*	SMD z-score (p-value)	Favorable Outcomes (%)
Valproate	4	140	2.08 [1.18–3.65]	2.54 (0.01)	4.4 [2.7–12]	3.01 (0.002)	0.452 [0.114–0.790]	2.62 [0.009]	2/4
Carbamazepine	1	70	1.84 [1.01–3.34]	1.98 (0.05)	3.4 [1.9–19]	2.39 (0.02)	0.209 [−0.291 to 0.709]	0.82 [0.0.41]*	0/1
Olanzapine+Fluoxetine	1	437	1.84 [1.44–2.36]	4.84 (<0.001)	1.8 [2.7–7.2]	4.28 (<0.001)	0.453 [0.211–0.695]	3.67 [<0.0001]	1/1
Lurasidone	1	485	1.72 [1.33–2.22]	4.15 (<0.001)	4.6 [3.3–7.8]	4.78 (<0.001)	0.318 [0.128–0.508]	3.29 [0.001]	1/1
Quetiapine	5	2 485	1.36 [1.24–1.49]	6.32 (<0.001)	5.9 [4.7–7.8]	7.73 (<0.001)	0.373 [0.284–0.462]	8.19 [<0.0001]	5/5
Olanzapine	2	1 220	1.25 [1.08–1.44]	3.03 (0.002)	11* [7.0–30]	3.12 (0.002)	0.187 [0.072–0.302]	3.18 [0.001]	1/2
Lamotrigine	5	1 071	1.25 [1.07–1.46]	2.81 (0.005)	10* [6.1–32]	2.86 (0.004)	0.131 [−0.018 to 0.280]	1.72 [0.09]*	1/5
Lithium	1	265	1.12 [0.92–1.44]	1.10 (0.27)*	15* [5.4–20]	1.11 (0.27)	0.142 [−0.099 to 0.383]	1.15 [0.25]*	0/1
Aripiprazole	2	690	0.88 [0.74–1.04]	0.69 (0.49)*	>100* [58–∞]	1.53 (0.13)	0.077 [−0.072 to 0.227]	1.07 [0.28]*	0/2
Ziprasidone	2	928	1.02 [0.90–1.17]	0.34 (0.73)*	87* [14–∞]	0.34 (0.74)	0.103 [−0.036 to 0.241]	1.47 [0.14]*	0/2
All Agents Pooled	**24**	**7 456**	**1.29 [1.19–1.40]**	**6.25 (<0.0001)**	**8.2 [6.4–11]**	**6.85 [<0.0001]**	**0.232 [0.167–0.297]**	**6.98 [<0.0001]**	**11/24**

(q) **Smith LA et al, Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis, J Affect Disord. 2010, PMID: 19926140.** *"…Four randomized, controlled, doubleblind trials of* ***142 participants*** *were included. Trial quality was good, although individual study sample sizes were small. Study duration was six weeks (2 studies) and eight weeks (2 studies).* ***Meta-analysis showed a significant difference in favour of valproate for reduction in depressive symptoms****, both on depression symptom scales (standardized mean difference (SMD) -0.35 (95% confidence interval, -0.69, -0.02****), and participants with at least 50% improvement in symptoms*** *- relative risk (RR) 2.00 (1.13, 3.53). Effects on anxiety symptoms were small, SMD -0.32 (-0.72, 0.08) and inconclusive (p=0.12).. Nausea occurred more frequently with valproate compared with placebo though the difference was not significant, RR 2.01 (0.98, 4.11).. There was a significant reduction in depression based on symptom scores, and significantly more participants with at least 50% improvement in depression symptoms. The absolute difference in effect between valproate and placebo for at least 50% improvement in depression symptoms was about 22% indicating that five patients would need to be treated in order for one to respond. The evidence for a greater reduction in anxiety symptoms with valproate was inconclu- sive. There was no evidence for an increased risk of mania. Valproate was well tolerated with no evidence for a difference in withdrawal rates between valproate and placebo. For the adverse events included in the meta-analyses no significant differences between valproate and placebo were detected, however, the data suggest that nausea may occur more frequently with valproate.." Note: the small number of patients and a short trial duration seriously compromises the value of this study.*

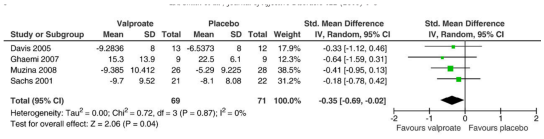


Fig. 2. Random effects meta-analysis of standardized difference in mean scores on depression symptom scales in RCTs of valproate versus placebo for treatment of bipolar depression.

Adverse effect	Studies	Valproate events/N	Placebo events/N	RR (95% CI)	Heterogeneity I^2
Diarrhoea	3	11/58	7/59	1.60 [0.68, 3.77]	0
Dizziness	2	4/35	5/31	0.84 [0.19, 3.75]	25
Dry mouth	2	5/35	3/37	1.56 [0.40, 6.09]	0
Dyspepsia	1	4/23	4/22	0.96 [0.27, 3.36]	–
Fatigue or myalgia/weakness	3	10/58	7/59	1.48 [0.61, 3.57]	0
Headache	2	6/32	4/31	1.48 [0.25, 8.92]	48
Nausea	3	18/58	9/59	2.01 [0.98, 4.11]	0
Sedation	1	6/9	3/9	2.00 [0.71, 5.62]	–
Vomiting	1	1/23	3/22	0.32 [0.04, 2.84]	–
Weight gain	Not reported				

Table 2 Random effects meta-analysis of adverse effects in RCTs of valproate versus placebo

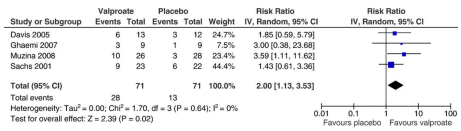


Fig. 3. Random effects meta-analysis of at least 50% improvement in depression symptoms in RCTs of valproate versus placebo for treatment of bipolar depression.

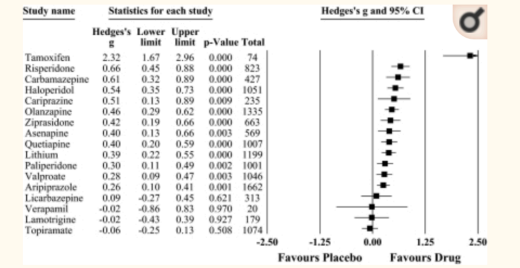
(r) **Weisler RH et al, A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes, J Clin Psychiatry. 2004, PMID: 15119909.** *"…Following a single-blind placebo lead-in, DSM-IV-defined bipolar disorder patients with manic or mixed episodes were randomly assigned to receive ERC-CBZ (N = 101) or placebo (N = 103) for 3 weeks… Starting at week 2, ERC-CBZ was associated with significantly greater improvements in YMRS (p =.032) using last-observation-carried-forward analyses. At end point, the responder rate (patients with at least a 50% decrease in YMRS score) also favored ERC-CBZ (41.5% vs. 22.4%; p =.0074)."*

(s) **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.*

(t) **Zeid M et al, Acute pharmacological treatment strategies for bipolar depression, Neuropsychiatry, 2016, https://goo.gl/UR9goc**. *"…All five trials of lamotrigine in acute bipolar depression were negative… Pooled data from all five studies also suggest a modest, but probably not clinically significant acute antidepressant effect of lamotrigine…" "…Sodium Valproate & Carbamazepine - Data regarding these two medications is limited…." "… The bulk of evidence [for antipsychotics] in the acute treatment of bipolar depression… rests with quetiapine… Quetiapine has also been approved by the US FDA for the treatment of acute bipolar II depression…"*

Results of Random Effects Meta-analyses for the Outcomes of Response as Risk Ratio, Absolute Difference in Responder Rates, and NNT with Drug *vs* Placebo Comparisons

Drug	*N*	Patients (*n*, ITT)	Risk ratio (CI)	*P*-value	Drug response (CI)	Placebo response (CI)	Rate difference (CI)	*P*-value	$NNT_{benefit}$ (1/RD; CI)
Aripiprazole	6	1662	1.35 (1.16–1.58)	<0.0001	0.46 (0.40–0.51)	0.34 (0.29–0.38)	0.12 (0.06–0.19)	<0.0001	8.3 (5.3–16.7)
Asenapine	2	569	1.41 (1.05–1.90)	0.021	0.42 (0.33–0.51)	0.30 (0.22–0.39)	0.13 (0.02–0.24)	0.026	7.7 (4.2–50)
Cariprazine	1	235	1.95 (1.27–3.0)	0.002	0.48 (0.35–0.62)	0.25 (0.16–0.37)	0.24 (0.08–0.39)	0.004	4.2 (2.6–12.5)
Olanzapine	5	1134	1.62 (1.34–1.97)	<0.0001	0.51 (0.44–0.57)	0.31 (0.26–0.37)	0.20 (0.12–0.27)	<0.0001	5 (3.7–8.3)
Paliperidone	4	1001	1.20 (1.0–1.44)	0.057	0.49 (0.42–0.55)	0.40 (0.34–0.47)	0.08 (0.001–0.16)	0.048	12.5 (6.3–1000)
Quetiapine	4	1007	1.53 (1.26–1.86)	<0.0001	0.50 (0.43–0.57)	0.33 (0.27–0.39)	0.18 (0.10–0.26)	<0.0001	5.6 (3.9–10)
Risperidone	3	823	1.75 (1.41–2.16)	<0.0001	0.55 (0.47–0.63)	0.32 (0.26–0.39)	0.24 (0.15–0.33)	<0.0001	4.2 (3.0–6.7)
Ziprasidone	3	663	1.59 (1.21–2.09)	0.001	0.44 (0.37–0.52)	0.28 (0.21–0.36)	0.17 (0.07–0.26)	0.001	5.9 (3.9–14.3)
SGAs	*28*	*7094*	*1.47 (1.36–1.59)*	*<0.0001*	*0.48 (0.46–0.51)*	*0.33 (0.30–0.35)*	*0.16 (0.13–0.19)*	*<0.0001*	*6.3 (5.3–7.7)*
Haloperidol	4	1051	1.57	<0.0001	0.52	0.33	0.20	<0.0001	5 (3.6–8.3)
FGAs	*4*	*1051*	*1.57 (1.29–1.91)*	*<0.0001*	*0.52 (0.45–0.59)*	*0.33 (0.27–0.39)*	*0.20 (0.12–0.28)*	*<0.0001*	*5 (3.6–8.3)*
Carbamazepine	2	427	2.03 (1.49–2.77)	<0.0001	0.51 (0.41–0.61)	0.25 (0.18–0.34)	0.26 (0.14–0.37)	<0.0001	3.9 (2.7–7.1)
Lithium	6	1199	1.51 (1.26–1.80)	<0.0001	0.47 (0.41–0.53)	0.32 (0.27–0.37)	0.16 (0.09–0.23)	<0.0001	6.3 (4.4–11.1)
Valproate	4	824	1.51 (1.20–1.90)	<0.0001	0.46 (0.38–0.53)	0.30 (0.24–0.37)	0.17 (0.08–0.26)	<0.0001	5.9 (3.9–12.5)
MSs	*12*	*2450*	*1.59 (1.39–1.82)*	*<0.0001*	*0.47 (0.43–0.52)*	*0.30 (0.26–0.34)*	*0.18 (0.13–0.23)*	*<0.0001*	*5.6 (4.4–7.7)*
Tamoxifen	2	74	7.46 (1.88–29.6)	0.004	0.48 (0.31–0.66)	0.07 (0.02–0.24)	0.42 (0.23–0.61)	<0.0001	2.4 (1.6–4.4)
PKC inhibitor (tamoxifen)	*2*	*74*	*7.46 (1.88–29.6)*	*0.004*	*0.48 (0.31–0.66)*	*0.07 (0.02–0.24)*	*0.42 (0.23–0.61)*	*<0.0001*	*2.4 (1.6–4.4)*
D/P contrasts significant	*46*[a]	*10669*	*1.52 (1.42–1.62)*	*<0.0001*	*0.48 (0.46–0.50)*	*0.31 (0.30–0.34)*	*0.17 (0.15–0.20)*	*<0.0001*	*5.9 (5–6.7)*
Lamotrigine	1	179	0.95 (0.64–1.41)	0.803	0.44 (0.30–0.59)	0.46 (0.33–0.60)	−0.02 (−0.20–0.16)	0.805	NNTH 50 (NNTH 5–∞–6.3)
Licarbazepine	1	313	1.02 (0.70–1.49)	0.920	0.36 (0.24–0.49)	0.35 (0.25–0.47)	0.007 (−0.14–0.16)	0.930	142.9 (6.3–∞–NNTH 7.1)
Toniramate	4	1074	0.96	0.757	0.27	0.28	−0.01	0.798	NNTH 100



[17] **Anticonvulsant FDA warnings**.

Epoctrates, Valproic Acid, Black Box Warnings. https://goo.gl/xcbmCi.

Oshea T, 10 Black Box Warnings Every Pharmacist Should Know, Pharmacy Times, 2016, https://goo.gl/1NtTPs. *"…Lamictal has a black box warning for causing cases of life-threatening serious rashes, including*

Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death. The rate of serious rash has been greater in pediatric patients than adults…"

US Food and Drug Administration. FDA Alerts Health Care Providers to Risk of Suicidal Thoughts and Behavior With Antiepileptic Medications. 2008, https://goo.gl/anx1JY. *"…An FDA analysis of suicidality reports from placebo-controlled studies of 11 antiepileptic drugs shows that patients taking these drugs have about twice the risk of suicidal thoughts and behaviors (0.43 percent), compared with patients receiving placebo (0.22 percent). This risk corresponds to an estimated 2.1 per 1,000 more patients in the drug treatment groups who experienced suicidality than in the placebo groups… The analysis included 27,863 patients in drug treatment groups and 16,029 patients in placebo groups. There were four suicides among patients in the drug treatment groups and none among patients in placebo groups. There were 105 reports of suicidal thoughts or behaviors in the drug-treated patients and 35 reports in placebo-treated patients. The higher risk of suicidal thoughts and behaviors was observed at one week after starting a drug and continued to at least 24 weeks. The results were generally consistent among all the different drug products studied and were seen in all demographic subgroups. There was no clear pattern of risk across age groups."*

FDA Highlights of prescribing information, Depacon (valproate sodium), for intravenous injection, https://goo.gl/kNc6SS. "…Hepatotoxicity, including fatalities, usually during the first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum liver testing prior to therapy and at frequent intervals thereafter (5.1). **Fetal Risk**, particularly neural tube defects, other major malformations, and decreased IQ (5.2, 5.3, 5.4). **Pancreatitis**, including fatal hemorrhagic cases (5.5)…"

NBC News, FDA Strengthens FDA epilepsy drug warning, NBCNews.com, 2007, https://goo.gl/ZicKsP. "…The Food and Drug Administration Wednesday strengthened warnings on certain drugs used to treat epilepsy, bipolar disorder and nerve pain, discussing the possibility of rare skin disorders and recommending that patients of Asian ancestry undergo genetic testing before using the drugs... The FDA said prescribing information for the drugs already carried a warning about the possibility of rare but severe — and sometimes life-threatening — skin reactions for all patients starting carbamazepine therapy… However, the warning will be moved to a more prominent location on the drugs' labels and be placed in an existing black box warning that discusses risks for developing anemia… The FDA said studies have found a strong association between certain serious skin reactions and an inherited variant of a gene that is found almost exclusively in people of Asian ancestry."

Michigan Medicine Confluence, Carbamazepine, 2013, https://goo.gl/TzgsWh. *"…FDA Black Box Warning. Serious and sometimes **fatal dermatologic reactions** (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported, especially in patients with the inherited allelic variant HLA-B*1502, found almost exclusively in patients of Asian descent. Screen genetically at-risk patients prior to receiving carbamazepine. Do not start carbamazepine in patients who test positive for the allele... **Aplastic anemia** (2/MM) and agranulocytosis (6/MM) have been reported. Obtain pretreatment hematological testing and periodically monitor CBC. Consider drug discontinuation if significant bone marrow depression develops or if serious dermatologic reactions occur…"*

[18] **Anticonvulsant side effects and risks**. See footnote #1 for definitions. **Tremors** 10% from Leo, **Liver Enzymes** 10% Leo midpoint of 5-15%, **rash** 10% for lamotrigine from Leo. **Suicide increase risk** of 2X from Patorno giving a rough average of the varied anticonvulsants. **Valproate fetal risk** of 4X from Medsafe, Vadja, and Campbell.

a) **Hitti M, WebMD, Epilepsy Drugs Get Suicide Risk Warning, https://goo.gl/WK8FqE.** *"...Dec. 16, 2008 -- The FDA today announced that it will require makers of epilepsy drugs to add a warning about increased risk of suicidal thoughts and behaviors.."* Note: 21 anti-epileptic meds carry FDA warning for increased suicide risk, though this warning is not as severe as a black box.

b) **Bellivier F, Anticonvulsants and suicide attempts in bipolar I disorders, Acta Psychiatr Scand. 2017, PMID: 28190254**. *"…A total of 3390 manic or mixed cases with bipolar disorder (BD) type I recruited from 14 European countries were included in a prospective, 2-year observational study… A total of 302 SA [suicide attempts] were recorded prospectively…In cases with a prior history of SA, risk of SA repetition was associated with… and initiation of an anticonvulsant at study entry… In cases with no previous SA, the first SA event was associated with… initiation of an anticonvulsant at study entry."*

c) **Campbell E et al, 'Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers' J Neurol Neurosurg Psychiatry, 2014, PMID: 24444855.** *"…ntiepileptic drug (AED) exposure during pregnancy increases the risk of major congenital malformations (MCMs)… The MCM risk with valproate monotherapy exposure in utero was 6.7% (95% CI 5.5% to 8.3%) compared with 2.6% with carbamazepine (95% CI 1.9% to 3.5%) and 2.3% with lamotrigine (95% CI 1.8% to 3.1%). A significant dose effect was seen with valproate (p=0.0006) and carbamazepine (p=0.03) exposed pregnancies. A non-significant trend towards higher MCM rate with increasing dose was found with lamotrigine. MCM rate for high-dose lamotrigine (>400 mg daily) was lower than the MCM rate for pregnancies exposed to <600 mg daily of valproate, but this was not significant (3.4% vs 5.0%, p=0.31)."*

d) **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"*

e) **Leon A et al, Antiepileptic Drugs for Bipolar Disorder and the Risk of Suicidal Behavior: A 30 -Year Observational Study, Am J Psychiatry, 2012, PMCID: PMC3643204.** *"…A prospective observational study was conducted at five U.S. academic medical centers from 1978 to 2009. Analyses included 199 participants with bipolar disorder for whom 1,077 time intervals were classified as either exposed to an antiepileptic (carbamazepine, lamotrigine, or valproate) or not exposed to an antiepileptic, an antidepressant, or lithium during 30 years of follow-up… Mixed-effects grouped-time survival models revealed no elevation in risk of suicide attempt or suicide during periods when participants were receiving antiepileptics relative to periods when they were not… "*

f) **Patorno E et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA. 2010, PMID: 20388896.** *"…The study identified 26 completed suicides, 801 attempted suicides, and 41 violent deaths in 297,620 new episodes of treatment with an anticonvulsant… This exploratory analysis suggests that the use of gabapentin, lamotrigine, oxcarbazepine, and tiagabine, compared with the use of topiramate, may be associated with an increased risk of suicidal acts or violent deaths. "*

g) **Patorno E et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA, 2010, PMID: 20388896.** *"…The incidence of the composite outcomes of completed suicides, attempted suicides, and violent deaths for anticonvulsants used in at least 100 treatment episodes ranged from 6.2 per 1000 person-years for primidone to 34.3 per 1000 person-years for oxcarbazepine**. The risk of suicidal acts was increased for gabapentin (hazard ratio [HR], 1.42; 95% confidence interval [CI], 1.11-1.80), lamotrigine (HR, 1.84; 95% CI, 1.43-2.37), oxcarbazepine (HR, 2.07; 95% CI, 1.52-2.80), tiagabine (HR, 2.41; 95% CI, 1.65-3.52), and valproate (HR, 1.65; 95% CI, 1.25-2.19), compared with topiramate.** *The analyses including violent death produced similar results."*

h) **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.** "…Up to 50% of patients receiving carbamazepine experience side effects."

i) **Medsafe, Trans-Tasman Early Warning System - Alert Communication, 2015, copied Jan 2019, https://goo.gl/iUVXjB.** *"…Congenital malformations have been estimated to affect between 6.7% and 12.4% of children exposed to Epilim [sodium valproate] in the womb. The rate of malformations in the general population is 2-3%. The most common types of malformations in children exposed to Epilim are: neural tube defects, cleft lip and palate, heart defects, limb defects and unusual facial features 2. Developmental delay is also common (30-40%) in children exposed to Epilim in the womb2. The IQ of Epilim exposed children is 7-10 points lower than the IQ of children exposed to other anti-epileptics 2. The risk of autism in children exposed to Epilim has been estimated at 2.5%. This is about five times higher than the rate in the general population.2 Epilim should not be used in female children or in women of child-bearing age, unless other treatments are ineffective or not tolerated. It is important that girls (and their caregivers) and women of child-bearing age taking Epilim are aware of these risks."*

j) **Vajda FJ et al, 'Dose dependence of fetal malformations associated with valproate' Neurology, 2013, PMID: 23911758.** *"… Analysis of data in the Australian Register of Antiepileptic Drugs in Pregnancy collected from 1999 to 2012. The specific type of fetal malformation in offspring exposed to valproate in utero was correlated with the dose of valproate taken by the mother in the first trimester… Compared with other malformations, the mean dose of valproate taken during the first trimester was higher in mothers whose offspring had spina bifida (2,000 ± 707 vs 1,257 ± 918 mg/d) and hypospadias (2,417 ± 1,320 vs 1,235 ± 715 mg/d) (both p < 0.05)."*

[19] **Antipsychotic efficacy**. We focus on response, not remission numbers. We have chosen efficacy values using the following rationale:

- **For acute mania Ketter (2011)** NNT=4-8, **Yildiz (2011)** pooled NNT=6.3, with a range of 4.2-8.3 for the more commonly used SGAs). We choose to use the Yildiz range 1/ 4.2 = 24%, 1 /8.3 = 12%.
- **For acute depression Fruty (2012)** NNT range from 6-7 for Quetiapine and NNT=12 for Olanzapine with pooled NNT= 8, **Ketter (2011)** gives Quetiapine NNT = 6, Olanzapine = 12. **Citrome (2014) Lurasidone monotherapy** NNT**=**5. We choose to specify range from Lurasidone (NNT=5, AAR=20%) to Olanzapine (NNT=12, ARR = 8%)
- **For long-term mood episode/relapse. Popovic** provides comprehensive information in table 2 and 3 which includes both stand-alone and adjunctive treatments. His monotherapies range from NNT=3 for Quetiapine to NNT=6 for aripiprazole (AAR range 17-33%)**. Ketter (2011)** shows maintenance NNTs of Olanzapine=3, Resperidone=4, Quentiapine=4, Aripiprazole=6**. Lindstrom** offers a larger and more recent review but is not NNT oriented. **Hayes (2016)** is more recent and offers a maintenance monotherapy failure analysis which shows lithium superior to stand alone antipsychotics with about double the duration until failure. Popovic and Ketter offer the same range (17-33%) for monotherapies so we go with that, though their values by SGA are somewhat different.

a) **Popovic D et al, Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder, Psychopharmacology (Berl). 2011, PMID: 21052983, https://goo.gl/dpcJJo**. *"…Due to the episodic and chronic nature of bipolar disorder (BD), maintenance therapy represents a critical part of treatment; however, there is a paucity of studies comparing effectiveness of available long-term treatments…The aim of this study is to determine and compare the efficacy of pharmacological treatments for maintenance treatment of BD "* Note: for antipsychotic mania NNTs = 3-9, depression NNTs = 4-7, and 3-8 any episode.

b) **Fruty J et al, Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis, J Psychopharmacol. 2012, PMID: 21940761, https://goo.gl/aYbgxq**. *Note: From table #3, page 37, NNT to gain response for all SGAs pooled was 8 NNT to gain remission for all SGAs pooled was 9.*

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.** *"... in this review, in the interest of brevity, the NNT calculations focused on response (rather than remission or recovery) and relapse/recurrence prevention, and NNH calculations focused on primarily on weight gain and sedation (rather than extrapyramidal symptoms, akathisia, and other adverse effects)."* Note: Figure 3 shows 2nd generation antipsychotics as mania monotherapy range in NNT = 4-8 and NNH = 5-11 and a 30% placebo response rate. For acute bipolar depression, quetiapine monotherapy had NNT=6 (40% placebo, 59% treatment). Quetiapine has NNH = 5 for sedation (30.4% adverse effects in treatment, 8.1% in placebo). CBT has NNT=4 for relapse (75.0% for treatment and 43.8% for no treatment). Figure 1 shows Olazapine+fluoxetine NNT=5 for acute depression (58% treatment response, 34% placebo response).

d) Lindstrom L et al, Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis, J Affect Disord. 2017. PMID: 28222360. *"…Primary outcomes were relapses (mood episode recurrence) and discontinuation. We identified 15 RCTs on SGA in bipolar disorder with follow-up-time of 6 months up to 2 years, and one observational study reporting long-term effects of up to 4 years. A total of 6142 patients were included in the randomized trials. No long-term RCTs beyond 2 years follow-up was identified. All RCTs except for one included patients with bipolar disorder type I only. All RCTs except for two included patients pre-stabilized on the drug under investigation prior to randomization (enrichment design).* ***For SGA as adjunctive therapy to lithium or valproate, meta-analyses showed that treatment with either aripiprazole (RR: 0.65, 95% CI 0.50-0.85), quetiapine (RR: 0.38, 95% CI 0.32-0.46) or ziprasidone (RR: 0.62, 95% CI 0.40-0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase****. Adjunctive therapy with quetiapine was the only drug that reduced both manic and depressive episodes.* ***For SGA as monotherapy, only quetiapine was shown to be better than lithium/ valproate for both manic and depressive relapses, but only for patients stabilized on quetiapine during the acute phase. As monotherapy, olanzapine, quetiapine and risperidone were shown to be superior to placebo in reducing the overall risk of relapses****… There were considerable limitations to the evidence base of maintenance treatment with SGA in bipolar disorder. Most studies used stabilized patients, i.e. enrichment design (selection bias), had considerable dropout levels (attrition bias), and variable degree of reporting bias. No long-term RCT data on efficacy is available beyond 2 years, and almost all studies are on bipolar disorder type I patients only. Despite these limitations, we elucidate quantitative findings from meta-analyses conducted on the randomized trials published on the topic."*

e) **Selle V et al, Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics, Pharmacopsychiatry. 2014, PMID: 24549862.** *"… We searched for reports of placebo-controlled, monotherapy trials of mood-stabilizing anticonvulsants, second-generation antipsychotics, or lithium for acute major depressive episodes in patients diagnosed with type I or II bipolar disorder and applied random-effects meta-analysis to evaluate their efficacy, comparing outcomes based on standardized mean drug-placebo differences (SMD) in improvement, relative response rates (RR), and number-needed-to-treat (NNT)… Overall, pooled drug-over-placebo responder-rate superiority (RR) was moderate (29% [CI: 19-40%]), and NNT was 8.2 (CI: 6.4-11)… Notably, drugs were superior to placebo in only 11/24 trials (5/5 with quetiapine, 2/4 with valproate), and only lamotrigine, quetiapine and valproate had > 2 trials. Treatment-associated mania-like reactions were uncommon (drugs: 3.7%; placebo: 4.7%). ".*

f) **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.** *"…NNT vs. placebo for response was 5 for lurasidone monotherapy (both dose ranges) and 7 for adjunctive therapy. NNT vs. placebo for remission for lurasidone monotherapy was 6 for 20-60mg/d and 7 for 80-120mg/d and 7 for adjunctive lurasidone… Lurasidone was not associated with any clinically meaningful mean weight or metabolic changes compared to placebo; NNH vs. placebo for weight gain ≥7% was 29 for 20-60mg/d and 5550 for 80-120mg/d and 42 for adjunctive lurasidone. The three most frequently occurring AEs with the largest difference in incidence for lurasidone vs. placebo were nausea,*

akathisia, and somnolence, with NNH values for lurasidone vs. placebo ranging from 11 (nausea with lurasidone monotherapy 80-120mg/d) to 130 (somnolence with lurasidone monotherapy 20-60mg/d)."

g) **Derry S et al, Atypical antipsychotics in bipolar disorder: systematic review of randomised trials, BMC Psychiatry. 2007, PMC2020469.** *"…With mania or mixed presentation atypical antipsychotics produced significantly better rates of response and symptomatic remission than placebo, with NNTs of about 5 up to six weeks, and 4 at 6–12 weeks, but more adverse event withdrawals (NNH of about 22) in studies of 6–12 weeks. In comparisons with established treatments, atypical antipsychotics had similar efficacy, but significantly fewer adverse event withdrawals (NNT to prevent one withdrawal about 10). In maintenance trials atypical antipsychotics had significantly fewer relapses to depression or mania than placebo or active comparator. Atypical antipsychotics are effective in treating both phases of bipolar disorder compared with placebo, and as effective as established drug therapies."*

h) **Fountoulakis K et al, Aripiprazole monotherapy in the treatment of bipolar disorder: A meta-analysis, J Affect Disord. 2011, PMID: 21040979, https://goo.gl/Yexkc3.** *"…Two thousand three hundred and three patients took part in the aripiprazole acute mania RCTs. At week 3 the pooled aripiprazole vs. placebo effect size was 0.34 and the NNT was 6 for response and 14 for remission… The meta-analysis of acute bipolar depression RCTs revealed a significant difference at week 8 with a weak effect size equal to 0.17… The current meta-analysis supports the usefulness of aripiprazole during all phases of bipolar illness. Its effect against acute bipolar depression is weak and the efficacy during the maintenance phase is proven only against new manic episodes in patients with an index manic episode who had previously responded to aripiprazole during the acute phase.."*

i) **Hayes J et al, Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records, World Psychiatry. 2016, PMC4780296.** *"…It is unclear which maintenance treatment for bipolar disorder is superior in clinical practice. Randomized controlled head-to-head trials of available drugs either do not exist or are inconclusive. We aimed to* ***compare rates of monotherapy treatment failure*** *in individuals prescribed lithium, valproate, olanzapine or quetiapine by a population-based cohort study using electronic health records.* ***5,089 patients with bipolar disorder*** *were prescribed lithium (N=1,505), valproate (N=1,173) olanzapine (N=1,366) or quetiapine (N=1,075) as monotherapy… Treatment failure was defined as time to stopping medication or add-on of another mood stabilizer, antipsychotic, antidepressant or benzodiazepine. In unadjusted analyses,* ***the duration of successful monotherapy was longest in individuals treated with lithium****. Treatment failure had occurred in* ***75% of those prescribed lithium by 2.05 years*** *(95% CI: 1.63-2.51), compared to 0.76 years (95% CI: 0.64-0.84) for those prescribed quetiapine****, 0.98 years (95% CI: 0.84-1.18) for those prescribed valproate****, and 1.13 years for those prescribed olanzapine (95% CI: 1.00-1.31)."*

j) **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... "* Note: Table 3 shows for pooled SGAs for mania an NNT=6.3 (5.3-7.7) with overall effect size of 0.4 and ARR=16%.

Table 3

Results of Random Effects Meta-analyses for the Outcomes of Response as Risk Ratio, Absolute Difference in Responder Rates, and NNT with Drug *vs* Placebo Comparisons

Drug	*N*	Patients (*n*, ITT)	Risk ratio (CI)	*P*-value	Drug response (CI)	Placebo response (CI)	Rate difference (CI)	*P*-value	$NNT_{benefit}$ (I/RD; CI)
Aripiprazole	6	1662	1.35 (1.16–1.58)	<0.0001	0.46 (0.40–0.51)	0.34 (0.29–0.38)	0.12 (0.06–0.19)	<0.0001	8.3 (5.3–16.7)
Asenapine	2	569	1.41 (1.05–1.90)	0.021	0.42 (0.33–0.51)	0.30 (0.22–0.39)	0.13 (0.02–0.24)	0.026	7.7 (4.2–50)
Cariprazine	1	235	1.95 (1.27–3.0)	0.002	0.48 (0.35–0.62)	0.25 (0.16–0.37)	0.24 (0.08–0.39)	0.004	4.2 (2.6–12.5)
Olanzapine	5	1134	1.62 (1.34–1.97)	<0.0001	0.51 (0.44–0.57)	0.31 (0.26–0.37)	0.20 (0.12–0.27)	<0.0001	5 (3.7–8.3)
Paliperidone	4	1001	1.20 (1.0–1.44)	0.057	0.49 (0.42–0.55)	0.40 (0.34–0.47)	0.08 (0.001–0.16)	0.048	12.5 (6.3–1000)
Quetiapine	4	1007	1.53 (1.26–1.86)	<0.0001	0.50 (0.43–0.57)	0.33 (0.27–0.39)	0.18 (0.10–0.26)	<0.0001	5.6 (3.9–10)
Risperidone	3	823	1.75 (1.41–2.16)	<0.0001	0.55 (0.47–0.63)	0.32 (0.26–0.39)	0.24 (0.15–0.33)	<0.0001	4.2 (3.0–6.7)
Ziprasidone	3	663	1.59 (1.21–2.09)	0.001	0.44 (0.37–0.52)	0.28 (0.21–0.36)	0.17 (0.07–0.26)	0.001	5.9 (3.9–14.3)
SGAs	*28*	*7094*	*1.47 (1.36–1.59)*	*<0.0001*	*0.48 (0.46–0.51)*	*0.33 (0.30–0.35)*	*0.16 (0.13–0.19)*	*<0.0001*	*6.3 (5.3–7.7)*
Haloperidol	4	1051	1.57 (1.29–1.91)	<0.0001	0.52 (0.45–0.59)	0.33 (0.27–0.39)	0.20 (0.12–0.28)	<0.0001	5 (3.6–8.3)
FGAs	*4*	*1051*	*1.57 (1.29–1.91)*	*<0.0001*	*0.52 (0.45–0.59)*	*0.33 (0.27–0.39)*	*0.20 (0.12–0.28)*	*<0.0001*	*5 (3.6–8.3)*
Carbamazepine	2	427	2.03 (1.49–2.77)	<0.0001	0.51 (0.41–0.61)	0.25 (0.18–0.34)	0.26 (0.14–0.37)	<0.0001	3.9 (2.7–7.1)
Lithium	6	1199	1.51 (1.26–1.80)	<0.0001	0.47 (0.41–0.53)	0.32 (0.27–0.37)	0.16 (0.09–0.23)	<0.0001	6.3 (4.4–11.1)
Valproate	4	824	1.51 (1.20–1.90)	<0.0001	0.46 (0.38–0.53)	0.30 (0.24–0.37)	0.17 (0.08–0.26)	<0.0001	5.9 (3.9–12.5)
MSs	*12*	*2450*	*1.59 (1.39–1.82)*	*<0.0001*	*0.47 (0.43–0.52)*	*0.30 (0.26–0.34)*	*0.18 (0.13–0.23)*	*<0.0001*	*5.6 (4.4–7.7)*
Tamoxifen	2	74	7.46 (1.88–29.6)	0.004	0.48 (0.31–0.66)	0.07 (0.02–0.24)	0.42 (0.23–0.61)	<0.0001	2.4 (1.6–4.4)
PKC inhibitor (tamoxifen)	*2*	*74*	*7.46 (1.88–29.6)*	*0.004*	*0.48 (0.31–0.66)*	*0.07 (0.02–0.24)*	*0.42 (0.23–0.61)*	*<0.0001*	*2.4 (1.6–4.4)*
D/P contrasts significant	*46*[a]	*10669*	*1.52 (1.42–1.62)*	*<0.0001*	*0.48 (0.46–0.50)*	*0.31 (0.30–0.34)*	*0.17 (0.15–0.20)*	*<0.0001*	*5.9 (5–6.7)*
Lamotrigine	1	179	0.95 (0.64–1.41)	0.803	0.44 (0.30–0.59)	0.46 (0.33–0.60)	−0.02 (−0.20–0.16)	0.805	NNTH 50 (NNTH 5–∞–6.3)
Licarbazepine	1	313	1.02 (0.70–1.49)	0.920	0.36 (0.24–0.49)	0.35 (0.25–0.47)	0.007 (−0.14–0.16)	0.930	142.9 (6.3–∞–NNTH 7.1)
Topiramate	4	1074	0.96 (0.77–1.21)	0.757	0.27 (0.22–0.33)	0.28 (0.23–0.34)	−0.01 (−0.09–0.07)	0.798	NNTH 100 (NNTH 11.1–∞–14.3)
Verapamil	1	20	2.25 (0.47–10.8)	0.310	0.38 (0.12–0.73)	0.17 (0.04–0.49)	0.21 (−0.20–0.62)	0.319	4.8 (1.6–∞–NNTH 5)
D/P contrasts NSig.	*7*[a]	*1586*	*0.98 (0.82–1.18)*	*0.866*	*0.31 (0.26–0.36)*	*0.32 (0.27–0.37)*	*−0.003 (−0.07–0.06)*	*0.928*	*NNTH 333.3 (NNTH 14.3–∞–16.7)*

Abbreviations: ∞, infinity; CI, 95% confidence interval; D/P, drug–placebo; FGAs, first generation antipsychotic (only haloperidol); ITT, intent to treat; N, number of trials; n, number of patients; NNT, numbers-needed-generation antipsychotics.

[a]For obtaining placebo response rates with each comparison drug, placebo response rates and CI are reported for 53 trials.

NNT: the estimated number of patients who need to be treated for one additional patient to benefit ($NNT_{benefit}$) or be harmed (NNT_{harm}: NNTH), all based on response rate differences.

[20] **Antipsychotic side effects.** See footnote #1 for definitions, there is a mix of NNH and prevalence in treatment group. **Tremors** (17%) Brooks NNH=6 ; **Sexual Dysfunction** (66%) Kumar; **Weight gain** (90%+) Bak and Nihalani; sedation (13%) Brooks NNT=8; **fatigue (35%)** Serretti; metabolic syndrome (13%) Vancampfort. References to reducing long-term recovery in schizophrenia (Harrow, Wunderink). Brain shrinkage references in **Brain shrinkage**. Cognitive functioning decrease in **Rehse (2016)**.

a) **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."*

b) **Brain Shrinkage. Fusar-Poli P et al, Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies, Neurosci Biobehav Rev. 2013, PMCID: PMC3964856; Beng-Choon H, Long-term Antipsychotic Treatment and Brain Volumes A Longitudinal Study of First-Episode Schiz., Arch Gen Psych, 2011, PMID: 21300943, http://goo.gl/fSS4eC. J Moncrieff, Antipsychotics and brain shrinkage: an update, 2013, http://goo.gl/M7pj1U.**

c) **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."*

d) **Citrome L, Treatment of bipolar depression: making sensible decisions, CNS Spectr. 2014, PMID: 25407667.** *"…NNH values less than 10 (vs placebo) were observed for the spontaneously reported adverse events of weight gain and diarrhea for olanzapine/fluoxetine combination (7 and 9, respectively) and somnolence and dry mouth for quetiapine (3 and 4, respectively). There were no NNH values less than 10 (vs placebo) observed with lurasidone treatment. NNH values vs placebo for weight gain of at least 7% from baseline were 6, 16, 58, and 36, for olanzapine/fluoxetine combination, quetiapine, lurasidone monotherapy, and lurasidone combined with lithium or valproate, respectively."*

e) **DiBonaventura M et al, A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia, BMC Psychiatry. 2012, PMCID: PMC3342101.** *"…Data were analyzed from a 2007-2008 nationwide survey of adults who self-reported a diagnosis of schizophrenia and were currently using an antipsychotic medication (N = 876). The presence of side effects was defined as those in which the patient reported they were at least "somewhat bothered"… Among patients with schizophrenia, medication side effects are highly prevalent and significantly associated with medication nonadherence… A majority of patients reported experiencing at least one side effect due to their medication* ***(86.19%)****. Only 42.5% reported complete adherence. Most side effects were associated with a significantly reduced likelihood of adherence. Those who reported complete adherence to their medication were significantly less likely to report a hospitalization for a mental health reason (OR = 0.51, p = 0.0006), a hospitalization for a non-mental health reason (OR = 0.43, p = 0.0002), and an emergency room (ER) visit for a mental health reason (OR = 0.60, p = 0.008). " Note: NNT = 5 = 1/(51%-30%) for minimal response, but NNT = 11 = 1/(23%-14%) for good response.*

f) Harrow M, Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study, Psychological Medicine, 2012, PMID: 22340278, https://goo.gl/HwUOj8

g) **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. Erectile dysfunction was present in 42% of the sample population and it was the most common type of sexual dysfunction reported…patients of Bipolar I disorder experience sexual side effects of antipsychotics frequently. Erectile dysfunction is the most common sexual dysfunction among men and this is significantly higher with typical than atypical antipsychotics…In this study, 71 out of 108 patients complained of sexual dysfunction, that amounts to a frequency of 65.7%...Overall, 66% of the patient population were having at least one type of sexual dysfunction. Apart from erectile dysfunction, 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."

h) **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."*

i) Rehse M et al, Influence of Antipsychotic and Anticholinergic Loads on Cognitive Functions in Patients with Schizophrenia, Schiz Research and Treatment, 2016, https://goo.gl/MvW4of. *"…There is evidence that, beyond a certain dose of antipsychotic medication, the antipsychotic daily dose (ADD) may impair cognitive performance… we conducted a retrospective record-based analysis of a sample of in patients with a diagnosis of schizophrenia…Results showed significant negative effects of ADD on performance in tests of information processing speed and verbal memory. "*

j) **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.** *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.

k) **Vancampfort D et al, Metabolic Syndrome and Metabolic Abnormalities in Bipolar Disorder: A Meta-Analysis of Prevalence Rates and Moderators, Am J Psychiatry. 2013, PMID: 23361837, https://goo.gl/uQ3TM4.** *"… Metabolic syndrome was significantly more prevalent in patients currently treated with antipsychotics (45.3% [95% CI=39.6–50.9] than in patients who were antipsychotic free (32.4% [95% CI=27.5–37.4]; odds ratio=1.72[95% CI=1.24–2.38])." Note: absolute risk = 45.3%-32.4% = 12.9%.*

l) Wunderink et al, Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial, JAMA Psychiatry. 2013, PMID: 23824214.

[21] **Psychiatric News, FDA Extends Black-Box Warning to All Antipsychotics, 2008, https://goo.gl/7vB6tY.** *"… Three years after the Food and Drug Administration (FDA) instituted a black-box warning for all second-generation antipsychotic (SGA) medications about increased risk of death in elderly dementia patients, a similar warning is being added to the labels of first-generation antipsychotics (FGAs) such as haloperidol and perphenazine. The FDA announced its decision in mid-June after reviewing two epidemiological studies, both conducted in Canada, that were published in 2007. The two studies found mortality rates in elderly patients taking FGAs to be comparable to or higher than the rates in patients taking SGAs…"*

[22] **Benzodiazepine efficacy and prescribing.** Very short-term use, Ashton, "very short (1 to 7 days) or short (2 to 4 weeks) course".

a) **Otheman Y et al, The use of benzodiazepines in bipolar disorders, Addict Clin Res, 2018, https://goo.gl/zVXip6.** *"… Benzodiazepines (BZD) are one of the most prescribed pharmacological agents in the world despite the risks of dependence, abuse and other concerns… Benzodiazepines are frequently prescribed for patients with BD. The use of BZD as adjunctive treatment in depressive episodes is common, especially to reduce associated anxiety, insomnia, and risk of suicide during the first days of treatment. Benzodiazepines have also demonstrated efficacy for the acute management of mania as adjuncts to mood stabilizers or antipsychotic drugs, to improve sleep and control anxiety, restlessness, agitation and aggressiveness… [In a] 6-month, randomized, multi-site comparison of a sample of 482 patients with bipolar I or II disorder… researchers compared clinical measures, in BZD users and nonusers, including the Bipolar Inventory of Signs and Symptoms (BISS), Clinical Global Impressions-Bipolar scale (CGIBP) and Clinical Global Impression Efficacy Index (CGI-EI). Although both groups demonstrated improvement,* ***BZD users experienced significantly less improvement in BISS and CGI-BP scores than non-users did****… **These findings highlight the fact that Practitioners use benzodiazepines to overcome the lack of alternatives in some difficult clinical situations**."*

b) **Ashton H, Guidelines for the rational use of benzodiazepines. When and what to use, Drugs 1994, PMID: 7525193. "…** *As hypnotics, benzodiazepines are mainly indicated for transient or short term insomnia, for which prescriptions should if possible be limited to a few days, occasional or intermittent use, or courses not exceeding 2 weeks…Diazepam is usually the drug of choice, given in single doses, very short (1 to 7 days) or short (2 to 4 weeks) courses, and only rarely for longer term treatment."*

c) **Levin J et al, Psychotropic drug prescription patterns among patients with bipolar I disorder, Bipolar Disord. 2000, PMID: 11252651.** *"… Approximately 40% of subjects received benzodiazepines. Only 18% of subjects received monotherapy, and nearly 50% received three or more psychotropic agents…."*

d) **Jurdi R et al, Prescription Patterns of Psychotropic Medications in Elderly Compared to Younger Participants Who Achieved a "Recovered" Status in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Am J Geriatr Psychiatry, 2009, PMCID: PMC2630050.** *"…A "recovered" status was defined if a participant reported less than two affective symptoms with moderate or greater severity for eight weeks or more, while "recovering" if a participant reported less than two affective symptoms with moderate or greater severity for less than eight weeks…. Of the 3,615 STEP-BD participants who had a lifetime diagnosis of bipolar*

subtypes I or II, 67.6% (n=2442) achieved a recovered status during their participation. 78.5% (n=193) of older patients recovered compared to 66.8% of the younger cohort. … the psychotropic medications taken by patients who reached recovered status. In our sample, the least prescribed medication was carbamazepine with approximately 5% of prescriptions. About 20% of patients in each age group took benzodiazepines, followed by 20% – 25% taking lamotrigine. Atypical antipsychotics were used by 30–33% of participants. Valproate was prescribed to 34.0% of younger patients compared to 39.4% of older participants (Fisher's exact test, p=.1340). Of those 20–59, 37.8% took Li whereas only 29.5% of the older group were prescribed this medication… More than half of all subjects were receiving concomitant antidepressants, of whom nearly 50% received the SSRI antidepressants and nearly 25% received buproprion."

[23] **Benzodiazepine long-term use. Sexual dysfunction** (33%) from Arbanas**, fatigue** (50%) from Arbanas.

a) **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."*

b) **Bobo WV, Effect of adjunctive benzodiazepines on clinical outcomes in lithium- or quetiapine-treated outpatients with bipolar I or II disorder: results from the Bipolar CHOICE trial, J Affect Disord. 2014, PMCID: PMC4113323.** *"…The study sample consisted of 482 patients with bipolar I or II disorder enrolled in a 6-month, randomized, multi-site comparison of lithium- and quetiapine-based treatment. Changes in clinical measures (BISS total and subscales, CGI-BP, and CGI-Efficacy Index) were compared between participants who did and did not receive benzodiazepine treatment at baseline or during follow-up…* ***Benzodiazepine users (at baseline or during follow-up) experienced significantly less improvement in BISS total, BISS irritability, and CGI-BP scores than did benzodiazepine non-users…"***

c) **Wingård L et al, Initiation and long-term use of benzodiazepines and Z-drugs in bipolar disorder, Bipolar Disord. 2018, PMID: 29450954.** *"…Increasing evidence points to the* ***harmful effects of long-term benzodiazepine treatment****. Our objective was to study the incidence of, and predictors for, long-term use of benzodiazepines and Z-drugs in bipolar disorder… We conducted a population-based cohort study, using data from Swedish national registers. Swedish residents aged 18-75 years with a recorded diagnosis of bipolar disorder or mania between July 2006 and December 2012, and no history of benzodiazepine/Z-drug use in the past year, were included. Patients were followed for 1 year with regard to prescription fills of benzodiazepines/ Z-drugs… Out of the 21 883 patients included, 29% started benzodiazepine/Z-drug treatment, of whom* ***one in five became long-term users*** *[20%]…* ***The incidence of subsequent long-term use among bipolar benzodiazepine initiators is high. Patients on clonazepam, alprazolam or benzodiazepine/Z-drug polytherapy have the highest risk of becoming long-term users, suggesting that these treatments should be used restrictively."***

d) **Perlis RH et al, Benzodiazepine use and risk of recurrence in bipolar disorder: a STEP-BD report, J Clin Psychiatry. 2010, PMID: 20193647.** *"…Benzodiazepines are* ***widely prescribed*** *to patients with bipolar disorder, but their impact on relapse and recurrence has not been examined… We examined prospective data from a cohort of DSM-IV bipolar I and II patients who achieved remission during evidence-guided naturalistic treatment in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. Risk for recurrence among individuals who did or did not receive benzodiazepine treatment was examined using survival analysis… After adjusting for potential confounding variables,* ***the hazard ratio for mood episode recurrence among benzodiazepine-treated patients was 1.21 (95% CI, 1.01-1.45). The effects of benzodiazepine treatment on relapse remained significant after excluding relapses occurring within 90 days***

of recovery… Benzodiazepine use may be associated with greater risk for recurrence of a mood episode among patients with bipolar I and II disorder…"

e) **Bobo WV, Effect of adjunctive benzodiazepines on clinical outcomes in lithium- or quetiapine-treated outpatients with bipolar I or II disorder: results from the Bipolar CHOICE trial, J Affect Disord. 2014, PMCID: PMC4113323.** *"…The study sample consisted of 482 patients with bipolar I or II disorder enrolled in a 6-month, randomized, multi-site comparison of lithium- and quetiapine-based treatment. Changes in clinical measures (BISS total and subscales, CGI-BP, and CGI-Efficacy Index) were compared between participants who did and did not receive benzodiazepine treatment at baseline or during follow-up…* ***Benzodiazepine users (at baseline or during follow-up) experienced significantly less improvement in BISS total, BISS irritability, and CGI-BP scores than did benzodiazepine non-users…"***

[24] **Dodds TJ, Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature, Prim Care Companion CNS Disord. 2017, PMID: 28257172.** *"…The majority of studies found that benzodiazepines were associated with increased suicide risk. This finding was consistent across various populations and different types of research…"*

[25] *Benzodiazepines prescribing is controversial.*

(a) Dell'Osso B et al, Bridging the gap between education and appropriate use of benzodiazepines in psychiatric clinical practice, Neuropsychiatr Dis Treat. 2015, PMCID: PMC4525786. "…the treatment of bipolar disorder is complex and use of BDZs [Benzodiazepines] is controversial…"

[26] **Benzodiazepine withdrawal. Withdrawal syndrome** 30% midpoint of Higgit 15-44%.

(a) 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."*

(b) Pétursson H, The benzodiazepine withdrawal syndrome, Addiction, 1994, PMID: 7841856. *"…Physiological dependence on benzodiazepines is accompanied by a withdrawal syndrome which is typically characterized by sleep disturbance, irritability, increased tension and anxiety, panic attacks, hand tremor, sweating, difficulty in concentration, dry wretching and nausea, some weight loss, palpitations, headache, muscular pain and stiffness and a host of perceptual changes.… Physiological dependence on benzodiazepines can occur following prolonged treatment with therapeutic doses…"*

(c) American Addiction Centers, How Long Do Benzo Withdrawal Symptoms Last?, 2018, https://goo.gl/wvrWoq. *"…Benzodiazepines are Schedule IV controlled substances per the Drug Enforcement Administration (DEA)… Withdrawal side effects are not generally lethal, although they are best managed with professional medical attention and supervision… The early withdrawal phase usually starts within a few hours to a few days of stopping the medication and may last a few days. During early withdrawal, an individual may experience a return of anxiety and insomnia symptoms as the brain rebounds without the drugs… After a few days of stopping a benzodiazepine, acute withdrawal may begin. This phase constitutes the bulk of withdrawal. Symptoms may include anxiety, panic, insomnia, muscle spasms or tension, nausea and/or vomiting, diarrhea,*

blurred vision, seizures, hallucinations, short-term memory impairment, trouble concentrating, clouded thinking, mood swings, agitation, drug cravings, twitching and weight loss due to a decreased appetite… ***Some people, around 10 percent according to a study published by ABC News, may experience protracted withdrawal syndrome that can extend several months or even years after stopping use of a benzodiazepine…"***

(d) Tapiainen V et al, The risk of Alzheimer's disease associated with benzodiazepines and related drugs: a nested case-control study. Acta Psychiatrica Scandinavica, 2018; https://goo.gl/efxMpn. *"…The study was conducted in the nationwide MEDALZ cohort which included all Finnish community dwellers with newly diagnosed Alzheimer's disease in 2005-2011 (70,719 persons), and their age, sex and region of residence matched controls (282,862 persons). Medicine use since 1995 was extracted from the Finnish Prescription Register. Many chronic disorders, substance abuse, socioeconomical position and use of antidepressants and antipsychotics were taken into account. To account for reverse causality, drug use within 5 years before Alzheimer's disease diagnosis was not taken into account… The use of benzodiazepines and related drugs (Z drugs) is associated with a modestly increased risk of Alzheimer's disease…"*

[27] FDA Warnings

a) FDA, FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use, 2016, https://goo.gl/cRk3pk.

b) FDA, FDA Requiring Labeling Changes for Benzodiazepines, News Release, 2020, https://bit.ly/3hYTVzW.

[28] **Approved treatments for bipolar depression.** OFC shows benefit over olanzapine of ARR=17% (Silva). This is the attributable risk for fluoxetine, the antidepressant, over and above olanzapine, the antipsychotic. "similarly likely to yield harms" from Ketter.

(a) **McIntyre M et al, A review of FDA-approved treatment options in bipolar depression, CNS Spectr. 2013,** PMID: 24237641. *"… 3 agents are now currently approved for the acute treatment of bipolar depression… Olanzapine-fluoxetine combination (OFC) was approved for the treatment of bipolar I depression in 2003... Quetiapine was approved as monotherapy for the treatment of bipolar depressive episodes by the FDA in October 2006… Lurasidone was approved for the treatment of adults with bipolar I depression as a monotherapy or an adjunct to lithium or divalproex…"*

(b) **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). …"*

(c) **Silva MT et al, Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis, J Affect Disord. 2013, PMID: 23218251. https://goo.gl/uKo5hd.** *"…four RCTs were included (1330 patients). OFC improved the response compared to olanzapine (relative risk [RR]=1.58; 95% confidence interval [95% CI]: 1.27, 1.97) and to placebo (RR=1.99; 95% CI: 1.49, 2.65) but not to lamotrigine (low-quality evidence).* ***The results of OFC therapy compared to olanzapine mono-therapy showed a significant improvement in response rate (Fig. 2****, NNT=6 [ARR=17%]; 95% CI: 4, 13)…* ***Statistically significant results favoring OFC were also found in comparison to a placebo (NNT=4****; 95% CI:3, 7) but not in comparison to lamotrigine**." **Although underlying data is not available, since OFC beat placebo by 25% (1/4) and OFC beat Olanzapine by 16% (1/6), the ARR for Olanzapine can be calculated as 25%-16% = 9%, for below other studies on Olanzapine.**

[29] **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..

Goodwin (2016) indicates antidepressants are over-prescribed.

(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 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 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)…* ***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)."* 7 trials N=350.

(e) **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%)…"

(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) **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**. *“…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…”*

(j) 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*** *…”*

(k) **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…”.***

(l) **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…”*

(m) **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."

(n) 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]"***

(o) 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****)…."*

(p) **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)…".*

(q) 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."*

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

(s) **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.**

(t) 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.**"*

(u) 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). Moreover, adjunctive-AD treatment did not increase rehospitalization rates of manic episode. 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**."*

(v) 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…"*

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

(x) 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.

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

(z) 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… "

(aa) 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 ($\chi 2 = 17.7$, $p < 0.0001$)… 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."*

(bb) 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.");*

[30] **Antidepressant Side effects**. **Sexual dysfunction** 58% from Kelly, **fatigue** 21% from Ashton, **weight gain** 15% from midpoint of Mahalani 10-20%.

a) 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)."*

b) Ferguson J et al, SSRI Antidepressant Medications: Adverse Effects and Tolerability, Prim Care Companion J Clin Psychiatry. 2001, PMC181155. *"…Uncontrolled studies have reported mean weight gains of 15 lb (6.75 kg) for sertraline, 21 lb (9.45 kg) for fluoxetine, and 24 lb (10.80 kg) for paroxetine after 6 to 12 months of therapy. Although studies to date suggest that citalopram is less likely to cause weight gain, one clinical series of 18 patients reported 8 patients with mixed anxiety and mood disorders who had an average weight gain of 15.7 lb (7.1 kg) after receiving citalopram for 5 weeks."*

c) **Hu et al, Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate, J Clin Psychiatry. 2004, PMID: 15291685.** *"…Patients who received an SSRI for a new or recurrent case of depression… were interviewed by telephone 75 to 105 days after initiation of SSRI therapy… Of 401 patients who completed the phone interview, 344 patients (86%) reported at least 1 side effect, and 219 patients (55%) experienced 1 or more bothersome side effect(s). The most common bothersome side effects were* ***sexual dysfunction and drowsiness (17% each)****. While most side effects first occurred within the first 2 weeks of treatment, the majority of patients were still experiencing the same side effects at the time of interview, most notably blurred vision (85%) and sexual dysfunction (83%). Overall, physicians (N = 137) significantly underestimated the occurrence of the 17 side effects explored, and they tended to underrate how bothersome those side effects were to their patients."*

d) **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".*

e) **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**. "…There is a 1–3 kg average weight gain on antidepressants in 10–20% of the population treated with them."*

[31] **STEP-D Results.** Note: STEP-BD is a large $26.8M study across 22-sites with 4,360 bipolar patients. It was funded by the National Institute of Mental Health to determine effective treatments for bipolar. Here are two view of this study. **Rapid Cycling** 3.8X from Schneck.

a) **Schneck C, The Prospective Course of Rapid-Cycling Bipolar Disorder: Findings From the STEP-BD, Amer J of Psychiatry, 2008, PMID: 18198271, https://goo.gl/BIaasb.** *"… Antidepressant use during the follow-up year was consistently associated with more frequent cycling… we found that patients who received antidepressants were 3.8 times (95Vo CI=|.7-8.5, p=9.961; as likely to experience rapid cycling…"*

b) **El-Mallakh R et al, Antidepressants Worsen Rapid-Cycling Course in Bipolar Depression: A STEP-BD Randomized Clinical Trial, J Affect Disord. 2015, PMCID: PMC4519402**. *"… long-term continuation of antidepressants was associated with more mood episodes in patients with rapid-cycling bipolar disorder, particularly with three-fold increased rate of depressive episodes in the first year of follow-up… [the sample was] a selected population of patients who had responded to antidepressants for acute bipolar depression, without manic switch. Thus, this was an 'enriched' sample of antidepressant-responsive patients… Further, all patients took baseline mood stabilizers, indicating that mood stabilizers were not protective against such antidepressant-related worsening of mood episodes in rapid-cycling bipolar disorder, at least in the depressive people... This decreased efficacy of antidepressants supports previous claims of limited clinical utility and lack of safety in long term treatment of (bipolar disorder) patients with [antidepressants]…"*

[32] **Antidepressant mania**. Mania 2.6X a-Baldessarini.

a) **Baldessarini RJ et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. J Affect Disord. 2013, J Affect Disord. 2013 J Affect Disord. 2013 J Affect Disord. 2013, PMID: 23219059.** *"…In 51 reports of patients diagnosed with MDD and treated with an AD, the overall risk of mood-switching was 8.18% (7837/95,786) within 2.39 ± 2.99 years of treatment, or 3.42 (95% CI: 3.34-3.50) %/year. **Risk was 2.6 (CI: 2.5-2.8) times greater with/without AD-treatment by meta-analysis of 10 controlled trials.** Risk increased with time up to 24 months of treatment, with no secular change (1968-2012). Incidence rates were 4.5 (CI: 4.1-4.8)-times greater among juveniles than adults (5.62/1.26 %/year; p<0.0001). In 12 studies the overall rate of new BPD-diagnoses was 3.29% (1928/56,754) within 5.38 years (0.61 [0.58-0.64] %/year), or 5.6-times lower (3.42/0.61) than annualized rates of mood-switching."*

b) **Schneck C, The Prospective Course of Rapid-Cycling Bipolar Disorder: Findings From the STEP-B, Amer J of Psychiatry, 2008, PMID: 18198271, https://goo.gl/BIaasb.** *"…Antidepressant use during follow-up was associated with more frequent mood episodes."*

c) **Truman CJ et al, Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), J Clin Psychiatry. 2007, PMID: 17960960**. *"… Antidepressant safety and efficacy remain controversial for the treatment of bipolar depression…"*

d) **Martin A, Age Effects on Antidepressant-Induced Manic Conversion, Archives of Pediatric Adolescent Medicine, 2004, PMID 15289250, https://goo.gl/G8yxLl;** *"…During median follow-up of 41 weeks (range, 8-251 weeks), manic conversion occurred in 4786 patients (5.4%). Multivariate analyses using time-dependent Cox proportional hazards models indicated that an **increased risk of manic conversion was associated with antidepressant category vs no antidepressant exposure (hazard ratios: 2.1** for selective serotonin reuptake inhibitors, P<.001; 3.8 for "other" antidepressants, P<.001; and 3.9 for tricyclic antidepressants, P =.002)."*

e) **Patel R et al, Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study, BMJ Open. 2015, PMCID: PMC4679886.** *"…In people with unipolar depression, antidepressant treatment is associated with an increased risk of subsequent mania/*

bipolar disorder. These findings highlight the importance of considering risk factors for mania when treating people with depression."

f) Goldberg JF et al, Antidepressant-induced mania: an overview of current controversies, Bipolar Disord. 2003, PMID: 14636364. *"…**Antidepressant-induced manias have been reported with all major antidepressant classes in a subgroup of about 20-40% of bipolar patients**. Lithium may confer better protection against this outcome when compared with other standard mood stabilizers, although switch rates have been reported with comparable frequencies on or off mood stabilizers. Evidence across studies most consistently supports an elevated risk in patients with (i) previous antidepressant-induced manias, (ii) a bipolar family history, and (iii) exposure to multiple antidepressant trials… About one-quarter to one-third of bipolar patients may be inherently susceptible to antidepressant-induced manias. Bipolar patients with a strong genetic loading for bipolar illness whose initial illness begins in adolescence or young adulthood may be especially at risk. Further efforts are needed to better identify high-vulnerability subgroups and differentiate illness-specific from medication-specific factors in mood destabilization."*

[33] **Antidepressant diabetes risk**.

(a) **Andersohn F et al, Long-Term Use of Antidepressants for Depressive Disorders and the Risk of Diabetes Mellitus, Am J Psych, 2009, PMID: 19339356.** *"…Compared with no use of antidepressants during the past 2 years, recent long-term use (>24 months) of antidepressants in moderate to high daily doses was associated with an increased risk of diabetes (incidence rate ratio=1.84, 95% CI=1.35-2.52)."*

[34] **Antidepressants and adult suicide and violence**.

(a) 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%)**."*

[35] **Antidepressant withdrawal**. 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.

[36] **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."*

[37] National Institute of Health, Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers, https://goo.gl/oRFBZZ.

[38] **75-85% of people do not see substantial benefit due to bipolar drugs.** See definitions from Footnote #1. This statement is equivalent to saying that bipolar drugs have overall ARRs in the 15%-25% range. ARRs reflect the percent of people who respond *attributable* to treatment ("due to" treatment), so subtracting from 100% gives percentage of people who do NOT respond. Examining individual response rates for bipolar drugs, **Antipsychotic** NNTs average 5.5, ARR=18% For **Lithium** ARRs 16%-21%, A**ntidepressants** have very low ARR, best estimate is likely NNT=29, ARR=3%. **Anticonvulsants** range from 0%-<25%. Although individual studies sometimes arrive at NNTs less than 5 meta-analyses usually do not. Speaking to overall ARR values aids understanding an important point: an individual is far more likely NOT to gain substantial benefit attributable to a treatment than to gain it.

[39] **Benzodiazepines, Antidepressant, and lamotrigine prescribing is controversial.** We omit lamotrigine from our number since it is one drug in the class.

(a) Dell'Osso B et al, Bridging the gap between **education and appropriate use of benzodiazepines in psychiatric clinical practice, Neuropsychiatr Dis Treat. 2015, PMCID: PMC4525786.** "…the treatment of bipolar disorder is complex and use of BDZs [Benzodiazepines] is controversial…"

(b) Cascade EF et al, Antidepressants in Bipolar Disorder, Psychiatry (Edgmont). 2007, PMCID: PMC2922360. *"… The use of antidepressants in bipolar disorder is perhaps the most controversial topic in the treatment of bipolar…"*

(c) 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…* ***Lamotrigine has become a highly controversial option****."*

[40] **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, but are also associated with greater suicide in health adults (Bielefeldt above).

(a) ***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…"*

(b) ***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. …"*

(c) ***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.** *"…. 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%).*

(d) ***Benzodiazepines*****. Dodds TJ, Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature, Prim Care Companion CNS Disord. 2017, PMID: 28257172.** *"…Benzodiazepines appear to cause an overall increase in the risk of attempting or completing suicide…"*

[41] **5 of 5 bipolar drugs carry black box warning.** See footnotes # 14, 16, 20, 26, and 36.

[42] **Searching for and treating causative factors of mental distress.** Research shows that scores of factors are associated with and appear to influence mental health. 25% of the time mental distress is caused or influenced

by physical issues (Koranyi, Hall). One simple conceptual model that pulls these together is the web of causation which acknowledges the interaction of our body, mind, and emotions (see here). Little success has been found in treating bipolar by seeking universal solutions that apply to everyone with the symptoms of depression and mania. However, some success is being found looking deeply into the causative factors for each individual to determine potential strongly influencing issues unique to the individual. This is the basis of nutrient therapy that in open label trials has resulted in significantly improved bipolar symptoms in about 75% of cases (Walsh). Testing helps uncover nutrient imbalances, hormonal issues, amino acid irregularities, food allergies, inflammation, and other issues that are directly associated with bipolar symptoms. Likewise, the success of psychosocial therapies points to the causative influence of trauma (people with bipolar are 2.6 times as likely to have experienced childhood trauma - Read), unhelpful thinking, stress, destructive relationships, and more. It is reasonable to suspect that the success of psychosocial therapies is caused at least in part by addressing these underlying psychosocial factors.

(a) **Koranyi EK et al, Physical illnesses underlying psychiatric symptoms, Psycho Psychosom. 1992, PMID: 1488499, http://goo.gl/V9Wi23.; Koran L, MEDICAL EVALUATION FIELD MANUAL, 1991, http://goo. gl/TPNL9t, copied 10/30/2013**.

(b) **Hall RC, Physical illness manifesting as psychiatric disease. II. Analysis of a state hospital inpatient population, Arch Gen Psychiatry. 1980, PMID: 7416911.**

(c) **Read J et al, Child Maltreatment and Psychosis: A Return to a Genuinely Integrated Bio-Psycho-Social Model. Clinical, 2008, Clinical Schizophrenia, https://goo.gl/nMLrx4**.

(d) **Walsh W, Nutrient Power Heal Your Biochemistry and Heal your Brain, Skyhorse Publishing, 2014, http://goo.gl/DxoIvQ**.

[43] **Few side effects of nondrug options.** Scanning the breadth of nondrug options for mental health (Wagner), very few demonstrate meaningful side effects, and those that do, are typically mild. A review of nondrug options by practicing psychiatrists (Brown, Lake) conclude the same. “The safety of nondrug options should encourage us to prudently experiment with them under a practitioner’s care” (Brown).

(a) **Brown R et al, How to Use Herbs, Nutrients and Yoga in Mental Health Care, WW Norton & Co, 2009, http://goo.gl/cWlG0g.**

(b) **Lake J MD and Spiegel D MD, Complementary and Alternative Treatments in Mental Health Care, American Psychiatric Publishing, 2007, http://goo.gl/viTvLs.**

(c) **Wagner C, Choices in Recovery, Onward Mental Health Press, 2018, https://goo.gl/FSJm35.**

[44] **Nondrug options are crucial**. Case studies abound of people recovering from serious mental illness using nondrug options, finding approaches that may not have broad applicability, but that work extremely well for them. Dr. Kenneth Duckworth, Medical Director of the National Alliance on Mental Illness, is clear: "... psychiatric medications... are rarely enough to promote recovery alone... Use of non-medication strategies is crucial for most clinical situations."

(a) **Duckworth K, The Sensible Use of Psychiatric Medications, NAMI Advocate Magazine, Winter 2013, https://goo.gl/GMIuSU.**