BIPOLAR GUIDELINES 2018

Evidence Ratings

Level 1: Meta-analysis with narrow CI or replicated double-blind RCT
Level 2: Meta-analysis with wide CI or one double-blind RCT
Level 3: 1+ double-blind RCT or health system admin data
Level 4: Uncontrolled trial, anecdotal reports, expert opinion

Treatment Ratings

First line: Level 1 or 2 evidence for efficacy and
- Clinical support for safety/tolerability + no risk of treatment-emergent switch

Second line: Level 3+ evidence for efficacy and
- Clinical support for safety/tolerability + low risk of TES

Third line: Level 4+ evidence for efficacy and
- Clinical support for safety/tolerability

Not recommended:
- Level 1 evidence for LACK of efficacy or
- Level 2 evidence for LACK of efficacy + expert opinion

1: FOUNDATIONS OF MANAGEMENT

Epidemiology

- **Prevalence** - World MH Survey Initiative: 2.4% (total lifetime), 1.5% (12-month)
    - Canadian Community Health Survey: BDI 0.87%, BDII 0.67% (12-month)
- **Age of onset** - overall average 25 years old
    - For BDI, three age of onset sub-groups
        - 42% early (~17), 25% middle (24), 34% late (32)
    - Earlier onset → longer delay to treatment, greater depressive sx severity, higher levels of comorbid anxiety, higher levels of substance use
- **Burden of illness** - symptomatic for approximately half of life-time, decreased QoL
    - Impairment more pronounced in those with depressive sx, more previous episodes or longer duration of illness, and lower cognition

Diagnostic assessment

- **DSM-5** - Spectrum of cyclothymia (subthreshold depressive/manic sx) → BDII → BDI
- **Staging** - based on clinical progression and neuroprogression, limited by heterogeneity
    - # previous episodes associated with:
        - Increased duration and symptomatic severity of subsequent episodes
        - Decreased threshold for future episodes
        - Increased risk of dementia
    - 3 broad clinical stages:
        - 1) At increased risk for developing BD due to family history and subsyndromal sx predictive of conversion to BD
        - 2) Fewer episodes and optimal functioning in interepisodic period
        - 3) Recurrent episodes and decline in function and cognition
- **Screening and diagnosis** - often delayed due to depressive sx onset, variable help-seeking, temporal instability of sx, high rate of comorbidity; often dx 10 years after sx onset

- Delay associated with inadequate initial tx and worse prognosis
- Most frequent misdiagnosis is MDD, followed by SCZ/other psychotic disorders
- Features of depression that increase suspicion of bipolarity:
  - Earlier age of onset, recurrent depressive episodes, family hx BD, depression with psychotic features, psychomotor agitation, atypical depressive sx (hypersomnia, hyperphagia, leaden paralysis), post-partum depression/psychosis, past suicide attempts, AD-induced mania or rapid cycling

TABLE 6 Features of depression that may increase suspicion of a bipolar vs unipolar illness

Feature	Suggestive of bipolarity	Suggestive of unipolarity
Symptomatology and mental state signs	Hypersomnia and/or increased daytime napping Hyperphagia and/or increased weight Other "atypical" depressive symptoms such as leaden paralysis Psychomotor retardation Psychotic features and/or pathological guilt Lability of mood; irritability; psychomotor agitation; racing thoughts	Initial insomnia/reduced sleep Appetite and/or weight loss Normal or increased activity levels Somatic complaints
Course of illness	Early onset of first depression (<25 years) Multiple prior episodes (≥5 episodes)	Late onset of first depression (>25 years) Long duration of current episode (>6 months)
Family history	Positive family history of bipolar disorder	Negative family history of bipolar disorder

- Possible over-diagnosis in BPD, SUD, ADHD
- Mood Disorders Questionnaire (MDQ) - use as adjunct for screening, not for dx
- Complete a careful psych hx, including collateral if possible, and ongoing mood charting
  - Confirmation of dx more confident with episodes prospectively observed

- **Comorbidity and mimics** - SUDs, impulse-control disorders, anxiety disorders, cluster B
- **Suicide risk** - 6-7% of patients with BD die by suicide; 43% report SI, 16% have SA (past year)
  - Factors associated with suicide attempt:
    - Female, younger age of illness onset, first episode depressed, comorbid anxiety/SUD/cluster B, first-degree family hx of suicide, past attempts
  - Factors associated with suicide death: male, first-degree family hx of suicide
  - Highest risk during/following hospital admission
  - Risk stratification assessment tools NOT sufficiently accurate to predict risk
    - Focus on modifiable risk factors that can be targeted

TABLE 8 Summary of main factors associated with suicide attempt and suicide deaths in bipolar disorder (BD)

Variable	Increased likelihood of suicide attempts	Increased likelihood of suicide deaths
Sex	Female	Male
Age	Younger Older—higher lethality	Older—higher ratio of deaths/attempts
Race	Minorities—youth only	
Marital status	Single, divorced, single parents	
Age of onset	Younger	
First episode polarity	Depression Mixed symptoms Mania—more violent attempts	
Predominant polarity	Depressive	
Current episode polarity	Depressive Mixed	Depressive Mixed Manic with psychotic features
Other episode characteristics	Mixed features Greater number/severity of episodes Rapid cycling Anxiety Atypical features Suicidal ideation	Hopelessness Psychomotor agitation
Psychiatric comorbidity	Substance use disorder Cigarette smoking Coffee intake Anxiety disorder Eating disorder	Anxiety disorder
Personality disorders	Present—particularly borderline or cluster B	
Physical comorbidity	Obesity or high BMI	
First-degree family history	Mood disorders BD Suicide	Mood disorders BD Suicide
Prior suicide attempts	Present	Present
Early life trauma	Childhood abuse Early life stress	
Psychosocial precipitants	Interpersonal problems Occupational problems Bereavement Social isolation	Present within 1 week of death
Sexual dysfunction	Present	

con't →

- Lithium and anticonvulsants (lesser extent) may prevent suicide attempts/deaths
- Most common method of suicide = self-poisoning (this is specific to bipolar d/o)

- **Chronic disease management** - ideally connect patient with health care team
  - **TABLE 9** The chronic disease management model

Self-management support	Empower and prepare patients to manage their health and health care
	Use effective self-management support strategies that include assessment, goal setting, action planning, problem solving, and follow-up
Decision support	Promote clinical care that is consistent with scientific evidence and patient preferences
	Embed evidence-based guidelines into daily clinical practice and share this and other information with patients to encourage their participation
	Use proven provider education materials
Community	Encourage patients to participate in effective community programs
	Form partnerships with community organizations
Delivery system design	Provide clinical care and self-management support that patients understand and that fits with their cultural background
	Ensure regular follow-up by the care team, with defined tasks for different team members
	Provide clinical case management services for complex patients
Clinical information systems	Provide timely reminders for providers and patients
	Facilitate individual patient care planning
	Share information with patients and providers to coordinate care
Health system	Measure outcomes and use information to promote effective improvement strategies aimed at comprehensive system change
	Develop agreements that facilitate care coordination within and across organizations

  - Specialized team-based interventions combining pharmacotx + psychoeducation more effective than standard community care
  - Regular monitoring of mood sx and other measures (sleep, cognition, function, QoL) encouraged - i.e. NIMH Life Chart Method-Self Rating Scale

---

2: PSYCHOSOCIAL INTERVENTIONS - **adjunctive**, useful for depressive episode and maintenance

TABLE 10 Strength of evidence and recommendations for adjunctive psychological treatments for bipolar disorder[a]

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

- NO evidence for specific interventions for acute mania
    - *Note - think of psychotherapy in maintenance as "relapse prevention"*
- Positive evidence for: psycheducation, CBT, FFT, IPSRT, peer support

- **Psychoeducation -** for <u>all</u> patients and family, recommended for relapse prevention/**maintenance**
    - Includes info about nature of illness, treatment, key coping strategies
        - Skill development to detect/manage prodrome, stress management, problem-solving, decreasing stigma, enhancing med adherence, healthy lifestyle measures
    - Deliver individually or in group, with focus on therapeutic alliance, empathy, sx monitoring
    - Enhanced when features active learning, active skill development, and homework
    - **2 models of psyched** (group format, manualized, euthymic patients) with lvl 2 evidence:
        - <u>Barcelona BDs Program</u> and <u>Life Goals Program</u>
        - Individual psychoeducation of 5+ sessions = first line for relapse prevention
    - Psychoed does NOT have significant evidence of utility in acute depressive/manic eps
- **CBT** - Usually 20 sessions/6 months, however results in trials are mixed
    - Recommended as **adjunctive second-line tx** for acute bipolar **depression**
    - **Second-line for maintenance** treatment (for those with few eps and less severe illness)
    - No evidence or recommendation for acute mania
- **FFT** - outcomes enhanced with support of family, especially if high level of EE
    - Focuses on <u>communication styles</u> between patients and family; 21 sessions/9 months
    - Adjunctive second-line for acute depression and maintenance; no evidence for mania
- **IPSRT** - IPT + regulation of social/sleep rhythms; specific for BD, 24 individual session/9 months
    - Adjunctive third-line for acute depression and maintenance; no evidence for mania
- **Peer interventions** - can reduce stigma, isolation, and improve engagement in treatment
    - More online resources - dbsalliance, crest.bd, moodswings, revivre
    - Adjunctive third-line for maintenance only
- **Others** - may help decrease sx (i.e. residual mood or anxiety sx) in those with BD
    - Family/caregiver interventions - may also help the pt; bipolarcaregivers.org
    - DBT - may reduce depressive sx and SI
    - MBCT - may reduce anxiety
    - Cognitive/functional remediation - may help with cog/fn deficits
    - Online/digital strategies - for self-monitoring/management; accessible and acceptable

3: ACUTE MANAGEMENT OF BIPOLAR MANIA

Presentations of mania

- Distinct period of abnormally and persistently elevated/expansive/irritable mood AND increased activity/energy present most of the day, nearly every day, for 1+ week (or less if hospitalization needed)
    - AND 3+ (4+ if mood irritable) of GST PAID
- BDI can be dx in those with MDD if mania emerges during tx and persists at a fully syndromal level beyond the physiological effect of the treatment

Management of agitation

- Key step - rapidly treating manic episode → consider antimanic agents with rapid onset first
    - If agitation persists, additional rapid-acting pharmacotherapy may be needed
- Clinically PO is effective, however consider ODT or inhalation if at risk of cheeking
    - If PO ineffective, agitation is severe and patient refusing PO, or PO cannot be safely/reliably administered → consider IM

Level of recommendation	Agent	Formulation	Level of evidence
First-line	Aripiprazole	IM	2
	Lorazepam	IM	2
	Loxapine	Inhaled	1
	Olanzapine	IM	2
Second-line	Asenapine	Sublingual	3
	Haloperidol	IM	3
	Haloperidol + midazolam	IM	3
	Haloperidol + promethazine	IM[e]	3
	Risperidone	ODT[e]	3
	Ziprasidone	IM[e]	3
Third-line	Haloperidol	PO[d]	4
	Loxapine	IM	4
	Quetiapine	PO[d]	4
	Risperidone	PO[e]	4

Pharmacological treatment of manic episodes

- Clinician to decide between monotx and combination tx
    - Combination works faster; consider patient's previous tx history, mania severity, tolerability, and patient willingness to take combination tx
- Evaluate efficacy and tolerability at **end of week 1 and 2**, and modify PRN

First line	First line adjunct	Second line	Third line	NOT recommended
Lithium Quetiapine Divalproex Asenapine Aripiprazole Paliperidone (>6mg) Risperidone Cariprazine	Li/DVP AND Quetiapine Aripiprazole Risperidone Asenapine	Olanzapine Carbamazepine Olanzapine + Li/DVP Li + DVP Ziprasidone Haloperidol ECT	Chlorpromazine Clonazepam Clozapine rTMS Tamoxifen Carbamazepine + Li/DVP Haloperidol + Li/DVP Tamoxifen + Li/DVP	Allopurinol Es/licarbazepine Gabapentin Lamotrigine Omega 3 FA Topiramate Valnoctamide Zonisamide

- ***Step 1: review general principles and assess medication status***
    - Assess for risk of aggression, violence, suicidality, insight, comorbidity, social supports
    - R/O sx secondary to substances, medications, other tx or AMC
    - If there is a dx of BD → immediate start antimanic agent
    - If first presentation of mania, monitor patients after antidepressants d/c and get collateral
    - Antidepressants should be d/c, and support d/c of stimulants, caffeine and ETOH
- ***Step 2: initiate or optimize therapy, and check adherence***
    - First-line **mono**therapy - 50% respond, with improvements within 3-4 weeks
        - Consider Li first **unless** mixed ft, comorbid substance use, past non-response
    - First-line **combo** therapy - greater efficacy than monotx with Li or DVP
        - Generally preferred to mood stabilizer monotx - 20% more patients will respond
        - Some evidence that combo is also **>** atypical antipsychotic monotx

    - All antimanic agents separated from placebo within 1 week - response expected within 1-2 weeks; if not, then repeat step 2
- ***Step 3: add on/switch therapy (alternate first-line agents)***
    - Only paliperidone and cariprazine DON'T have combo therapy recommendation
- ***Step 4: add on/switch therapy (second-line agents)***
    - Consider after unsuccessful trials of multiple first-line strategies
    - Good evidence but safety/tolerability concerns
    - ECT - 80% show marked improvement; suggest brief-pulse, 2-3 x/week, bifrontal
- ***Step 5: add on/switch therapy (third-line agents)***
    - Only if patient has not responded to **all** first and second-line options; no hierarchy
    - Note - CLZ adjunct also third line; rTMS at 110% motor threshold to Rt PFC
- No specific recommendations for:
    - Paliperidone and ziprasidone + Li/DVP (methodological issues)
    - OLZ or risperidone + CBZ negative (enzyme-inducing effects of CBZ)
    - Some evidence for BCAA, folic acid, L-tryptophan, medroxyprogesterone, memantine, mexiletine, levetiracetam, phenytoin, glasses that block blue light, verapamil

- **Clinical features to direct treatment choice in BIPOLAR I MANIA:**
    - **Lithium:** Classic euphoric grandiose mania, few prior episodes of illness, mania-depression-euthymia course, family hx of BD, family hx Li response
    - **Divalproex:** Equally effective in classic and dysphoric mania; multiple prior episodes, predominant irritable or dysphoric mood and/or **comorbid substance use**, hx of head trauma
    - **Carbamazepine:** Hx of head trauma, comorbid **anxiety and substance use**, **SCZA presentations with mood-incongruent delusions**, negative family hx of BD (first-degree relatives)
    - **Combination with Li/DVP + AAP:** faster response needed, patients judged at risk, previous hx of partial acute or prophylactic response to monotherapy, or more severe manic episode
    - **Anxious distress:** predictor of poor outcome
        - Greater severity of mania, longer time to remission, more reported medication SE
        - Possible anxiolytic benefit for DVP, quetiapine, olanzapine and carbamazepine
    - **Mixed features:** 10-30% of cases; more severe/disabling course and higher suicide rate
        - Preferential use of AAP, DVP; combination therapy often required
        - Asenapine, aripiprazole, olanzapine, ziprasidone are equally effective in treating classical mania and mania w/ mixed features
    - **Psychotic features:** 50%+ of cases
        - Mood-incongruent features = more severe illness w/ poorer long-term prognosis
        - Evidence - no benefit of any first-line option
        - Clinical experience - Li/DVP + AAP more appropriate for mood-incongruent psychotic features, or if SCZA a diagnostic possibility
    - **Rapid cycling:** Course of illness that includes 4+ mood episodes/year; ⅓ of BDI patients
        - Associated with hypothyroidism, AD use, substance use
        - No evidence for superiority among any first-line options - choose based on effectiveness in the maintenance phase
        - More likely to need combination of mood stabilizers
    - **Seasonal pattern:** no evidence for superiority of any agent

---

4: ACUTE MANAGEMENT OF BIPOLAR DEPRESSION

Presentations of bipolar depression

- Often more pervasive and debilitating; accounts for ⅔ time spent unwell even with treatment
- Subsyndromal depressive sx may persist despite tx, are common, and should be treated aggressively

Diagnostic and treatment challenges

- Misdiagnosis common (MDD)
- *Increased likelihood of BD in depressed patients*:
    - Earlier age of onset, brief/recurrent depressive episodes, family hx of BD, depression with psychotic features, atypical features (hypersomnia, hyperphagia, leaden paralysis, psychomotor agitation), postpartum depression/psychosis, AD-induced irritability, rapid cycling
- Consider applying BD depression tx recommendations for those at high risk (rather than AD monotx)
- **Suicide risk** → 70% of attempts and deaths during the bipolar DEPRESSED phase
    - All patients at risk should be encouraged to **develop and share a written safety plan** listing coping strategies and sources of support
    - Opioids and benzos most common meds ingested at lethal levels
        - *Recall - poisoning is #1 cause of suicide in bipolar d/o*
- **Cognitive and functional impairment** - avoid tx that may further cognitive difficulties
    - Cognitive enhancement therapies = experimental

Psychological interventions

- No first-line options; **second-line adjunct CBT, FFT**; **third-line IPSRT**

Pharmacological treatment of acute bipolar I depression

First line	Second line	Third line	NOT recommended
Quetiapine Lurasidone + Li/DVP Lithium Lamotrigine Lurasidone Lamotrigine *adjunct*	Divalproex SSRI/Bupropion *adjunct* ECT Cariprazine OLZ-Fluoxetine	Carbamazepine Olanzapine Aripiprazole *adjunct* Armodafinil *adjunct* Asenapine *adjunct* EPA *adjunct* Ketamine IV *adjunct* Light therapy *adjunct* Levothyroxine *adjunct* Modafinil *adjunct* NAC *adjunct* Pramipexole *adjunct* rTMS *adjunct* SNRI/MAOi *adjunct*	AD monotherapy Aripiprazole Lamotrigine + folic acid Mifepristone *adjunct* Ziprasidone Ziprasidone *adjunct*

- ***Step 1: review general principles and assess medication status***
    - Support patient to d/c stimulant use, limit nicotine/caffeine/drug/ETOH use
    - Offer psychoed/psychosocial strategies alongside pharmacological treatment
- ***Step 2: initiate or optimize therapy, and check adherence***
    - **First-line**: QTP, Li, LTG (+adj), Lurasidone (+adj)
        - No evidence for QTP + Li, however can consider this option
        - No difference in efficacy between QTP 300 and 600mg; 300mg/day = target
        - Lithium levels 0.8 - 1.2 meq/L; LTG target 200+ mg/day

- ***Step 3: add on/switch therapy (alternate first-line agents)***
    - Lack of improvement → robust predictor of non-response (except LTG - slow titration)
    - Generally switch is preferred to limit polypharmacy, but add-on often required

- ***Step 4: add on/switch therapy (second-line agents)***
    - Consider after unsuccessful trials of all first-line strategies
    - AD generally should be avoided or used cautiously in those w/ a history of AD-induced mania or hypomania, current/predominant mixed features, or recent rapid cycling
    - ECT for tx-refractory patients when rapid treatment response needed (i.e. imminent suicide risk, catatonia, psychotic depression, need medical stabilization)
        - BP, Rt unilateral

- ***Step 5: add on/switch therapy (third-line agents)***
    - Only if patient has not responded to all first and second-line options; no hierarchy
    - rTMS adj applied to Lt or Rt DLPFC
    - If using SNRI or MAOi adj, careful because higher risk to induce manic switch
    - Possible benefit of light therapy and total sleep deprivation
    - IV ketamine only for those with severe sx, significant SI, and other tx unsuccessful

- No specific recommendations for:
    - Insufficient data - ASA (adj), celecoxib (adj), gabapentin (monotx), levetiracetam (adj), lisdexamfetamine (adj), memantine (adj), pioglitazone (adj), riluzole, risperidone (adj)

Clinical features that help direct treatment choices

- **Need for rapid response:** QTP, lurasidone
    - Can consider ECT, cariprazine, OLZ-fluoxetine
- **Previous tx response:** Consider adjunct AD if previous response and no hx of switch
- **Anxious distress:** Consider QTP, OLZ-fluoxetine
- **Mixed features**: Often need combo therapy
    - Consider AAP, OLZ-fluoxetine, asenapine, lurasidone; avoid antidepressant
- **Melancholic features:** ECT very effective
- **Atypical features:** Efficacy for MAOi tranylcypromine (anergic bipolar depression)
- **Psychotic features:** ECT and antipsychotics effective
- **Rapid cycling:** No evidence for lamotrigine; avoid antidepressants
- **Seasonal pattern:** No evidence for superiority

5: MAINTENANCE THERAPY FOR BIPOLAR DISORDER

Need for long-term strategies

- Almost all patients with BD need maintenance treatment - there is a subgroup in which BD may be a neuroprogressive disease
    - Recurrence → reduced brain volume, worsened cognitive impair, decreased recovery and fn, more severe and frequent relapse, reduced rate of tx response (meds and psychotx)
- Effective maintenance tx can reverse cognitive impair, preserve brain plasticity, and improve prognosis
- Lithium may be superior to QTP in volumetric and cognitive outcomes
- Recurrence risk factors: younger age of onset, psychotic ft, rapid cycling, more frequent episodes, comorbid anxiety, comorbid SUDs
- Psychosocial support and lower stress may protect against recurrence

Treatment adherence

- Important, up to half of patients non-adherent → hospitalization, suicide, lost productivity
- Tx withdrawal may ppt recurrence - 50-90% of patients d/c Lithium and experience recurrence in 3-5 months
- Engaging patients in tx may double adherence - i.e. brief psychoeducational interventions

Psychosocial interventions (First-line: psychoeducation only; second-line: CBT, FFT; third-line IPSRT, peer support**)**

- On average, adjunct psychosocial tx reduce recurrent rate by **15%**

Pharmacological treatments - *Prevention of any mood episode, mania, and depression:*

First line	Second line	Third line	NOT recommended
Lithium Quetiapine Divalproex Lamotrigine Asenapine Quetiapine + Li/DVP *Aripiprazole + Li/DVP, *Aripiprazole, *Aripiprazole OM	Olanzapine *Risperidone LAI Risperidone LAI *adjunct* Carbamazepine *Paliperidone (> 6mg) Lurasidone + Li/DVP *Ziprasidone + Li/DVP ** = no data to prevent depression*	Aripiprazole + LTG Clozapine adjunct Gabapentin adjunct OLZ + fluoxetine	Perphenazine TCAs

- ***Step 1: review general principles and assess medication status***
    - Generally, meds effective in acute phase should be continued
        - Careful with antidepressant - generally not recommended, unless responded to combo tx and are stable
    - Most AAP good at preventing mania, efficacy at preventing depression weaker
- ***Step 2: initiate or optimize therapy, and check adherence***
    - Risk of recurrence is reduced with antipsychotic combined with Li/DVP, especially for first 6 mo
        - Re-evaluate after **6 mo of sustained response** to determine if maintenance combo therapy justified
- ***Step 3-5: add on/switch therapy (alternate first-line, second-line, third-line)***

Clinical features that direct treatment choices

- Very few patients manage a lifetime with monotherapy
- Some reports suggest that long-term tx becomes less effective w/ longer duration of untreated illness
- Factors associated with good prognosis:
    - Good treatment adherence, lack of early adversity, intermediate age of onset, good social support, absence of rapid cycling or personality d/o
- Lithium - gold standard for maintenance tx - prevents mania and depression, anti-suicide
    - Some genetic/biological basis to lithium response
- Lamotrigine - responders predominantly depressive polarity, with comorbid anxiety
- Quetiapine - particularly valuable for mixed features
- Asenapine - effective for mania and depression (efficacy mania > depression)
- Lack of data to differential antipsychotic responders/non-responders

Treatment-refractory bipolar disorder

- Do comprehensive assessment to determine factors responsible for refractoriness
- Address comorbidities with pharmacological/psychological strategies
- Consider genotyping CYP450 enzymes to exclude possibility of ultra rapid metabolizers
- Adjunct clozapine may be effective

6: BIPOLAR II DISORDER

Presentation

- Diagnosis of BDII generally stable over time, with higher risk of conversion to BDI early in illness
- Economic burden of BDII x4 greater than BDI - mood is mainly depressed
- Similar rate of **suicide attempts (⅓) and completions (1/25)**

Pharmacological treatment

- *General considerations for interpreting recommendation* - Tx of BDII understudied

Acute management of hypomania

- D/c agents that may worsen or prolong sx (i.e. AD, stimulant)
- All antimanic agents also effective for hypomania - generally consider Lithium or divalproex, and/or AAP

Acute management of depression

First line	Second line	Third line	NOT recommended
Quetiapine	Lithium Lamotrigine Bupropion *adjunct* ECT Sertraline Venlafaxine	Agomelatine *adjunct* Bupropion *adjunct* Divalproex EPA *adjunct* Fluoxetine - For pure depression Ketamine *adjunct* NAC *adjunct* Pramipexole *adjunct* T3/T4 *adjunct* Tranylcypromine *adj* Ziprasidone - For depression/mixed hypomania	Paroxetine

- **No recommendations** - CES, DM+quinidine, light therapy, lisdexamfetamine, OLZ, pioglitazone, pregnenolone, celecoxib, levetiracetam, modafinil, rTMS, memantine

Maintenance

First line	Second line	Third line
Quetiapine Lithium Lamotrigine	Venlafaxine Fluoxetine (per text)	Carbamazepine Divalproex Escitalopram Fluoxetine Other antidepressants Risperidone

7: SPECIFIC POPULATIONS

Bipolar disorder in women at various stages of reproductive cycle

- **Preconception** - Provide counselling to all women of child-bearing age, at least 3 mo before pregnancy
  - Review med effects, illness recurrence, genetic risk, effect of BD on risk for gestational HTN, antepartum hemorrhage, induction of labour, C/S, instrumental delivery, PTD, and neonatal size
  - Pregnant BD women more likely overweight, smoke, have poor diet, and have SUDs
  - If women want off meds, can consider gradual taper prior to conception if stable x **4-6 mo+**
  - If possible, **monotherapy at minimum effective dose** recommended
- **Contraceptive counselling** - CBZ, topiramate, LTG can decrease OCP levels; OCP can decrease LTG level
  - Not enough evidence that high dose folic acid protects against anticonvulsant-spina bifida
  - Generally avoid DVP in females (children, childbearing age, and pregnant) per Health Canada, if used should be on effective contraceptive
  - Develop monitoring schedule and treatment plan if sx emerge
- **Screening for BD during pregnancy/postpartum**
  - If depressive sx - i.e. Mood Disorder Questionnaire or Edinburgh Postnatal Depression Scale
- **Pharmacological management of BD during pregnancy**
  - Psych and OB team should liaise
  - High recurrence rate - 85% (meds dc) and 37% (on meds)
    - Predominantly depressive/mixed, in the **first trimester within 2 weeks of med d/c**
  - Psychosocial strategies preferred over meds in first trimester
  - Monitor closely and screen during pregnancy
  - May need higher doses in second/early third trimester
  - Use prenatal vitamins, high doses folic acid (5mg/d)
- **Pharmacological management of BD during postpartum** - high risk period of time
  - Highest relapse risk if mood episode occurred during pregnancy and not on meds
  - Some evidence for benzo, AAP, Lithium and QTP (but basically use the general guidelines)
  - Encourage pts to initiate/optimize maintenance tx ASAP
  - Counsel patients about risks/benefits of meds while breastfeeding, early recognition of drug toxicity, monitoring in infants
  - Use antidepressants cautiously due to risk of first onset mania/hypomania in women w/ MDD
- **Impact of menstrual cycle on symptoms**
  - Women with PMS exacerbation more likely to have more sx, more relapse
  - **PMDD** associated with earlier disease onset, more comorbid axis I, more hypomanic/manic/depressive episodes, higher rate of rapid cycling
  - PMS and PMDD more common on women with BD
- **Menopause** - STEP-BD suggests more depressive sx during menopause transition

	Pregnancy risk category[b]	Lactation risk category[c]
Lithium	D	L4
Anticonvulsants		
Carbamazepine	D_m	L2
Divalproex	D_m	L4
Lamotrigine	C_m	L2
Atypical antipsychotics		
Aripiprazole	C_m	L3
Clozapine	B_m	L3
Olanzapine	C_m	L2
Quetiapine	C_m	L2
Risperidone	C_m	L2
Ziprasidone	C_m	L2
SSRI antidepressants		
Citalopram	C_m	L2
Escitalopram	C_m	L2
Fluoxetine	C_m	L2
Fluvoxamine	C_m	L2
Paroxetine	D_m	L2
Sertraline	C_m	L2
Other antidepressants		
Bupropion	B_m	L3

Management of BD in children and adolescents

TABLE 22 Differential diagnosis of manic symptoms in children and adolescents

Symptom	Bipolar mania hypomania	Attention deficit hyperactivity disorder	Oppositional defiant disorder
Elation	Episodic, prolonged, pathological (inappropriate to context or uncharacteristic), associated with change in functioning, "travels" with ≥3 other manic symptoms	If present, not clearly episodic or pathological	If present, not clearly episodic or pathological
Irritability	Episodic, prolonged, pathological, associated with change in functioning, "travels" with ≥4 other manic symptoms	Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (eg, ODD)	Diagnostic criterion, lacks distinct prolonged episodes, does not "travel" with other manic symptoms
Sleep	Reduced need for sleep (ie, significantly less sleep than usual without increased daytime fatigue or somnolence); change must be mood-related	Insomnia (ie, difficulty falling asleep); can be an associated feature or associated with stimulants, but need for sleep is unchanged	Not a symptom or common characteristic; may defy bedtime rules or routine
Grandiosity	Distinct uncharacteristic increase in confidence or self-importance; change must be mood-related	Not a symptom or common characteristic	Defiance toward authority figures is common but not necessarily mood-related
Hyperactivity and distractibility	Episodic; if comorbid ADHD is diagnosed, then distinctly "worse than usual" change must be mood-related	Diagnostic criteria, nonepisodic	Not prominent or episodic

- **Presentation and diagnosis** - ⅓ to ⅔ of BD patients have first mood episode as child/adolescent
    - Make dx on same set of criteria as adults
    - Lower rates of treatment and higher rates of SI/comorbidity
    - Overlapping sx should only count towards dx of mania/hypomania if they intensify during intervals of elation/irritability
    - DMDD has BD as an exclusion criteria
    - **28% of children/youth with MDD eventually develop BD**; risk factors:
        - Family hx mood d/o, earlier age of onset, emotional/behavioural dysregulation, subthreshold manic sx, cyclothymia, atypical depression, psychosis

- **Pharmacological treatment**
    - Same general principles as treating adults with BD
    - Consider comorbid ADHD (may need concurrent tx), CV risk factors, metabolic side effects (more susceptible than adults) and lifestyle measures
    - **Acute mania:**
        - **First line** - Lithium, risperidone, aripiprazole, asenapine, quetiapine
            - Risperidone > Lithium if non-obese with **ADHD**
        - **Second line -** Olanzapine, ziprasidone, quetiapine adjunct
        - **Third line** - Divalproex
        - **NOT recommende**d - oxcarbazepine
    - **Acute bipolar depression:**
        - **First line** - Lurasidone
        - **Second line** - Lithium, lamotrigine
        - **Third line** - OLZ-fluoxetine, quetiapine
        - **NOT recommended** - oxcarbazepine
    - **Maintenance treatment:**
        - **First line** - Aripiprazole, lithium, divalproex, lamotrigine adjunct (13+ yrs)
        - **Third line** - Asenapine, quetiapine, risperidone, ziprasidone
    - Comorbid **ADHD** - stimulants if stable/euthymic on optimal doses of antimanic meds
    - Comorbid **substance use** - tx concurrently, Lithium may reduce use, consider FFT

Management of BD in older age

- **Presentation and course**
  - Late-life BD 1-2% prevalence; related to neurological/physical comorbidity
  - Less prominent mania/hypomania - more depressive/cognitive sx
  - Lower psych comorbidity (anxiety and SUD most common)
  - Less likely to use inpt/outpt/ER, more likely to use case management/conservator service
  - Cognitive dysfunction significant - related to # mood episodes earlier in life
    - Lithium use associated with **lower** rates of cognitive disorders in BD
- **Medical comorbidity**
  - Those with BD have average 3-4 medical comorbidities - metabolic syndrome, HTN, DM, CVD, arthritis, endocrine abnormalities most common
  - Life expectancy reduced by **10-15 yrs**
- **Pharmacological treatment**
  - Generally same as recommendations for adults, but consider tolerability and changes in PK/PD
  - Lithium associated with adverse neurological effects and renal disease
    - Monitor level and renal function at least q3-6 months, and 5-7 days after change in dose of Li, NSAIDs, ARBs, ACEi, or thiazide diuretics
  - Divalproex associated with motor SE and metabolic effects
  - CBZ induces CYP450
  - Association between mortality and antipsychotics in those with dementia
  - **Acute mania:**
    - **First line** - Lithium, divalproex
    - **Second line** - Quetiapine
    - **Third line** - Asenapine, aripiprazole, risperidone, CBZ
    - **Tx-resistant** - Clozapine, ECT
  - **Bipolar depression:**
    - **First line -** Quetiapine, lurasidone (consider trying Lithium or Lamotrigine even though evidence only level 4)
    - **Second line - ?**
    - **Third line -** Divalproex, aripiprazole, CBZ
    - **Tx-resistant** - ECT
    - Can consider SSRI/bupropion + mood stabilizer
  - **Maintenance:**
    - Lithium, lamotrigine, divalproex have data (but consider con't whatever was started)

Management of comorbid condition in BD

- **Comorbid psychiatric d/o**
  - Most common = SUDs, anxiety, personality, impulse-control disorders
  - Increase tx resistance, suicide risk, and time with impairing sx
  - Implement hierarchical approach - tx disorder with greater morbidity/mortality first
  - SUDs: tx both simultaneously *(seems like Li and DVP better in general… and not QTP)*
    - AUD - **combination** of Divalproex and Lithium - careful with electrolytes and liver fn
      - Quetiapine NOT recommended - lack of efficacy
    - CUD - Lithium and/or Divalproex
      - Quetiapine failed to provide benefit
    - Stimulant UD - **Adjunct citicoline** for cocaine u/d
      - Bupropion, and lithium and/or divalproex for cocaine u/d
      - Quetiapine or risperidone for cocaine, amphetamine, meth u/d
    - OUD - Methadone
    - Others - OLZ can decrease mania and cravings; abilify can decrease ETOH cravings and cocaine use in polysubstance users
  - Anxiety disorders: affect 24-56% of patients with bipolar d/o, esp in women
    - GAD and PD → quetiapine (negative trials for risperidone and ziprasidone)
      - Consider olanzapine, gabapentin
    - OCD - high rate of co-occurrence - possible shared neurobiology
      - OCD sx may remit during effective tx of BD
      - Case reports support Li, anticonvulsants, OLZ, risperidone, QTP, aripiprazole
  - Personality disorders: affect 42% of patients with BD
    - **OCPD** > borderline > avoidant > paranoid > histrionic
    - Divalproex and LTG may help with BPD
  - ADHD: affect 10-20% of BD (and BD affects 20% of those with ADHD)
    - More tx-refractory, mood eps, fn impair and risk of suicide
    - Generally tx bipolar sx first, then ADHD sx

- **Comorbid metabolic d/o**
  - Metabolic syndrome present in 20-65% of patients with BD - also worsens BD outcomes
  - Work with multidisciplinary team
  - Consider “primary care-based medical homes”
  - Include non-pharmacological lifestyle interventions, choosing meds with more favourable profile, bariatric sx if BMI 27+
  - **Lithium** may reduce risk of stroke, cancer and dementia

---

8: SAFETY AND MONITORING

Medical evaluation and lab investigations

- Lithium - thyroid and renal fn at baseline, 6 months and at least annually
- Divalproex - menstrual sx (re: PCOS), heme profile, LFTs Q3-6 month in first year, then annually
- LTG, CBZ - educate about risk of skin rash, SJS, and TEN
    - For CBZ, Han Chinese/Asian patients should have genotyping for HLA-B*1502 (high risk SJS/TEN)
        - CBZ - also check Na+ annually (risk of hypoNa+)
- AAP - weight monthly x 3 mo, then q3mo
    - BP, fasting glc, lipid profile assessed at 3 mo, 6 mo, then annually

Medication serum levels

- For Lithium (0.8-1.2 acute, 0.6-1 mEq/L maintenance), divalproex (350-700 mM/L), and CBZ
- Check trough - 12 hrs after last dose
    - Ensure **2 consecutive serum levels are in the therapeutic range**, then repeat q3-6mo
    - However for CBZ - no clear relationship between serum level and efficacy (for toxicity)
- Patients tx with concurrent CBZ or hepatic-enzyme inducing agents should have serum levels of all psychotropics measured

Safety and tolerability

- **Weight gain** - less for CBZ, LTG, ziprasidone, lurasidone
- **GI symptoms** - common for Li/DVP
- **Renal toxicity** - Li associated with nephrogenic DI, TIN, ATN, CKD
    - Especially if higher [Li], multiple daily doses, concurrent meds, somatic illness, older age
    - No clear eGFR cutoff - **consider nephro consult if <45**
- **Hematological effects** - CBZ is a risk factor for leukopenia, BM suppression
- **CV effects** - Li increases risk of QT prolongation and T-wave abnormalities
    - Lurasidone and aripiprazole are the safest AAPs
- **Endo effects** - Li associated with hypothyroid, hyperparathyroid (high calcium)
    - DVP associated with PCOS
    - AAP associated with hyperPRL
- **Cognition** - only LTG NOT associated with cognitive impair
- **Sedation** - most common in DVP and AAP
- **Neurological/EPS** - Li and DVP can cause tremor
    - DVP can cause hyperammonemic encephalopathy (new onset neuro sx)
- **Derm -** LTG will cause non-serious rash in 10% of pts (0.3-1% develop serious rash)
    - CBZ also associated with rash and SJS
    - Li associated w/ acne, psoriasis, eczema, hair loss, hidradenitis suppurativa, nail/mucous issues
- **Metabolic** - least with aripiprazole, ziprasidone, asenapine, lurasidone
- **Fracture risk and OP** - something to screen in some pts