CANMAT Bipolar 2018

Complete Guidelines

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1 Introduction – Sections (Table 3)

1. Introduction
2. Foundations of management
3. Acute management of bipolar mania
4. Acute management of bipolar I depression
5. Maintenance therapy or bipolar I disorder
6. Bipolar II disorder
7. Specific populations
8. Safety and monitoring

1 – Introduction

1 Introduction

Table 1. Criteria for Level of Evidences and Line of Treatment	
1	• Meta-analysis with narrow confidence intervals • Replicated DB RCTs with placebo/active control (n ≥30 arms)
2	• Meta-analysis with wide confidence intervals • 1 DB RCT with placebo/active control (n ≥30 arms)
3	• 1 DB RCT with placebo/active control (n = 10-29 arms) • Health system administrative data
4	• Uncontrolled trial, anecdotal reports, expert opinion

Table 2. Criteria for Line of Treatment	
First-line	• Level 1/2 evidence, plus clinical support for safety/tolerability • No risk of treatment-emergent switch
Second-line	• Level 3+ evidence, plus clinical support for safety/tolerability • Low risk of treatment-emergency switch
Third-line	• Level 4+ evidence, plus clinical support for safety/tolerability
NOT recommended	• Level 1 evidence for LACK of efficacy • Level 2 evidence for LACK of efficacy + expert opinion

2 – Foundations of Management

2.1 Epidemiology

- 2.1.1 | Prevalence
  - Lifetime prevalence (CCHS-MH, Canada)
    - Bipolar I = **0.87%**
    - Bipolar II = **0.67%**

- 2.1.2 | Age of Onset
  - Typically **late adolescence, young adulthood**
    - Average age of onset = **age 25**
    - 3 subgroups
      - **Early age 17** (42%), **middle age 24** (25%), **late age 32** (34%)
  - Earlier onset features
    - **Longer delay to treatment**
    - **Greater depressive sx** severity
    - **Higher anxiety + substance use** comorbidity

2.1 Epidemiology

- 2.1.3 | Burden of Illness
  - **Symptomatic 50% of life** → sub/syndromal, esp depressive sx
  - **Reduced quality of life** → regardless if symptomatic
    - Physical, sleep, mood, cognition, spirituality, self-esteem
    - Independence, finances, household, education, leisure, social
    - 30% unable to maintain **proper work role function**
  - More pronounced impairment if:
    - **Previous episodes**
    - **Longer duration of illness**
    - **Depressive sx**
    - **Lower cognition**

2.1 Epidemiology

- 2.1.3 | Burden of Illness
  - Global Burden of Disease Study
    - **16th leading cause** of YLD (years lost to disability)
    - 6th leading cause of DALYs in age 10-24 **(greater impact if young)**
  - **Higher costs with:**
    - Bipolar I, delayed/misdiagnosis
    - Frequent psychiatric interventions
    - Use of AAPs, treatment non-adherence
    - Poor prognosis, relapse, comorbidity

Table 4. Clarifying overlapping terminology	
Mood stabilizer	• Inconsistent use in literature, not used in guidelines
Divalproex	• Encompasses valproate, valproic acid, valpromide, divalproex sodium
Conventional antipsychotics	• First-generation antipsychotics with high affinity for D2 receptors
Atypical antipsychotics	• Second-generation antipsychotics with affinity for D2 + 5HT2 receptors, and those with partial agonist effects at D2/D3 receptors
Recurrence	• Re-emerging episodes of mania or depression • Includes both “relapse” & “recurrence”
Maintenance	• Prophylactic therapy after stabilization of acute mood episode

2.2 Diagnostic Assessment

- 2.2.2 | DSM5 Specifiers
  - **With mixed features** → replaced mixed episodes
    - Can give rise to multiple complex presentations of mixed states

Table 5. DSM-5 specifiers for bipolar & related disorders			
Specifier	*Manic Episode*	*Depressive Episode*	*Illness Course*
Melancholic features		**X**	
Atypical features		**X**	
Anxious distress	**X**	**X**	
Mixed features	**X**	**X**	
Psychotic features	**X**	**X**	
Catatonia	**X**	**X**	
Peripartum onset	**X**	**X**	
Remission	**X**	**X**	
Episode severity	**X**	**X**	
Rapid cycling			**X**
Seasonal pattern			**X**

2.2 Diagnostic Assessment

- 2.2.3 | Staging Bipolar Disorder
  - **Number of previous episodes** → assoc with **incr recurrence risk**
    - **Duration + sx severity** of future episodes
    - **Decr threshold** for future episodes
    - Incr risk of **dementia** in long-term
  - Staging models (not used clinically)
    - 1) At risk → family hx, subsyndromal sx predictive of bipolar
    - 2) Pts with fewer episodes, optimal function between episodes
    - 3) Pts with recurrent episodes, functional + cognitive decline
  - Importance of early identification, treatment, illness trajectories

2.2 Diagnostic Assessment

- 2.2.4 | Screening + Diagnosis
  - Many not accurately dx until up to **10 years after onset of sx**
    - Frequent **depressive onset**
    - Variable help-seeking during hypomania/mania
    - Temporal instability of sx
    - High rates of comorbidity
    - Delay → inadequate initial tx, **worse prognosis**
  - **MDD is MOST frequent misdiagnosis**
    - Schizophrenia/other psychotic disorders = 2nd most (30%)
  - May be over-diagnosis too
    - **Borderline PD, SUD, ADHD** → overlapping sx, often COMORBID
  - Self-report instruments → only as screening (not for dx/tx)
    - Poor sensitivity + specificity
      - (esp in community, highly comorbid populations)

2.2 Diagnostic Assessment

Table 6. Features of depression that may increase suspicion of bipolar vs unipolar illness

Bipolarity	*Unipolarity*
• **Mood lability, irritability, racing thoughts** • **Psychomotor agitation/retardation** • **Atypical depressive sx** (hypersomnia, hyperphagia, leaden paralysis) • **Psychotic features** (or pathological guilty)	• Normal/increased activity levels • Decr appetite, weight loss • Initial insomnia, decr sleep • Somatic complaints
• **Early onset** (age <25) • **Highly recurrent** episodes (≥ 5) • **Rapid cycling** • **Post-partum depression/psychosis** • **Antidepressant-induced manic sx**	• Late onset (age >25) • Long duration of current episode (>6 mo)
• **Family hx of bipolar disorder** • **Past suicide attempt**	• No family hx of bipolar disorder

2.2 Diagnostic Assessment

- 2.2.5 | Comorbidities & Mimics
  - Comorbidity common
    - **SUDs**
    - **Impulse control**
    - **Anxiety**
    - **Personality disorders** (esp Cluster B)

2.2 Diagnostic Assessment

Table 7. Differential diagnosis of bipolar disorder	
MDD/PDD	• **NO manic or hypomanic episodes**
Bipolar due to AMC	• Consequence of medical condition, temporal relationship • E.g. TBI, frontal lobe meningiomas, MS, stroke, Cushing's, hyperthyroid
Substance/med-induced	• Consequence of substance or medication (intoxication/withdrawal) • E.g. stimulants, steroids, L-dopa, antidepressants
Cyclothymic disorder	• Hypomanic & depressive sx do NOT meet full criteria
Psychotic disorders	• Psychotic sx in ABSENCE of prominent mood sx • Consider onset, accompanying sx, previous course, family hx
Borderline PD	• Rarely true euphoria or prolonged well-functioning intervals
Narcissistic PD	• Grandiosity NOT assoc with mood changes or functional impairments
Antisocial PD	• Disregard for rights of others NOT only during manic episode

2.3 Suicide Risk

- **6 – 7% die by suicide** (10x higher than gen pop)
  - Higher **fatality** of suicide attempts
  - Higher risk in **MALES** (M 0.37 vs F 0.22 per 100 person years)
  - Higher risk **during/after hospitalization**
    - 14% of suicides during inpatient, 26% within 6 weeks of discharge

- Past year
  - **43% suicidal ideation**, 21% plan, 16% suicide attempt

- Risk factors for suicide ATTEMPT
  - **Female**, **younger age of onset**, previous suicide attempt
  - **Depressive polarity** of first episode, current/recent episode
  - Comorbid anxiety disorder, SUD, cluster B/borderline PD
  - 1º family hx of suicide

- Risk factors for suicide COMPLETION
  - **Male, 1º family hx of suicide**

2.3 Suicide Risk

- **Self-poisoning** → most common method
  - Antipsychotics (32%), opioids (29%), benzos (27%)
  - Carbamazepine (21%), diphenhydramine (15%)
  - Lithium (3%)

- Treatment & suicide risk
  - **Lithium** → **may prevent** suicide attempts + deaths
  - Lesser extent → anticonvulsants
  - (limited data for antipsychotics, antidepressants)

Factors Associated with Suicidality (1)

Table 8. Main factors associated with suicide attempt and suicide deaths in BD		
Variable	***Increased likelihood of suicide attempts***	***Increased likelihood of suicide deaths***
Sex	• Female	• Male
Age	• Younger (if older, more lethal methods)	• Older (higher ratio of deaths/attempts)
Race	• Minorities (youth only)	
Marital	• Single or divorced, single parents	
Onset	• Younger	
First episode polarity	• Depression • Mixed symptoms • Mania (more violent attempts)	
Main polarity	• Depressive	
Current episode polarity	• Depressive • Mixed	• Depressive • Mixed • Manic with psychotic features
Other episode features	• Mixed features • Greater number/severity of episodes • Rapid cycling • Anxiety • Atypical features • Suicidal ideation	• Hopelessness • Psychomotor agitation

Factors Associated with Suicidality (2)

Table 8. Main factors associated with suicide attempt and suicide deaths in BD		
Variable	***Increased likelihood of suicide attempts***	***Increased likelihood of suicide deaths***
Psychiatric comorbidity	• Anxiety disorder • Eating disorder • Personality disorder (esp BPD or cluster B) • Substance use disorder • Cigarette smoking • **Coffee intake**	• Anxiety disorder
Physical comorbidity	• **Obesity or high BMI** • Sexual dysfunction	
First-degree family history	• Mood disorders • Bipolar disorder • Suicide	• Mood disorders • Bipolar disorder • Suicide
Prior attempt	• 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

2.4 Chronic Disease Management

- Long-term multidisciplinary approach
  - Basic clinical management
    - Establish diagnosis, comorbidity, medical health
    - **Patient health education + pharmacotherapy** = initial foundational steps
  - Strong therapeutic alliance → **shared decision-making approach**
    - Include family + key friends
  - Ongoing monitoring of mood symptoms (mood diary, rating scales)
    - Sleep, cognition, functioning, quality of life
    - **Early warning signs of relapse**

2.4 Chronic Disease Management

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

2.5 Dealing With Stigma

- May impact individual + family members
  - Prevent seeking/engaging in treatment
  - Cause them conceal illness
  - Reducing social support, functioning, quality of life

- Stereotypes
  - Personal weakness
  - Violence + criminal behavior

- Strategies to reduce stigma
  - Enhancing **coping skills**
  - Improve **self-esteem, empowerment, help-seeking behavior**

2.6 Psychosocial Interventions

- Adjunctive psychosocial interventions
  - **Maintenance treatment** → positive evidence + recommended
    - **Psychoeducation, CBT, FFT** (family-focused therapy)
    - **IPSRT** (interpersonal & social rhythm therapy)
    - More studies needed for → DBT, MBCT, cognitive/functional remediation
  - **Acute depressive episodes → CBT, FFT, IPRST** may be useful
    - Prevent relapse, restore quality of life
  - Acute mania → NO evidence for specific psychosocial intervention
- Psychoeducation → recommended for all pts + family
  - **Maintenance/prevention of relapse** (esp at illness onset)
    - NOT useful in acute depressive episode of manic episodes

2.6 Psychosocial Interventions

Table 10. Recommendations for Adjunctive Psychological Treatments			
Modality	*Maintenance*	*Depression*	*Mania*
Psychoeducation (PE)	**FIRST LINE**	*Insuff evidence*	*Insuff evidence*
CBT	**SECOND LINE**	**SECOND LINE**	*Insuff evidence*
Family-focused therapy (FFT)	**SECOND LINE**	**SECOND LINE**	*Insuff evidence*
IPSRT	**THIRD LINE**	**THIRD LINE**	*Insuff evidence*
Peer support/intervention	**THIRD LINE**	*Insuff evidence*	*Insuff evidence*
Family/caregiver interventions	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
DBT	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
MBCT	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
Cognitive + functional remediation	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
Online interventions	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*

2.6 Psychosocial Interventions

- 2.6.1 | Psychoeducation
  - Teach **detecting + managing** prodromes of depression + mania
    - Stress management, **problem solving**
    - Diminish effects of **stigma + denial** of illness
    - Enhance **medication adherence**
    - Develop **healthy lifestyles** (substances, exercise, sleep)
  - May be delivery individually or in groups → **active learning**
    - Monitor development of understanding, active skills, homework
    - **Peer support + group learning** → may add efficacy
    - Maximize therapeutic alliance, convey empathy, monitor sx
  - KEY GOAL = **prevent mood relapse** (maintenance)
    - Barcelona BDs, Life Goals, individual → all first line

Maintenance	Acute Depression	Acute Mania
FIRST LINE (adj)	*Insufficient evidence*	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.2 | Cognitive Behavioral Therapy
  - Typically 20 individual sessions over 6 months, plus booster sessions
  - **MIXED results in bipolar** (unlike efficacy for MDD, psychosis)
    - Acute bipolar depression → adjunctive second-line
    - Maintenance → adjunctive second-line (for less severe illness)
    - Acute mania → NO evidence

Maintenance	Acute Depression	Acute Mania
SECOND LINE (adj)	SECOND LINE (adj)	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.3 | Family-Focused Therapy
  - Communication styles between pts + families/spouses
  - 21 sessions over 9 months → goal to **improve relationship function**

Maintenance	Acute Depression	Acute Mania
SECOND LINE (adj)	SECOND LINE (adj)	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.4 | Interpersonal & Social Rhythm Therapy
  - Expands on IPT (grief, role transition, role dispute, I/P deficits)
  - Also includes regulation of **social + sleep rhythms**

Maintenance	Acute Depression	Acute Mania
THIRD LINE (adj)	THIRD LINE (adj)	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.5 | Peer Interventions
  - Reduce **self-stigma + isolation → improve tx engagement**
  - Risks → if not properly trained, or promote inappropriate views

Maintenance	Acute Depression	Acute Mania
THIRD LINE (adj)	*Insufficient evidence*	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.6 | Other Psychosocial Interventions
  - No others specifically targeted for bipolar depression or mania
    - Some designed to **reduce episode recurrence**
  - **Family/caregiver interventions**
  - **DBT**
  - **MBCT**

Maintenance	Acute Depression	Acute Mania
Insufficient evidence	*Insufficient evidence*	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.7 | Cognitive & Functional Remediation
  - Cognitive deficits during acute episodes, between episodes
  - **Functional remediation**
  - **Cognitive remediation**

Maintenance	Acute Depression	Acute Mania
Insufficient evidence	*Insufficient evidence*	*Insufficient evidence*

2.6 Psychosocial Interventions

- 2.6.8 | Online & Digital Strategies
  - Self-monitoring, self-management → online tools, mobile apps
    - Good fidelity, good acceptability, ease of access, ease of use
  - Mainly pilot studies → no benefit in larger studies

Maintenance	Acute Depression	Acute Mania
Insufficient evidence	*Insufficient evidence*	*Insufficient evidence*

3 – Acute Management of Mania

3.1 Presentations of Mania

- Bipolar I can be dx from **tx-emergent mania in MDD**

- **"Mixed features" specifier**
  - Replaces "mixed episode"

- Other specifiers
  - Anxious distress
  - Rapid cycling
  - Psychotic features (mood-congruent or incongruent)
  - Catatonia
  - Peripartum onset
  - Seasonal pattern

3.2 Management of Agitation

- Agitation is manifestation of mania (rule out **akathisia**)
  - Common if **mixed features**
  - "Excessive motor activity, assoc with feeling of inner tension"
  - Pacing, fidgeting → uncooperative, threatening, aggressive

- Prevention + mitigation is key
  - **Antimanic agents with rapid onset** → consider first

- If agitation persists (despite antimanic agents)
  - May need additional **rapidly acting pharmacotherapy**
    - **Oral (level 3)** → also ODT, liquids, inhalation
    - If oral refuse/cannot be given → **intramuscular (level 2)**

3.2 Management of Agitation

Table 11. Recommendations for Short-Term Pharmacological Management of Agitation				
Recomm	*Agent + Single dose*	*Route*	*Evi*	*Max/24h*
FIRST LINE	**Aripiprazole** 9.75 mg	**IM**	2	*15mg*
	Lorazepam 2 mg	**IM**	2	
	Loxapine 5 mg	**INH**	1	*10 mg*
	Olanzapine 2.5 mg	**IM**	2	*10 mg*
SECOND LINE	**Asenapine** 10 mg	**SL**	3	
	Haloperidol 5 mg	**IM**	3	*15 mg*
	Haloperidol 2.5 mg **+ midazolam** 7.5 mg	**IM**	3	*5 mg/15 mg*
	Haloperidol 2.5 mg **+ promethazine** 25 mg	**IM**	3	*5 mg/50 mg*
	Risperidone 2 mg	**ODT**	3	*4 mg*
	Ziprasidone 2 mg	**IM**	3	*20 mg*
THIRD LINE	**Haloperidol** 5 mg	**PO**	4	*15 mg*
	Loxapine	**IM**	4	*N/A*
	Quetiapine	**PO**	4	*486 mg/day*
	Risperidone 2 mg	**PO**	4	

3.3 Pharmacological Treatment of Manic Episodes

- Hierarchy considers
  - Efficacy for acute mania
  - Efficacy in preventing mania/depression
  - Treating acute bipolar depression
  - Safety/tolerability
  - Risk of treatment-emergent switch

- Consider higher up first
  - Unless previous non-response, pt preferences preclude

3.3 Pharmacological Treatment of Manic Episodes

TABLE 12 Hierarchical rankings of first and second-line treatments recommended for management o acute mania

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

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.1 | Step 1: Review General Principles + Med Status
  - Immediate **risk assessment** (aggression, violence, suicide)
  - Degree of insight, ability to adhere
  - Comorbidity, social network
  - **Physical exam + labs** → rule out other causes, perpetuating factors
  - **Discontinue antidepressants, stimulants** if presenting manic

- If prev bipolar, THEN can immediately start antimanic agents
- If first episode, watch + confirm bipolar disorder

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.2 | Step 2: Initial or Optimize Therapy, Adherence
  - **First-line MONOTHERAPY**
    - **50% will respond** to monotherapy within **3-4 weeks**
      - All show **comparable efficacy**
    - ***Lithium***
    - ***Quetiapine***
    - ***Divalproex***
    - ***Asenapine***
    - ***Aripiprazole***
    - ***Paliperidone***
    - ***Risperidone***
    - ***Cariprazine***
  - ***LQDAsArPRC***

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.2 | Step 2: Initial or Optimize Therapy, Adherence
  - **First-line COMBO THERAPY**
    - **20% MORE will respond** → preferred over monotherapy
      - Greater efficacy than monotherapy with Li/DVP alone
    - ***Quetiapine + Li/DVP***
    - ***Aripiprazole + Li/DVP***
    - ***Risperidone + Li/DVP***
    - ***Asenapine + Li/DVP***

L/D + QARA

  - **If sx NOT controlled with first-line mono/combo therapy**
    - **Optimize dose, address non-adherence, consider substance use**
    - BEFORE adding/switching
    - Most antimanic agents effect within 1-2 weeks

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.3 | Step 3: Add or switching therapy (alt FIRST-line)
  - Add or switch **alternative first-line agent**
    - Exception → NOT paliperidone + ziprasidone combo
  - Only go to second or third-line agents if unsuccessful

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.4| Step 4: Add or switching therapy (SECOND-line)
  - **Second-line**
    - **Strong evidence, but safety/tolerability**
      - ***Olanzapine*** → first choice
      - ***Carbamazepine***
      - ***Ziprasidone***
      - ***Haloperidol***
      - ***Olanzapine + Li/DVP***
    - **Limited evidence for**
      - ***Lithium + divalproex***
    - **ECT** → 80% show marked clinical improvement
      - Brief pulse, bifrontal, 2-3x per week

TABLE 13 Additional agents evaluated for use in acute mania

	Agent	Level of evidence
Third-line	Carbamazepine/oxcarbazepine + Li/DVP	Level 3
	Chlorpromazine	Level 2
	Clonazepam	Level 2
	Clozapine	Level 4
	Haloperidol + Li/DVP	Level 2
	rTMS	Level 3
	Tamoxifen	Level 2
	Tamoxifen + Li/DVP	Level 2
Not recommended	Allopurinol	Level 1 negative
	Eslicarbazepine/licarbazepine	Level 2 negative
	Gabapentin	Level 2 negative
	Lamotrigine	Level 1 negative
	Omega-3 fatty acids	Level 1 negative
	Topiramate	Level 1 negative
	Valnoctamide	Level 2 negative
	Zonisamide	Level 2 negative

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.5| Step 5: Add or switching therapy (THIRD-line)
  - **Third-line** (not hierarchal)
    - ***Chlorpromazine***
    - ***Clonazepam***
    - ***Clozapine (mono or adjunct)***
    - ***Tamoxifen*** → risk of uterine cancer, lack of clinical experience
    - ***Carbamazepine + Li/DVP***
    - ***Oxcarbazepine + Li/DVP***
    - ***Haloperidol + Li/DVP***
    - ***Tamoxifen + Li/DVP***
    - ***rTMS (right PRF at 110% motor threshold)***

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.6| Agents NOT recommended for acute mania tx
  - **No demonstrated antimanic effect**
    - ***Lamotrigine***
    - ***Topiramate***
    - ***Gabapentin***

    - ***Allopurinol***
    - ***Eslicarbazepine/licarbazepine***
    - ***Valnoctamide***
    - ***Zonisamide***

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.7| Agents requiring further study, no recommendation
  - *Paliperidone + Li/DVP*
  - *Ziprasidone + Li/DVP*
  - *Olanzapine + carbamazepine*
  - *Risperidone + carbamazepine*
  - *Nutraceuticals (BCAAs, folic acid, L-tryptophan)*
  - *Medroxyprogesterone*
  - *Memantine*
  - *Mexiletine*
  - *Levetiracetam*
  - *Phenytoin*
  - *Glasses that block blue light*
  - *Verapamil*

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.8| Clinical features that help direct treatment choices

Mania features that direct treatment choice		
Lithium (> DVP)	**DVP** (> Lithium)	**Carbamazepine**
• Classical euphoric, **grandiose mania**	• Equally effective for dysphoria vs classical mania	• **Schizoaffective presentation** with mood-incongruent delusions
• **Few prior episodes** of illness	• **Multiple prior episodes**	
• **Mania-depression-euthymia** course	• Predominant **irritable or dysphoric** mood	
• **Family hx of bipolar** (esp if lithium response)	• Hx head trauma • Comorbid substance abuse • *caution in women of childbearing age	• Hx head trauma • Comorbid anxiety + substance abuse • **NO family hx** in 1° relatives

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.8| Clinical features that help direct treatment choices

  - **Combination AAP + Li/DVP if:**
    - Response needed **FASTER**
    - Patients at risk
    - Previous hx of partial response to monotherapy
    - **More severe manic episodes**

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.8| Clinical features that help direct treatment choices
  - **Anxious distress**
    - Common during manic episode → predictor of poor outcome
      - **Greater severity** of manic sx
      - **Longer time to remission**
      - More **medication SE**
    - ***DVP, quetiapine, olanzapine*** (maybe carbamazepine)
  - **Mixed features**
    - Depressive sx in **10-30% of manic episodes**
      - May indicate **more severe + disabling course**
      - **Higher suicide** rates
    - **Combination therapy** → ***AAP + DVP***
      - ***Asenapine, aripiprazole, olanzapine, ziprasidone***

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.8| Clinical features that help direct treatment choices
  - **Psychotic features**
    - Psychosis in **50% of manic episodes**
      - Mood-CONGRUENT → same prognosis as no psychotic sx
      - Mood-INCONGRUENT → **more severe illness, poorer prog**
    - **Combination therapy** → ***AAP + Li/DVP***
      - No superior combination
      - Use in mood-congruent, possible schizoaffective
  - **Rapid cycling** (4+ mood episodes per year)
    - **One-third** of bipolar I
      - Assoc with hypothyroidism, AD use, substance abuse
    - No superior first-line tx → based on **maintenance phase tx**
  - **Seasonal pattern** → NO superiority of any agents

3.3 Pharmacological Treatment of Manic Episodes

- 3.3.8| Clinical features that help direct treatment choices

Specifiers that help direct treatment choices	
Anxious distress	• ***DVP, quetiapine, olanzapine*** • (maybe carbamazepine)
Mixed features	• Combination therapy → ***AAP + DVP*** • ***Asenapine, aripiprazole, olanzapine, ziprasidone***
Psychotic features	• Combination therapy → ***AAP + Li/DVP*** • No superior combination • Use in mood-congruent, possible schizoaffective
Rapid cycling	• **No superior first-line tx** • Based on maintenance phase tx
Seasonal pattern	• **NO superiority of any agents**

4 – Acute Management of Bipolar Depression

4.1 Presentations of Bipolar Depression

- For many bipolar pts
  - Depressive polarity → **more pervasive + debilitating** (vs mania)
    - May account for **two-thirds of time** spent unwell (even with tx)
    - Subsyndromal depressive sx → major source of impairment

- Specifiers

4.2 Diagnostic + Treatment Challenges

- 4.2.1 | Misdiagnosis & Delayed Diagnosis
  - Bipolar depression frequently **misdiagnosed with MDD**
    - Esp if mania/hypomania not requiring hospitalizations
  - **Features increasing likelihood of bipolar** (table 6)
  - Monitor high risk bipolar pts carefully
    - Risk of iatrogenic effects of AD monotherapy
  - Effective psychosocial interventions

4.2 Diagnostic + Treatment Challenges

- 4.2.2 | Suicide Risk in Bipolar Depression
  - **>70% of suicide deaths/attempts** during depression (in bipolar pts)
    - **Mixed features** → esp high risk
  - **Self-poisoning** → most common method
    - Fewer deaths due to lithium
    - (vs carbamazepine, opioids, benzos) → ineffective in bipolar dep

4.2 Diagnostic + Treatment Challenges

- 4.2.3 | Cognitive & Functional Impairment
  - Avoid treatment that may exacerbate cognitive difficulties
  - Cognitive enhancement therapies → experimental

4.3 Psychological Interventions for Bipolar Depression

Table 10. Recommendations for Adjunctive Psychological Treatments			
Modality	*Maintenance*	*Depression*	*Mania*
Psychoeducation (PE)	**FIRST LINE**	*Insuff evidence*	*Insuff evidence*
CBT	**SECOND LINE**	**SECOND LINE**	*Insuff evidence*
Family-focused therapy (FFT)	**SECOND LINE**	**SECOND LINE**	*Insuff evidence*
IPSRT	**THIRD LINE**	**THIRD LINE**	*Insuff evidence*
Peer support/intervention	**THIRD LINE**	*Insuff evidence*	*Insuff evidence*
Family/caregiver interventions	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
DBT	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
MBCT	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
Cognitive + functional remediation	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
Online interventions	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.1 | Step 1: Review General Principles + Med Status
  - Severity of depression, associated sx, risk of suicide, self-harm
  - Ability to adhere to treatment, social supports, impairment
  - Treatment setting
  - **Discontinue stimulants, limit nicotine, caffeine, drug, alcohol**
  - Restart discontinued medications (if coinciding with depression)
  - Offer psychoeducation + other psychosocial strategies

3.3 Pharmacological Treatment of Manic Episodes

TABLE 14 Hierarchical rankings of first and second-line treatments recommended for management of acute bipolar I depression

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

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

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.2 | Step 2: Initiate or optimize therapy, adherence
  - **FIRST-line**
    - ***Quetiapine***
    - ***Lithium***
    - ***Lamotrigine (monotherapy, adj)***
    - ***Lurasidone (monotherapy, adj)***

  - If presenting with acute bipolar depressive episode
    - If without treatment → ***quetiapine***
    - If on lithium → **ADD *lurasidone, lamotrigine, quetiapine***
      - Or **SWITCH TO *quetiapine, lurasidone (monotherapy)***

    - Quetiapine → target dose = **300 mg/day** (no diff at 600 mg)
    - Lithium → target level **0.8 – 1.2 mEq/L**
    - Lamotrigine → minimum **200 mg/day**

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.3 | Step 3: Add on or switch therapy (alt first-line)
  - **Early improvement → predictor of overall response**
    - Except lamotrigine (necessary slow titration)
  - Medication may be selected to address several goals
    - Lithium → acute depression, anti-manic prophylaxis
  - If on antidepressant
    - Consider discontinuing or switch class of antidepressant
    - Overlap/taper manner

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.4 | Step 4: Add on or switch therapy (second-line)
  - **SECOND-line**
    - ***Divalproex (monotherapy)***
    - ***SSRI + Li/DVP/AAP***
    - ***Bupropion + Li/DVP/AAP***
    - ***ECT***
    - ***Cariprazine***
    - ***Olanzapine-fluoxetine combo***

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.4 | Step 4: Add on or switch therapy (second-line)
  - **SECOND-line**
    - Antidepressants → **no longer first-line** (ISBD: ideally avoid)
      - Risk of switch or rapid cycling → discontinue if emerging
      - **Do NOT use monotherapy**
    - ECT (brief pulse, RUL)
      - Treatment-refractory, rapid tx response needed
      - Severe depression, imminent suicidal risk
      - Catatonia, psychotic depression

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.5 | Step 5: Add on or switch therapy (third-line)
  - **THIRD-line monotherapy**
    - *Carbamazepine (monotherapy)*
    - *Olanzapine (monotherapy)*
  - **THIRD-line adjunctive**
    - *Aripiprazole +*
    - *Asenapine +*
    - *Levothyroxine +*
    - *Modafinil/armodafinil +*
    - *Pramipexole +*
    - *rTMS (L/R DLPFC) +*
    - *SNRIs +*
    - *MAOIs +*
    - *EPA +*
    - *NAC +*
    - *Light therapy ± total sleep deprivation +*
    - *Ketamine IV +* → fast acting, effective, but invasive, short duration
      - Lack of safety data, potential of abuse

4.4 Pharmacological Treatment for Bipolar Depression

- 4.4.6 | Agents NOT recommended
  - ***Antidepressant monotherapy***
  - ***Aripiprazole monotherapy***
  - ***Ziprasidone monotherapy or adjunctive***
  - ***Lamotrigine + folic aid***
  - ***Mifepristone***

- 4.4.7 | Agents requiring further study (no recommendation)
  - *Risperidone (adjunctive)*
  - *Gabapentin (monotherapy)*
  - *Levetiracetam (adj)*
  - *Lisdexamfetamine (adj)*
  - *Memantine (adjunctive)*
  - *Aspirin (adj)*
  - *Celecoxib (adj)*

4.5 Clinical Features That Help Direct Treatment

- Need for rapid response
  - Incr risk of **suicide, medical complications, dehydration**
  - First-line = ***quetiapine, lurasidone*** → effect as early as week 1
  - Second-line = ***ECT, cariprazine, olanzapine-fluoxetine***
  - **NOT lamotrigine** (slow titration)
    - May be better for depressive cognitions, psychomotor slowing

- Previous treatment response
  - **Adjunctive antidepressants** may be appropriate
    - Prior response with NO treatment-emergent switch

4.5 Clinical Features That Help Direct Treatment

- Anxious distress
  - Common during depressive episode
    - Predictive of more **persistent depressive sx + incr SI**
  - Bipolar depression + anxiety → ***quetiapine, olanzapine-fluoxetine***
  - MDD with mixed features + anxiety → ***lurasidone***
  - Limited effect → *risperidone, lamotrigine, divalproex*

- Mixed features
  - Often **subsyndromal hypomanic/manic features**
    - More severe depressive sx, substance use, cardiovascular disease
  - ***Atypical antipsychotics*** effective → many require ***combination tx***
    - ***Olanzapine-fluoxetine, asenapine, lurasidone***
  - **AVOID antidepressants**

4.5 Clinical Features That Help Direct Treatment

- Melancholic features
  - No specific studies about **predictive ability**
  - Clinical experience → ***ECT very effective***

- Atypical features
  - ***Tranylcypromine + Li/DVP/AAP (adj only)***
    - Consider interactions with food, other medications

- Psychotic features (mood congruent/incongruent)
  - Among inpatient bipolar depressive episode → **20% have psychosis**
  - No studies on relative efficacy
  - Clinical experience → ***ECT, antipsychotics***

4.5 Clinical Features That Help Direct Treatment

- Rapid cycling
  - May be assoc with hypothyroidism, ADs, substance abuse
  - No evidence for specific agent for depression during rapid cycling
  - Recommendation based on acute + maintenance effectiveness
    - ***Lithium, divalproex, olanzapine, quetiapine***
      - All comparable maintenance efficacy
  - NOT recommended
    - **Lamotrigine NOT effective** (vs placebo)
    - **Antidepressants may destabilize pts** (even with mood stabilizer)

- Seasonal pattern
  - No evidence for specific agent
  - Mixed data whether bipolar mania/depression follows seasonal pattern

4.5 Clinical Features That Help Direct Treatment

Bipolar depression specifiers that help direct treatment	
Anxious distress	• Bipolar depression + anxiety → ***quetiapine, olanzapine-fluoxetine*** • MDD with mixed features + anxiety → ***lurasidone***
Mixed features	• ***Atypical antipsychotics*** effective → many require ***combination tx*** • ***Olanzapine-fluoxetine, asenapine, lurasidone*** • **AVOID antidepressants**
Psychotic features	• Clinical experience → ***ECT, antipsychotics***
Melancholic features	• Clinical experience → ***ECT very effective***
Atypical features	• ***Tranylcypromine + Li/DVP/AAP (adj only)***
Rapid cycling	• ***Lithium, divalproex, olanzapine, quetiapine*** • **Lamotrigine NOT effective** (vs placebo) • **Antidepressants may destabilize pts** (even with mood stabilizer)
Seasonal pattern	• No evidence for specific agent

5 – Maintenance Therapy for Bipolar Disorder

5.1 Need for long-term strategies

- Almost all with bipolar require maintenance tx
  - Prevent more episodes, reduce residual sx
  - Restore function + quality of life

- May be neuroprogressive disease
  - Reduction in brain **grey + white matter** volume
  - Worsening **cognitive impairment**
  - Decr **inter-episodic recovery + function**
  - Higher **rate + severity of relapse**
  - Decr rate of **tx response**

- Effective maintenance tx early in course
  - May reverse cognitive impairment, preserve brain plasticity
  - Esp if remains episode free
  - ** ***Lithium*** → may be superior to quetiapine for first episode

5.1 Need for long-term strategies

- Recurrence, if on treatment → **19-25% per year**

- Recurrence risk
  - **Younger** onset
  - **Psychotic** features
  - Persistent **subthreshold** sx
  - **Residual** sx
  - **Rapid cycling**
  - More **prev episodes**
  - Comorbid **anxiety**
  - Comorbid **SUDs**

- Protective factors
  - Psychosocial support
  - Lower stress levels

5.2 Treatment Adherence

- Concordance of clinical + pt views → crucial determinant
  - Risks of **unrecognized** treatment non-adherence
  - **Tx engagement interventions → can double adherence**
    - Brief psychoeducational interventions
    - Flexible + collaborative engagement

- Non-adherence or discontinuation
  - **Predicts recurrence** (lithium, other mood stabilizers)
    - Lithium d/c → **50-90% recurrence within 3-5 months**
    - Greater risk if more rapid discontinuation
  - **Hospitalization, suicide, lost productivity**

5.3 Psychosocial Intervention for Maintenance Tx

- Adjunctive psychosocial tx
  - May **decr recurrence rates by 15%**

Table 10. Recommendations for Adjunctive Psychological Treatments

Modality	*Maintenance*	*Depression*	*Mania*
Psychoeducation (PE)	**FIRST LINE**	*Insuff evidence*	*Insuff evidence*
CBT	**SECOND LINE**	**SECOND LINE**	*Insuff evidence*
Family-focused therapy (FFT)	**SECOND LINE**	**SECOND LINE**	*Insuff evidence*
IPSRT	**THIRD LINE**	**THIRD LINE**	*Insuff evidence*
Peer support/intervention	**THIRD LINE**	*Insuff evidence*	*Insuff evidence*
Family/caregiver interventions	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
DBT	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
MBCT	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
Cognitive + functional remediation	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*
Online interventions	*Insuff evidence*	*Insuff evidence*	*Insuff evidence*

5.4 Efficacy of maintenance pharmacological tx

- Limitations of RCTs
  - **Limited follow-up time frames**
    - Maintenance therapy may extend across decades
  - New medication with **enriched design studies**
    - Limits generalizability

5.5 Pharmacological tx for maintenance therapy

- 5.5.1 | Step 1: Review General Principles + Med Status
  - Many agents have **prophylactic efficacy**
  - Most meds effective in acute → should **continue into maintenance**
    - Exception → **do NOT continue adjunctive ADs** (switch risk)
      - (but may be destabilizing in some)

  - **Many AAPs effective** in maintenance
    - Mainly **prevention of manic episodes** (most studies index mania)
    - Efficacy of preventing depressive relapse UNKNOWN

  - If not receiving/responding to pharmacological tx
    - Review clinical course, response to previous tx
    - Family hx, psychiatric comorbidity, polarity of episodes
    - **Medication blood levels**

5.5 Pharmacological tx for maintenance therapy

- 5.5.2 | Step 2: Initiate or Optimize Therapy, Adherence
  - Follow **recommendation hierarchy**
    - **But should continue treatment** for acute mood episode
    - If first-line maintenance, but lower down (may need decr dose)

  - **AAP + Li/DVP** → reduces recurrence risk
    - Clear benefit in **first 6 months after response** (then r/a)

5.5 Pharmacological tx for maintenance therapy

TABLE 17 Hierarchical rankings of first- and second-line treatments recommended for maintenance treatment in bipolar disorder

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

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5.5 Pharmacological tx for maintenance therapy

- 5.5.2 | Step 2: Initiate or Optimize Therapy, Adherence
  - **FIRST-line monotherapy**
    - ***Lithium***
    - ***Quetiapine***
    - ***Divalproex***
    - ***Lamotrigine***
    - ***Asenapine***
    - ***Aripiprazole PO/depot***
  - **FIRST-line combination**
    - ***Quetiapine + Li/DVP***
    - ***Aripiprazole + Li/DVP***

5.5 Pharmacological tx for maintenance therapy

- 5.5.3 | Step 3: Add on or switch therapy (alt first-line)
  - Before adding/switching
    - Optimize dose
    - Address non-adhere
  - Try alternate first-line before second-line

5.5 Pharmacological tx for maintenance therapy

- 5.5.4 | Step 4: Add on or switch therapy (second-line)
  - **SECOND-line**
    - ***Olanzapine***
    - ***Risperidone depot (monotherapy, adjunctive)***
      - Not for preventing depressive episodes
    - ***Carbamazepine***
    - ***Paliperidone***
    - ***Ziprasidone oral (adjunctive)***
    - ***Lurasidone (adjunctive)***
      - For any mood episode (not manic or depressive individually)

5.5 Pharmacological tx for maintenance therapy

- 5.5.5 | Step 5: Add on or switch therapy (third-line)
  - **THIRD-line**
    - ***Aripiprazole + lamotrigine***
    - ***Clozapine***
    - ***Gabapentin***
    - ***Olanzapine-fluoxetine***

5.5 Pharmacological tx for maintenance therapy

- 5.5.6 | Agents requiring further study, no recommendation
  - *Cariprazine*
  - *Flupenthixol*
  - *Oxcarbazepine (adj)*
  - *Topiramate*

- 5.5.7 | NOT recommended
  - ***Perphenazine***
  - ***TCA (monotherapy, adjunctive)***

5.5 Pharmacological tx for maintenance therapy

- 5.5.8 | Clinical features that help direct treatment
  - Most will require combination therapy at some point

  - **Good prognostic factors**
    - Good adherence
    - No early adversity
    - Intermediate age at onset
    - Social support
    - NO spontaneous rapid cycling
    - NO personality disorder features

5.5 Pharmacological tx for maintenance therapy

- 5.5.8 | Clinical features that help direct treatment
  - **Predictors of lithium response**
    - Episode, remitting pre-treatment clinical course
    - **Family hx of bipolar** (67% if lithium responsive family)
    - Low rates of comorbidity
    - Mania-depression-euthymic pattern in biphasic episodes or typical clinical presentation

    - ***Biological factors***
      - **No EEG abnormalities**
      - Higher brain lithium concentrations
      - Increased *N*-acetyl aspartate
      - Lower myo-inositol peaks (magnetic resonance spectroscopy)

5.5 Pharmacological tx for maintenance therapy

- 5.5.8 | Clinical features that help direct treatment
  - **Lamotrigine responders**
    - Predominantly **depressive polarity, comorbidity anxiety**
    - NOT appropriate for frequent manic episodes
  - **Quetiapine**
    - May particular useful for **mixed features**
  - **Asenapine**
    - Effective for both **mania + depression** (more in mania)
  - **Carbamazepine** (vs lithium)
    - **Atypical illness, bipolar II, schizoaffective disorder**
  - **Rapid cycling**
    - Address stimulants, ADs, hypothyroidism
    - May require **combination of mood stabilizers**
      - Monotherapy often ineffective

5.5 Pharmacological tx for maintenance therapy

- 5.5.8 | Clinical features that help direct treatment
  - **Treatment-refractory bipolar disorder**
    - Consider non-adherence, failure to optimize, comorbidities, true resistance to pharmacotherapy
    - **CYP450 genotyping NOT routinely recommended**
      - Consider if not responding to 1st/2nd/3rd-line treatments
      - Exclude **ultra rapid metabolic status**
    - **Non-adherence** → psychosocial strategies (psychoeducation)
      - **Long-acting injectable AAPs** → effective in preventing relapse
    - Limited data for refractory bipolar treatments
      - **Clozapine** → may be effective in treatment-resistant pts

6 – Bipolar II Disorder

6.1 Presentation of Bipolar II Disorder

- Canadian prevalence = **0.67%** (vs BDI 0.87%)
  - BDII diagnosis stable over time
  - Risk of conversion to BDI **higher early in illness** (factor/prodrome)

- BDII disability comparable to BDI
  - **4x economic burden** → similar time symptomatic, more depressive
  - **Similar suicide rates** (attempt + completed)
    - Lifetime SA → 1/3
    - Complete → 1/25

- 6.2.1 | General Considerations for Recommendations
  - Common for trials to enroll BDI + BDII, not separate results
  - Fewer tx with high-quality evidences, fewer first-line tx

6.2 Pharmacological tx for Bipolar II

- 6.2.2 | Acute Management for Hypomania
  - For some, causes minimal functional impairment
    - May even have above-normal functioning
    - If prolonged, severe, mixed or irritable → may be impairing
  - Many medications for mania → LIMITED studies in hypomania
    - Incl **lithium, most AAPs**
    - Trials with DVP, NAC, quetiapine, risperidone (acute hypomania)
      - Only level 4 evidence
    - Clinical experience → **anti-manic agents effective** for hypomania

6.2 Pharmacological tx for Bipolar II

- 6.2.3 | Acute Management for Bipolar II Depression

TABLE 19 Strength of evidence and treatment recommendations for acute management of bipolar II depression

Recommendation	Agent	Level of evidence
First-line	Quetiapine	Level 1
Second-line	Lithium	Level 2
	Lamotrigine	Level 2
	Bupropion (adj)	Level 2
	ECT	(Level 3)
	Sertraline[a]	Level 2
	Venlafaxine[a]	Level 2
Third-line	Agomelatine (adj)	Level 4
	Bupropion (adj)	Level 4
	Divalproex	Level 4
	EPA (adj)	Level 4
	Fluoxetine[a]	Level 3
	Ketamine (IV or sublingual) (adj)[c]	Level 3
	N-acetylcysteine (adj)	Level 4
	Pramipexole (adj)	Level 3
	T3/T4 thyroid hormones (adj)	Level 4
	Tranylcypromine	Level 3
	Ziprasidone[b]	Level 3
Not recommended	Paroxetine	2 negative

6.2 Pharmacological tx for Bipolar II

- 6.2.3 | Acute Management for Bipolar II Depression
  - **FIRST-Line**
    - ***Quetiapine (monotherapy, adjunctive)***
  - **SECOND-Line**
    - ***Lithium 0.8-1.2***
    - ***Sertraline (pure depression)***
    - ***Venlafaxine (pure depression)***
    - ***Lamotrigine***
    - ***ECT (tx-refractory, rapid response)***

6.2 Pharmacological tx for Bipolar II

- 6.2.3 | Acute Management for Bipolar II Depression
  - **THIRD-Line monotherapy**
    - *Divalproex (monotherapy)*
    - *Fluoxetine (pure depression)*
    - *Tranylcypromine*
    - *Ziprasidone (depression, mixed hypomania)*
  - **THIRD-Line adjunctive**
    - *Agomelatine +*
    - *Bupropion +*
    - *EPA +*
    - *NAC +*
    - *Pramipexole +*
    - *Thyroid hormones +*
    - *Ketamine IV (refractory, rapid onset) +*

6.2 Pharmacological tx for Bipolar II

- 6.2.3 | Acute Management for Bipolar II Depression
  - **Require further study, no specific recommendation**
    - *Olanzapine*
    - *rTMS*
    - *Light therapy*
    - *Lisdexamfetamine (adjunctive)*
    - *Modafinil (adjunctive)*
    - *Memantine*
    - *Levetiracetam*

    - *Cranial electrotherapy stimulation (CES)*
    - *Dextromethorphan + quinidine*
    - *Pioglitazone, celecoxib*
    - *Pregnenolone (adjunctive)*
    - *S-adenosylmethionine, acetyl-L-carnitine, ALA*

6.2 Pharmacological tx for Bipolar II

- 6.2.3 | Acute Management for Bipolar II Depression
  - **NOT RECOMMENDED**
    - ***Paroxetine***

6.2 Pharmacological tx for Bipolar II

- 6.2.4 | Maintenance Treatment for Bipolar II
  - **FIRST-Line**
    - *Quetiapine*
    - *Lithium*
    - *Lamotrigine*
  - **SECOND-Line**
    - *Venlafaxine*

TABLE 20 Strength of evidence and treatment recommendations for maintenance treatment of bipolar II disorder

Recommendation	Agent	Evidence level
First-line	Quetiapine	Level 1
	Lithium	Level 2
	Lamotrigine	Level 2
Second-line	Venlafaxine	Level 2
Third-line	Carbamazepine	Level 3
	Divalproex	Level 3
	Escitalopram	Level 3
	Fluoxetine	Level 3
	Other antidepressants	Level 3
	Risperidone[a]	Level 4

[a]Primarily for prevention of hypomania.

6.2 Pharmacological tx for Bipolar II

- 6.2.4 | Maintenance Treatment for Bipolar II
  - **THIRD-Line**
    - ***Fluoxetine***
    - ***Divalproex***
    - ***Carbamazepine***
    - ***Escitalopram***
    - ***Other antidepressants***
    - ***Risperidone***
  - **Requires further study, no specific recommendation**
    - *Olanzapine*

7 – Specific Populations

7.1 Management of Women of Reproductive Age

- 7.1.1 | Pre-conception, contraceptive counselling

  - Pre-conception counselling for **ALL WOMEN of childbearing ages**
    - Provide **at least 3 months prior** to considering pregnancy
    - Or **immediately for those pregnancy**

  - For medication-free pregnancy
    - **Stable for min 4-6 months** → low risk of relapse

  - Important topics to review
    - Gestational HTN, antepartum hemorrhage
    - Induction of labor, **preterm delivery, neonatal size**
    - Caesarean sections, instrumental delivery

7.1 Management of Women of Reproductive Age

- 7.1.1 | Pre-conception, contraceptive counselling

  - Most common issues/fears
    - Effects of meds on fetus
    - Illness recurrence
    - Genetic transmission to offspring

  - Pregnant women with bipolar → more likely:
    - **Overweight , poorer diet**
    - Hx of tobacco, alcohol, drug misuse during pregnancy

7.1 Management of Women of Reproductive Age

- 7.1.1 | Pre-conception, contraceptive counselling
  - Counselling → reduces chance of **unintended pregnancies**
    - Some **anticonvulsants** may **DECREASE effectiveness of OCP**
      - **Carbamazepine, topiramate, lamotrigine**
      - OCP may decr lamotrigine levels
    - **Divalproex should NOT be used** → high teratogenic potential
      - Must use effective contraception during treatment
    - **Folic acid 5 mg** → prevents spontaneous spina bifida
      - Unclear if protects against anticonvulsant spina bifida
      - May reduce lamotrigine levels
    - May need to **stop FGA or risperidone** → incr conception chance
      - (incr serum prolactin → may interfere with ovulation, fertil

7.1 Management of Women of Reproductive Age

- 7.1.2 | Screening for bipolar disorder during peripartum
  - Screen all women with **depressive sx**
    - **Mood Disorder Questionnaire**
    - **Edinburgh Postnatal Depression Scale**
  - Follow with clinical interview to confirm
  - Also assess with common co-occurring psychiatric disorder
    - Anxiety disorders, OCD

7.1 Management of Women of Reproductive Age

- 7.1.3 | Pharmacological tx of bipolar disorder in pregnancy
  - **High risk of RECURRENCE** during pregnancy (among bipolar pts)
    - 85% of those who discontinue mood stabilizers
      - If abrupt → average 2 weeks to recurrence
      - If gradual → average 22 weeks to recurrence
    - 37% of those maintained on 1+ mood stabilizers
    - Predominantly **depressive or mixed episodes**
    - 50% recurrence in **first trimester**
  - **Follow hierarchies for general population**
    - With consideration of specific peripartum risks of each agent
      - Prefer **monotherapy, lowest effective dose**
    - If possible → **prefer psychosocial tx in first trimester**
      - Period of highest teratogenic risk

7.1 Management of Women of Reproductive Age

- 7.1.3 | Pharmacological tx of bipolar disorder in pregnancy
  - **Monitoring & Screening**
    - Lithium in 1st trimester → **fetal ultrasound**
    - Divalproex → AVOID
      - **NTD 5%**, other **congenital abnormalities**
      - **Neurodevelopmental delay** (loss of 9 IQ points, age 3)
    - Physiological changes in 2nd – early 3rd trimesters
      - Incr plasma volume, hepatic activity, renal clearance
      - May need **higher doses**

7.1 Management of Women of Reproductive Age

- 7.1.4 | Pharmacological tx of bipolar disorder postpartum
  - **Higher risk of recurrence** of mood episode AFTER delivery
    - 66% if medication free
    - 23% if on treatment
    - Highest if mood disorder during pregnancy + no prophylactic tx
  - **Postpartum mania**
    - *Benzodiazepines*
    - *Antipsychotics*
    - *Lithium*
  - **Postpartum bipolar depression**
    - *Quetiapine*
    - NO studies for psychotherapy

7.1 Management of Women of Reproductive Age

- 7.1.4 | Pharmacological tx of bipolar disorder postpartum
  - **Initiate + optimize maintenance ASAP after delivery**
    - Close monitoring near delivery → signals of mood/psychosis
    - Follow general hierarchies
      - Preference for previously effective medications
  - **Consider safety in breastfeeding** (most meds excreted in milk)
    - Schedule medication AFTER breastfeeding
    - ***Quetiapine, olanzapine*** PREFERRED (lower relative infant dose)
    - May be able if too disorganized in postpartum psychosis/mania
  - **Consider formula** (vs benefits of breastfeeding)
    - **Sleep disruption** may incr risk of mood episodes
    - Bottle feeding at night (maintain sleep schedule)

7.1 Management of Women of Reproductive Age

- 7.1.4 | Pharmacological tx of bipolar disorder postpartum
  - **Childbirth can be trigger for first onset hypomania/mania**
    - Caution with ADs → risk of switch
      - Esp if **family hx** of bipolar
      - If **first onset depression** in postpartum period
      - If **recurrence of depression** in early postpartum

7.1 Management of Women of Reproductive Age

- 7.1.5 | Impact of Menstrual Cycle on Symptoms
  - **Hormonal changes may impact illness course**
    - If **premenstrual sx exacerbation**
      - More likely highly symptomatic + relapse prone
    - If **PMDD (premenstrual dysphoric disorder)**
      - Earlier illness onset (closer to age of menarche)
      - More comorbid Axis I disorders
      - More hypomanic/manic/depressive episodes
      - More rapid cycling
    - PMS + PMDD → more frequent in women with bipolar

7.1 Management of Women of Reproductive Age

- 7.1.6 | Menopause
  - Stress + hormone changes → may incr/trigger mood sx
  - STEP-BD → incr rates of **depressive episodes** during transition
    - (no incr in manic episodes)

7.2 Management of Bipolar in Children & Adolescents

- 7.2.1 | Presentation & Diagnosis
  - 33% community, 66% clinical samples → first mood episode in C&A
    - Earlier onset → **more severe illness** (sx burden + comorbidity)
    - High rates of symptomatic recovery
      - But **high rates of recurrence**

  - **Adolescent bipolar**
    - Low rates of treatment (risk of incorrect/delayed dx)
    - High rates of suicidality + comorbidity

  - **Symptomatic overlap** (early-onset mania/hypomania vs others)
    - ADHD, ODD, DMDD, GAD, substance abuse, personality disorders
    - Episodic vs persistent sx (chronic irritability NOT exclusion)
      - DMDD phenotype in 25% of adolescents with bipolar

7.2 Management of Bipolar in Children & Adolescents

- 7.2.1 | Presentation & Diagnosis
  - Of C&A with MDD → **minority (28%)** develop bipolar

  - **Risk factors for switch to mania** (after MDE)
    - **Family hx of mood disorders** (esp if parents with bipolar)
    - **Earlier age of onset**
    - **Psychotic sx**
    - Emotional + behavioral dysregulation
    - Subthreshold manic sx, cyclothymia, atypical depression

  - If parent with bipolar → no uniform strategy
    - Caution with antidepressants, stimulants (risk of switch)
    - Self/parent-report questionnaires to screen

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

7.2 Management of Bipolar in Children & Adolescents

- 7.2.2 | Pharmacological Management
  - **General Principles**
    - **Comorbid ADHD** is common
      - ADHD sx often do NOT improve with mood stabilization
      - May require concurrent ADHD tx
    - Assess **cardiovascular risk factors** regularly
    - **Lifestyle management** (diet, exercise, substances, smoking)
    - Risk of **metabolic SE** (esp with AAPs)
    - Judicious use of **polypharmacy**

7.2 Management of Bipolar in Children & Adolescents

- 7.2.2 | Pharmacological Management in C&A

	Acute Mania	Bipolar Depression	Maintenance
First-line	• Lithium • Risperidone • Aripiprazole • Asenapine • Quetiapine	• Lurasidone	• Aripiprazole • Lithium • Divalproex • Risperidone + Li/DVP • Lithium + DVP/CBZ • Lamotrigine (adj)
Second-line	• Olanzapine • Ziprasidone • Quetiapine (adj)	• Lithium • Lamotrigine	• None
Third-line	• Divalproex	• Olanzapine-fluoxetine • Quetiapine • Antidepressants	• Asenapine • Quetiapine • Risperidone • Risperidone LAI • Ziprasidone
NOT REC	• Oxcarbazepine	• Oxcarbazepine	• None

7.2 Management of Bipolar in Children & Adolescents

- 7.2.2 | Pharmacological Management
  - **Treatment of comorbid conditions**
    - **ADHD**
      - ***Adjunctive stimulants*** *(mixed AMP, MPH)*
      - Potential benefit of *atomoxetine* (risk of switch)
    - **Substance use**
      - ***Lithium, FFT*** → may also reduce substance use
      - NAC → cannabis use disorders, smoking, bipolar depression

7.3 Management of Bipolar in Older Age

- 7.3.1 | Presentation & Course
  - **Bipolar in geriatric psychiatric patients**
    - 6% of outpatients, 10% of inpatients
      - High users of psychiatric + physical health services
    - Of all bipolar patients → **25% age >60** (>50% by 2030)
    - Of OA bipolar → **90-95% initial episode before age 50**
  - **Late-life bipolar**
    - Lifetime prevalence = **1 – 2%**
    - 12-month prevalence = **0.1 – 0.7%**
    - Often related to neurological/physical comorbidity

7.3 Management of Bipolar in Older Age

- 7.3.1 | Presentation & Course
  - **Symptomatology in older adults**
    - Mania/hypomania sx → less prominent
    - **Depressive + cognitive sx** → MORE frequent
    - Hyperactivity, aggressive, insomnia, impulsivity, self-neglect risks
    - Psychiatric comorbidity → generally lower (vs younger)
      - Less likely to utilize inpt, outpt, ER services
    - More likely to use **case-management, conservator services**

  - **Cognitive dysfunction**
    - **>30% population** → deficits across all mood states + euthymia
      - Related to number of mood episodes
      - Does NOT exceed normal aging in 2-5 year f/u
    - **Lithium** → lower rates of cognitive disorders in bipolar
      - Higher levels in drinking water → ? lower dementia risk

7.3 Management of Bipolar in Older Age

- 7.3.2 | Medical Comorbidity
  - **OA with bipolar** → average 3-4 medical comorbidities
    - Metabolic syndrome, HTN, DM2, CVD, arthritis, endocrine abn
    - Overall decr life expectancy by **10-15 years**

7.3 Management of Bipolar in Older Age

- 7.3.3 | Pharmacological Treatment
  - Limited data → only 1 RCT in geriatric patients
  - STEP-BD → similar number of meds needed, but **lower doses**
  - Clinical experience → general adult tx work

  - **Medication considerations**
    - Lithium → adverse neurological effects, renal disease
    - Lithium level + renal monitoring → **q3-6 months**
      - **5-7 days after dose Δ** (lithium, NSAIDS, ARBs, ACEs, thiazides)
    - Divalproex → motor SE, metabolic effects
    - Carbamazepine → CYP450 induction, decr DVP levels
    - Antipsychotics → side effects, assoc mortality

7.3 Management of Bipolar in Older Age

- 7.3.3 | Pharmacological Treatment in Older Age

	Acute Mania	Bipolar Depression	Maintenance
First-line	• Lithium • Divalproex	• Quetiapine • Lurasidone	• Lithium • Lamotrigine • Divalproex
Second-line	• Quetiapine	• Lithium • Lamotrigine	• None
Third-line	• Asenapine • Aripiprazole • Risperidone • Carbamazepine • Clozapine • ECT	• Divalproex • Aripiprazole • Carbamazepine • ECT • Antidepressants + mood stabilizers	• None
NOT REC	• None	• None	• None

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Epidemiology**
    - Most pts with bipolar → **at least 1 psychiatric comorbidity**
      - SUD, anxiety, personality, impulse-control (ADHD, ODD, CD)
    - Incr likelihood of **treatment resistance, suicide risk**
    - Incr time spent with **impairing sx**
    - Address disorder/sx with greatest morbidity/mortality first

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Substance use disorders**
    - Among bipolar → **33% have comorbid SUD** (45% in clinical)
    - Negative impact on course of bipolar
      - Lower remission rates
      - More hospitalizations
      - Incr risk of **suicide attempts** (maybe suicide deaths)
    - Address ASAP → likely to interfere with bipolar tx
      - Should treat **simultaneously** (low levels of evidence)

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Alcohol use disorders**
    - **Combination *lithium + divalproex*** (level 2)
      - Decr # drinks per drinking day, per heavy drinking days
    - ***Lamotrigine*** (level 3)
    - ***Divalproex*** *(monotherapy, adjunctive)* (level 3)
    - Quetiapine NOT recommended

    - AUD tx guidelines may have benefit in bipolar
      - **Naltrexone, gabapentin, disulfiram**
      - (no recommendations for acamprosate yet)

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Cannabis use disorder**
    - **20% of bipolar pts**
      - Younger age
      - Manic/mixed episode polarity
      - More time in affective episodes
      - Rapid cycling
      - Psychotic features
      - Nicotine dependence, AUD, other SUDs
    - ***Lithium and/or divalproex*** (level 3)
    - No benefit from quetiapine

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Stimulant use disorders** (cocaine, meth/amphetamines)
    - *Citicoline (adjunctive)*
    - ***Quetiapine*** *(monotherapy, adjunctive)*
    - ***Risperidone*** *(monotherapy, adjunctive)*

  - **Cocaine use disorder only**
    - ***Lithium and/or divalproex***
    - *Bupropion*
    - NOT lamotrigine

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Opioid use disorder**
    - ***Methadone***
    - National guidelines
  - **Others**
    - *Olanzapine (adjunctive)* → decr cravings + manic sx
    - *Aripiprazole* → decr alcohol cravings
      - Decr cocaine use in polysubstance users

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Anxiety disorders**
    - **24-56% of bipolar pts** → highest in WOMEN
      - More mood episodes
      - More depressive sx (incl suicidality, sleep disturbance)
      - Greater psychosocial impairment
      - Worse quality of life
      - High use of antidepressants
    - **Mood stabilization is priority** (over specific anxiety tx)
      - Caution with serotonergic agents, benzos
      - CBT still **FIRST-LINE** for anxiety

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **GAD, panic disorder**
    - ***Quetiapine monotherapy*** → superior to placebo, DVP (level 2)
    - If euthymic + on lithium → ***lamotrigine, olanzapine*** (level 3)
    - ***Olanzapine-fluoxetine*** (level 3)
    - ***Olanzapine monotherapy***
    - ***Gabapentin adjunctive*** (level 4)
    - Negative trials → risperidone, ziprasidone

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **OCD**
    - **10-20% of bipolar pts**
      - May be more common in C&A with bipolar
      - Earlier onset of bipolar
      - More previous mood episodes
      - Rapid cycling
      - Seasonality
      - Substance misuse
      - Lower overall functioning
      - Incr risk of **pharmacological switch**

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **OCD**
    - **OCD sx tend to fluctuate with mood changes**
      - OCD sx may remit during effective bipolar tx
      - **Mood stabilizers ± AAPs** (ADs may not be necessary)
      - If ADs → SSRIs preferred (+ prophylactic antimanic agents)
    - CANMAT 2012 recommendations for comorbid OCD (level 4)
      - *Lithium, anticonvulsants*
      - *Olanzapine, risperidone, quetiapine, aripiprazole*
    - More recently, some evidence for
      - *ECT*
      - *Topiramate (adjunctive)*

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **Personality disorders**
    - **42% of bipolar pts** → predicts poor tx response
      - OCPD 18%, BPD 16%, AvPD 12%, PaPD 11%, HPD 10%
    - CANMAT 2012
      - For BPD → ***divalproex*** (level 3), ***lamotrigine*** (level 4), **DBT**
      - ***Psychoeducation*** for any PD (level 3), STEPPS

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.1| Comorbid Psychiatric Disorders
  - **ADHD**
    - **10-20% of adult bipolar pts** (20% of ADHD meet bipolar criteria)
      - More treatment-refractory course
      - More mood episodes
      - More functional impairment
      - Higher risk of suicide
    - **Stabilize mood first** (mood stabilizer, AAPs), then ADHD adj tx
      - Mixed amphetamine salts (level 3)
      - Methylphenidate (level 3) → incr mania if monotherapy
      - Atomoxetine (level 4)
      - Bupropion (level 4)
      - Lisdexamfetamine (level 4)

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.2| Comorbid Metabolic Disorders
  - **Epidemiology of Metabolic Syndrome**
    - **20-65% of bipolar pts** (not always incr BMI)
      - Abdo adiposity, HTN, impaired fasting glucose, DM2, DLD
      - Incr risk of CVD, DM2, **premature mortality**
      - Worsens **bipolar clinical outcomes**
    - Contributors to metabolic syndrome
      - **AAPs,** insulin dysfunction,
      - Insufficient access to primary healthy care
      - Low SES, habitual inactivity, childhood adversity
      - Peripheral + neuroinflammation, oxidative stress
  - **Principles of management**
    - Multidisciplinary → "primary care-based medical homes"

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.2| Comorbid Metabolic Disorders
  - **Treatment recommendations**
    - Replace “high metabolic risk” medications
    - **Bariatric surgery** if unsuccessful attempts
      - BMI ≥27 with weight-related morbidity
      - BMI ≥30 without weight-related morbidity
    - No specific tx for comorbid HTN, DLD
      - Statins, aspirin, ACEi/ACRBs → may benefit mood

7.4 Management of Comorbid Conditions in Bipolar

- 7.4.3| Other Comorbid Medical Conditions
  - **Taiwan study of lithium for bipolar**
    - Decr risk for stroke, cancer
    - Even when adjusted for risk of antipsychotics
  - **Incr risk of dementia in bipolar**
    - May be decreased with lithium tx, lithium in drinking water

8 – Safety & Monitoring

8.1 Medical Evaluation + Lab Investigations

- Before starting pharmacotherapy
  - Complete medical history, BMI, baseline labs
  - Rule out pregnancy

Maintenance monitoring	
Lithium	• Thyroid, renal function, plasma Ca (at 6 mo, then yearly)
Divalproex	• Menstrual hx (PCOS), CBC, LFTS (q3-6mo 1st year, then yearly)
Lamotrigine	• SJS, TENS
Carbamazepine	• If Asian (esp Han Chinese) → HLA-B*1502 allele (SJS/TENS risk) • Serum Na yearly (risk of hyponatremia)
AAPs	• Weights (monthly x 3 mos, then q3mo) • BP, fasting glucose, lipids (at 3 mo, 6 mo, then yearly) • More freq monitoring if age <10, seniors, medically ill, combo tx

8.2 Monitoring medication serum levels

- Lithium, divalproex, carbamazepine → regular serum levels
  - Measure at **trough point → 12 hrs after last dose**
  - For **lithium/divalproex**
    - In acute phase, 2 consecutive levels in therapeutic range, then q3-6mo
  - For **carbamazepine** → ensure level not toxic → q6-12mo

- Lithium levels
  - Acute = **0.8 – 1.2 (adults)**, 0.4 – 0.8 (older adults)
  - Maintenance = **0.6 – 1.0**
  - Take **5 days after** dose change
  - Toxic levels → assoc with risk of kidney damage

- Divalproex levels
  - Acute = 350-700 mM/L (50-100 ug/mL)
    - Higher levels → greater efficacy in acute mania
  - Take **3-5 days after** dose change

TABLE 24 Safety/tolerability concerns and risks of treatment-emergent switch with pharmacological agents indicated for use in bipolar disorder

	Safety concerns		Tolerability concerns		Risk of treatment emergent switch	
	Acute	Maintenance	Acute	Maintenance	Mania/hypomania	Depression
Lithium	+	++	+	++	–	–
Anticonvulsants						
Carbamazepine	++	++[a]	+	++	–	–
Divalproex	–	++[a]	+	+	–	–
Gabapentin	–	–	+	+	–	–
Oxcarbazepine	+	+	+	+	–	–
Lamotrigine	++	–	–	–	–	–
Atypical antipsychotics						
Aripiprazole	–	–	+	+	–	–
Asenapine	–	–	+	+	–	–
Cariprazine	–	–	+	–	–	–
Clozapine	++	+++	++	+++	–	–
Lurasidone	–	–	+	+	–	–
Olanzapine	+	+++	++	++	–	–
Paliperidone	–	+	+	++	–	–
Quetiapine	+	++	++	++	–	–
Risperidone	–	+	+	++	–	–
Ziprasidone	++	++	++	+	–	–
Conventional antipsychotics						
Haloperidol	+	+++	++	++	–	++
Loxapine	+	+	+	+	–	nk

TABLE 24 Safety/tolerability concerns and risks of treatment-emergent switch with pharmacological agents indicated for use in bipolar disorder

	Safety concerns		Tolerability concerns		Risk of treatment emergent switch	
	Acute	Maintenance	Acute	Maintenance	Mania/hypomania	Depression
Antidepressants (adjunctive[b])						
Agomelatine	+	–	–	–	+	–
Bupropion	+	–	+	–	+	–
Ketamine IV	++	nk	++	nk	nk	nk
MAOIs	++	++	+	++	++	–
SNRIs	–	+	+	–	++	–
SSRIs	–	–	+	+	+	–
TCAs	++	++	++	++	+++	–
Stimulants						
Amphetamines	–	++	+	–	+++	–
Modafinil	–	–	–	–	++	nk
Dopamine agonists						
Pramipexole	–	+	–	–	++	nk

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.1 | Weight gain
  - Most commonly assoc with
    - **Olanzapine, clozapine, risperidone, quetiapine**
    - **Gabapentin, divalproex, lithium**
  - Possible weight gain (long-term use)
    - Asenapine, aripiprazole
    - Lurasidone (minimal)
  - Safer options
    - **Carbamazepine, lamotrigine, ziprasidone**

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.2 | GI symptoms
  - **35-45% of lithium/divalproex**
    - Nausea, vomiting, diarrhea
    - Esp during lithium initiation/dose increase
  - May mitigate by
    - Gradual dose titration
    - Take at bedtime
    - Take with food
    - Slow release preparations

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.3 | Renal toxicity
  - **Lithium**
    - Nephrogenic diabetes insipidus → 20-40% of pts
    - Chronic tubulointerstitial nephropathy
    - Acute tubular necrosis
    - Polyuria → 70% of chronic lithium pts
    - **Lithium toxicity** → incr risk of renal dysfunction

    - CKD (decr GFR) → long-term lithium tx (>10 years)
      - Higher lithium levels
      - Multiple daily dose (vs once daily)
      - Concurrent meds (NSAIDs, ACEIs, ARBs, diuretics)
      - Somatic illnesses (HTN, DM2, CAD)
      - Older age (2x risk of CKD with lithium)

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.3 | Renal toxicity
  - **Lithium**
    - Measure eGFR q3-6mo
    - Consult nephrology if
      - Rapidly declining eGFR (>5 per year, >10 within 5 years)
      - eGFR <45 in 2 consecutive readings
    - **Acute lithium intoxication** → can decr GFR

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.4 | Hematological effects
  - **Carbamazepine**
    - Risk of **leukopenia**
      - Generally reversible with dose reduction/discontinuation
    - Concern about **bone marrow suppression** (esp elderly)
  - **Clozapine**
    - Risk of **neutropenia/agranulocytosis**
    - Clozapine monitoring program

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.5 | Cardiovascular effects
  - **Lithium**
    - Incr risk of **QT prolongation**, **T-wave abn**
    - More pronounced with age → **60% of older pts** with ECG abn
  - **Risperidone, olanzapine, ziprasidone, Asenapine**
    - Also assoc with **QT prolongation**
  - **Clozapine**
    - **Myocarditis,** dilated cardiomyopathy, pericarditis

  - Safe AAPs from cardiac perspective
    - ***Lurasidone***
    - ***Aripiprazole*** (may incr risk of hypotension)

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.6 | Endocrine effects
  - **Lithium maintenance**
    - **Hypothyroidism** → affective episodes, rapid cycling, depression
      - NOT indication for stopping lithium → use thyroid supplement
    - **Hyperparathyroidism** → serum calcium
  - **Divalproex**
    - **Oligomenorrhea, hyperandronism**
    - May have incr PCOS (mixed studies)
  - **Hyperprolactinemia**
    - **Risperidone, paliperidone, amisulpride**
    - Short-term → **amenhorrhea, sexual dysfunction, galactorrhea**
    - Long-term → **gynecomastia, osteoporosis**

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.7 | Cognition
  - **Many pts experience cognitive impairment**
    - May be attributable to disease itself
    - More pronounce if more severe or chronic illness
  - Potential negative impact of several medications
    - Antipsychotics → MOST significant
    - Lithium → impaired **processing speed + memory**
      - (may not be as bad as quetiapine)
    - Anticonvulsants → **subjective cognitive impairment**
      - (except lamotrigine)

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.8 | Sedation
  - **>50% report as reason for tx non-adherence**

  - Most likely
    - **AAPs (30-50%)**
      - *Quetiapine, clozapine, olanzapine*
      - (more than ziprasidone, risperidone, aripiprazole)
    - **Divalproex (21-29%)**
      - (more than lamotrigine, lithium)

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.9 | Neurological effects, EPS
  - **Tremor** → 10% of lithium or divalproex
  - **Hyperammonemic encephalopathy** → potentially fatal!
    - Consider if new onset neurological sx while on ***divalproex***
    - Detect early + stop divalproex
    - Sustained release formulation, dose reductions may limit sx
  - **EPS** → parkinsonism, dystonia, tardive dyskinesia, akathisia
    - More often with **FGA** (e.g. haloperidol)
    - AAPs more likely → ***risperidone, aripiprazole, cariprazine, ziprasidone, lurasidone***
      - Linked to **impaired swallowing + dysphagia** in older pts

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.9 | Neurological effects, EPS
  - **NMS** → potentially fatal!
    - Very low risk with AAPs, but still assoc
    - Risk greatest during:
      - **Initial phase of treatment, dose changes**
      - **High doses, IV/IM administration**
      - Polypharmacy, medical/psychiatric comorbidities
      - Physically restrained, dehydrated, high ambient temp
      - Hx of NMS, personal/family hx of **catatonia**
  - **Thermoregulation** → affected by AAPs
    - Heat-related illnesses
    - Hypothermia

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.10 | Dermatological reactions
  - **Lamotrigine**
    - 10% → non-serious rash
    - 0.3-1% → serious rash (SJS, TENS)
      - If slow titration (start 25 mg, incr 25 mg biweekly) → 0.02%
  - **Carbamazepine**
    - **First 8 weeks** → incr risk of rash, SJS
    - (baseline risk extremely low)
  - **Divalproex** → extremely low risk of same rashes
  - **Lithium** → **3-45%** skin conditions (most managed without stopping)
    - Acne, psoriasis, eczema, hair loss
    - Hidradenitis suppurativa, nail dystrophy, mucosal lesions

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.11 | Metabolic syndrome, hyperglycemia, DM2, DLD
  - Bipolar pts **already at incr risk** of these illness
    - Further incr risk by AAPs + mood stabilizers
      - Lithium, divalproex → both assoc with weight gain
  - Hierarchy of risk with AAPs
    - **Clozapine, olanzapine**
    - **Quetiapine**
    - **Risperidone**
    - Minimal → **aripiprazole, ziprasidone, asenapine, lurasidone**
  - Monitor blood glucose + lipids in all pts on AAPs

8.3 Safety & Tolerability of Pharmacotherapy

- 8.3.12 | Fracture risk & osteoporosis
  - Some anticonvulsants, antidepressants, antipsychotics
    - May **decr bone mineral density**
    - May **incr fracture risk** in high-risk pts
  - Also incr risk from present of **mood disorder**
    - Also **physical inactivity, smoking, poor diet** quality