Pharmacology:

How to Start, Titrate, & Monitor Challenging Medications

TA Veeder, MD
Assistant Professor
Dept of Psychiatry, OHSU

Emotional Specifiers for MDD

1. With anxious distress (obsessional sxs, trauma-related sxs)
   - Consider SSRI use
2. With mixed features (questionable manic/hypomanic sxs or those with marked mood instability)
   - Short $t_{1/2}$ SSRI medications, avoid duloxetine (Cymbalta), consider adjunctive strategies more – use of antipsychotics, lamotrigine (Lamictal)
3. With melancholic features (unresolved grief, note if there is poor concentration/focus
   - Use Bupropion (Wellbutrin)
4. With atypical features (increased sleep, overeating, social anxiety/rejection, etc.)
   - Consider use of SSRIs, SNRIs
5. With mood-congruent or incongruent psychotic features
   - Will clearly require use of adjunctive antipsychotic use
6. With pain
   - SNRI, TCA
7. With anorexia
   - Consider mirtazapine (Remeron)

Case #1 – 28yo F

Major complaint is depression.

History of substance use, impulsivity, affective instability.

Noted social anxiety, “freezing up during school projects/social functions”

Depression sxs: poor sleep, appetite, and concentration; crying spells

Family history of schizophrenia, substance use, and Bipolar disorder; personal history of childhood sexual trauma.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Not particularly homogenous: isomers explain side effects
  - Lipophilic
  - Hepatic metabolism and clearance
- Major mechanism of action: selective reuptake inhibition of serotonin → increased 5-HT output & increased post-synaptic sensitivity
- Side effects: HA, dizziness, nausea, decreased REM, rare SIADH, tremor, sexual dysfunction, blunting of affect
- **Discontinuation syndrome**: dysphoria (crying spells, irritability), anxiety, restlessness, dizziness, N/V, GI distress, flu-like syndrome (myalgias, chills, fatigue, lethargy)
- Note: black-box warning for increased depression and suicidal ideation in children and adolescents; **consider using higher doses with obsessionality**; **no major monitoring**

Selective Serotonin Reuptake Inhibitors (SSRIs)

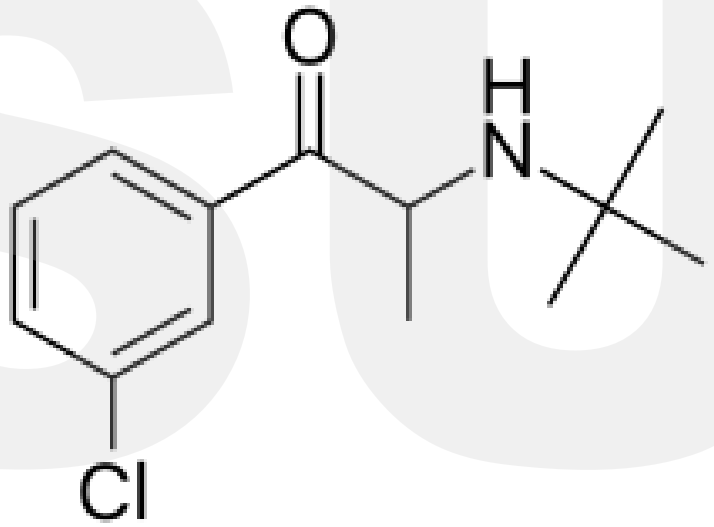
Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Citalopram (Celexa) Escitalopram (Lexapro)	36	20-40 10-30	MDD, GAD	Low GI side effects, watch for QTc prolongation (not in elderly)
Fluoxetine (Prozac)	88-384	20-80	MDD, OCD, Panic d/o, Bulimia, PMDD	Activating, 2D6 inhibition, safe in pregnancy, old and effective, very long $t_{1/2}$
Sertraline (Zoloft)	26-32	50-200	MDD, OCD, PTSD, Panic d/o	Variable side effects, GI distress, don't take w/ food, DA-I
Paroxetine (Paxil)	24	20-50	MDD, OCD, panic d/o, GAD, PTSD	Anticholinergic, NE-I, NO in pregnancy, very short $t_{1/2}$
Fluvoxamine (Luvox)	15	50-300	OCD	BID dosing, monitor Clozapine & Coumadin, QTc prolongation

Case #2 – 33yo M

- Chief complaint is depression
  - Lack of motivation
  - Low energy
  - Melancholia
  - Struggles w/ concentration
- History is complicated with multiple trials of several medications in different classes.
- Definitely important to consider his comorbid ADHD

Bupropion (Wellbutrin)

- **Dose Range: 100mg → 450mg/d**
- **Structurally similar to amphetamine**: has DA- & NE-reuptake inhibition
- Has three formulations: IR (75mg & 100mg), SR (100mg, 150mg, & 200mg), & XL (150mg & 300mg)
- Approved for MDD, SAD, and smoking cessation (SR formulation); off-label use for sexual-dysfunction with SSRI use and ADHD
- Major side effects: dry mouth, dizziness, nausea, and insomnia
- Risk for seizures – monitor when co-administered with other agents that lower the seizure threshold; **do not use in anorexia or bulimia** (electrolyte abnormalities); **no major monitoring**



Case #3 – 44yo M

- Major complaint is depression and pain
- Long history of substance use, familial trauma
- Successful at work, but struggling – need to return to work to support family
- Odd symptoms emerged - **?psychosis**
  - Visual experiences
  - Physical sensations

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Serotonin reuptake inhibition at lower doses, norepinephrine reuptake at higher doses
- Use with comorbid chronic pain
- Similar side effect burden as SSRIs, with a few notably exceptions
  - Cymbalta has higher yawning and night seats, slight weight loss vs placebo, and liver issues
  - Milnacipran has higher dysuria
  - Overall, more dry mouth, sweating
- Go slow in titration and discontinuation schedules

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine (Effexor) – 37.5mg → 225mg/d
  - Short $t_{1/2}$ = 5h
  - Can increase blood pressure, so monitor in patient's with known h/o HTN
  - Approved for MDD, GAD, panic d/o, Social anxiety d/o
- Desvenlafaxine (Pristiq) – 50mg → 100mg/d
  - Primary active metabolite O-Desmethylvenlafaxine (ODV)
  - Approved for MDD
- Duloxetine (Cymbalta) – 30mg → 120mg/d
  - Approved for use in chronic pain as well as psychiatric conditions: MDD, GAD, chronic pain, fibromyalgia, diabetic neuropathic pain
  - Can increase hepatic transaminases
- Milnacipran (Savella) – 12.5mg → 200mg
  - Strict titration schedule: 12.5 mg day 1, then 12.5 mg BID days 2 & 3, then 25 mg BID on days 4 - 7, then 50 mg BID thereafter.
  - Preferentially blocks NE-reuptake over 5-HT-reuptake; Off label for MDD

Titration Schedules

- Discontinuing antidepressant medications:
  - If <3w treatment, significant adverse reactions, or not extreme doses: can cold turkey or titrate off in 5-7d by decreasing by 50%
  - If >3w treatment, high doses: titrate off over 2-4w; note: increase titration schedule q4w if using a drug with short $t_{1/2}$ (eg, paroxetine, venlafaxine), prior history of antidepressant withdrawal symptoms, or high doses of antidepressants (APA 2010; Hirsch 2019).
- Switching antidepressant medications:
  - Cross-titration is preferred: over course of 1-4 weeks, lower original medication at 50% increments while gradually increasing the newer medication per guidelines
  - Direct switch is useful in three scenarios:
    1. When switching to another agent in the same or similar class
    2. When original antidepressant has been used for <1 week
    3. When the discontinuation is due to adverse effects

Psychosis & Antipsychotics

- *The Narrow Definition* – typical definition from DSM-5
  1. Delusions
  2. Hallucinations
  3. Disorganized Thinking
  4. Disorganized Behavior
- *The Broader Definition* – often seen in medically induced psychosis, OCD, personality disorders, or trauma-based conditions
  1. Loss of reality testing – one's inability to attend to and establish a relationship with the objective or real world
  2. Loss of self – experience of inner subjectivity is lost;

     "who am I?" or "what do I want?"
  3. Inability to communicate; loss of ability to symbolize; concrete symbolization

Antipsychotics – Typicals

- Strong D2-antagonism
  - Antipsychotic mechanism in mesolimbic pathway
  - Side effect profile w/ increased EPS in nigrostriatal pathway
- See some anticholinergic side effects, especially at higher doses
- Easy to titrate on and off these medications

Antipsychotics – Atypicals

- Two main theories for mechanism of action:
  1. Partial agonist activity at D2 & D3 w/ faster K_D
  2. Serotonin agonist to modulate DA levels more
- Side effect profile related to interaction with other monoamine receptors
  - H1-R: weight gain, sleepiness
  - α-R: orthostasis, rebound HTN
  - AcH-R: anticholinergic effects of dry mouth, constipation, bladder incontinence
- May need slower titrations as a result of R profiles
- Monitoring: baseline – CBC, CMP (fasting gluc, LFTs), HbA_{1C}, fasting lipid, AIMS; CBC, CMP – yearly; HbA_{1C} & fasting lipid – repeat after 3mo of initiating antipsychotic, then yearly; AIMS – at dose increases or q6mo.

Antipsychotics – Atypicals

Drug Name	Dose Range (mg/d)	Notes
Quetiapine (Seroquel)	50-800	Very sedating, large amount of weight gain; FDA approved for monotherapy in Bipolar depression
Risperidone (Risperdal) & Paliperidone (Invega)	0.5-6 6-12	Most typical; use lower doses in MDD, OCD, and agitation; Consta: 2w depot injection & Sustenna: 4w/12w depot injection
Olanzapine (Zyprexa)	5-30	Clozapine-like; major weight gain and sedation; monitor for metabolic syndrome with DMII and possibility of DKA
Aripiprazole (Abilify)	2-30	Monitor for akathisia, N/V, orthostatic hypotension, weight gain, and mild sedation
Lurasidone (Latuda)	20-60	FDA-approved for bipolar depression; take w/ meals
Ziprasidone (Geodon)	40-160	BID dosing; take with meals; initial 2w of anxiety
Clozapine (Clozaril)	25-200	Strict dosing & monitoring schedule; see REMS

Antipsychotics – Depot Injections

First, establish efficacy and tolerability with PO formulation

1. Haldol decanoate: 50-450mg q4w
   - With PO Haldol on board: initial IM dose is 10x the oral dose (if dose 100mg, administer 2 doses given 3-7d apart)
   - Without PO Haldol on board: initial IM dose is 20x oral dose (if dose 100mg, administer 2 doses given 3-7d apart)
   - Oral overlap: Following the first ER decanoate dose, taper the oral dose by ~25% at weekly intervals during the second or third month of decanoate treatment.
2. Prolixin decanoate: 6.25-100mg q2-3w
   - 12.5mg q3w decanoate is equivalent to 10mg PO
   - Decrease PO dose by ½ after the initial injection; consider DC of PO after second injection (McEvoy 2006)
3. Abilify Maintena: 400mg IM q4w
   - Overlap w/ oral dosing for 2w
   - For missed doses >5w, administer oral aripiprazole for 14 days with next400mg injection

Antipsychotics – Depot Injections

4. Risperdal Consta & Invega Sustenna
   - For Risperdal: initiate 25mg q2w; increase dose in increments of 12.5mg q4w to max of 50mg IM q2w (Hawley 2010; Turner 2004); will require concomitant dosing of PO medication x 3w (overlap)
   - For Invega: initiate 234mg IM on day 1, then 156mg IM 1 week later; magic number is 6; no need for PO overlap

Risperdal PO	Risperdal Consta	Invega Sustenna 4w	Invega Sustenna PO
2mg PO qd	25mg IM q2w	117mg IM q4w	<6mg PO qd
3mg PO qd	37.5mg IM q2w	117mg IM q4w	6mg PO qd
4mg PO qd	50mg IM q2w	156mg IM q4w	9mg PO qd
5-6mg PO qd	50mg IM q2w	234mg IM q4w	12mg PO qd

Mood Stabilizers

1. Lithium: 300mg-1800mg/d; level 1.0
   - Typically give in BID dosing to avoid long-term renal issues; can increase dose by 300mg every 1-5d
   - After 5-7d at a stable therapeutic dose, obtain Lithium trough level; aiming for Lithium level of 0.6-**1.2**
   - Monitoring: baseline – CBC, CMP, TSH/FT4; BUN/Cr & Thyroid – q3mo x2, then q12mo; Lithium – on stable dose 5-7d following last dose increase, then q3mo once dose/levels are stable; Fluid status – with AMS
   - Side effects: **Abd pain, N/V, sedation, weight gain, diarrhea**, decreased appetite, **tremor**, **metallic taste**, confusion, ataxia, **poor cognition**/memory impairment
2. Valproic Acid (Depakote): 250-2500mg/d; level 100
   - IR dosing is BID, ER is qHS (horse pill)
   - Note that starting dose for seizures is 15-20mg/kg
   - Increase by 250-500mg q1-3d until desired clinical effect [Goodwin 2016]
   - Monitoring: baseline – CBC, CMP (liver functions), then yearly; Ammonia – lethargy, vomiting, AMS; VPA level – at stable dose (trough at 7d) or with si/sxs of toxicity: malaise, edema (facial or LE), anorexia, jaundice, N/V, abd pain, AMD
   - Side effects: **abd pain**, **dizziness**, HA, **sedation**, **alopecia**, N/V, **weight gain**, thrombocytopenia, tremor, **amenorrhea**, elevated AST/ALT
   - Note: safest mood stabilizer in BREAST FEEDING.

Mood Stabilizers

3. Carbamazepine (Tegretol): 200-1200mg/d; level of 10
   - Start 200mg/d; increase in increments of 200mg/d q1-4d
   - If DC, do so by 200mg increments over 2mo, unless a more rapid titration is required
   - Monitoring: Baseline – CBC, CMP, then q6mo-1y; Tegretol – 5d following last dose change; only needed during initial induction phase and then at steady dose
   - Side effects: **dizziness**, ataxia, **sedation**, **N/V**, **constipation**, low Na^+
4. Lamotrigine (Lamictal): 50-200mg/d (doses up to 400mg have been used)
   - Strict titration schedule: 25mg/d x 2w, then 50mg/d x 2w, then 100mg/d x 2w, then 200mg/d
   - When using inducers (CBZ, phenytoin): 50mg/d x2w, then 100mg/d x2w, then 200mg/d x1w, then 300mg/d (max 400mg/d)
   - When using inhibitors (VPA): 25mg every other day x2w, then 25mg/d x2w, then 50mg/d x1w, then 100mg/d x1w, then 200mg/d
   - Honestly, see insert when discontinuing concomitant inducers or inhibitors
   - No major monitoring except in pregnancy; DC immediately w/ signs of rash; check LFTs, renal panel yearly; monitor other anticonvulsants closely

Bipolar Disorder

- If unable to obtain mood control: ensure there are NO serotonergic medications on board, increase dose of antimanic agent, AND refer to psychiatry – these are complex situations
- If depression emerges: follow FDA-approved guidelines for treatment of depression or refer to psychiatry; can use SSRIs or other adjunctive strategies ONLY when mood has been stabilized

	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	◑	◔	◔	◔	◔	+	++	+	++	–

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

●, level 1 evidence; ◔, level 2 evidence; ◑, level 3 evidence; ◴, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◩, level 4 negative evidence; n.d., no data; –Limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Although monotherapies are listed above combination therapies in the hierarchy, combination therapies may be indicated as the preferred choice in patients with previous history of partial response to monotherapy and in those with psychotic mania or in situations where rapid response is desirable.

[b]Did not separate from placebo in those with index mania; no studies available in index depression.

[c]No controlled trials; however, clinical experience suggests that it is a useful strategy.

[d]Did not separate from placebo on core symptoms of depression.

[e]Divalproex and carbamazepine should be used with caution in women of childbearing age.

	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.

	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]	+

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.

●, level 1 evidence; ◔, level 2 evidence; ◐, level 3 evidence; ◴, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◰, level 4 negative evidence; n.d., no data; – limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Did not separate from placebo in those with index mania; no studies available in index depression.

[b]Did not separate on core symptoms of depression.

[c]Divalproex and carbamazepine should be used with caution in women of child bearing age.

[d]Trend for superiority on the primary efficacy measure, hence the lower rating.

[e]Effective in those with an index episode of depression.

References

1. Bauer M, et al. (2015). *World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder*. World J Biol Psychiatry. 16(2):76-95.
2. Calabrese JR, et al. (2005). *A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder*. Am J Psychiatry. 162(11):2152-2161.
3. Geddes JR, et al. (2009). *Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials*. Br J Psychiatry. 194(1):4-9.
4. Gitlin M. (2016). *Lithium side effects and toxicity: prevalence and management strategies*. Int J Bipolar Disord. 4(1):27.
5. Hawley C, et al. (2010). *Switching stable patients with schizophrenia from depot and oral antipsychotics to long-acting injectable risperidone: reasons for switching and safety*. Hum Psychopharmacol. 25(1):37-46.

References

6. Levenson JL. (2011). *Textbook of Psychosomatic Medicine. Psychiatric Care of the Medically Ill, Second Edition*. Arlington, VA: American Psychiatric Publishing, Inc.
7. McEvoy JP. (2006). *Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry*. 67(Sup5):15-18.
8. Panksepp J. (1998). *Affective Neuroscience: the foundations of human and animal emotions*. New York City, NY: Oxford University Press.
9. Schatzberg A, et al. (2013) *Essentials of Clinical Psychopharmacology, Third Edition*. Arlington, VA: American Psychiatric Publishing.
10. van der Westhuizen et al. (2015). *Basic emotional foundations of social dominance in relation to Panksepp's affective taxonomy*. Neuropsychoanalysis. 17(1):19-37.
11. Yatham LN, et al. (2018). *Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder*. Bipolar Disord. 20(2):97-170.