Measurement-Based Care Training:
3. Antidepressant Treatment Algorithms

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Disclosure Statement 2019-2021

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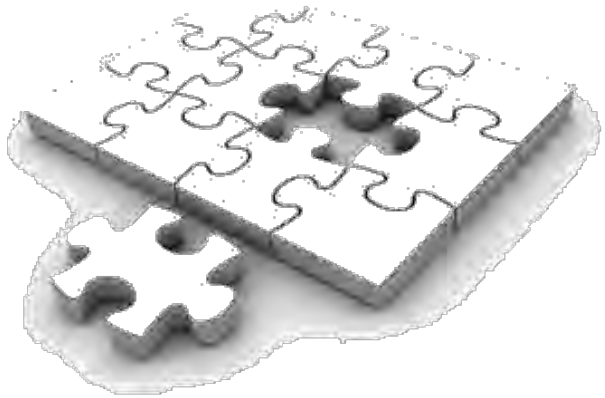
www.DrRaymondLam.ca

Objectives

At the end of this presentation, participants will be able to:

- Describe the rationale for treatment algorithms.
- Use a simple algorithm for selecting an antidepressant.
- Compare and contrast switching versus adjunctive strategies for incomplete response to the first antidepressant

www.WorkingWithDepression.psychiatry.ubc.ca



Features of EMBED MBC Implementation

For Doctors


Scales package


Monitoring form for chart


Medication algorithm


MBC training

For Patients


Patient information


WeChat mood tracking


WeChat "Feeling Better"

For Hospital


Workflow training


Champions


Expert consultation

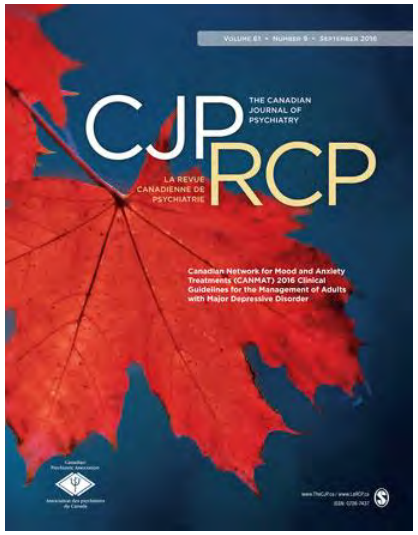
Icons by DinosoftLabs

Treatment Algorithms

Treatment Algorithm:
An ordered sequence of clinical decisions to help solve a clinical problem

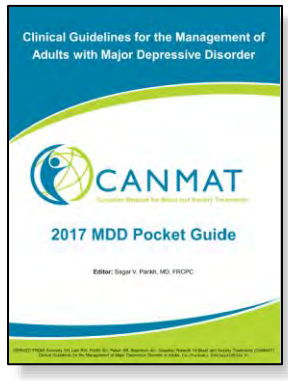
- Standardizes care, reduces variability
- Can be used alongside measurement-based care
- Not a fixed recipe – can deviate based on the clinical situation

CANMAT Depression Guidelines 2016



Available at www.canmat.org

- Evidence-based major update of 2009 CANMAT guidelines
  1. Burden and principles of care
  2. Psychological treatments
  3. Pharmacological treatments
  4. Neurostimulation treatments
  5. Complementary and alternative medicine treatments
  6. Special populations (youth, women, elderly)
- For specialists; Question-Answer format; Pocket Guide soon available
- No external/pharma funding
- Published as theme issue in Canadian Journal of Psychiatry, September 2016



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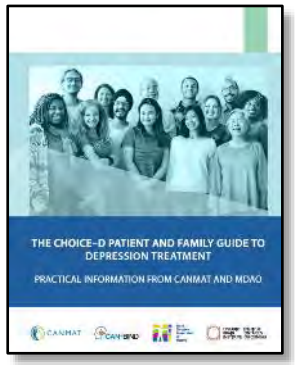
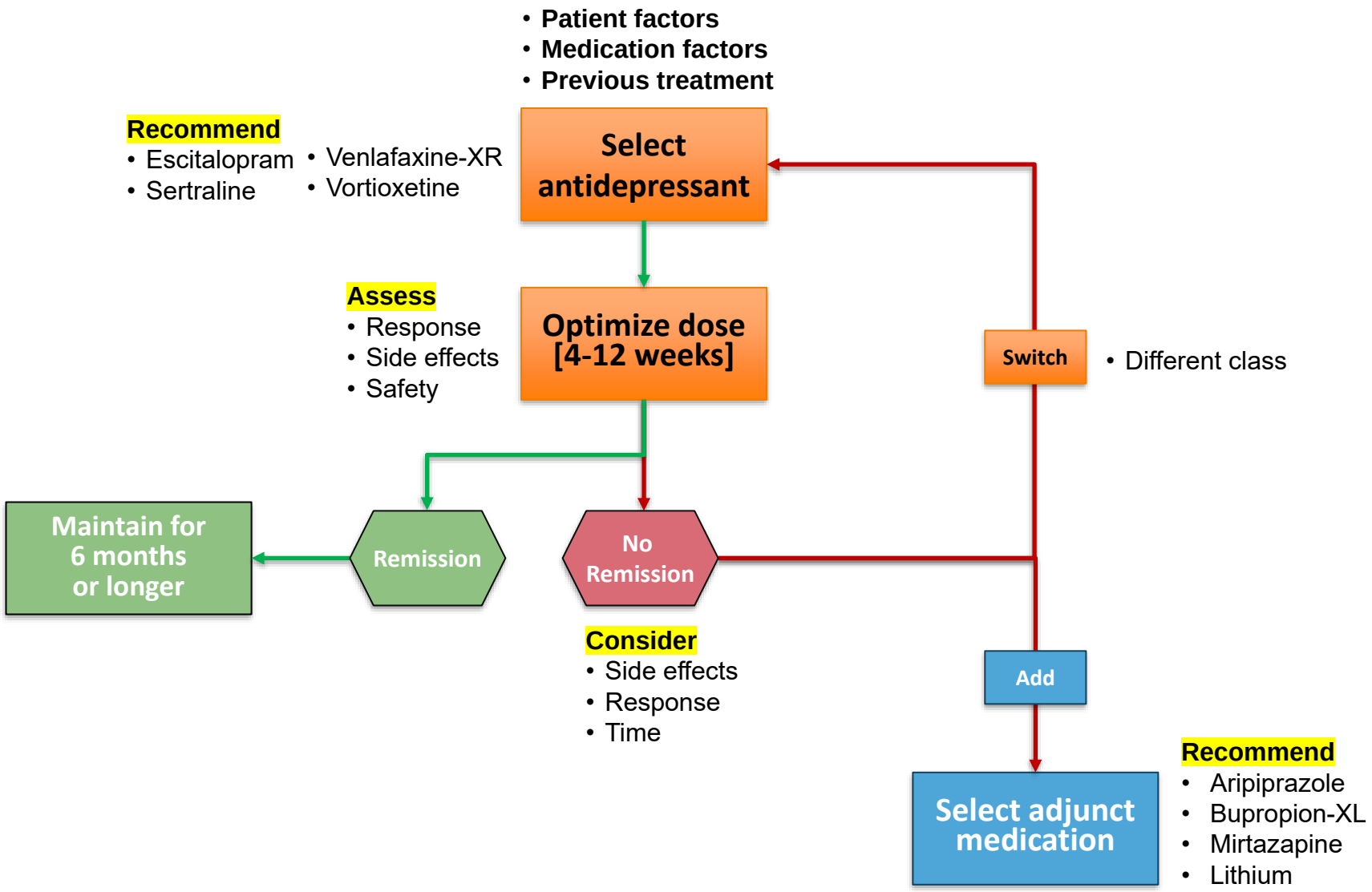


CHOICE-D

Simplified Algorithm for Antidepressant Treatment



How do you select the right antidepressant for your patient?

Recommendations for Antidepressants

1st Line

- Agomelatine* (MT_1, MT_2 agonist; 5-HT_2 antagonist)
- Bupropion (NDRI)
- Citalopram (SSRI)
- Desvenlafaxine (SNRI)
- Duloxetine (SNRI)
- Escitalopram (SSRI)
- Fluoxetine (SSRI)
- Fluvoxamine (SSRI)
- Mianserin* (α_2-adrenergic, 5-HT_2 antagonist)
- Milnacipran* (SNRI)
- Mirtazapine (α_2-adrenergic, 5-HT_2 antagonist)
- Paroxetine (SSRI)
- Sertraline (SSRI)
- Venlafaxine (SNRI)
- Vortioxetine (multimodal)

2nd Line

- Amitriptyline, clomipramine, others (TCAs)
- Levomilnacipran (SNRI)
- Moclobemide (reversible inhibitor MAO-A)
- Quetiapine (AAP)
- Selegiline transdermal* (irreversible inhibitor MAO-B)
- Trazodone (SRI; 5-HT_2 antagonist)
- Vilazodone (SRI, 5-HT_{1A} partial agonist)

3rd Line

- Phenelzine (irreversible inhibitor MAO)
- Tranylcypromine
- Reboxetine* (NRI)

All recommendations are level 1 evidence. *Not available in Canada.
Red indicates new since 2009.

MT, melatonin; 5-HT, serotonin; MAO, monoamine oxidase; NDRI, noradrenaline and dopamine reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA; tricyclic antidepressant; AAP, atypical antipsychotic

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Kennedy SH, Lam RW et al, Can J Psychiatry 2016;6:540-60.

Simplified Algorithm for Antidepressant Treatment

- Patient factors
- Medication factors
- Previous treatment

Select antidepressant

Factors to Consider in Selecting an Antidepressant

Patient Factors

- Clinical features and dimensions
- Comorbidities
- Response and side effects to previous antidepressants
- Patient preference

Medication Factors

- Comparative efficacy
- Comparative tolerability
- Potential drug interactions
- Simplicity of use
- Cost and availability

Antidepressant selection must be individualized since the relative differences between medications are small

Kennedy SH et al, Can J Psychiatry 2016;6:540-60.

How do you assess differences among antidepressants?

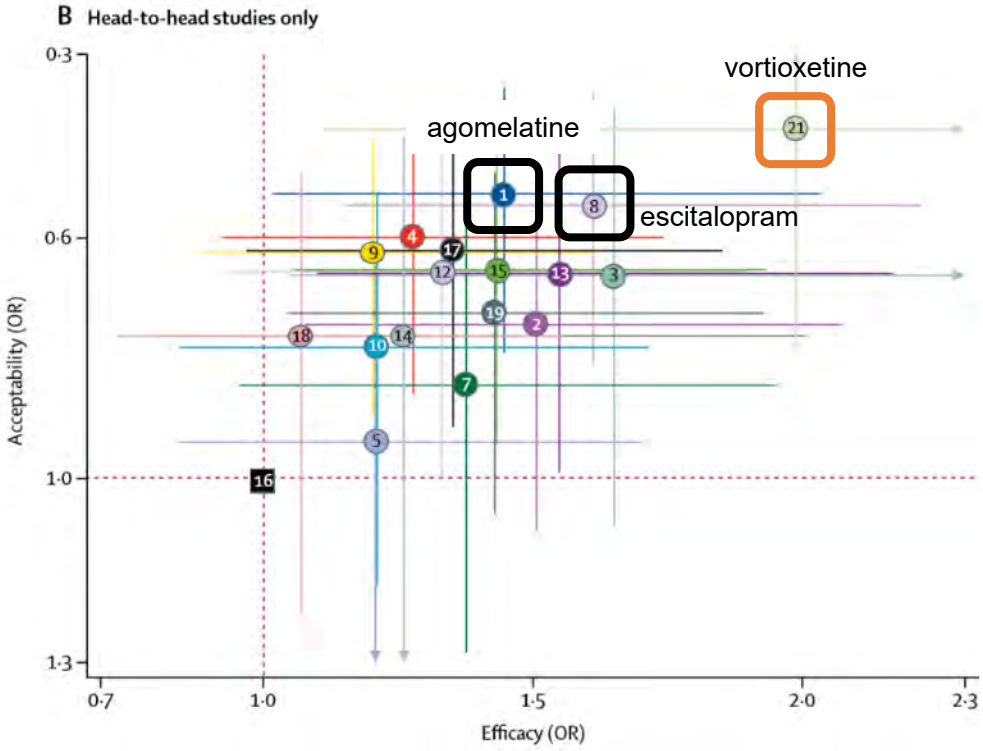
Antidepressants With Evidence for Superior Efficacy Based on Meta-Analyses

Antidepressant	Level of Evidence	Comparator Medication(s)
Escitalopram	LEVEL 1	Citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine
Mirtazapine	LEVEL 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine
Sertraline	LEVEL 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Venlafaxine	LEVEL 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Agomelatine	LEVEL 2	Fluoxetine, sertraline
Citalopram	LEVEL 2	Paroxetine

Meta-analyses continue to show that some ADTs have modest superiority for treatment response (5-6%), which may be relevant from a population basis

ADT, antidepressant

Combining efficacy and acceptability



Data are reported as ORs in comparison with reboxetine, which is the reference drug. Error bars are 95% CrIs. Individual drugs are represented by different coloured nodes. Desvenlafaxine, levomilnacipran, and vilazodone were not included in the head-to-head analysis because these three antidepressants had only placebo-controlled trials.

3 antidepressants had the most favourable profile for efficacy and acceptability:

- Agomelatine
- Escitalopram
- Vortioxetine

1	Agomelatine	12	Milnacipran
2	Amitriptyline	13	Mirtazapine
3	Bupropion	14	Nefazodone
4	Citalopram	15	Paroxetine
5	Clomipramine	16	Reboxetine
6	Desvenlafaxine	17	Sertraline
7	Duloxetine	18	Trazodone
8	Escitalopram	19	Venlafaxine
9	Fluoxetine	20	Vilazodone
10	Fluvoxamine	21	Vortioxetine
11	Levomilnacipran	22	Placebo

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Cipriani A. et al, Lancet 2018;391:1357-66

Medication Factors: influence on antidepressant selection

Side Effects?

- Differences between antidepressants are small and doctors have many different opinions about side effects.

Sexual side effects

- Lower risk with agomelatine, bupropion, desvenlafaxine, mirtazapine, vilazodone, vortioxetine.

Drug-drug interactions

- Minimal risk with desvenlafaxine, escitalopram, mirtazapine, sertraline, venlafaxine-XR.
- Avoid fluoxetine and paroxetine.

Kennedy SH et al, Can J Psychiatry 2016;6:540-60.

Simplified Algorithm for Antidepressant Treatment

- **Patient factors**
- **Medication factors**
- **Previous treatment**

Recommend

- Escitalopram
- Sertraline
- Venlafaxine-XR
- Vortioxetine

Select antidepressant

Antidepressants with the best evidence for efficacy and tolerability

- Escitalopram
- Sertraline
- Venlafaxine-XR
- Vortioxetine

Selecting an Antidepressant – Clinical Examples

Scenario 1

- Patient has anxious worrying, accompanied by agitation
- Has comorbid cardiovascular disease
- Has a family history of bipolar disorder

➢ **Use SSRI** – e.g., sertraline, escitalopram

Why?

- SNRIs may be more activating
- SNRIs have slightly higher risk of hypomanic responses
- Sertraline and escitalopram have cardiovascular safety
- Citalopram has QTc issue
- Fluoxetine and paroxetine have more potential for drug-drug interactions.

Selecting an Antidepressant – Clinical Examples

Scenario 2

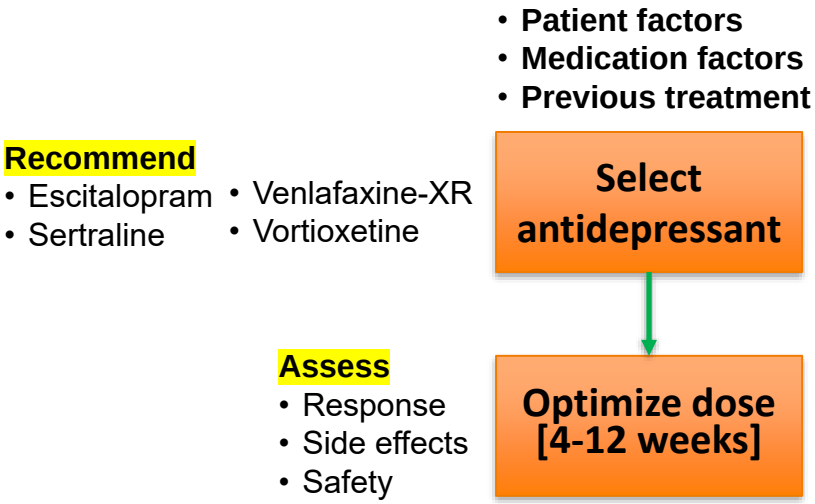
- Patient has flat mood (can't feel, not sad), cognitive symptoms (poor concentration, memory), low energy
- Has comorbid panic disorder, irritable bowel syndrome (IBS)

➢ **Use SNRI** – e.g., venlafaxine-XR, desvenlafaxine

Why?

- SNRIs may be more activating, less risk of emotional blunting
- SNRIs slightly better than SSRIs for cognition, energy
- Duloxetine and bupropion good for energy, but less evidence for efficacy in anxiety disorders.
- Vortioxetine good for cognition, but has higher rates of nausea

Simplified Algorithm for Antidepressant Treatment



When do you increase the dose?

Importance of early improvement for antidepressant response

- Contrary to previous beliefs, there is ample evidence for early onset of antidepressant effects, within 2 weeks
- Early improvement in symptoms (more than 20% reduction in depression score) may predict final symptom response
- Early improvement in symptoms also predicts final functional improvement
- **Lack of early improvement** may be a more clinically useful predictor
- **Less than 20%** improvement at **2-4 weeks** indicates low probability of final response at 6-12 weeks

Lam RW, Eur Neuropsychopharmacol 2012;22:S492-S498;
Kudlow PA et al, CNS Drugs 2014;28:601-9;
Lam RW et al, Int Clin Psychopharm, 2014;29:239-51.

How to define early improvement

Outcome	Definition	PHQ-9 example (baseline score = 15)
Improvement	≥ 20% reduction from baseline	PHQ-9 change ≥ 3
Response	≥ 50% reduction from baseline	PHQ-9 change ≥ 8
Remission	Score in “normal” range	PHQ-9 score = 0 to 4

A change in score of ± 5 points is clinically significant.

“20 in 4” Rule

If there is less than 20% improvement in 4 weeks:

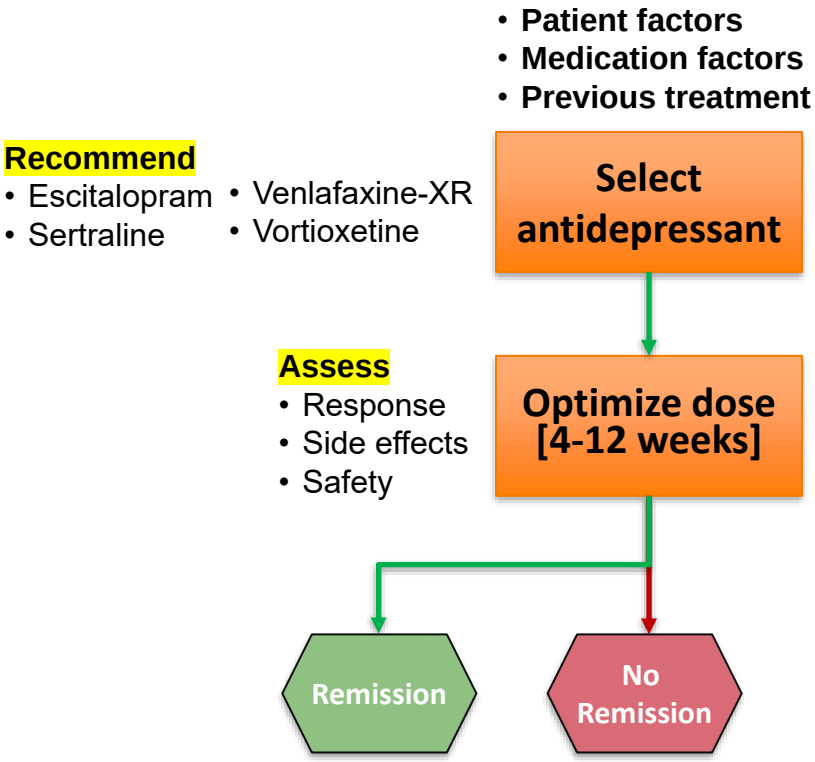
DO SOMETHING.

Mitigated by:

- Severity
- Side effects
- Previous treatments
- Stressful life events

Kudlow PA, McIntyre RS, Lam RW. CNS Drugs 2014;28:601-9.

Simplified Algorithm for Antidepressant Treatment



Two Phases of Treatment for Major Depressive Disorder

Treatment Phase	Duration	Goals	Activities
Acute "How do you get patients well?"	8-12 weeks	• Remission of symptoms • Restore functioning	• Establish therapeutic alliance • Educate • Select and use treatment(s) • Monitor progress
Maintenance "How do you keep them well?"	6-24 months or longer	• Return to full functioning and quality of life • Prevention of recurrence	• Educate • Rehabilitate • Treat comorbidities • Monitor for recurrence

How long do you continue an antidepressant?

All patients should continue antidepressants for 6 months after remission of symptoms, but longer-term (≥ 2 years) maintenance is recommended for patients with:

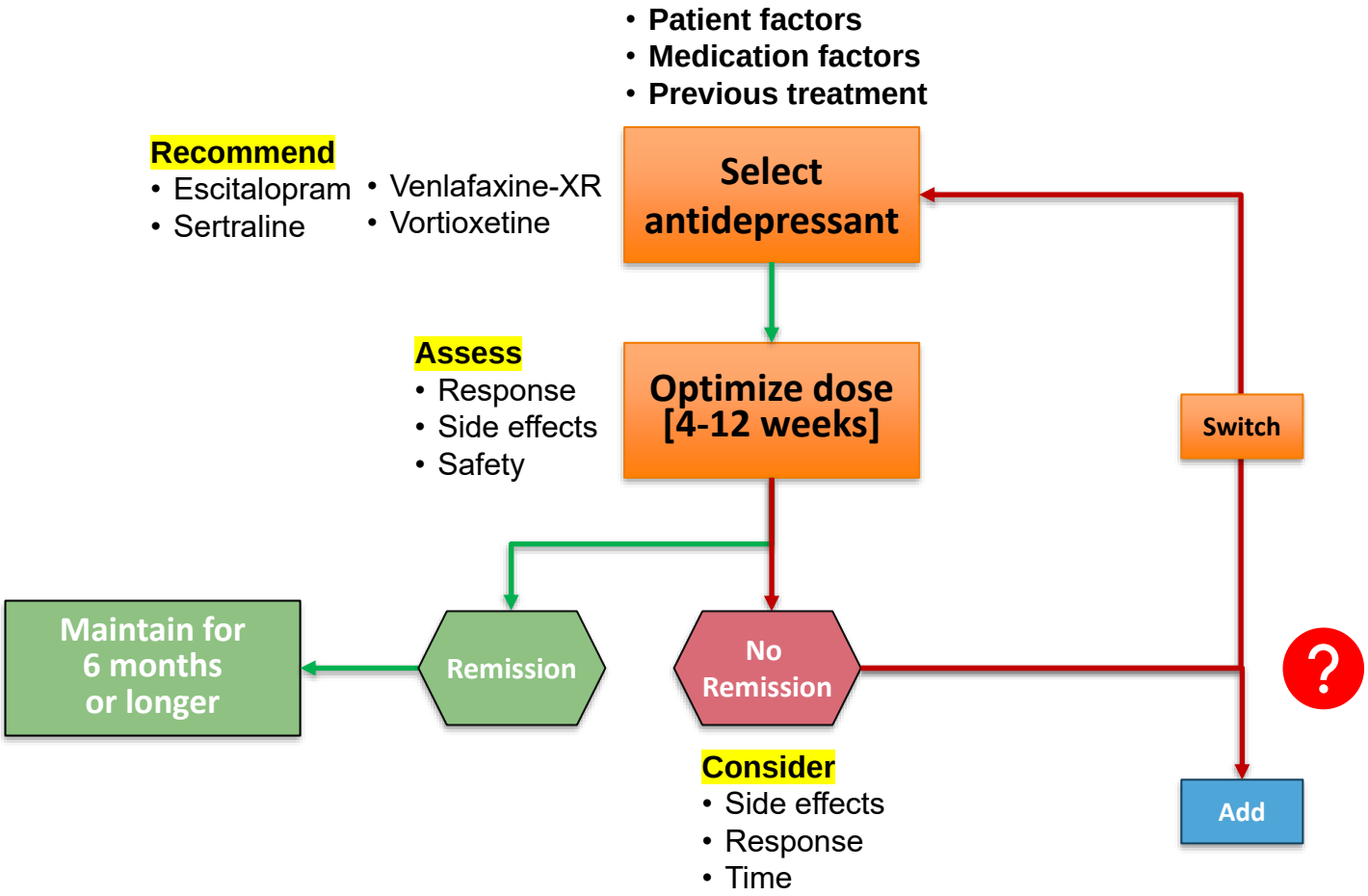
- ✓ Frequent, recurrent episodes
- ✓ Severe episodes (psychosis, severe impairment, suicidality)
- ✓ Chronic episodes
- ✓ Psychiatric or medical comorbidities
- ✓ Difficult-to-treat episodes

*Few RCTs have specifically evaluated risk factors to guide longer term treatment; therefore, these recommendations are Level 3 and Level 4 evidence

RCT, randomized controlled trial

Kennedy SH et al, Can J Psychiatry 2016;6:540-60.

Simplified Algorithm for Antidepressant Treatment



When do you switch the antidepressant?

Switching or Adding an Adjunctive Medication

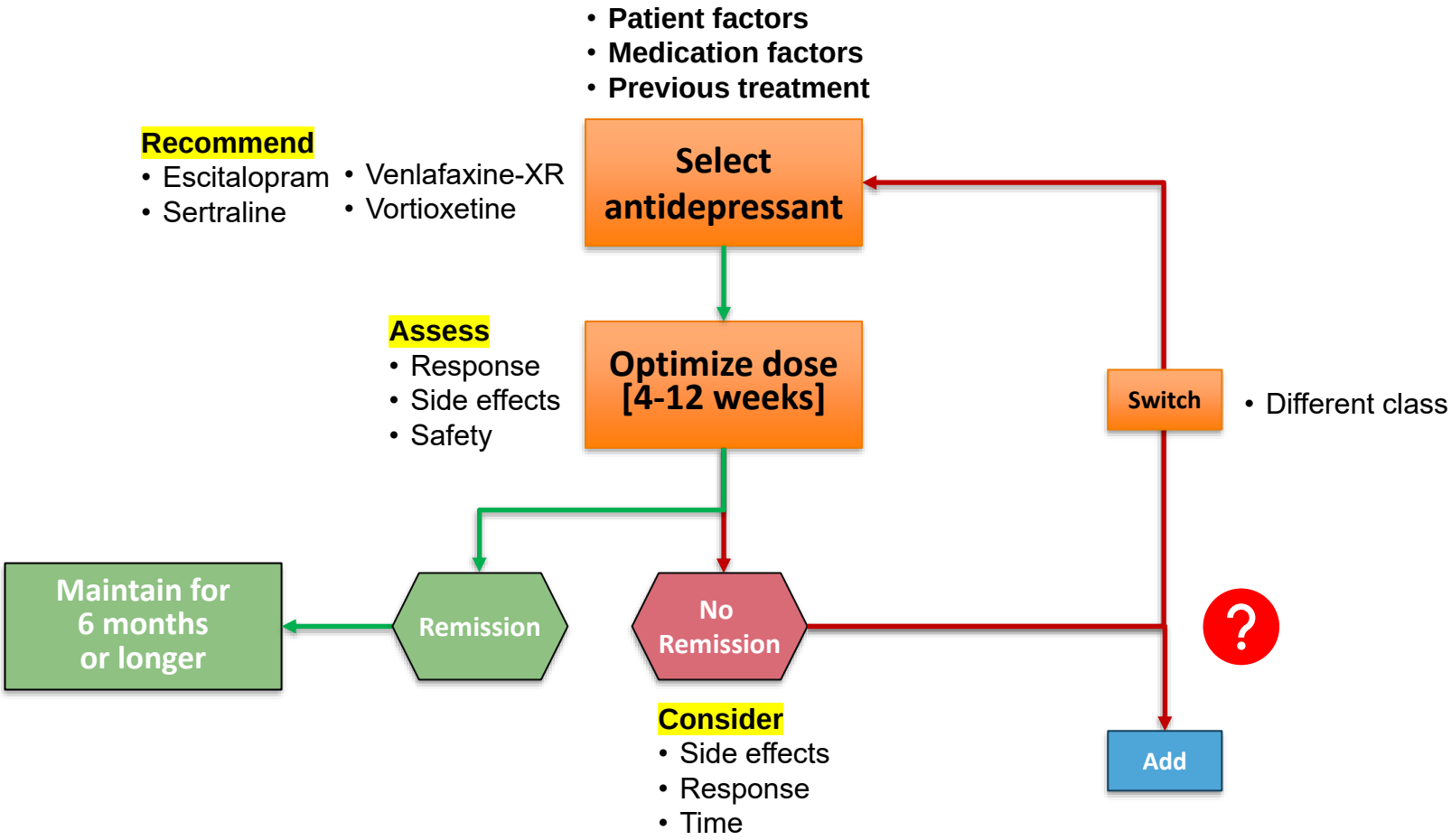
Factors to Consider

Consider Switching when:
• It is the 1st antidepressant trial
• Initial antidepressant is poorly tolerated
• No response (<25%) to the initial antidepressant*
• More time to wait for a response
• Patient prefers to switch

*For the initial antidepressant trial. In subsequent trials, lack of response (<25% improvement) may not be a factor for choosing between switch and adjunctive strategies.

Kennedy SH et al, Can J Psychiatry 2016;6:540-60.

Simplified Algorithm for Antidepressant Treatment



Switching or Adding an Adjunctive Medication

Factors to Consider

Consider Switching when:	Consider Adjunctive Therapy when:
• It is the 1st antidepressant trial	• ≥2 antidepressant trials
• Initial antidepressant is poorly tolerated	• Initial antidepressant is well tolerated
• No response (<25%) to the initial antidepressant*	• Partial response (>25%) to the initial antidepressant
• More time to wait for a response	• Less time to wait for a response
• Patient prefers to switch	• Patient prefers to add-on
	• Specific residual symptoms or side effects can be targeted

*For the initial antidepressant trial. In subsequent trials, lack of response (<25% improvement) may not be a factor for choosing between switch and adjunctive strategies.

Kennedy SH et al, Can J Psychiatry 2016;6:540-60.

Adjunctive Strategies for Non- or Partial Response

Recommendation	Adjunctive Agent (Dosing)	Level of Evidence
1st LINE	• Aripiprazole (2-15 mg) • Quetiapine (150-300 mg) • Risperidone (1-3 mg)	LEVEL 1
2nd LINE	• Brexpiprazole* (1-3 mg) • Olanzapine (2.5-10 mg)	LEVEL 1
	• Bupropion (150-300 mg) • Lithium (600-1200 mg [therapeutic serum levels]) • Mirtazapine/mianserin (30-60 mg) • Modafinil (100-400 mg) • Triiodothyronine (25-50 mcg)	LEVEL 2
3rd LINE	• TCAs (e.g. desipramine) (various)	LEVEL 2
	• Other ADTs (various) • Other stimulants (methylphenidate, lisdexamfetamine, etc) • Ziprasidone (20-80 mg bid)	LEVEL 3
Other		
Experimental	• Ketamine (0.5 mg/kg, single IV dose)†	LEVEL 1
Not recommended	• Pindolol (N/A)	

*Newly approved since the 2009 CANMAT guidelines.
†For acute treatment.

ADT, antidepressant; IV, intravenous; N/A, not applicable

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Kennedy SH et al, Can J Psychiatry 2016;6:540-60.

Add-On with Atypical Antipsychotics

- Side effect burden must be considered (especially in elderly):
  - Extrapyramidal symptoms, sedation*, hyperprolactinemia, weight gain*, metabolic syndrome*, QTc prolongation*

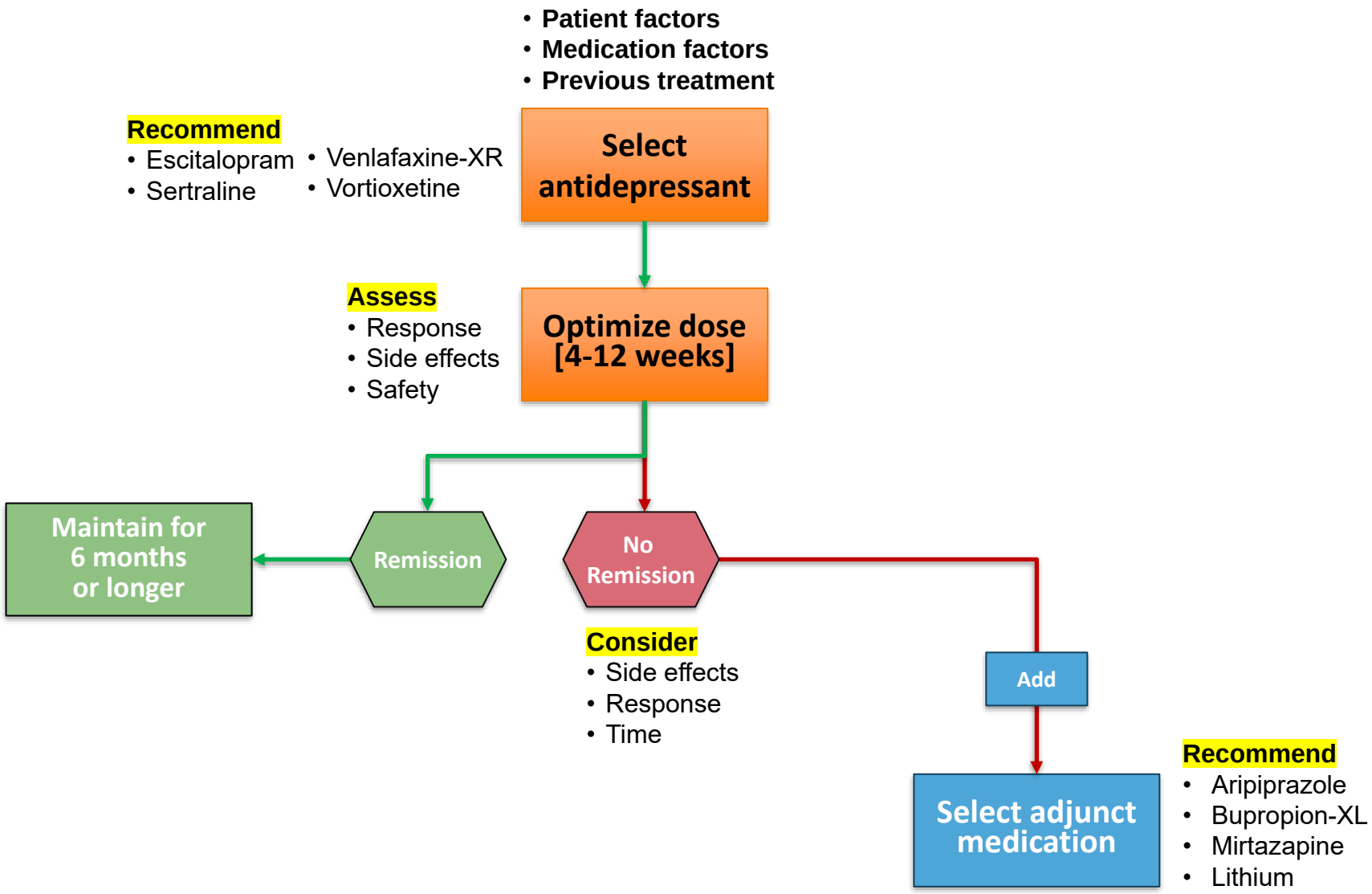
* Also seen in antidepressants

Agent	Dosing Recommendations	
	Initiate	Acute Treatment
Aripiprazole	▪ 2-5 mg/d	▪ Increase to 15 mg if needed
Quetiapine XR	▪ 50 mg XR qhs x 2 days ▪ 150 mg XR qhs on day 3	▪ Increase to 300 mg XR qhs if needed
Brexpiprazole	▪ 0.5-1.0 mg ▪ Target dose = 2 mg	▪ Increase to 3 mg if needed
Olanzapine	▪ 5 mg qhs x 1 week	▪ Increase to 7.5-10 mg if needed
Risperidone	▪ 0.25 mg qhs	▪ Increase to 2.0 mg qhs if needed

Side effect burden must be evaluated in specific patient population at specific doses

Kennedy SH, Lam RW et al, Can J Psychiatry 2016;6:540-60.

Simplified Algorithm for Antidepressant Treatment



Clinical scenarios for switching vs add-on

Switch patient scenario

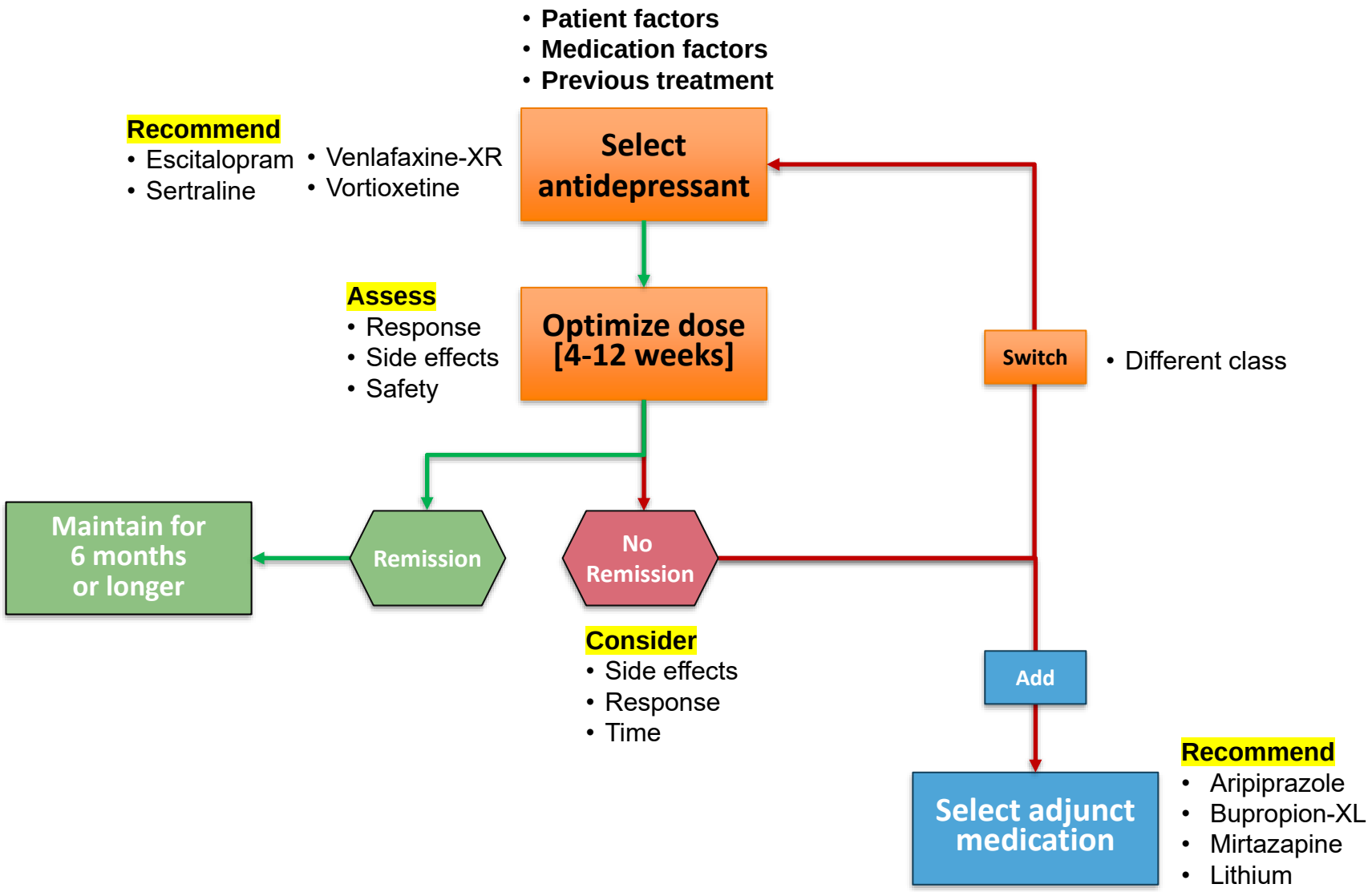
- First antidepressant – sertraline
- Baseline PHQ-9 = 15 (moderately depressed)
- SDS = 6/6/6 (moderate impairment)
- Minimal response: PHQ-9 = 14
- Also getting CBT
- Having some troublesome sexual side effects

Add-on patient scenario

- First antidepressant – sertraline
- Baseline PHQ-9 = 21 (severely depressed)
- SDS = 10/9/8 (severe impairment)
- Partial response: PHQ-9 = 14
- Tolerating medication

PHQ9, Personal Health Questionnaire;
SDS, Sheehan Disability Scale;
CBT, cognitive-behavioural therapy

Simplified Algorithm for Antidepressant Treatment



Summary

- Treatment decisions for depression must account for both acute and maintenance phases.
- Clinical guidelines can provide guidance for treatment, but the choice of an antidepressant medication depends on both patient and medication factors.
- Measurement-based care can help identify lack of symptom improvement and symptom remission to aid treatment decisions.