NEXT STEPS IN DEPRESSION TREATMENT

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Learning Objectives

- Describe consequences of discontinuing an antidepressant prematurely
- Determine when and how an antidepressant regimen should be adjusted based on patient response (i.e. is maximizing dose, switching, or augmenting most appropriate?)
- Recognize appropriate antidepressant combinations and non-antidepressant augmenting agents used in the treatment of refractory depression.
- Recommend next steps in antidepressant treatment for an individual patient.
- Identify key educational points that should be communicated to a patient continuing an antidepressant medication for depression.

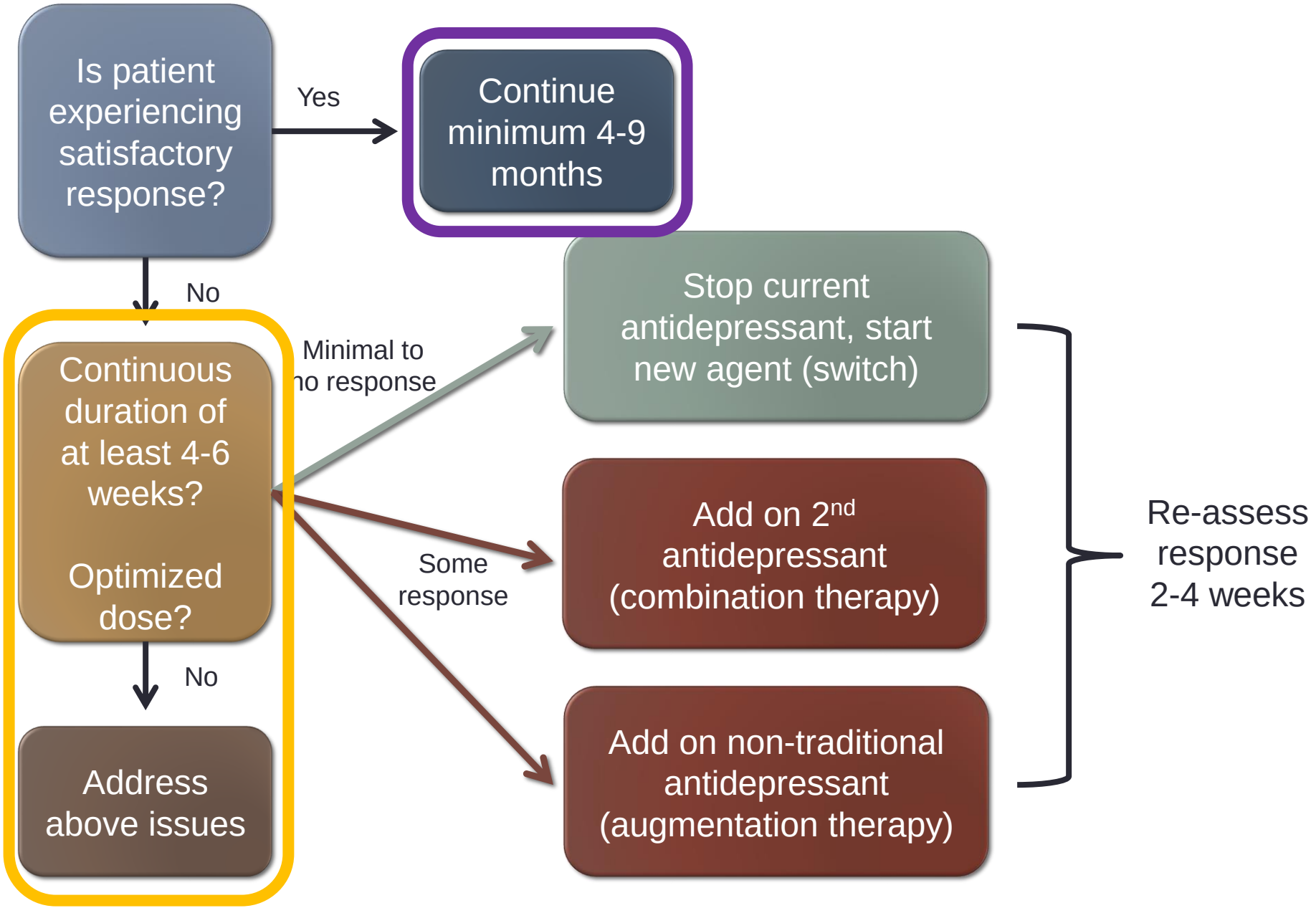
Goal of Antidepressant Treatment

- Remission is ultimate goal of treatment:
  - Improved functionality and long-term prognosis compared to non-response and response
- ~33% of patients do not achieve remission following multiple antidepressant trials

- Alternative goal: satisfactory response that improves functionality and quality of life to an acceptable level while minimizing intolerable antidepressant side effects (centered on patient perception and goals)

Trivedi MH, Rush AJ, Wisniewski SR. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implication for clinical practice. Am J Psychiatry. 2006;163:28-40.

4 – 6 week f/u: next steps in depression medication management



Antidepressant Adherence Challenges

- Non-adherence (10-60% of patients)
  - Failing to fill initial prescription
    - ~20% of patients never fill antidepressant prescription
  - Skipping or self-adjusting doses
  - Discontinuing prematurely
    - 50% by 6 months
    - 25% do not inform prescriber when discontinuing
  - May be intentional or unintentional
- Non-adherence associated with increased risk for relapse and recurrence of depression

Potential Contributors to Non-Adherence

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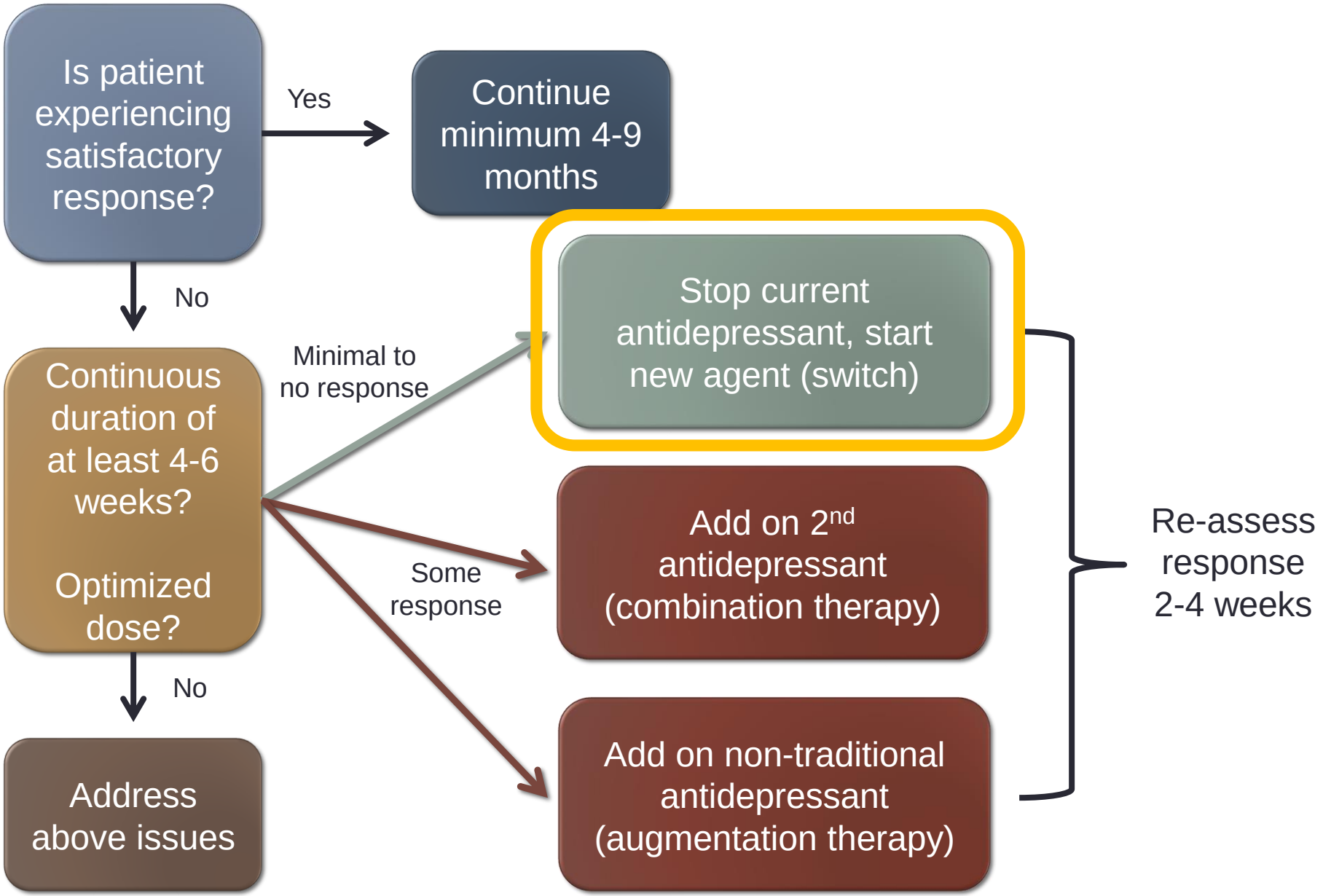


Antidepressant Discontinuation

- Educate patient not to abruptly stop antidepressant, risk of discontinuation symptoms:
  - Nausea, headache, chills, insomnia, dizziness
  - Start within 2-3 days of antidepressant discontinuation and will generally resolve within 1-2 weeks

- Taper dose over 2-3 weeks
  - Reduce daily dose weekly until initial starting dose reached
  - If withdrawal symptoms appear, resume previous dose and slow taper

Antidepressant Half-Life

Shorter Half-life	Longer Half-life
Fluvoxamine (15 hours) Paroxetine (21 hours) SNRIs (~12 hours, varies by agent)	Fluoxetine (4-6 days) Vortioxetine (2-3 days)

Greater withdrawal risk with missed doses or discontinuation

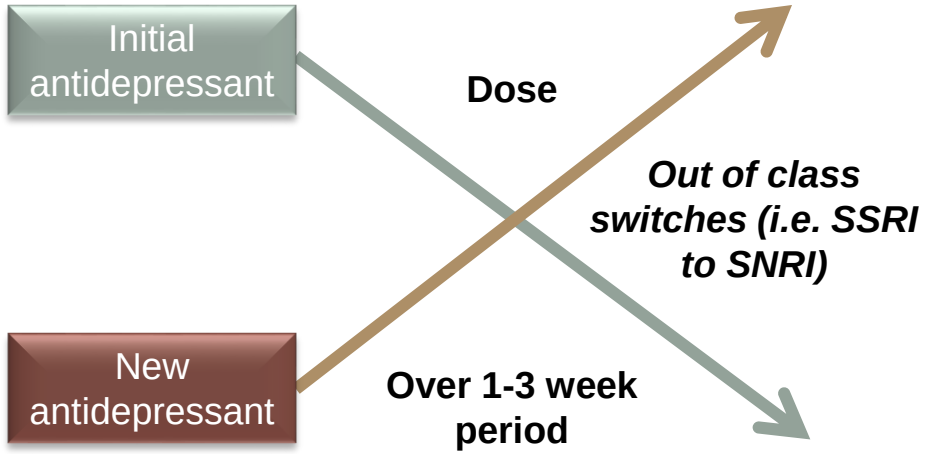
Requires slower, more gradual taper

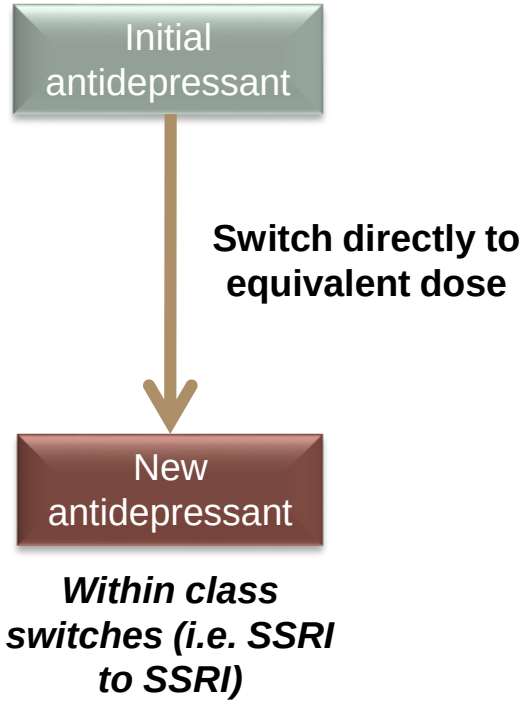
Less impact from missed doses

Fluoxetine considered self-tapering

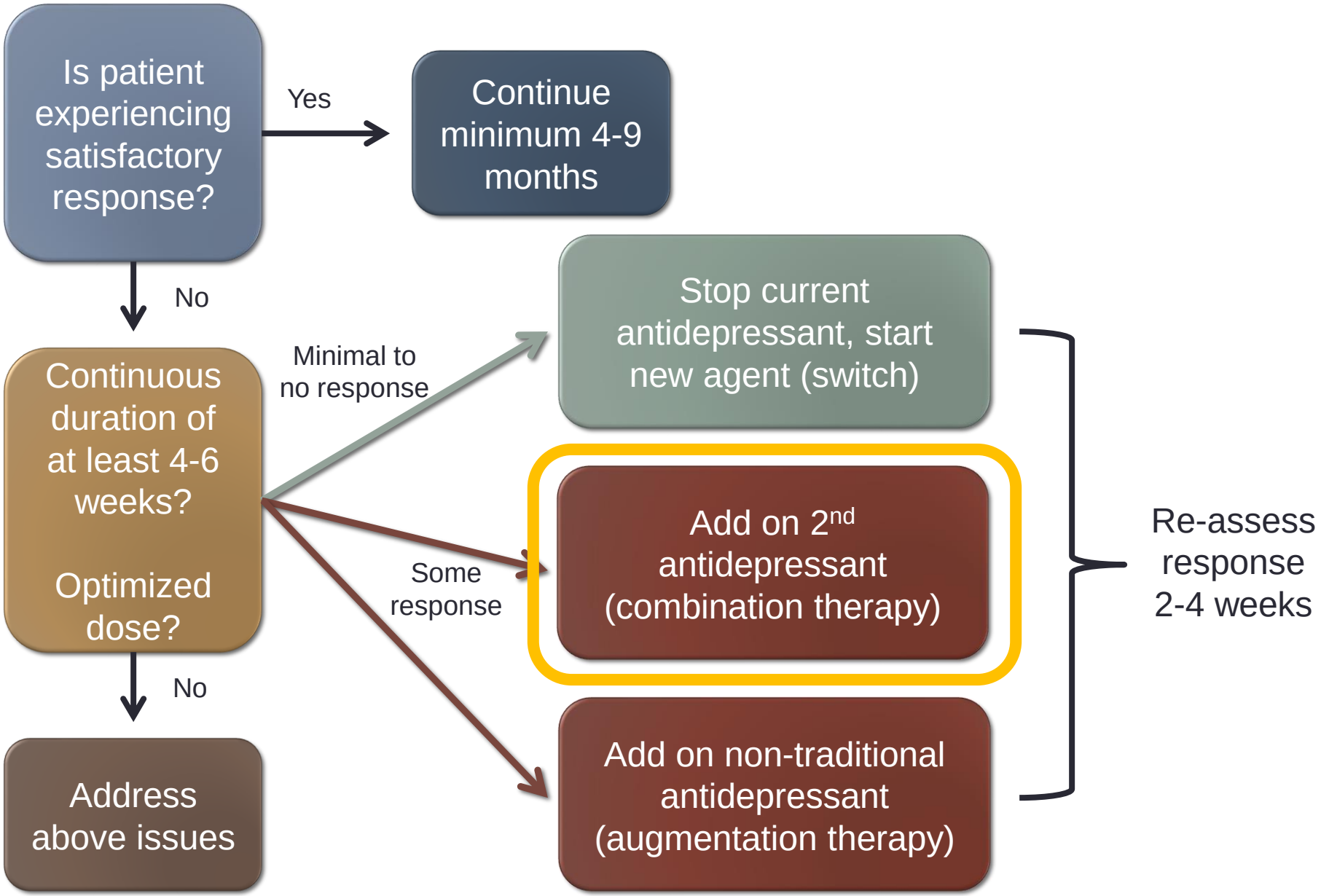
Switching Drug Therapy

- Within-class switch and across-class switch are equally effective strategies
- Expect an additional 25% of patients will achieve remission of depressive symptoms following switch in antidepressant medication





4 – 6 week f/u: next steps in depression medication management



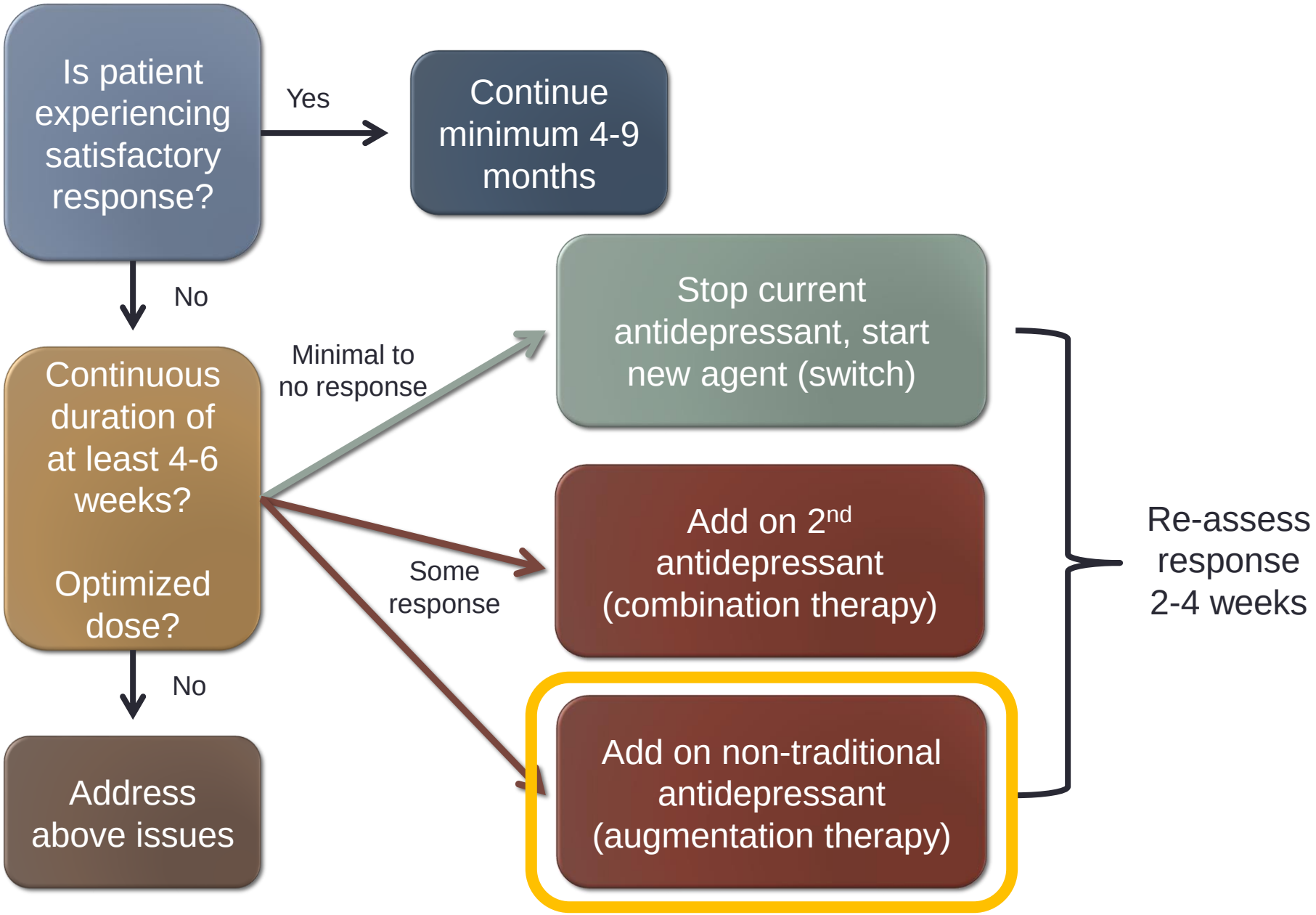
Antidepressant Combinations

- SSRI + mirtazapine OR bupropion
- SNRI + mirtazapine OR bupropion
- Mirtazapine + bupropion
- Trazodone or low dose TCA added at bedtime for sleep

- Always avoid combination of MAO-I with any other antidepressant
- Generally avoid combinations of antidepressants with similar mechanism of action (SSRI, SNRI, therapeutic dose TCA)

* Individual SSRIs, SNRIs and TCAs have unique CYP enzyme interactions and need to be evaluated separately

4 – 6 week f/u: next steps in depression medication management



Augmenting Agents

- Generally considered if patient has failed combination antidepressant therapy or has specific target symptoms such as anxiety/agitation, insomnia, fatigue, psychotic features, etc.

Strongest supporting evidence	• Second generation antipsychotics (aripiprazole, quetiapine, olanzapine, risperidone, ziprasidone, brexpiprazole) • Lithium • Esketamine • Liothyronine (T3)
Less evidence	• Buspirone • Anticonvulsants • Stimulants • Folate

Spravato™ (esketamine)

- N-Methyl-D-Aspartate (NMDA) receptor antagonist (ionotropic glutamate receptor)
- (S)-enantiomer of ketamine
- FDA-approved as nasal spray formulation
  - March 2019 for treatment resistant depression in adults (≥18 yo) in combination with an oral antidepressant
  - August 2020 for depressive symptoms in adults with MDD and acute suicidal ideation or behavior
- Short-term efficacy: shown to reduce depressive symptoms within 24 hours, and in as little as 4 hours
- Longer-term efficacy: statistically significantly longer time to relapse

https://www.spravatohcp.com/what-is-spravato#what-is-spravato

Challenges of Spravato™ Use

- Risk Evaluation and Mitigation Strategy (REMS)
  - Due to risks of sedation, dissociation, and abuse/misuse
  - Healthcare settings must be certified in the program and ensure Spravato is:
    - Only dispensed in healthcare settings and administered to patients who are enrolled in the program
    - Administered by patients under the direct observation of a healthcare provider and patients are monitored for at least 2 hours after administration
  - Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program
- Dosing
  - Twice weekly x 4 weeks (induction)
  - Once weekly x 4 weeks
  - Once weekly or every other week thereafter

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Identify Key Education Points

Category	Educational points
Administration	(i.e. when during the day should the antidepressant be taken?)
Time to Benefit	(i.e. when should the patient expect to first notice improvement in depression symptoms and when is max benefit expected? At what time points are specific symptoms expected to improve?)
Adverse Effects	(i.e. what effects should a patient monitor for, when are they expected to occur, and how long will they last? what should the patient do if they occur?)
Duration of Treatment	(i.e. if the antidepressant is safe and well tolerated, how long should the patient expect to continue it? what is the risk if the patient stops the antidepressant early?)
Safety	(i.e. what should a patient do to avoid/minimize problematic interactions? what should a patient do if they wish to discontinue an antidepressant?)
Follow-up	(i.e. when should a patient expect to f/u with a health care provider and what will be monitored at f/u?)

Questions??

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