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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

TREATMENT RESISTANT DEPRESSION

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project ECHO

SPEAKER DISCLOSURES

- ✓ No conflicts of interest

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OBJECTIVES

1. Discuss pros and cons of treatment guidelines
2. Walk through cases to determine best options
3. Improve confidence in decision making around treatment resistant depression

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RESISTANT VS REFRACTORY?

- Treatment-resistant depression
  - Inadequate response to 2 med trials
- Treatment-refractory depression
  - Inadequate response to multiple med trials

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APPROACH

- The correct diagnosis?
- Comorbidities
  - STOP-Bang
  - Thyroid-thyroid labs
  - Substance use
  - Others???
- Med adherence/adequacy of med trial

CASE 1

2017

23yo F with a history of depression presents with symptoms consistent with a moderate depressive disorder. Sertraline 200mg x 6 weeks PHQ9: 21. She would like to adjust her treatment.

PMH: none
Meds: Sertraline 200mg
Past Psych Meds: none
All: none
No substance use

PHQ9: 21 (#9 is 1)
-low energy
-poor concentration
-increased appetite
-passive SI

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CASE 1

23yo F with a history of depression presents with symptoms consistent with a moderate depressive disorder. Sertraline 200mg x 6 weeks PHQ9: 21. She would like to adjust her treatment.

What would you do next?

a) Refer for CBT
b) Switch antidepressants
c) Augment with Bupropion
d) Augment with Aripiprazole
e) Other?

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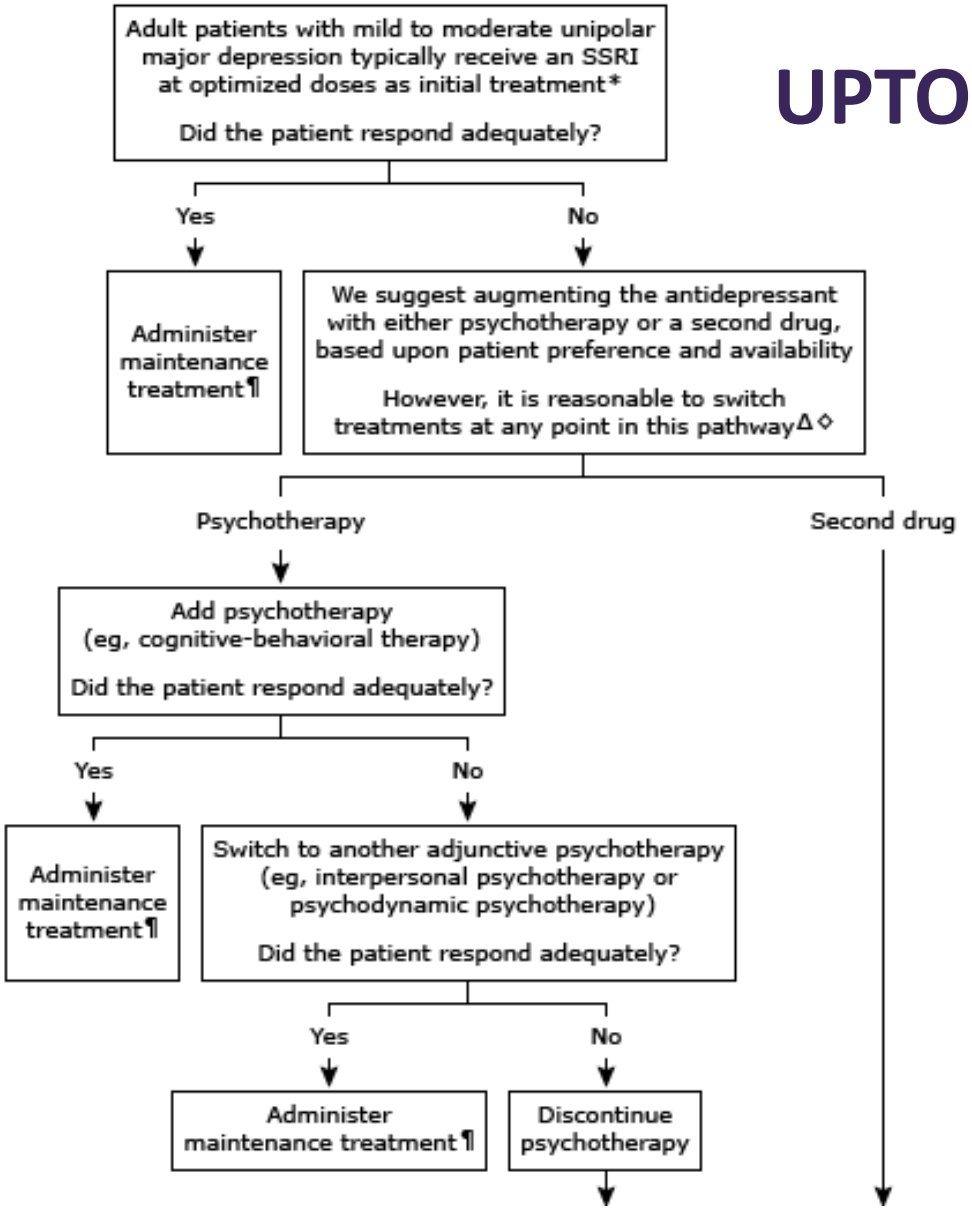
UPTODATE 2022



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Effectiveness of psychotherapy for treatment-resistant depression: a meta-analysis and meta-regression

Psychological Medicine
2018

Suzanne van Bronswijk[1], Neha Moopen[2], Lian Beijers[3], Henricus G. Ruhe[4,5,*] and Frenk Peeters[1,*]

- 21 randomized trials, N=3539
  - Switch (293) or add-on (1588) psychotherapy vs Treatment As Usual (N=1638)
  - 11 Different therapies (CBT, ICP, Mindfulness, DBT, etc.)
  - 8-60 sessions

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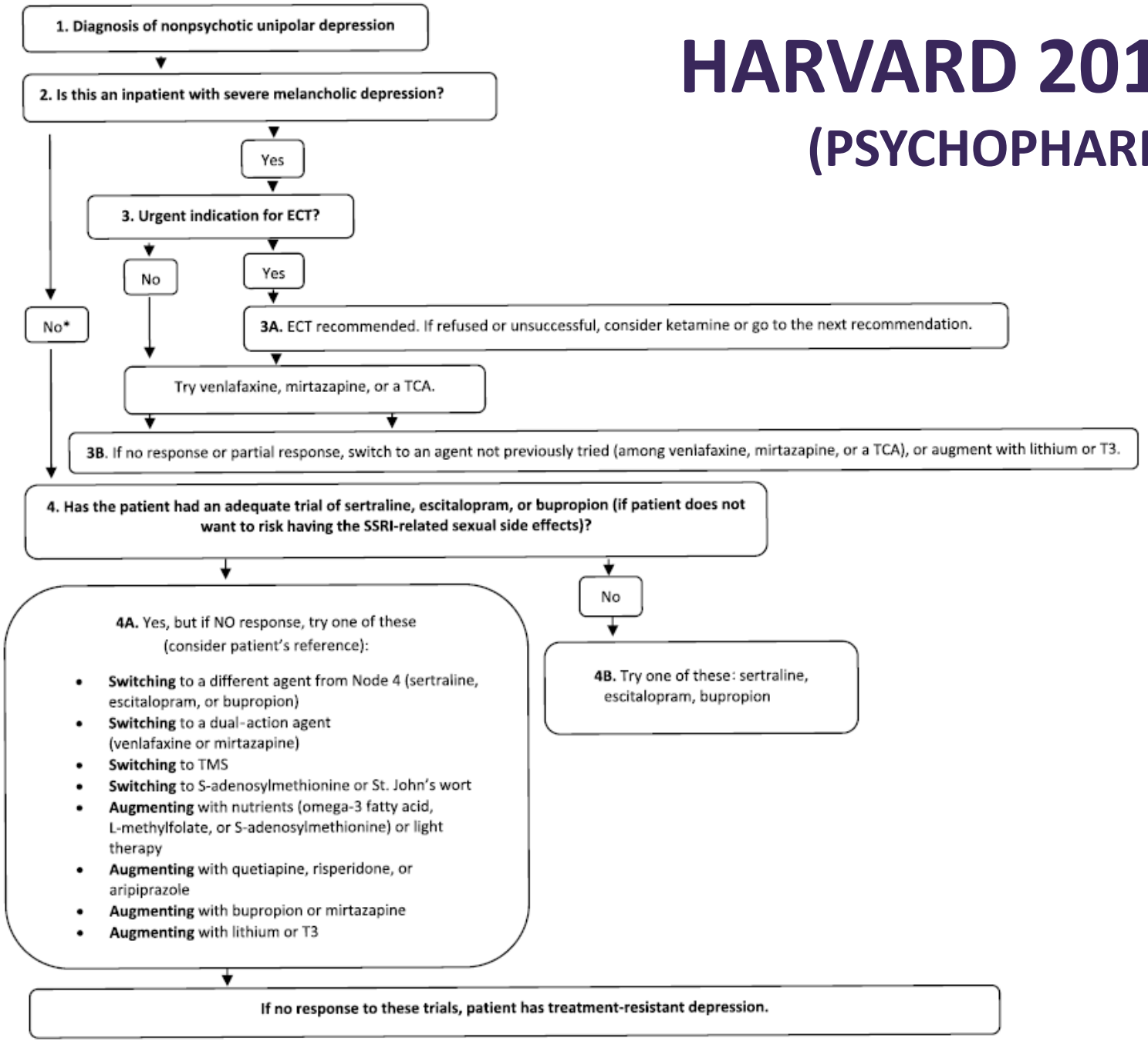
- 21 randomized trials, N=3539
  - Switch (N=293) or add-on (N=1588) psychotherapy vs Treatment As Usual (N=1638)

- Findings
  - Psychotherapy vs TAU: no difference (g -0.13)
  - ***Add-on: improved treatment (g 0.42)***
  - More severe→More effect
  - Group→More effect
  - Lack of association between effect size and number of sessions (not a consistent finding)

HARVARD 2019
(PSYCHOPHARM)



4. Has the patient had an adequate trial of sertraline, escitalopram, or bupropion (if patient does not want to risk having the SSRI-related sexual side effects)?

No

4A. Yes, but if NO response, try one of these (consider patient's reference):

- **Switching** to a different agent from Node 4 (sertraline, escitalopram, or bupropion)
- **Switching** to a dual-action agent (venlafaxine or mirtazapine)
- **Switching** to TMS
- **Switching** to S-adenosylmethionine or St. John's wort
- **Augmenting** with nutrients (omega-3 fatty acid, L-methylfolate, or S-adenosylmethionine) or light therapy
- **Augmenting** with quetiapine, risperidone, or aripiprazole
- **Augmenting** with bupropion or mirtazapine
- **Augmenting** with lithium or T3

4B. Try one of these: sertraline, escitalopram, bupropion

CASE 1: 23YO WITH MDD

- 5 months later, 2017.
- Switched to Escitalopram and titrated up to 20mg qday. She also started doing every other week therapy.
- PHQ9 went from a 21→14
- Currently endorsing significant sleep problems and had been taking Trazodone.

She would like to adjust her treatment.

Meds: Escitalopram 20mg, Trazodone 100mg qhs.

Past Psych Meds: Sertraline

What would you do next?

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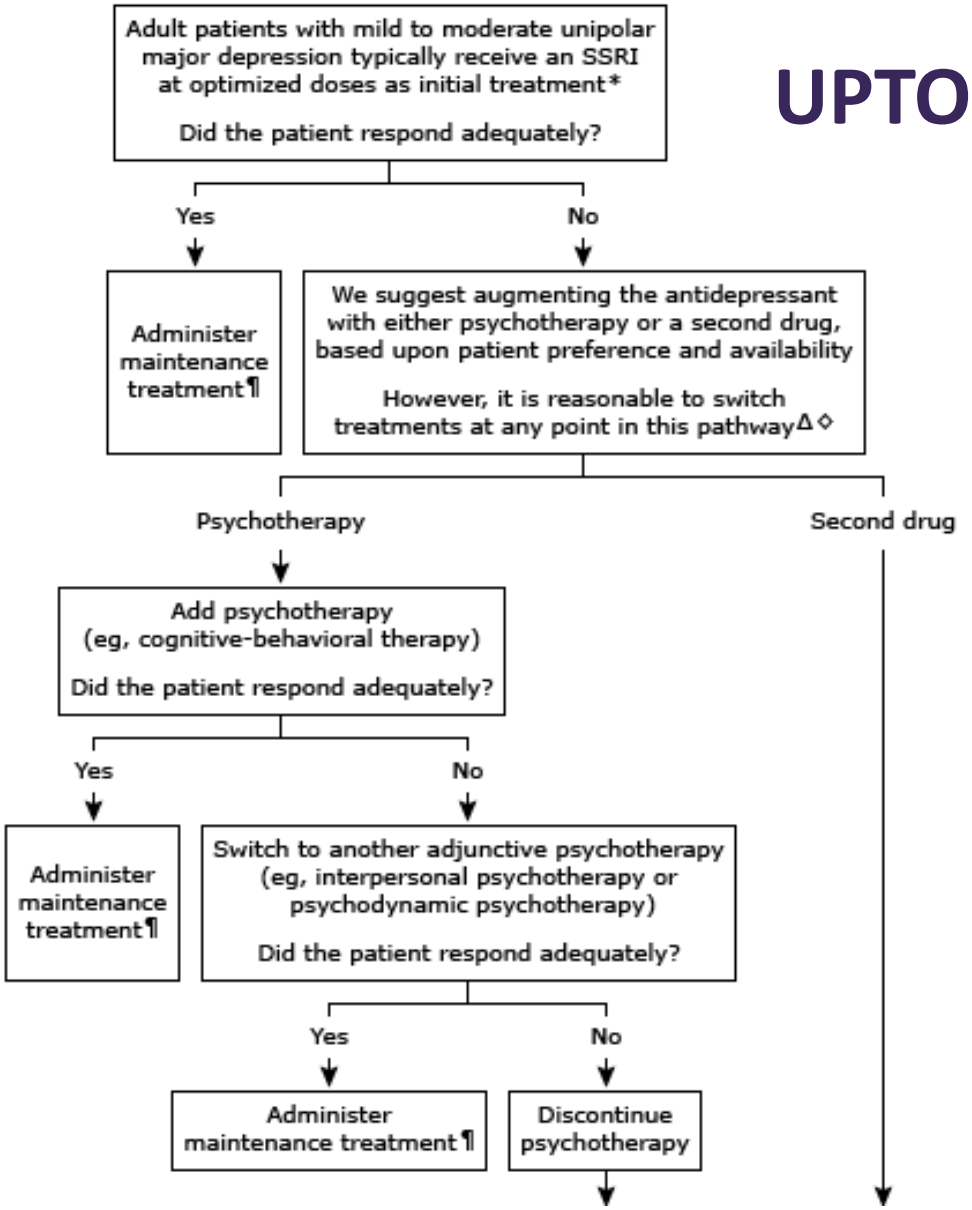

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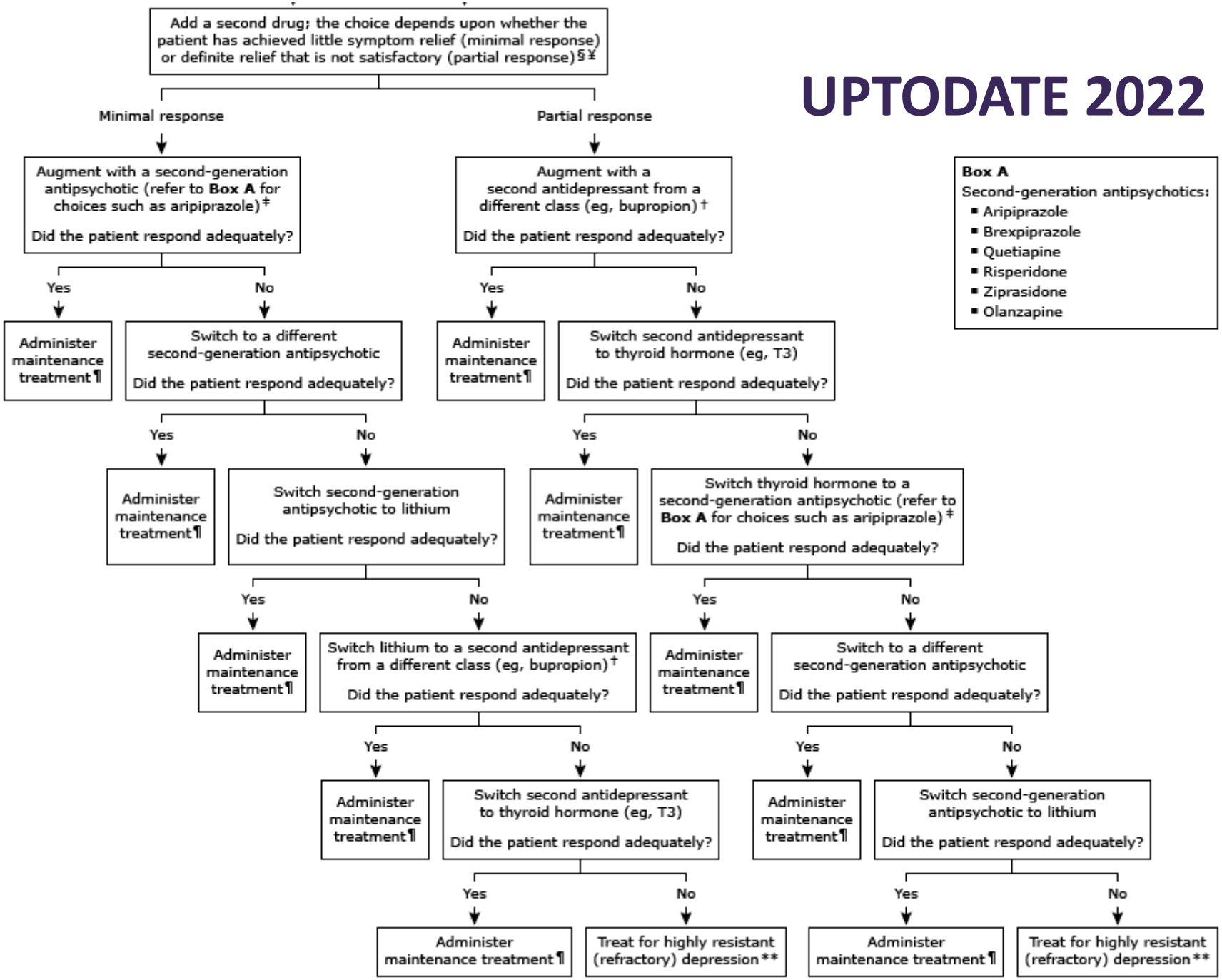

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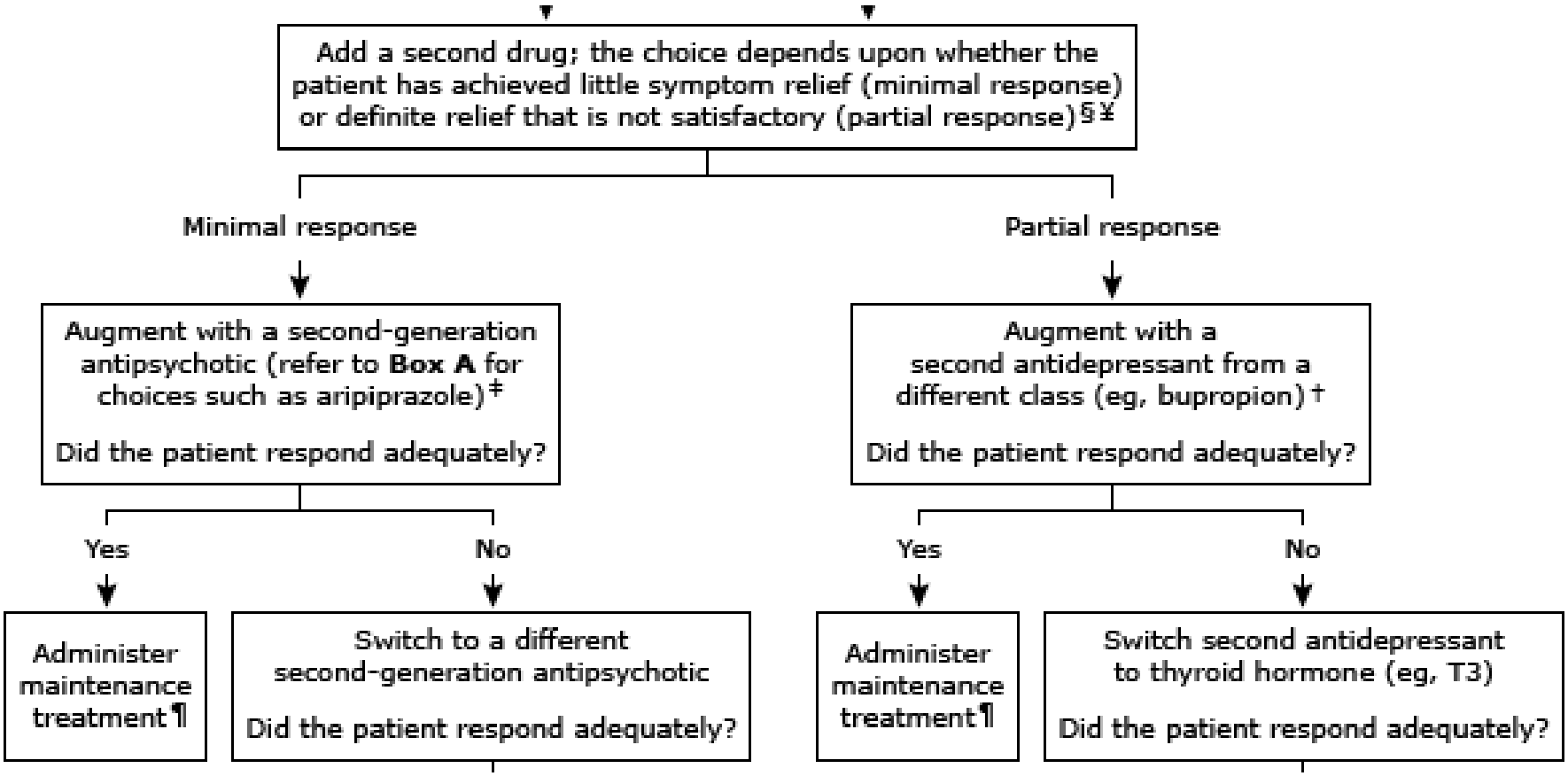

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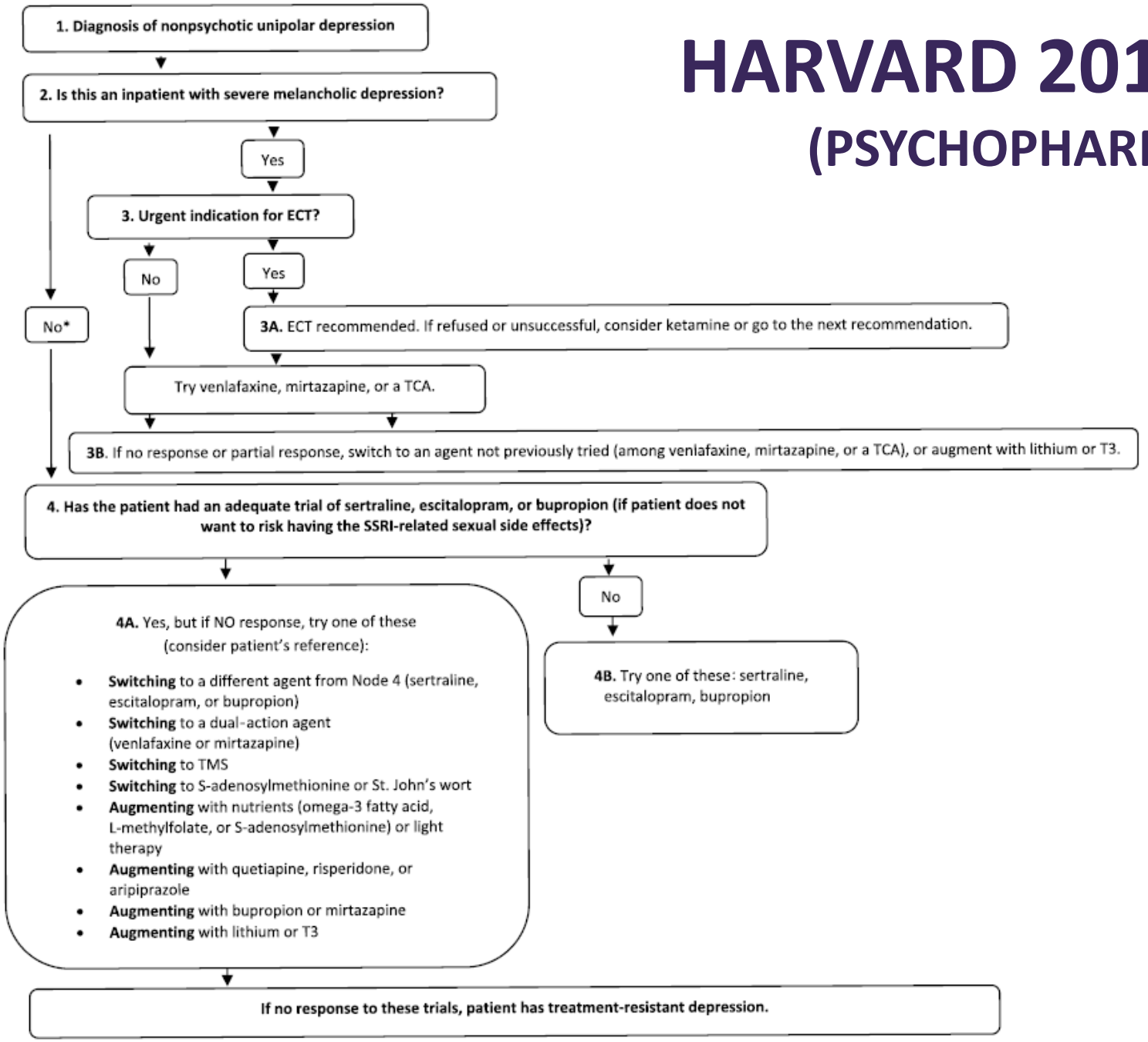
HARVARD 2019
(PSYCHOPHARM)



4. Has the patient had an adequate trial of sertraline, escitalopram, or bupropion (if patient does not want to risk having the SSRI-related sexual side effects)?

No

4A. Yes, but if NO response, try one of these (consider patient's reference):

- **Switching** to a different agent from Node 4 (sertraline, escitalopram, or bupropion)
- **Switching** to a dual-action agent (venlafaxine or mirtazapine)
- **Switching** to TMS
- **Switching** to S-adenosylmethionine or St. John's wort
- **Augmenting** with nutrients (omega-3 fatty acid, L-methylfolate, or S-adenosylmethionine) or light therapy
- **Augmenting** with quetiapine, risperidone, or aripiprazole
- **Augmenting** with bupropion or mirtazapine
- **Augmenting** with lithium or T3

4B. Try one of these: sertraline, escitalopram, bupropion

JAMA Psychiatry | Original Investigation

2022

Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression

A Systematic Review and Meta-analysis

Jonathan Henssler, MD; David Alexander; Guido Schwarzer, PhD; Tom Bschor, MD; Christopher Baethge, MD

- 39 RCTs, 6751 patients
  - Included both first line treatment and treatment resistance
- Findings
  - Combination treatment seems to be more effective vs monotherapy
  - Adding ***α2-autoreceptors*** (mirtazapine, trazodone) was associated with significantly **superior** outcomes vs monotherapy for both **1st line treatment and 2nd line**. (small effect size SMD .2)
  - Bupropion augmentation was barely(?) helpful in non-responders to the first med trial. (SMD 0.17)
  - Treatment effect not associated with baseline severity.

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CASE 1: 23YO WITH MDD

- PHQ9 21→14 on Escitalopram 20mg qday x 5 months. Failed Sertraline trial. Sleep problems.

What would you do next?

a) Augment with Mirtazapine
b) Augment with Aripiprazole
c) Augment with Quetiapine
d) Augment with Bupropion
e) Light Therapy
f) Other

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CASE 1: 23YO WITH MDD

- 2018-2019
- Quetiapine chosen over Mirtazapine to see if it would help with her depressive symptoms quicker as well as her sleep. This did help with sleep, but depressive symptoms persisted and her PHQ9 was a 17. Escitalopram replaced with Bupropion to deal with low energy (Quetiapine?) and ongoing depressive symptoms. Bupropion and Quetiapine helpful for mood and sleep. Over the next 8 months her depression and sleep problems returned, and she could not tolerate Quetiapine over 75mg qhs.

She would like to adjust her treatment.

Meds: Bupropion XL 450mg qday, Quetiapine 75mg qhs
Past Psych Meds: Sertraline, Escitalopram

What would you do next?

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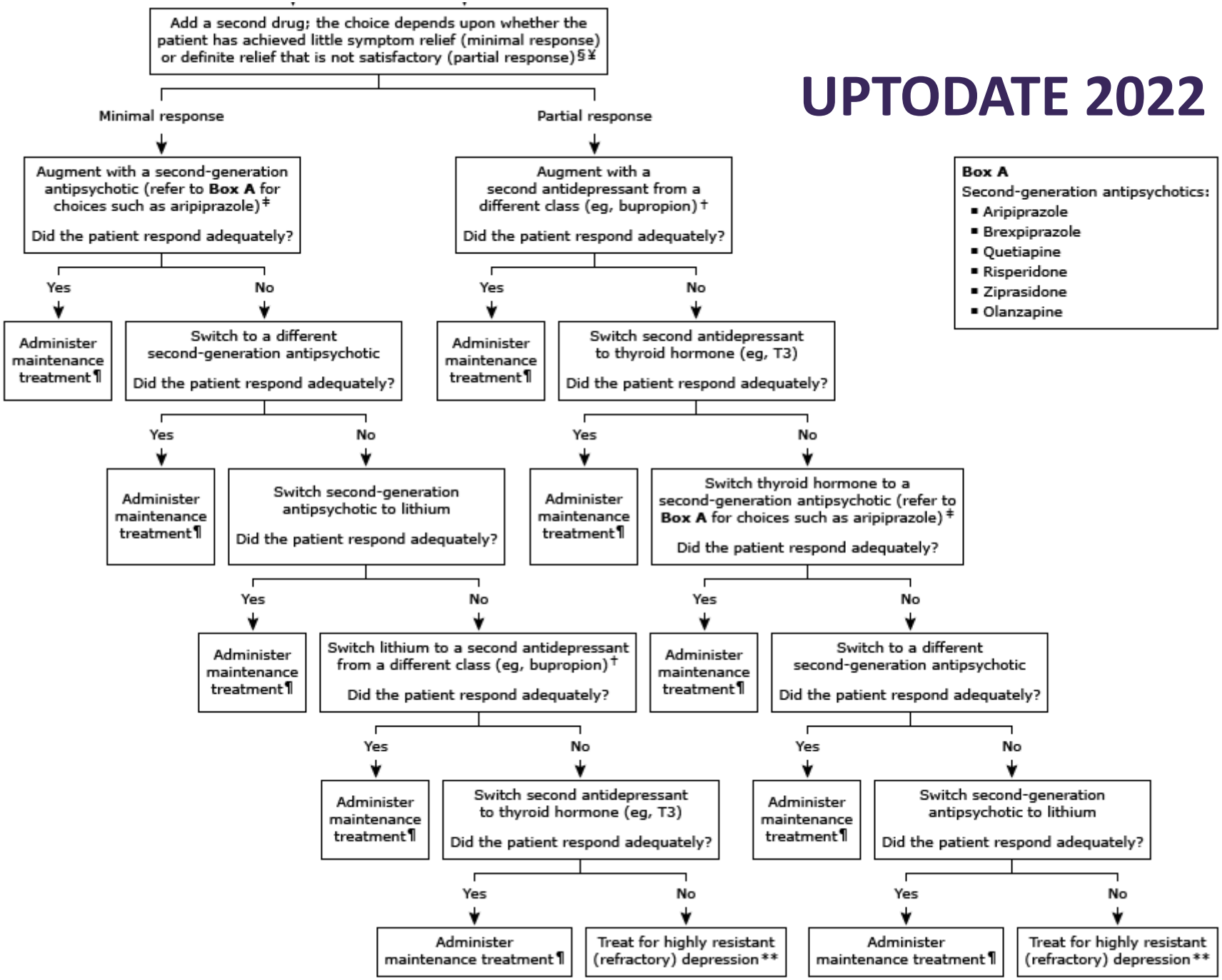
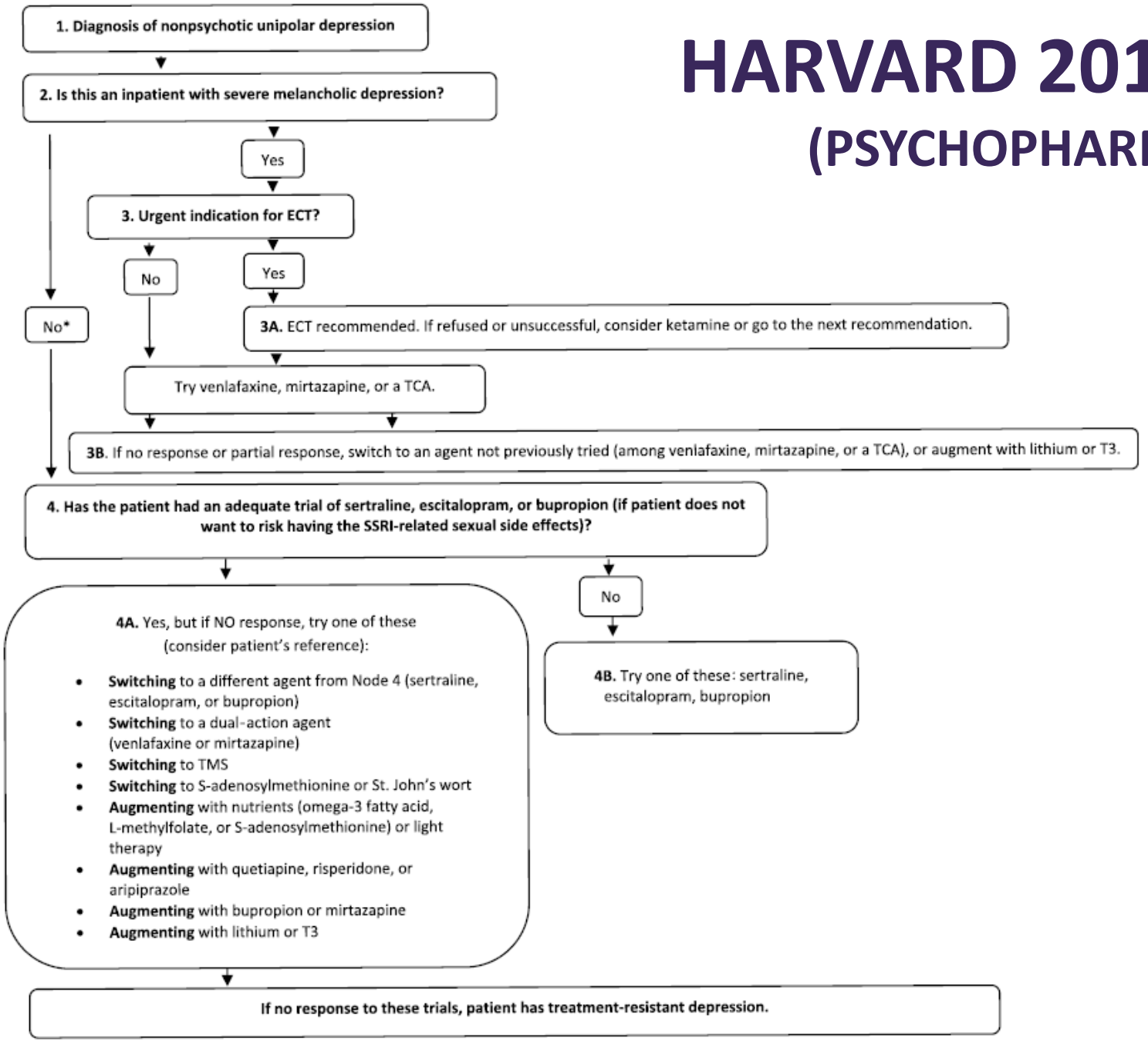
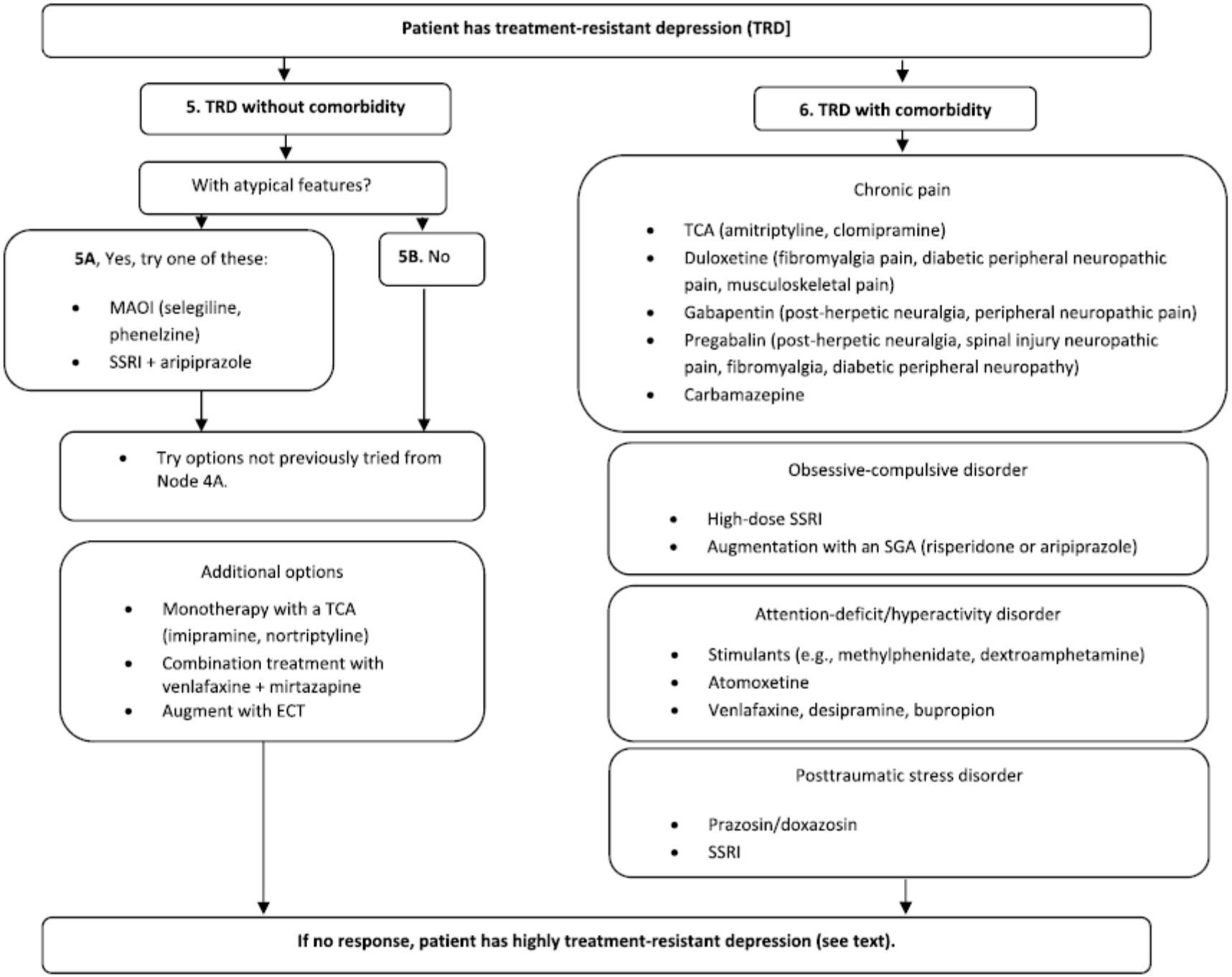


HARVARD 2019
(PSYCHOPHARM)




Patient has treatment-resistant depression (TRD]
5. TRD without comorbidity
With atypical features?
5A, Yes, try one of these:
MAOI (selegiline, phenelzine)
SSRI + aripiprazole
5B. No
Try options not previously tried from Node 4A.
Additional options
Monotherapy with a TCA (imipramine, nortriptyline)
Combination treatment with venlafaxine + mirtazapine
Augment with ECT
6. TRD with comorbidity
Chronic pain
TCA (amitriptyline, clomipramine)
Duloxetine (fibromyalgia pain, diabetic peripheral neuropathic pain, musculoskeletal pain)
Gabapentin (post-herpetic neuralgia, peripheral neuropathic pain)
Pregabalin (post-herpetic neuralgia, spinal injury neuropathic pain, fibromyalgia, diabetic peripheral neuropathy)
Carbamazepine
Obsessive-compulsive disorder
High-dose SSRI
Augmentation with an SGA (risperidone or aripiprazole)
Attention-deficit/hyperactivity disorder
Stimulants (e.g., methylphenidate, dextroamphetamine)
Atomoxetine
Venlafaxine, desipramine, bupropion
Posttraumatic stress disorder
Prazosin/doxazosin
SSRI
If no response, patient has highly treatment-resistant depression (see text).

ADD ANTIPSYCHOTIC OR ANTIDEPRESSANT?

JAMA | Original Investigation

2017

Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment

The VAST-D Randomized Clinical Trial

Somaia Mohamed, MD, PhD; Gary R. Johnson, MS; Peijun Chen, MD, PhD, MPH; Paul B. Hicks, MD, PhD; Lori L. Davis, MD; Jean Yoon, PhD; Theresa C. Gleason, PhD; Julia E. Vertrees, PharmD, BCPP; Kimberly Weingart, PhD; Ilanit Tal, PhD; Alexandra Scrymgeour, PharmD; David D. Lawrence, MS; Beata Planeta, MS; Michael E. Thase, MD; Grant D. Huang, MPH, PhD; Sidney Zisook, MD; and the VAST-D Investigators

- N=1522, MDD, Unresponsive to at least 1 antidepressant, VA population

- Intervention: randomly assigned to 1 of 3 groups
  - Switch to Bupropion
  - Augment with Bupropion
  - Augment with Aripiprazole

VAST-D TRIAL

2017

Results

- Remission Rates at 12 weeks
  - Bupropion switch: 22.3%
  - Bupropion augment: 26.9%
  - Aripiprazole augment: 28.9%

- Anxiety more frequent in Bupropion groups
- Lowest discontinuation and drop outs: Aripiprazole group
- Adverse effects more common in Aripiprazole group (somnolence, akathisia, and weight gain)
  - Weight gain: >7% from baseline in 25% of aripiprazole group

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CASE 1: 23YO WITH MDD

- 1 year later, PHQ9 17
- Meds: Bupropion XL 450mg qday, Quetiapine 75mg qhs
- Past Psych Meds: Sertraline, Escitalopram

What would you like to do next?

a) Refer for TMS/ECT
b) Switch to Mirtazapine from Quetiapine
c) Switch to Aripiprazole from Quetiapine
d) Augment with Lithium
e) MAOI-Trial
f) Other

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CASE 1: 23YO WITH MDD

- 2019-2020
- Quetiapine stopped and Aripiprazole started, which seemed to help. PHQ9 still 16. Aripiprazole increased to 7.5mg qday, which she was taking with Bupropion XL 300mg qday. Past trauma revealed, but she is not ready for therapy. Prazosin started which has helped. Maintaining employment. After 4 months on the Aripiprazole, PHQ9 14, and it was stopped. Anxiety is reportedly higher and Buspirone was started. Over the next 6 months she continued to take Bupropion XL 150mg and Buspirone 20mg BID which subjectively helped, but her PHQ9 remained 17. She was functioning well-working and starting a grad school program. Things got difficult in context of family member's suicide, stopping therapy, and school stopping.

She would like to adjust her treatment.

Meds: Bupropion XL 300mg qday, Buspirone 20mg BID, Prazosin 3mg qhs
Past Psych Meds: Sertraline, Escitalopram, Quetiapine, Aripiprazole

What would you do next?

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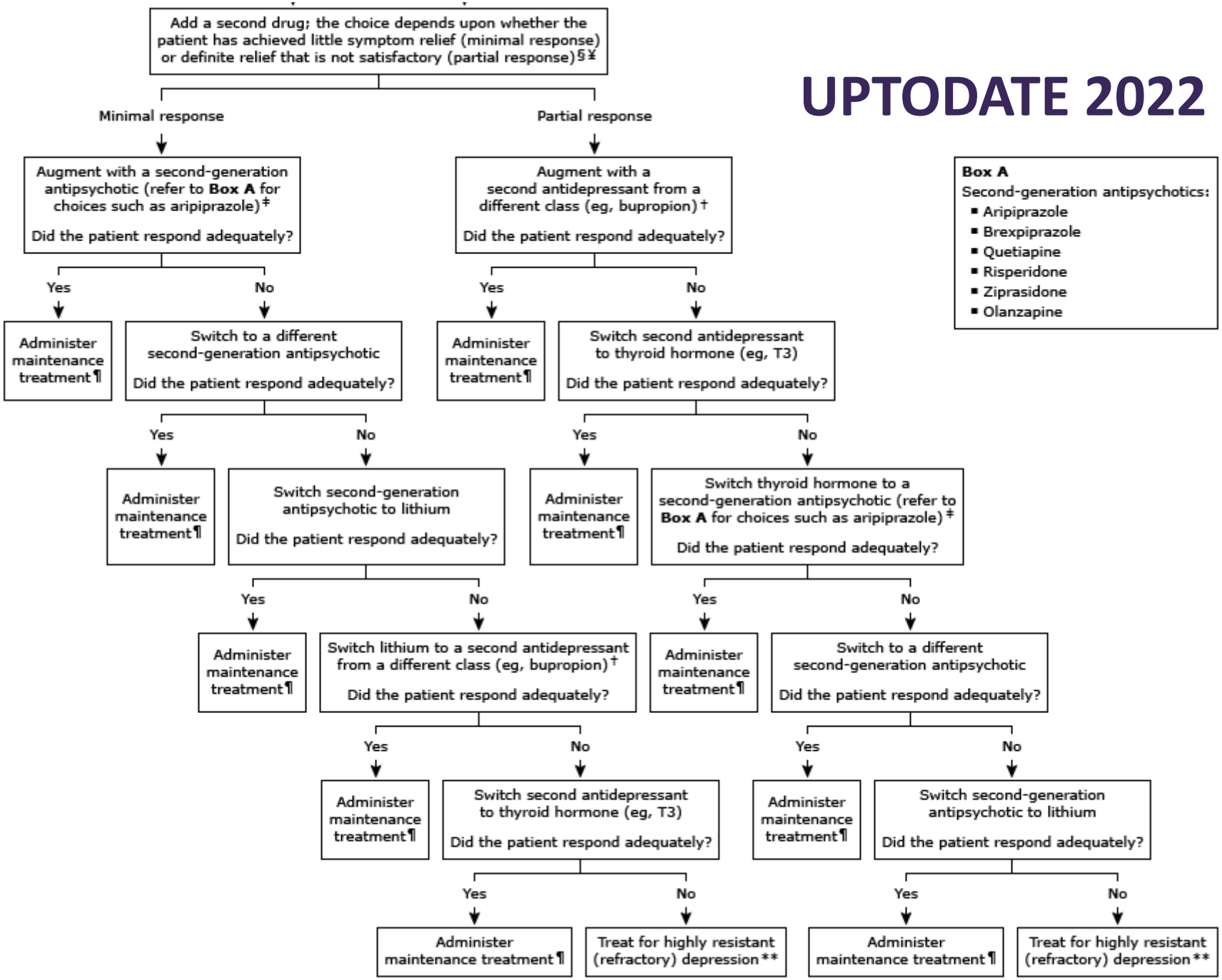

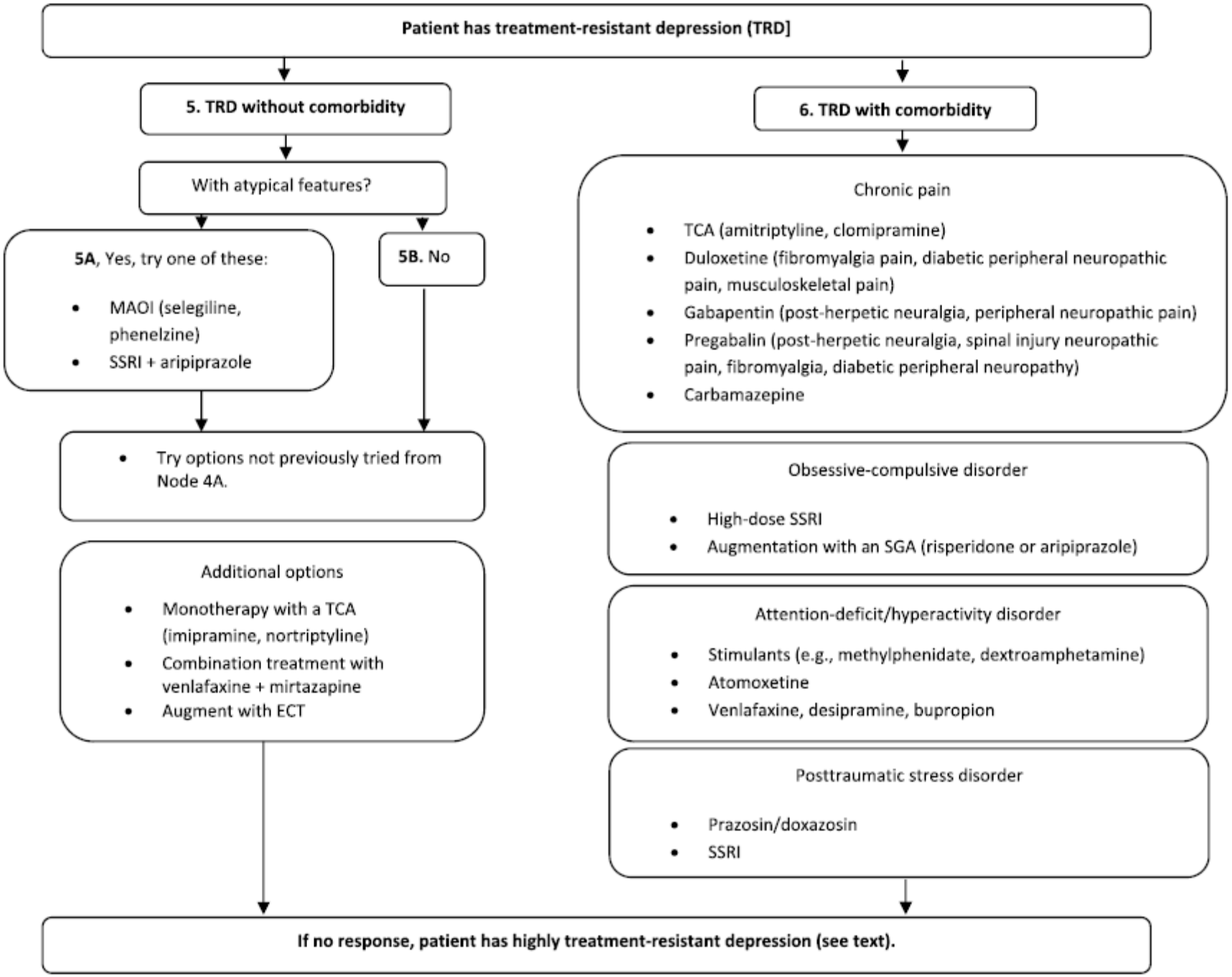
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Atomoxetine
Venlafaxine, desipramine, bupropion
Posttraumatic stress disorder
Prazosin/doxazosin
SSRI
If no response, patient has highly treatment-resistant depression (see text).

WHAT ABOUT PHARMACOGENETIC TESTING?

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PHARMACOGENETIC TESTING?

!!July 12,2022!!

JAMA | Original Investigation

Effect of Pharmacogenomic Testing for Drug-Gene Interactions on Medication Selection and Remission of Symptoms in Major Depressive Disorder

The PRIME Care Randomized Clinical Trial

David W. Oslin, MD; Kevin G. Lynch, PhD; Mei-Chiung Shih, PhD; Erin P. Ingram, BA; Laura O. Wray, PhD; Sara R. Chapman, MS, OTR/L; Henry R. Kranzler, MD; Joel Gelernter, MD; Jeffrey M. Pyne, MD; Annjanette Stone, BS; Scott L. DuVall, PhD; Lisa Soleymani Lehmann, MD, PhD, MSc; Michael E. Thase, MD; and the PRIME Care Research Group

- RCT, N=1944 (VA) with MDD
- Intervention: provision of pharmacogenetic testing to start or switch an antidepressant vs usual care

- Findings
  - 80-90% of participants had none or mod gene-drug interactions
  - Less meds used with drug-gene (45% vs 18%)
  - Remission of symptoms (PHQ9 < 5)
    - 12 weeks: 16.5% (gene testing) vs 11.2% (no gene testing)
    - 24 weeks: not significantly different

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CASE 1: 23YO WITH MDD

- 2019-2020, PHQ9 14
- Meds: Bupropion XL 300mg qday, Buspirone 20mg BID, Prazosin 3mg qhs
- Past Psych Meds: Sertraline, Escitalopram, Quetiapine, Aripiprazole

What would you do next?

a) Revisit diagnosis
b) Refer for Trauma-focused therapy
c) Get pharmacogenetic testing?
d) Start Modafinil
e) Refer for ECT/TMS
f) Other

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CASE 1: 23YO WITH MDD

- 2020-present
- Pharmacogenetic testing was ordered which showed the following.

ANTIDEPRESSANTS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
desvenlafaxine (Pristiq®)	**clomipramine** (Anafranil®)	1	**amitriptyline** (Elavil®)	1,6
levomilnacipran (Fetzima®)	**desipramine** (Norpramin®)	1	**doxepin** (Sinequan®)	1,6
vilazodone (Viibryd®)	**duloxetine** (Cymbalta®)	1	**imipramine** (Tofranil®)	1,6
vortioxetine (Trintellix®)	**fluoxetine** (Prozac®)	1		
	fluvoxamine (Luvox®)	1		
	mirtazapine (Remeron®)	1		
	nortriptyline (Pamelor®)	1		
	venlafaxine (Effexor®)	1		
	selegiline (Emsam®)	2		
	trazodone (Desyrel®)	3		
	citalopram (Celexa®)	1,4		
	escitalopram (Lexapro®)	1,4		
	paroxetine (Paxil®)	1,4		
	sertraline (Zoloft®)	3,4		
	bupropion (Wellbutrin®)	3,6		

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CASE 1: 23YO WITH MDD

- 2020-present
- Pharmacogenetic testing was ordered, and the patient chose to try Levomilnaciprin as she was also having some back and chronic pelvic pain. Prazosin no longer needed and stopped. Bupropion tapered off as it was not helping. Buspirone increased to 30mg BID. **Started Trauma-focused therapy, 7/2021**. Pain has become more of an issue. Mood remains 2-4 (it was a 3 when we started in 2017). Levomilnaciprin at 80mg (max 120mg)
- Last seen: 5/2022, PHQ9 17. But reports mood is better, functioning well at work, and still working with her therapist.

Meds: Levomilnaciprin 80mg qday

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TAKEAWAYS

- Algorthms can be useful to stay within the evidence base, but have their limits.
- Augmenting with psychotherapy is more effective then switching to psychotherapy.
- Augmenting with an antidepressant (esp Mirtazapine) or antipsychotic are evidence-based strategies to address treatment resistant depression as a second line option.
- Pharmacogenetic testing can help sort out additional medication options

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CASE 2: 29YO F WITH 10 YEARS OF MDD

Mood: 3/10-best. Low motivation, tearful, anhedonia-fun activities take a lot of effort. No psychosis. Current med: Mirtazapine 60mg qhs x 1 year, which has helped with SI. Lives at home. No substance use. No psychosis. Master's degree in engineering. Works at family business with parents.

PMH: Brain CA s/p surgery and chemo in remission x years.

Past Psych History

- Diagnoses: PTSD, Depression, Anxiety
- Inpatient: 2016 for depression with SI
- Outpatient: therapy briefly after her sister's death
- Suicide Attempts: took some unknown med, cutting back in 2016
- Past Medications: Duloxetine, Desvenlafaxine, Sertraline, Bupropion, Lithium, Aripiprazole, Modafinil, Buspirone

CASE 2: 29YO F WITH 10 YEARS OF MDD

Mood: 3/10-best. Current med: Mirtazapine 60mg qhs.

- Past Medications: Duloxetine, Desvenlafaxine, Sertraline, Bupropion, Lithium, Aripiprazole, Modafinil, Buspirone

What would you do next?

a) Refer for TMS
b) Refer for ECT
c) Partial hospitalization
d) Refer for Ketamine
e) Start Vilazodone
f) Refer for therapy

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QUESTIONS

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