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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

TREATMENT RESISTANT DEPRESSION

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UW Medicine
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Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ No conflicts of interest

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OBJECTIVES

1. Define treatment resistant depression
2. Highlight the importance of shared decision making
3. Improve confidence using augmentation approaches as the next step in treatment
4. Outline what augmentation approaches are available

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A COMMON PROBLEM

STAR*D Trial

- 37% remission after 1 trial of citalopram
  - N: 3671

Treatment-resistant depression is the norm.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006 Nov;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905. PMID: 17074942.

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RESISTANT VS REFRACTORY?

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

- What is an adequate med trial?

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MEASUREMENT BASED CARE

Why?

- Help Improve Patient Outcomes
  - Clinical judgement alone is not always enough
  - Enhanced precision and effectiveness
  - Help overcome clinical inertia
  - Provide providers monitor clinical effectiveness
  - Allow systems the ability to monitor effectiveness
  - Help streamline assessments
- Increase in remission
  - 53% remission with measure vs 43 % without

Fortney, J et al, 2017
Zhu M, Hong RH, Yang T, Yang X, Wang X, Liu J, Murphy JK, Michalak EE, Wang Z, Yatham LN, Chen J, Lam RW. The Efficacy of Measurement-Based Care for Depressive Disorders: Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Psychiatry. 2021 Sep 28;82(5):21r14034. doi: 10.4088/JCP.21r14034. PMID: 34587377.

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RISK FACTORS FOR TREATMENT RESISTANT DEPRESSION

- Comorbid medical conditions
- Chronic pain
- Comorbid psych conditions
- Severe symptoms
- Personality traits
- Low socioeconomic status

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TREATMENT RESISTANT VS ???

- The correct diagnosis?
- Comorbidities
- Med adherence/adequacy of med trial
  - What medication?
  - Did it help?
  - How long did you take it?
  - What dose?
  - Did you take it consistently?

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CASE 1

23yo F with a history of depression presents with symptoms consistent with a moderate depressive disorder. Patient's unemployment is running out. Finances are tight. 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. Unemployment ran out. 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 a different medication
d) Refer to social work to help with job resources
e) Other?

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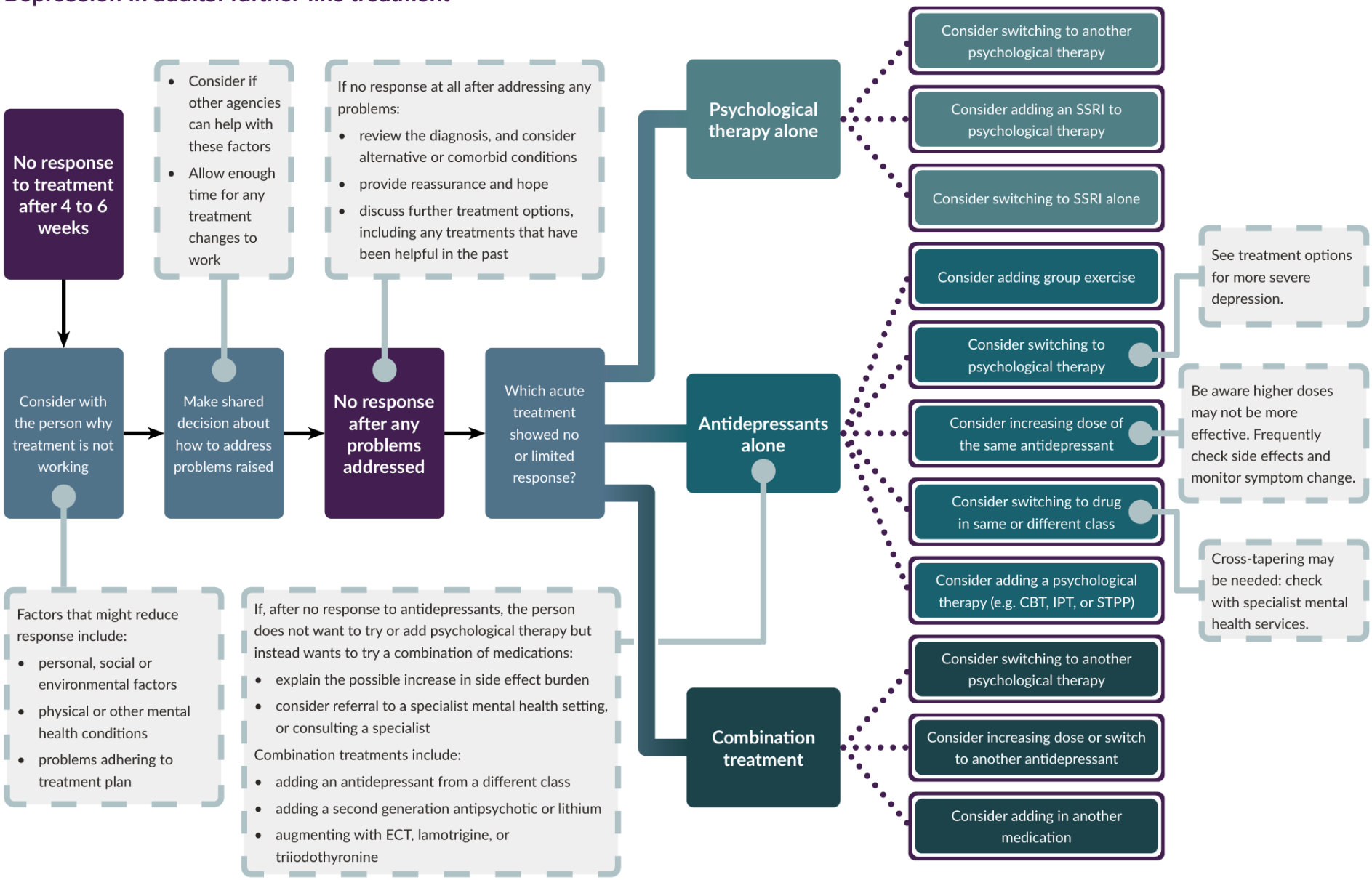
Depression in adults: further-line treatment



NICE National Institute for Health and Care Excellence

This is a summary of some of the advice in the NICE guideline on depression in adults: treatment and management.
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https://www.nice.org.uk/guidance/ng222/resources/furtherline-treatment-pdf-11131007009 -

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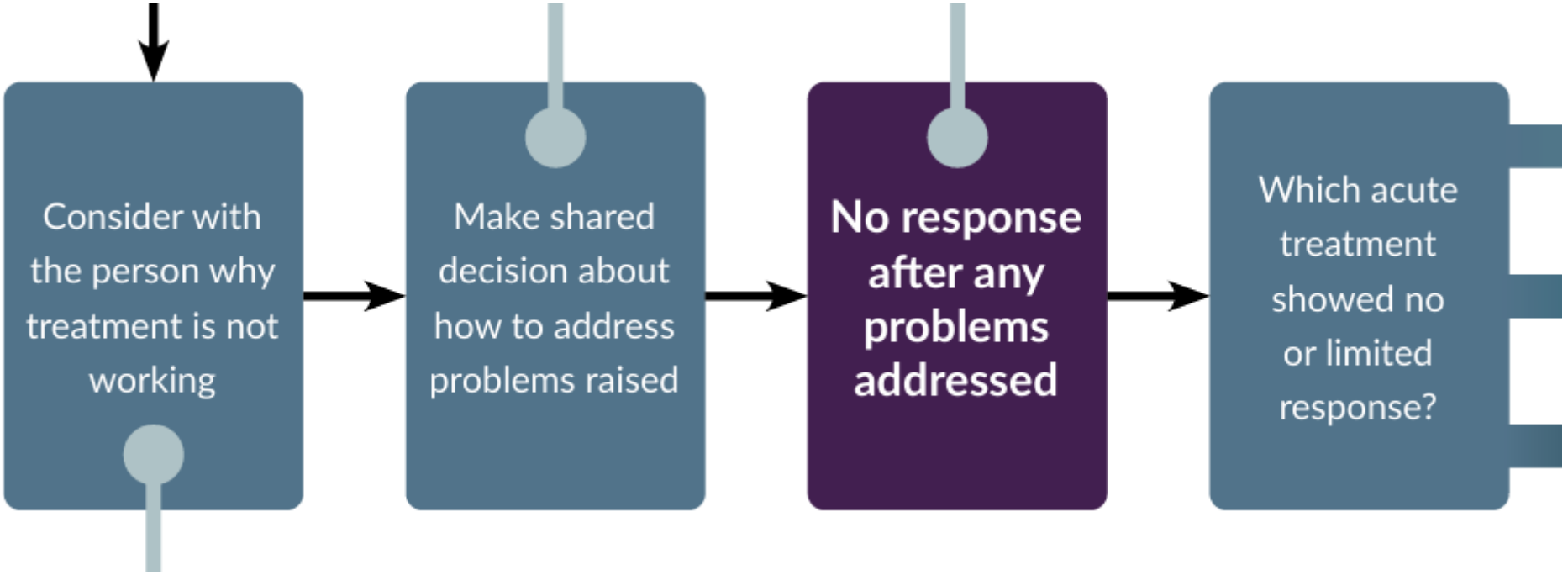
REASONS TREATMENT IS NOT WORKING



- What is the role of stressors in treatment-resistant depression?

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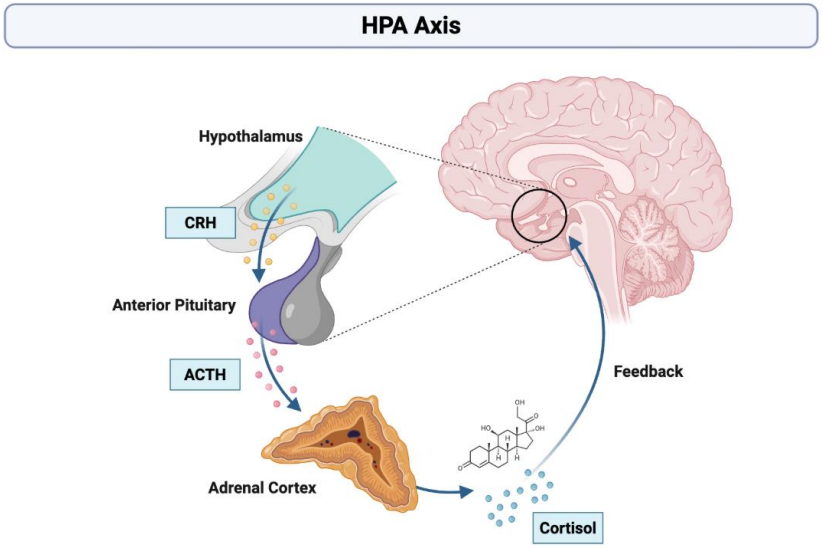
STRESS AND DEPRESSION

- Increase risk of non-remission
- Mediated via activation of hypothalamic-pituitary-adrenal axis and immune system
- **Blunts antidepressant response**



https://app.biorender.com/biorender-templates/details/t-65fc5afb9970e99daa4b45f5-hypothalamic-pituitary-adrenal-hpa-axis

Menke A, Nitschke F, Hellmuth A, Helmel J, Wurst C, Stonawski S, Blickle M, Weiß C, Weber H, Hommers L, Domschke K, Deckert J. Stress impairs response to antidepressants via HPA axis and immune system activation. Brain Behav Immun. 2021 Mar;93:132-140. doi: 10.1016/j.bbi.2020.12.033. Epub 2021 Jan 8. PMID: 33422640.

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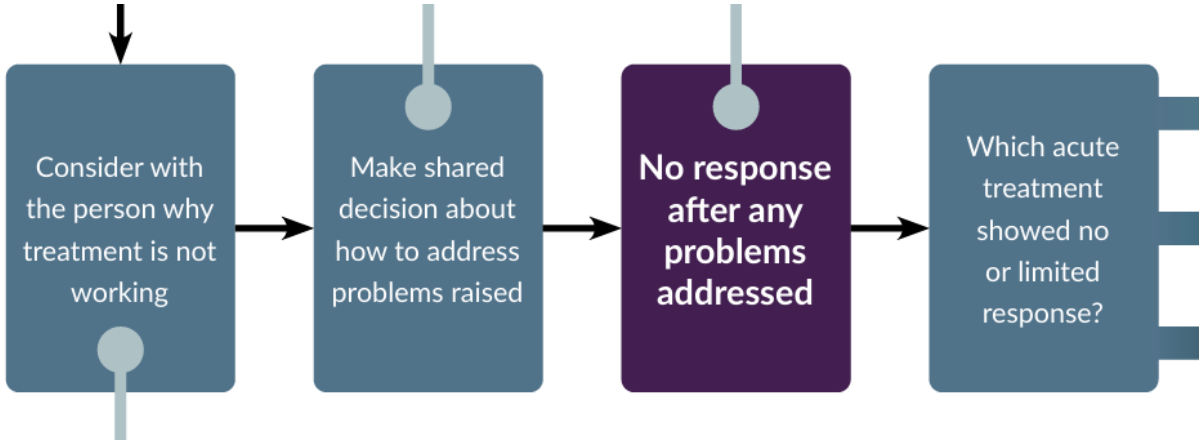
WHAT ARE WAYS TO APPROACH THE IMPACT OF STRESS ON DEPRESSION?



- Multimodal approach
  - Address social issues
  - Stress-reducing therapy
    - Mindfulness based CBT
    - SMART-D (stress management and resiliency training)
  - Meds: antipsychotics, lithium, ketamine→target stress affected areas of brain?

Cladder-Micus MB, Speckens AEM, Vrijsen JN, T Donders AR, Becker ES, Spijker J. Mindfulness-based cognitive therapy for patients with chronic, treatment-resistant depression: A pragmatic randomized controlled trial. Depress Anxiety. 2018 Oct;35(10):914-924. doi: 10.1002/da.22788. Epub 2018 Aug 8. PMID: 30088834; PMCID: PMC6175087.

Seshadri A, Fuller-Tyszkiewicz M, Harper L, Clark MM, Singh B, Chesak S, Kaur AS, McGillivray J, Frye MA. Randomized controlled trial of stress management and resiliency training for depression (SMART-D)-pilot study. PLoS One. 2025 Aug 19;20(8):e0328539. doi: 10.1371/journal.pone.0328539. PMID: 40828809; PMCID: PMC12364347.

Rosa I, Padula LP, Semeraro F, Marrangone C, Inserra A, De Risio L, Boffa M, Zoratto F, Borgi M, Guidotti R, Lorenzo GD, D'Addario C, Pettorruso M, Martinotti G. Endocannabinoids, depression, and treatment resistance: Perspectives on effective therapeutic interventions. Psychiatry Res. 2025 Oct;352:116697. doi: 10.1016/j.psychres.2025.116697. Epub 2025 Aug 16. PMID: 40840197.

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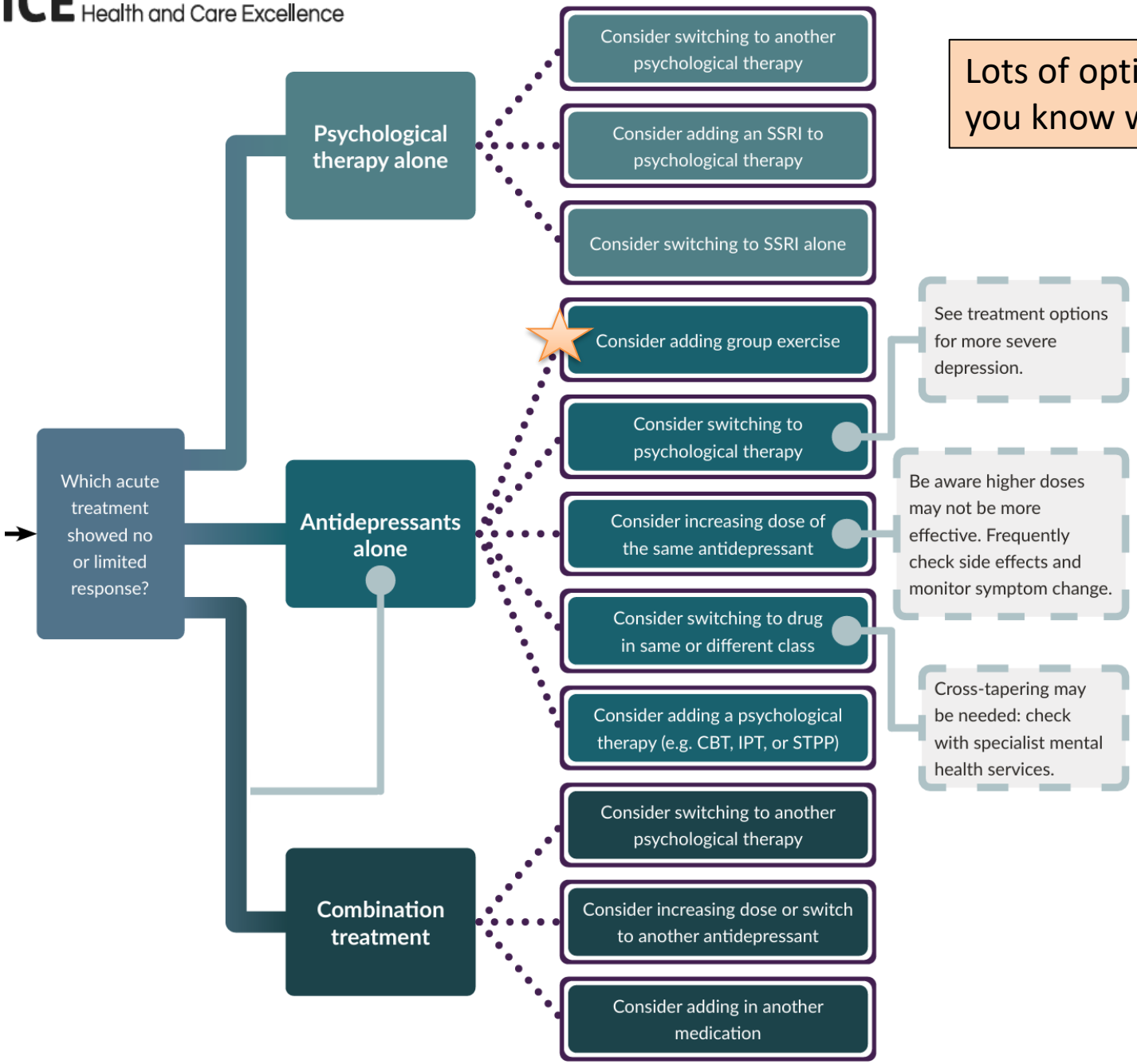

Lots of options-how do you know what is best?

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SHARED DECISION MAKING IN TREATMENT RESISTANT DEPRESSION

Definition

Collaborative process in which clinicians and patients jointly consider clinical evidence, risks, benefits, and patient values to individualize treatment plans

Benefits

Improved patient satisfaction

Engagement in decision making process

Improved med adherence

Improved patient outcomes

Samalin L, Genty JB, Boyer L, Lopez-Castroman J, Abbar M, Llorca PM. Shared Decision-Making: a Systematic Review Focusing on Mood Disorders. Curr Psychiatry Rep. 2018 Mar 27;20(4):23. doi: 10.1007/s11920-018-0892-0. PMID: 29589129.

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TREATMENT OPTIONS TO DISCUSS

- Add a medication
- Switch to a different medication
- Add therapy
  - May be at ***less risk of relapse vs meds*** when treatment is stopped

    Meta-analysis of 7 trials
    - CBT relapse/recurrence: 39%
    - Pharmacotherapy relapse/recurrence: 61%

Vittengl JR, Clark LA, Dunn TW, Jarrett RB. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. J Consult Clin Psychol. 2007 Jun;75(3):475-88. doi: 10.1037/0022-006X.75.3.475. PMID: 17563164; PMCID: PMC2630051.

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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)

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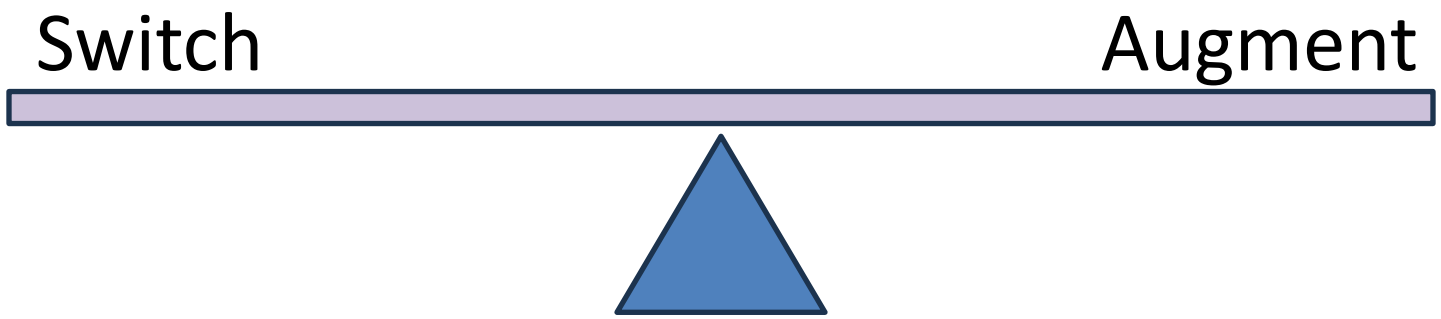
MEDICATION OPTIONS



Evidence suggests that augmentation is slightly more effective than switching.

Avoid adding on more meds.

(Try to keep it to two.)

No evidence for complex regimens.

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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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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

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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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MEDICATION AUGMENTATION

- Second-generation antipsychotics
- Lithium
- Different class antidepressant
- Thyroid hormone

Which one is the right one?

Ask the patient

  - Tolerability vs Efficacy

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ANTIPSYCHOTICS AND TREATMENT RESISTANT DEPRESSION

- Consistent benefit
  - Aripiprazole > risperidone > quetiapine > brexpiprazole
- May have more side effects
  - Avoid Olanzapine
  - If aripiprazole causes akathisia→brexpiprazole
- If no response in 6-12 weeks→switch augmenting option

Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Efficacy and safety/tolerability of antipsychotics in the treatment of adult patients with major depressive disorder: a systematic review and meta-analysis. Psychol Med. 2023 Jul;53(9):4064-4082. doi: 10.1017/S0033291722000745. Epub 2022 May 5. PMID: 35510505; PMCID: PMC10317805.
Frankel JS, Schwartz TL. Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole. Ther Adv Psychopharmacol. 2017 Jan;7(1):29-41. doi: 10.1177/2045125316672136. Epub 2016 Oct 17. PMID: 28101322; PMCID: PMC5228714.

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LITHIUM AND TREATMENT RESISTANT DEPRESSION

- Effective
- Potential reduced risk of suicide
  - Vs placebo
  - Vs TCAs, Lamotrigine
- Needs lab monitoring
  - Lithium toxicity
- Often considered after 2 rounds of antipsychotic augmentation

Nelson JC, Baumann P, Delucchi K, Joffe R, Katona C. A systematic review and meta-analysis of lithium augmentation of tricyclic and second generation antidepressants in major depression. J Affect Disord. 2014 Oct;168:269-75. doi: 10.1016/j.jad.2014.05.053. Epub 2014 Jun 2. PMID: 25069082.
Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry. 2005 Oct;162(10):1805-19. doi: 10.1176/appi.ajp.162.10.1805. PMID: 16199826.

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STILL NO RESPONSE…

- Switch antidepressant-different class
  - SNRIs
  - Serotonin modulator (vilazodone or vortioxetine)
  - Atypicals (mirtazapine or bupropion, Auvelity)

- Transcranial Magnetic Stimulation
  - In treatment resistant depression, response was 4 times more likely with active TMS vs sham

Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ. 2019 Mar 27;364:l1079. doi: 10.1136/bmj.l1079. PMID: 30917990; PMCID: PMC6435996.

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SEVERE DEPRESSION

- PHQ > 20
- Psychosis
- Severe functional impairment
- Catatonia

- Admission?
- ECT
- Ketamine

Anand A, Mathew SJ, Sanacora G, Murrough JW, Goes FS, Altinay M, Aloysi AS, Asghar-Ali AA, Barnett BS, Chang LC, Collins KA, Costi S, Iqbal S, Jha MK, Krishnan K, Malone DA, Nikayin S, Nissen SE, Ostroff RB, Reti IM, Wilkinson ST, Wolski K, Hu B. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. N Engl J Med. 2023 Jun 22;388(25):2315-2325. doi: 10.1056/NEJMoa2302399. Epub 2023 May 24. PMID: 37224232.

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CASE 1: 23YO WITH MDD

- PHQ9 21→19 on Escitalopram 20mg qday x 5 months. Failed Sertraline trial. Sleep problems. Passive SI. Unemployed.

What would you do next?

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

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SUMMARY

- Treatment resistant depression is the norm
- Offer shared decision making
- Augmenting baseline antidepressant with therapy or meds is typically the next step
- Avoid polypharmacy
- Neurmodulation is an option if failed trials persist

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