Depression and anxiety update

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Objectives

- Describe updates on the nonpharmacologic management of depression
- Prescribe appropriate medications for depression or anxiety, when indicated
- Identify appropriate nonpharmacologic therapies for anxiety

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Guideline updates

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1. American College of Physicians guideline on the treatment of acute depression in adults

- Systematic review + expert panel
- Patient-oriented outcomes (patient preferences/values)
- GRADE guidelines
- Recommendation for mild depression:
  - CBT
- Recommendation for moderate-severe depression:
  - CBT or SSRI/SNRI based on patient preference or a combo
- For non-responders:
  - Switching or augmentation with CBT, or switching or augmentation with medication

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2. VA/DOD guideline for major depression

- Systematic review + expert panel
- Screen for depression
- Use tools to monitor response to treatment
- Treat uncomplicated depression with psychotherapy or meds
  - Vague on specifics, but SSRIs/SNRIs
- Combo therapy for those with severe or refractory symptoms

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3. NICE guidelines for depression

- UK National Institute for Health and Care Excellence
- Recommend using not just symptom screeners but also functional impairment and history
- Less severe symptoms: CBT or group therapy
- More severe: CBT with meds or either alone
- Recommend lithium or antipsychotics for treatment-resistant depression

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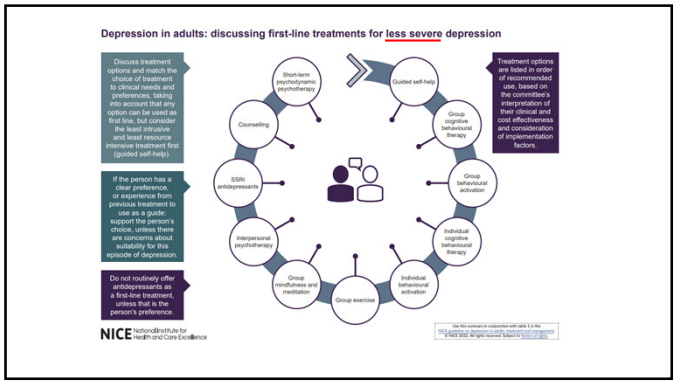

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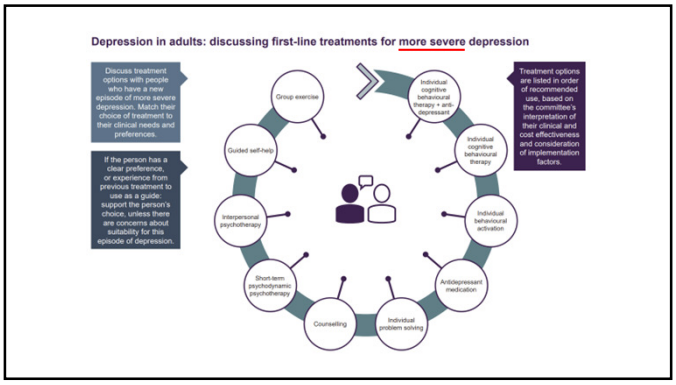

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Non-drug therapies for depression

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Exercise improves depression scores in older adults

- Systematic review and meta-analysis
- 80 studies, 5500 adults, average age in each study >65 years
  - Most at high or moderate risk of bias
- Evaluated effects of different kinds of exercise on depression scores
- Assessed patients with and without depression at baseline

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Exercise improves depression scores in older adults

Table 1. Describing the effect of each exercise modality on depression in older adults, stratified by baseline depression levels.

Exercise modality Sub-group	SMD [95% CI]	N. effect size	I^2%	*P*-value
Aerobic exercise				
Depressed	**−0.42 [−0.84, −0.01]**	7	75%	.043
Non-depressed	**−0.29 [−0.46, −0.12]**	14	12%	<.001
Resistance exercise				
Depressed	**−1.20 [−1.82, −0.59]**	11	85.5%	<.001
Non-depressed	**−0.34 [−0.53, −0.15]**	10	0	<.001
Mixed exercise				
Depressed	−0.28 [−0.67, 0.11]	8	78%	.166
Non-depressed	−0.18 [−0.42, 0.07]	7	25%	.166
Mind–body exercise				
Depressed	**−0.62 [−0.94, −0.31]**	14	67%	<.001
Non-depressed	**−0.47 [−0.67, −0.14]**	13	8%	<.001

Note: Cells in bold indicate significant results.

SMD values between 0.2 and 0.5 are small effect sizes, values between 0.5 and 0.8 are medium effect sizes, and values higher than 0.8 are large effect sizes

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6. Exercise prescriptions for patients with depression

- Systematic review and network meta-analysis
- 218 (!) studies; 14,000 patients with mild to severe depression
  - ~60% high risk of bias, often unblinded studies
- No benefit:
  - Counseling for exercise
  - Participant choice of activity
- Some benefit:
  - Prescribed exercise interventions included classes, walking, yoga, strength training
- More exercise/higher intensity was better

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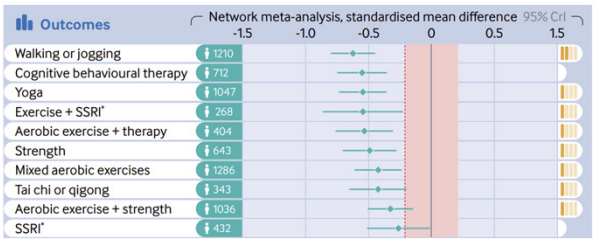
6. Exercise prescriptions for patients with depression



SMD values between 0.2 and 0.5 are small effect sizes, values between 0.5 and 0.8 are medium effect sizes, and values higher than 0.8 are large effect sizes

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7. Bright light therapy for nonseasonal depression

- Systematic review and meta-analysis
- 11 trials; 860 patients
- Bright light therapy with 10,000 lux x 30 minutes daily
- Control typically regular light, dim red light, or no light, with or without SSRI

- Bright light better than control
  - Remission: OR 2.42 (1.50-3.91)
  - Response to tx: OR 2.34 (1.46-3.75)
  - Remission within 4 weeks: OR 3.59 (1.45-8.88)
  - Remission after 4 weeks: OR 2.18 (1.19-4.00)
  - Response > and <4 weeks as well

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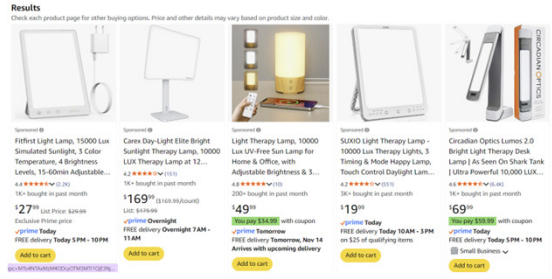
10,000 Lux light therapy: approximate cost



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8. Among psychedelics, only psilocybin has demonstrated benefit to treat depression

- Systematic review and network meta-analysis
- 15 RTCs; 810 patients with depression
- Compared trials of psychedelics, including MDMA, LSD, ayahuasca, and psilocybin
  - Generally small trials
  - Also included 4 trials of escitalopram for comparison in the NMA
- One concern with studies of psychedelics is lack of true masking/blinding due to effects of meds

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8. Among psychedelics, only psilocybin has demonstrated benefit to treat depression

- Compared psychedelics to
  - Studies with psychedelics + placebo
  - Studies with SSRI + placebo
- Compared high, low, and very dose dose psilocybin and MDMA
  - Escitalopram 10 and 20 mg
- Single trial compared escitalopram 20 mg to high dose psilocybin (20mg +)

- All psychedelics are better than placebo when compared head-to-head
- High dose psilocybin and ayahuasca are clearly better than the placebo response found in antidepressant trials
- High dose psilocybin has a small effect when compared to extremely low-dose psilocybin

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9. Single-dose esketamine for post-partum depression

- Randomized controlled trial
- 364 pregnant participants with at least mild depression at the time of delivery
- Randomized to esketamine 0.2mg/kg IV at the time of cord clamp or saline placebo
- Followed for 42 days
- Primary outcome was major depressive episode

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9. Single-dose esketamine for post-partum depression

Not used in this trial!

Outcomes
- Major depressive episode
  - Esketamine: 6.7%
  - Placebo: 25.4%
- HAM-D score of "no depression"
  - Esketamine: 71.1%
  - Placebo: 39%
- Neuropsych side effects
  - Esketamine: 33.5%
  - Placebo: 11.1%

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Treatment-resistant depression

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10. Esketamine is superior to quetiapine for remission of treatment-resistant depression

- Randomized controlled trial of patients with treatment-resistant depression
  - Persistent depression after 2-6 medications from at least 2 drug classes
- 811 patients screened->run in period->676 randomized
  - Esketamine nasal spray at tapering doses
  - Quetiapine 50 mg tapering to 300 mg
- Followed for 32 weeks
- Primary outcome was remission on the Montgomery-Åsberg Depression Rating Scale (score of <10) at week 8

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10. Esketamine is superior to quetiapine for remission of treatment-resistant depression

Used in this trial!

Adverse events leading to discontinuation
- Esketamine: 4.2%
- Quetiapine: 11%

Hospitalization for worsening depression or suicide was similar in both groups

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11. Single-dose psilocybin is beneficial in the short term for treatment-resistant depression

- Randomized controlled trial of patients with treatment-resistant depression
  - Persistent depression after 2-4 medications from at least 2 drug classes
- 233 patients randomized to receive
  - 1 mg psilocybin
  - 10 mg psilocybin
  - 25 mg psilocybin
- Followed for 3 weeks
- Primary outcome was change in the Montgomery–Åsberg Depression Rating Scale

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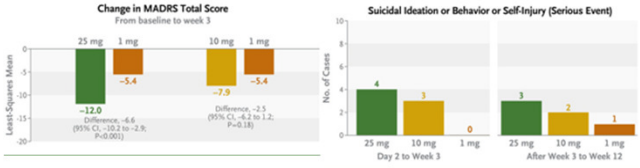
11. Single-dose psilocybin is beneficial in the short term for treatment-resistant depression



Small differences in outcomes, serious adverse effects to know about

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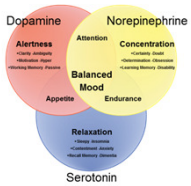
12. Combination antidepressant therapy for acute severe depression and nonresponding depression

- Systematic review and meta-analysis
- 39 trials; 6700 patients
- Comparing initiating a single antidepressant with initiating two antidepressants
  - Big range of medication combos: SSRI + TCA; SSRI + mirtazapine; SSRI + bupropion
- Follow up varied but generally <12 weeks



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12. Combination antidepressant therapy for acute severe depression and nonresponding depression

Results	SMD
All included studies	0.31 (0.19-0.44)
Initial + bupropion, all comers	0.10 (-0.07 – 0.31)
Initial + bupropion, initial non-responders	-0.17 (0.02-0.31)
Initial + bupropion, first line dual	0.04 (-0.20-0.29)
SSRI/SNRI + mirtazapine, all comers	0.37 (0.19-0.55)
SSRI/SNRI + mirtazapine, initial non-responders	0.24 (0.03-0.45)
SSRI/SNRI + mirtazapine, first line dual	0.64 (0.12-1.15)

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Anxiety updates

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13. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders

- Systematic review and meta-analysis
- 69 RCTs, 4100 patients
- Comparing CBT to control
- Range of therapies and controls
  - Individual, group, internet
  - Wait list, active controls, pill placebos, relaxation, education
- Follow up included short term (1-6 months) and longer term (6-12; 12+ months)

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13. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders

Diagnosis	Hedges g: End of Treatment (95% CI)	Hedges g: 1–6 Months (95% CI)	Hedges g: 6–12 Months (95% CI)	Hedges g: >12 Months (95% CI)
GAD	0.39 (0.12 to 0.66)	0.07 (−0.50 to 0.63)	0.40 (0.13 to 0.67)	0.22 (0.02 to 0.42)
Panic Disorder	0.22 (0.01 to 0.43)	0.27 (−0.01 to 0.55)	0.35 (0.11 to 0.59)	0.14 (−0.19 to 0.47)
Social Anxiety Disorder	0.38 (0.19 to 0.57)	0.60 (0.36 to 0.85)	0.34 (0.07 to 0.61)	0.42 (0.04 to 0.79)
Specific Phobia	0.49 (0.13 to 0.84)	0.72 (0.01 to 1.44)	NA	NA
PTSD	0.72 (0.52 to 0.93)	0.67 (0.46 to 0.88)	0.59 (0.42 to 0.77)	0.84 (0.03 to 1.64)
OCD	0.70 (0.29 to 1.12)	0.85 (0.47 to 1.22)	NA	NA

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14. Pharmacological treatments for GAD

- Systematic review and network meta-analysis
- 89 trials, 25,000 patients
- Range of medications
  - Most compared active med to placebo
- Follow up time varied
  - 4-26 weeks; median 8 weeks
- Most used the HAM-A as an outcome assessment
- Most studied medications were better than placebo with similar side effects
- Meds with bigger sample sizes were more likely to show benefit

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14. Pharmacological treatments for GAD

- Meds that were effective with decent acceptability:
  - Duloxetine
  - Pregabalin
  - Venlafaxine
  - Escitalopram
- Probably effective with decent acceptability (limited by sample size)
  - Mirtazapine
  - Sertaline
  - Fluoxetine
  - Buspirone
- High effectiveness, low tolerability
  - Quetiapine
  - Benzodiazepines
  - **Paroxetine**

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Bottom lines

- Recent guidelines are starting to emphasize accurate diagnosis of depression and first line talk therapy for non-severe depression.
- Effective non-drug options for depression include exercise and bright light therapy.
- High-dose psilocybin is slightly better than escitalopram for moderate to severe depression, but other psychedelics do not appear to be effective.
- Esketamine and psilocybin may be useful for treatment-resistant depression.
- Consider combination therapy for severe or non-responding depression.

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