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Increasing Your Confidence in Treating Pediatric Depression and Anxiety

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Feeling confident with what you recommend

- What might happen without treatment?
- What treatments work?
 - Data in the literature
 - Clinical experience*
- Availability of treatment*

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Depression

Some statistics to consider

- Adolescent depression affects 12-25% of adolescents
- Onset prior to age 12 linked to poor functioning, suicide attempts, more lifetime depression, psychiatric comorbidity.
- Generally associated with poor academic, social, and health outcomes; substance abuse, early pregnancy and parenthood, and increased healthcare costs
- Suicide is the 2nd leading cause of death for our youth ages 10-24
- More teenagers and young adults die from suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia, influenza, and chronic lung disease, **COMBINED**
- Despite these statistics, 80 % of adolescents do not receive appropriate treatment

CDC and Lewandowski RE, Auri MC, Hoagwood KE, Offton M, Clarke G, Gardner W, Scholle SH, Byron S, Kelleher K, Pincus HA, Frank S, Horwitz SM. Evidence for the management of adolescent depression. Pediatrics. 2013 Oct;132(4):e996-e1009

The Natural History of Depression

- 1580 high school students 14-18 yo
- Mean age of onset of first episode of MDD was 14.9
- MDE duration mean 26.4 weeks, median 8.0 weeks
 - Previous studies: Mean 32-36 weeks, median 16 weeks
- Relapse:
 - 5% within 6 months
 - 12% within a year
 - 33% within 4 years
- Previous studies: 26% relapse in 1 year, 40% in 2 years

Levinsohn et al. Major Depression in Community Adolescents: age at onset, episode duration, and time to recurrence. JAACAP 1994 33(6):809

TADS - Conclusions

- Treatment of depression with fluoxetine alone or in combo with CBT accelerates response
- Adding CBT to meds enhances the safety of meds
- Therefore, combined treatment superior to monotherapy



Initial treatment of depression

- Mild/uncomplicated/brief
 - Psychoeducation
 - Supportive management - active listening and reflection, restoration of hope, problem solving, coping skills, and strategies for maintaining participation in treatment
 - Case management – environmental stressors in family and school
- Moderate
 - CBT (or IPT)
 - Consider SSRI – not responding, not ready for therapy
- Severe/suicidal ideation
 - CBT (or IPT) and SSRI

Birmaher et al. J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY. 46:11, NOVEMBER 2007



Which SSRI to start with?

- Fluoxetine – multiple positive RCTs, FDA approved 8 and up
 - Very little SI signal in controlled studies
 - Long half life means no withdrawal symptoms from missed doses
 - Covered by all plans, and available generic
 - Available in once a week dosing:
 - Start patient on short acting fluoxetine and stabilize at 20 mg dose
 - Then stop fluoxetine 20 mg/day and start fluoxetine 90 mg/week capsule 7 days after last 20 mg dose
 - Caution: Medication interactions



Fluoxetine in the press this year!

August 2016 Lancet article by Cipriani et al. "Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis".

- Meta-analysis of 34 RCT's for the acute treatment of MDD, included 5260 patients
- For SSRI monotherapy for depression in adolescents, Fluoxetine is the only antidepressant with statistically significant change from placebo
- Take home: Fluoxetine should be first line treatment if choosing an SSRI for a depressed teen with moderate-to-severe depression without access to psychotherapy or who is not responding to therapy alone



Which SSRI to start with? (cont.)

- Sertraline* – 1 positive RCT
- Citalopram* – 1 positive RCT
 - Caution: QT prolongation, doses over 40 mg not recommended and caution advised with other QT prolonging medication or meds/conditions that would decrease citalopram metabolism
- Escitalopram – 1 mixed result RCT (only adolescent subset positive), FDA approved 12 and up

* Not FDA approved for depression treatment <18



Medicating Major Depression

- Start low, go slow
- Change one medicine at a time
- Use the full dose range, wait 4-6 weeks before each increase



Predictors of poor response to SSRIs with/without CBT

- Depression severity and chronicity
- Hopelessness
- Suicidal ideation
- Family conflict
- Functional impairment
- History of abuse
- Non-suicidal self injury (NSSI)
- Older age and lower family income (TADS study)
- Comorbidity (TADS)



Treatment of Resistant Depression in Adolescents (TORDIA)

- Design
 - 334 12-18 y.o. with MDD that had not responded to 2 mo on SSRI
 - Switch to: (1) 2nd SSRI, (2) 2nd SSRI and CBT, (3) venlafaxine, (4) venlafaxine and CBT
 - 12 weeks blind, 12 more open
- Results
 - Rates of response (12 weeks):
 - CBT plus either med 54.8% > med alone 40.5%
 - No difference in response between 2nd SSRI and venlafaxine
- Adverse Effects
 - No differential treatment effects on SI
 - More AEs with venlafaxine
 - increase diastolic BP and pulse
 - skin problems
 - associated with a higher rate of self-harm adverse events in those with higher SI



¹ Brent et al. JAMA 2008; 299:3001
² Ernst et al. Am J Psychiatry 2010; 167:792-794
³ Brent et al. Am J Psychiatry 2009; 166:418-426

TORDIA - Conclusions

- For adolescents with depression not responding to first SSRI:
 - Continued treatment results in remission in approximately 1/3 of patients
 - Eventual remission is evident within the first 6 weeks in many
 - Earlier intervention may be important
 - Switch to 2nd SSRI just as efficacious as a switch to venlafaxine
 - SSRI had fewer adverse effects
 - Combo of CBT + new med > new med alone



Once things stabilize. . .

- Treatment should be continued for 6 to 12 months during the continuation phase
 - Patients typically seen at least monthly, depending on clinical status, functioning, support systems, environmental stressors, motivation for treatment, and the presence of comorbid psychiatric or medical disorders.
- General rule of thumb: the longer it takes to recover or the higher the # of recurrences, the longer the period of maintenance.
 - ≥ 2 episodes of depression, 1 severe episode, or chronic episodes should have maintenance treatment for > 1 yr.





Anxiety

The natural history of anxiety

- Harvard/Brown Anxiety Research Project
 - Adult patients of psychiatric clinics
 - Remission at one year
 - Panic disorder - ~40%
 - Panic disorder with agoraphobia - ~15%
 - Social phobia - ~7%
 - GAD - ~10-15%
 - Remission at 8 years
 - Panic disorder - ~70-75%
 - Panic disorder with agoraphobia - ~35-40%
 - Social phobia - ~30%
 - GAD - ~45-55%



Yonkers et al. Depression and Anxiety 17: 173 (2003)

The natural history of anxiety

- Cumulative Probability of Relapse after 8 years
 - Panic disorder - ~20-65% (gender variable)
 - Panic disorder with agoraphobia - ~40-50%
 - Social phobia - ~30%
 - GAD - ~40%
- Important points
 - Anxiety disorders are chronic in majority of men and women
 - Patients who experienced remission were more likely to improve during first 2 years

Yorkers et al. Depression and Anxiety 17:173 (2003)



Child/adolescent Anxiety Multimodal Study (CAMS)

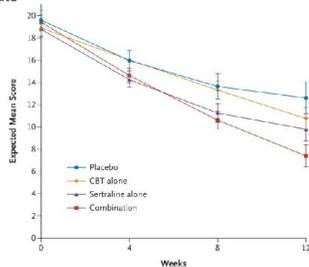
- Design
 - 488 7-17 y.o. with SAD, GAD or SP
 - 14 sessions of CBT, sertraline, combo, or placebo
 - 12 weeks
- Results
 - Very much or much improved:
 - 80.7% combo
 - 59.7% CBT
 - 54.9% sertraline
 - 23.7% placebo
 - Pediatric anxiety rating scale, similar results
 - SI no more frequent in sertraline than placebo, no suicide attempts



Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety. Walkup et al. *NEJM* 2008; 359(20): 2713

CAMS - Conclusion

- CBT and sertraline both work, combo of the two has superior response rate



CAMS - Conclusion

- CBT and sertraline both work, combo of the two has superior response rate



The Pediatric OCD Treatment Study (POTS)

- Design
 - 112 7-17 y.o. with OCD
 - Sertraline, CBT, combo, or placebo
 - 12 weeks
- Results
 - Improvement in CY-BOCS
 - Combo>CBT=sertraline>placebo
 - Clinical remission
 - Combo 53.6%
 - CBT 39.3%
 - Sertraline 21.4%
 - Placebo 3.6%
 - No patient became suicidal or made an attempt
- Conclusion
 - Youth with OCD should begin with CBT or CBT plus SSRI



Screening Measures for Anxiety—SCARED (child and parent versions)

- Free, ages 9-17
- Broad screen for global anxiety
- Also has subscales for specific anxiety diagnoses
- Brief version for tracking over time
- Available in several languages

Triggering is considered as child respondent age 2-8 and ≤ 18

Subscale	Trigger subscale when score ≥	Trigger respondent
Panic Disorder	7	Child, Parent (if account exists)
Generalized Anxiety	9	Child, Parent (if account exists)
Separation Anxiety	5	Child, Parent (if account exists)
Social Anxiety	8	Child, Parent (if account exists)
School Avoidance	3	Child, Parent (if account exists)

• Signs are based on cutoff scores developed by Dismukes and Colegrove
See Dismukes, B., Brent, D.A., Chappetta, L., Budge, J., Moga, S., & Baugher, M. (1999). Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): A replication study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(10), 1230-4.



Additional screeners for anxiety

- SPENCE Children's Anxiety Scale <http://scasweb.site>
 - Free, has child, parent and teacher scales
 - Ages 3-17
 - Available in many (28+) languages
 - 44 item measure for child and 38 item measure for parent
 - Screens for somatization, panic, GAD, separation anxiety and social phobia
- GAD7
 - Free
 - Brief, only 7 questions
 - Validated for ages 14 and up
 - Scores 0-21 with >5 (mild), >10 (moderate), >15 (severe)
 - Total score >10 should trigger extended evaluation

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Lava B, DuBois C, Muller S, Blumenthal E, Schatzberg D, Heston W, Heston P, Y
 Validation and psychometric properties of the Generalized Anxiety Disorder Screener (GAD-7) in the general population.
 Med Care. 2008;Mar;46(3):258-74

Initial treatment of anxiety

- Mild
 - CBT (or other therapy)
- Moderate
 - CBT
 - Consider SSRI- esp. if not responding, not ready for therapy
- Severe
 - CBT and SSRI

Corody et al. J. Am. Acad. Child Adolesc. Psychiatry. 2007;46(2):267-283

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Anxiety Medications

Starting at a very low dose of SSRI for the first week or two with anxiety disorders is especially essential to reduce the child's experience of side effects (augmented by associated somatic anxieties).

Drug Name	Dosage Form	Usual starting dose for adolescents	Increase increment (after 1-4 weeks)	RCT anxiety treatment benefits in kids	FDA anxiety approved for children?	Editorial Comments
Fluoxetine (Prozac)	10, 20, 40 mg 20mg/5ml	5-10 mg/day (60 max)*	10-20mg**	Yes	Yes (For OCD>7yr)	Long 1/2 life, no SE from a missed dose
Sertraline (Zoloft)	25, 50, 100 mg 20mg/ml	25 mg/day (200 max)*	25-50mg**	Yes	Yes (For OCD >6yr)	May be prone to SE from weaning off
Sertraline and Fluoxetine are both first line medications for child anxiety disorders, per the evidence base						
Fluvoxamine (Luvox)	25, 50, 100 mg	25 mg/day (300 max)*	50 mg **	Yes	Yes (For OCD >6yr)	Often more side effect than other SSRI's, has many drug interactions
Paroxetine (Paxil)	10, 20, 30, and 40 mg 10mg/5ml 11.5, 25, 37.5 mg CR forms	5-10 mg/day (60 max)*	10-20mg**	Yes	No	Not preferred if child also has depression. Can have short 1/2 life
Citalopram (Celexa)	10, 20, 40 mg 10mg/5ml	5-10 mg/day (40 max)*	10-20mg**	Yes	No	Very few drug interactions
Escitalopram (Lexapro)	5, 10, 20mg 5mg/5ml	2 1/2 to 5 mg/day (20 max)*	5-10mg**	No	No	No generic form. Active isomer of citalopram

* Recommend decrease maximum dosage by at least 1/3 for pre-pubescent children
 ** Recommend using the lower dose increase increments for younger children.
 Successful medication trials should continue for 6-12 months

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After two SSRIs don't work - anxiety

- Venlafaxine* (Effexor XR) – 2 positive RCTs combined in one to get benefit
 - Side effect profile makes this a 2nd tier option
- Mirtazapine* (Remeron) – no controlled trials
 - Consider if need sedation and appetite stimulation
- Buspirone* (Buspar) – 2 negative RCTs in youth with GAD
- Benzodiazepines*
 - Have not shown efficacy in RCTs with youth
 - Risk of tolerance and dependence
 - When used for severe anxiety - adjunctively & short term
- Beta-blockers*- no controlled trials
 - Used for performance anxiety
- Antihistamines- no controlled trials
 - Hydroxyzine used for as adjunctive, often for insomnia/anticipatory anxiety
- Tricyclic antidepressants
 - Clomipramine shown to be efficacious in OCD, FDA approved ≥ 10yo
 - Anticholinergic side effects, cardiac monitoring, risk of fatality with overdose



Conolly et al. J. Am. Acad. Child Adolesc. Psychiatry. 2007;46(2):207-215

*Not FDA approved for anxiety treatment <18



Other common concerns and recent updates

Sleep Troubles

- Commonly impacted by both depression and anxiety
- Impact from SSRIs
 - Serotonergic REM suppression may cause decreased dream frequency
 - Increased periodic limb movements of sleep
 - Vivid dreams
- Sleep hygiene
- CBT-Insomnia
- Sleep meds: no medication labeled for insomnia in children by FDA
 - Melatonin: 3-5 mg, 1 hour before bedtime
 - Diphenhydramine: 12.5-25 mg starting dose, max 50 mg QHS, short term only
 - Trazodone: 25-50 mg QHS, max 200 mg QHS
 - inhibits CYP 2D6, use with caution with fluoxetine or paroxetine, it may decrease their effect



SSRI Risk Benefits

TABLE 7 SSRI Side Effects

Side Effect	Management
Gastrointestinal distress	Typically self-resolves Symptomatic care
Headache	Typically self-resolves Symptomatic care
Appetite change	Counsel on healthy nutrition
Sedation	Administration at bedtime
Sleep disturbance	Administration in morning Counsel on sleep hygiene Consider melatonin as needed
Diaphoresis	No action if mild
Sexual side effects	Consider medication change
Activation (agitation, agitation, irritability, silly)	If persistent and significant, discontinue medication
Platelet dysfunction (rare)	Discontinue medication

If any symptoms are severe, prescriber may decrease medication dose or switch to another.



Southernmalkosane C, Schmitz K. Pediatric Psychopharmacology for Treatment of ADHD, Depression, and Anxiety. Pediatrics. 2015 Aug; 136(2):351-9. doi: 10.1542/peds.2014-1581. Epub 2015 Jul 6. Review.

SSRI Risk Benefits

TABLE 8

SSRI Benefit to Suicidal Risk Comparison

Diagnosis	Number Needed to Treat	Number Needed to Harm
Depression	10*	112
OCD	6	200
Non-OCD anxiety	3	143

- Data from ref 60. OCD, obsessive-compulsive disorder.
- * High number needed to treat likely secondary to high placebo response rate in pediatric depression studies (30% to 60% compared with 40% to 70% SSRI response rate). SSRI efficacy has been established, but pooled studies and this high number needed to treat underscore the importance of individualizing treatment.



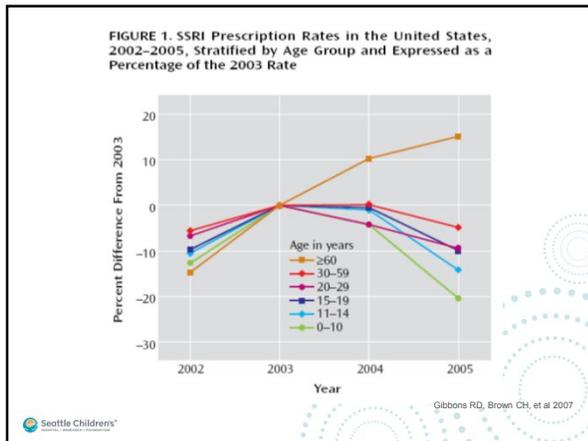
Southernmalkosane C, Schmitz K. Pediatric Psychopharmacology for Treatment of ADHD, Depression, and Anxiety. Pediatrics. 2015 Aug; 136(2):351-9. doi: 10.1542/peds.2014-1581. Epub 2015 Jul 6. Review.

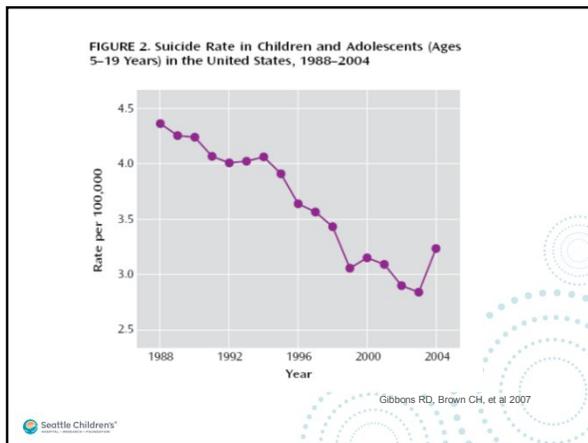
Discussing the black box warning

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PROZAC or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PROZAC is approved for use in pediatric patients with MDD and Obsessive Compulsive Disorder (OCD).







Black box warning, recent meta-analyses

- Bridge et al, JAMA. 2007;297:1683-1696
 - Meta-analysis of 27 RCTs for antidepressants relative to placebo for pediatric MDD and anxiety (OCD and non-OCD)
 - Results:
 - Overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt.
 - Pooled risk of suicidal ideation/suicide attempt for each indication were all less than 1%.
 - Depending on treatment indication, NNT ranges from 3 to 10, while NNH via emergence of suicidal ideation/suicide attempt ranges from 112 to 200

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Black box warning, recent meta-analyses (cont.)

- Conclusions:
 - Relative to placebo, antidepressants are efficacious for pediatric MDD and anxiety disorders
 - Effects strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD.
 - Benefits of antidepressants appear to be much greater than risks from SI/suicide attempt across indications
 - Comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.
 - "We believe that the strength of evidence presented here supports the **cautious and well monitored use** of antidepressant medications as one of the first-line treatment options"



Black box warning, recent meta-analyses

Gibbons et al, Arch Gen Psychiatry. Published online February 6, 2012

- Looked at >30 adult (fluoxetine and venlafaxine) and 4 youth (fluoxetine) studies
- Results:
 - Fluoxetine and venlafaxine decreased suicidal thoughts and behavior for adult and geriatric patients.
 - For youths, no significant effects of treatment on suicidal thoughts and behavior were found, although depression responded to treatment.
 - No evidence of increased suicide risk was observed in youths receiving active medication (fluoxetine).



Black box warning, recent meta-analyses

- Sharma et al. BMJ. 2016; 352:i65
 - Looked at meta-analysis of data from clinical study reports on double blind placebo controlled trials of SSRI medications
 - included 70 studies of duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine
 - included 18,526 patients, both adult and teen data was included.
 - mortality, suicidality, aggressive behavior and akathisia were outcome measures
 - No deaths in children or teens in the study
 - Odds ratios were 2.39 (1.31 –4.33) for suicidality, 2.79 (1.62-4.81) for aggression and 2.15 (0.48-9.65) for akathisia.
 - Values >1 indicate higher risk with drug than placebo
 - In children and adults, the **risk of suicidality and aggression doubled**
 - Argued morbidity data missing and misreported from reports likely underestimates potential harms



Refusal to engage in therapy

- Help him/her learn more about what therapy really is
 - http://www.dartmouthcoopproject.org/TeenMental/Cognitive_Behavioral2_PT.html
- Educate patient and family on the benefits of therapy
- Remind him/her that therapists are different, therapies are different, and the future experience may be nothing like the past
- Suggest starting with self-guided therapy
- Take a motivational stance



Motivational Interviewing

- Goal is to increase motivation to change
- Change talk is elicited from patient, rather than imparted by provider
- Has shown effectiveness in many types of behavior change, including
 - Adults with obesity
 - Teens with substance use
- Can be used at any point in treatment



MI Principles and Strategies

- Express empathy
- Develop discrepancy
- Avoid argumentation
- Roll with resistance
- Support self-efficacy
- Ask open-ended questions
- Listen reflectively
- Affirm
- Summarize
- Elicit self-motivational statements



Motivational Interviewing

- Brief Negotiation
 - <http://www.kphealtheducation.org/roadmap/index.html>
- <http://www.motivationalinterview.org>



Self-guided therapy (depression and anxiety)

- For parents:
 - Helping Your Anxious Child: A Step-by-Step Guide for Parents (Rapee et al).
 - Freeing Your Child From Anxiety: Powerful, Practical Solutions to Overcome Your Child's Fears, Worries, and Phobias. (Tamar Chansky)
 - Freeing Your Child From Negative Thinking: Powerful, Practical Strategies to Build a Lifetime of Resilience, Flexibility and Happiness. (Tamar Chansky)
 - The Depressed Child: Overcoming Teen Depression (Kaufman)
- For children:
 - What to Do When You Worry Too Much: A Kid's Guide to Overcoming Anxiety (Huebner and Matthews).
 - What to Do When Your Brain Gets Stuck (Huebner)
 - Taking Depression to School (2002), (Kathy Khalsa)
 - Where's Your Smile, Crocodile? (Clair Freedman)



Self-guided therapy (depression and anxiety)

- For adolescents/young adults:
 - Mastery of Your Anxiety and Worry: Workbook (Craske and Barlow)
 - Mastery of Your Anxiety and Panic: Workbook (Barlow and Craske)
 - Riding the Wave Workbook (Pincus et al)
 - Feeling Good: The New Mood Therapy (David Burns)
 - Relaxation Exercises
 - http://www.dartmouthcoopproject.org/TeenMental/using_relaxation_TN.html
 - http://palforkids.org/docs/Care_Guide/Anxiety_Care_Guide.pdf (Relaxation Therapy Tip Sheet)
 - Depression Self Care
 - <http://www.dartmouthcoopproject.org/TeenMental/teen-resources.html>



Useful Apps: mood and anxiety

- Positive Penguins: educational app to help kids understand why they feel the way they do and help them challenge their negative thinking
 - <http://positivepenguins.com/>
- Breathe2Relax: app designed by the National Center for Telehealth & Technology to teach breathing techniques to manage stress
- Worry Box: app to track worries
- Bellybio: interactive, guided deep breathing
- Optimism: mood tracking app



Useful apps: sleep

- Bedtime meditations for kids: guided meditations
- Deep Sleep with Andrew Johnson: guided progressive muscle relaxation to target anxiety and insomnia
- isleep: guided meditations with music for sleep





Questions?