



# Juvenile Depression

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# Disclosure (Past 12 Months)

- Dr. Wagner has received honoraria from Axsome Therapeutics, Physicians Postgraduate Press, Klingenstein Foundation, and Doris Duke Charitable Foundation.

# Off-Label Use

- Medications discussed in this presentation are off-label for the acute and maintenance treatment of major depression in youth, with the exception of fluoxetine and escitalopram

# National Trends in Prevalence of Depression in Adolescents

2005  
8.7%

2017  
13.2%

52%  
Increase

Source: National Survey on Drug Use and Health (n=212,913 adolescents, ages 12-17 years)  
Twenge JM, et al. *J of Abnormal Psychology*. 2019;128(3):185-199.



# Suicide Rates 2007–2018

## Ages 10 – 24 Years

|             |             |
|-------------|-------------|
| <u>2007</u> | <u>2018</u> |
| 6.3%        | 10.7%       |
| Per 100,000 | Per 100,000 |

57.4%  
Increase

Source: National Vital Statistics Reports. 2020. State Suicide Rates Among Adolescents and Adults Aged 10-24: United States, 2000-2018. Volume 69, Number 11.  
<https://www.cdc.gov/nchs/data/nvsr/nvsr69/nvsr-69-11-508.pdf>



# Long-Term Outcome of Adolescent Depression

- 140 adolescents with depressive disorders
- Psychosocial and/or antidepressant treatment
- Outcome 3-9 years (mean 6yrs)
  - 93% full remission from index episode
  - 53% recurrence of depressive disorder
  - 79% developed non-mood disorder (anxiety, substance use, eating disorders)
  - Only 15% had no subsequent depressive episode or other non-mood disorder

Melvin GA et al. *J Affective Disorders*. 2013, 151:298-305.

# Long-Term Psychosocial Outcomes of Adolescent Depression

- Meta-analysis of 31 articles on adult psychosocial outcomes in adolescents with and without depression
- Outcome
  - Adolescent depression associated with:
    - Failure to complete secondary school
    - Unemployment
    - Pregnancy / Parenthood

Clayborne ZM et al. *J Am Acad Child Adolesc Psychiatry*. 2019;58(1):72-79

# Major Factors Associated with Depression in Youth

- Parental depression
- Child abuse
- Bullying
- Substance abuse

1 - Weissman MM, et al., *American Journal of Psychiatry*. 2015 Apr 21;172(5):450-9; Lewinsohn PM, *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995 Sep 30;34(9):1221-9.

2 - Côté SM, et al., Why Is Maternal Depression Related to Adolescent Internalizing Problems? A 15-Year Population-Based Study. *J Am Acad Child Adolesc Psychiatry*. 2018 Dec;57(12):916-924. doi: 10.1016/j.jaac.2018.04.024. Epub 2018 Sep 20. PMID: 30522737.

3 - LeMoult J, et al. Meta-analysis: Exposure to Early Life Stress and Risk for Depression in Childhood and Adolescence. *J Am Acad Child Adolesc Psychiatry*. 2020 Jul;59(7):842-855. doi: 10.1016/j.jaac.2019.10.011. Epub 2019 Oct 30. PMID: 31676392.





# FDA Approval for **Acute** Treatment of Major Depressive Disorder

| <u>Medication</u>             | <u>Ages</u>  |
|-------------------------------|--------------|
| <b>Fluoxetine (3 studies)</b> | <b>8-17</b>  |
| <b>Escitalopram (1 study)</b> | <b>12-17</b> |

Prozac Prescribing Information. Lexapro Prescribing Information.

Emslie GJ et al. *Arch Gen Psychiatry*, 1997; 54:1031–1037; Emslie GJ et al, *J Am Acad Child Adolesc Psychiatry*, 2002;41:1205–1215. Treatment for Adolescents with Depression Study (TADS) Team. *JAMA*, 2004; 292:807–820. Emslie GJ et al: *J Am Acad Child Adolesc Psychiatry*. 2009; 48:721–729.



# Meta-analysis of Antidepressant Trials Depression in Youth

|                        | Response Rates |
|------------------------|----------------|
| <b>Antidepressants</b> | 61%            |
| <b>Placebo</b>         | 50%            |

Bridge JA et al, *JAMA*. 2007; 297:1683-1696.

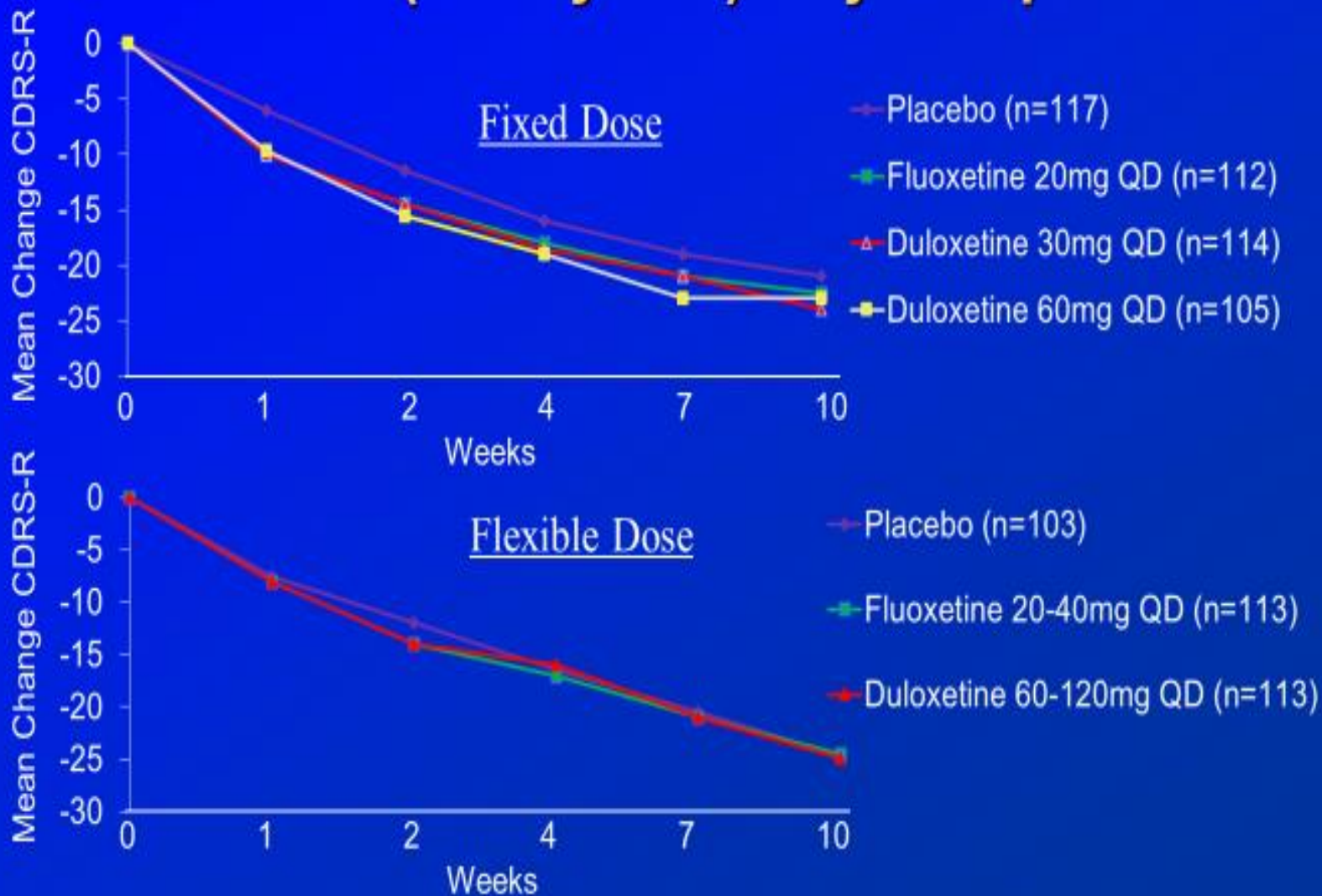
# Selegiline Treatment for Adolescent Depression

- 308 adolescents ages 12-17 with major depression
- Randomized to selegiline transdermal system flexible dosing (6 mg/24h, 9 mg/24h, or 12 mg/24h) or placebo

| CDRS-R   | EMSAM® | Placebo |
|----------|--------|---------|
| Baseline | 56.7   | 57.9    |
| Endpoint | 35.4   | 36.4    |

EMSAM: selegiline transdermal system. Delbello MP et al, *J Child Adol Psychopharm*. 2014; 24:1-7

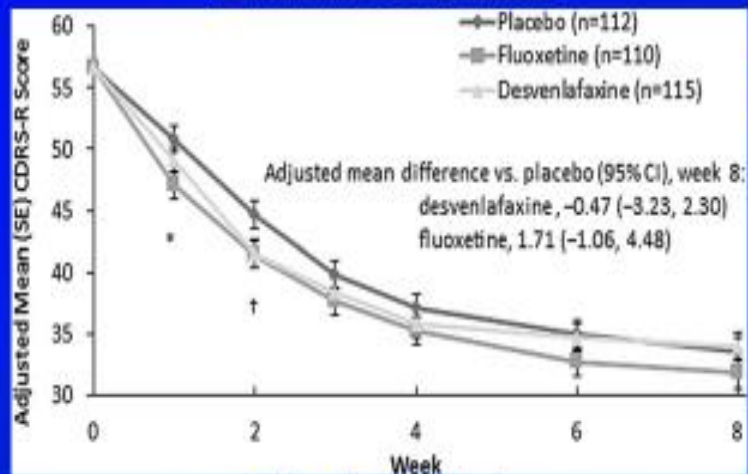
# Controlled Trials of Duloxetine for Pediatric (7–17 years) Major Depression



Emslie GJ et al. *J Child and Adol Psychopharm.* 2014; 24: 170-179; Atkinson SD et al. *J Child and Adol Psychopharm.* 2014; 24:180-189;

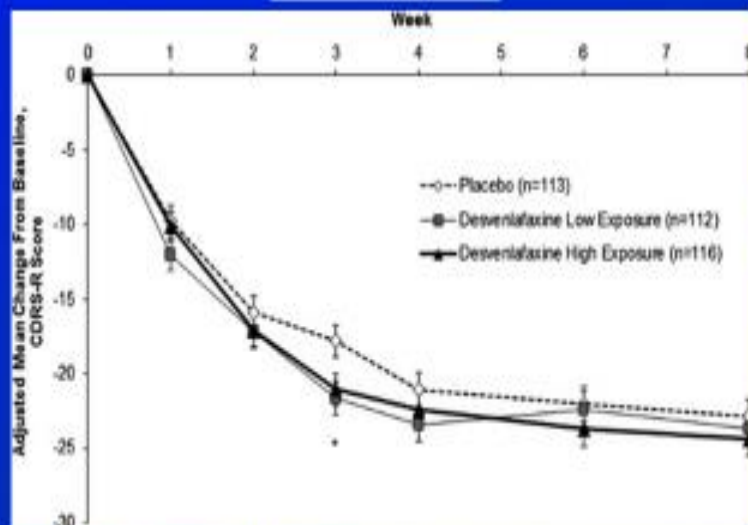
# Desvenlafaxine Treatment for Pediatric (7-17 years) Major Depression

## Fluoxetine Comparator



Fluoxetine 20mg/day  
Desvenlafaxine 25, 35 or 50mg/day

## Placebo Control

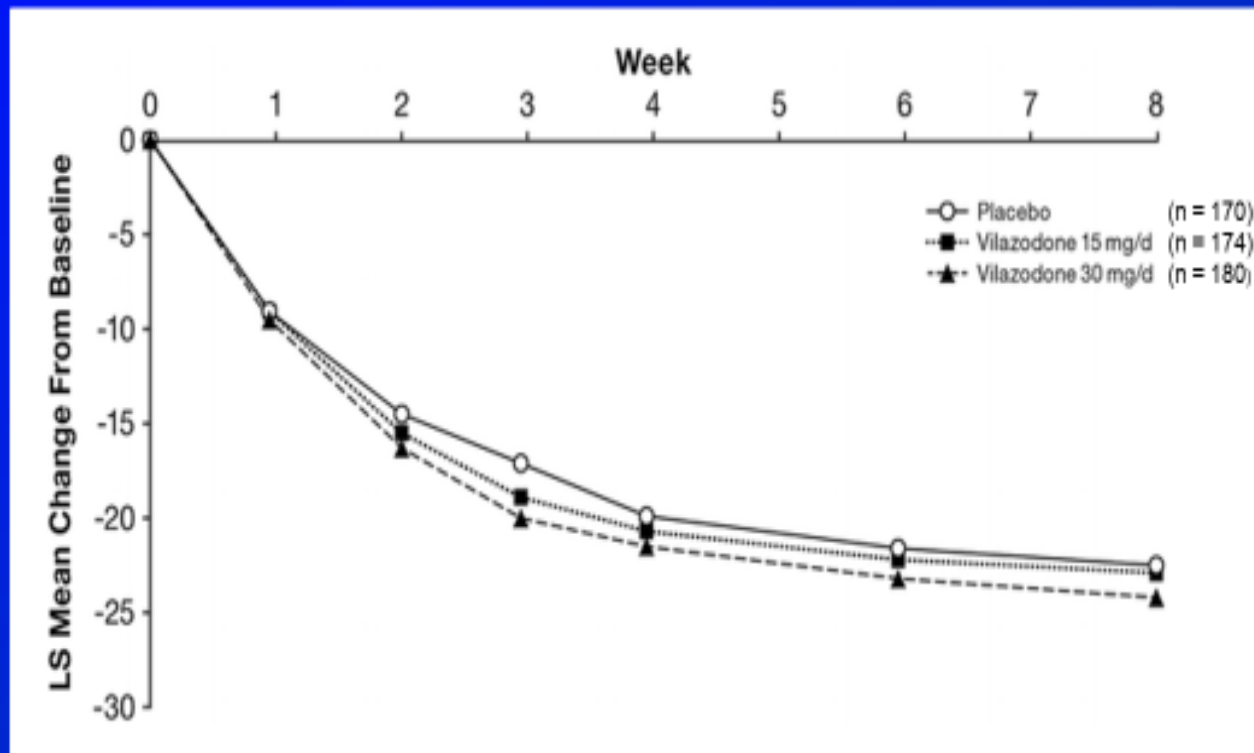


Dose: 20, 30, or 35mg/day  
Dose: 25, 35, or 50mg/day

Weihls KL et al. *JCAP*. 2018;28(1):36-46; Atkinson SD et al. *JCAP*. 2018;28(1):55-65.

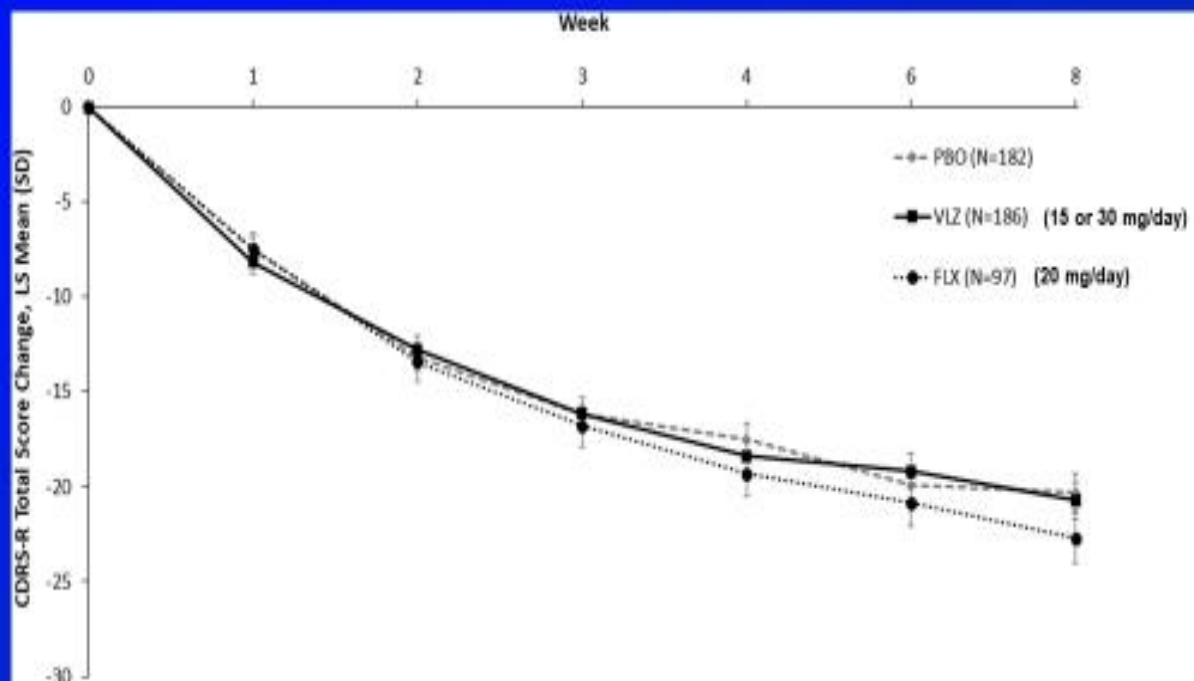
# Vilazodone for Adolescent (12–17) Major Depression Double-Blind Placebo-Controlled Trial

## Fixed Dose



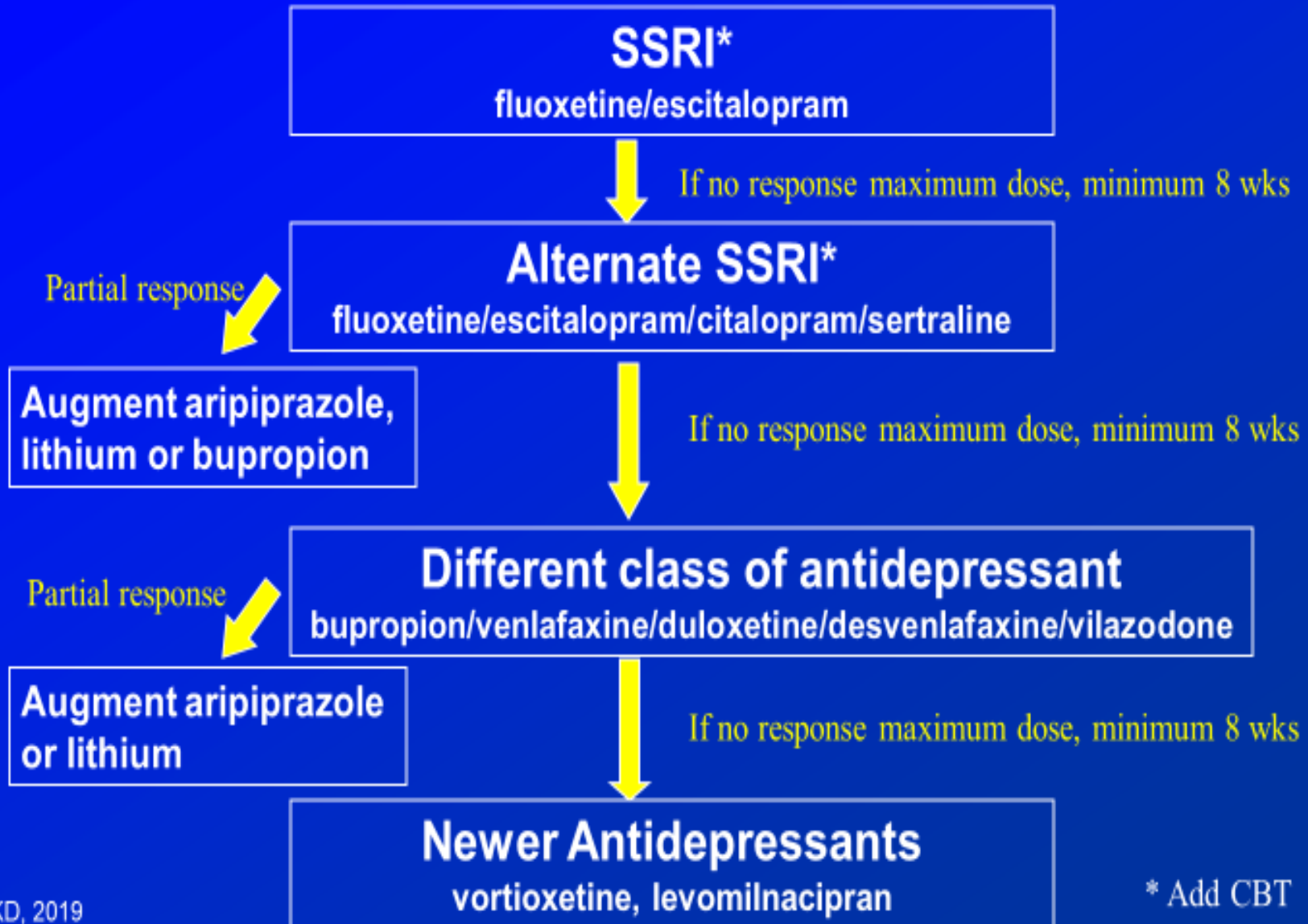
Durgam, S. et al., *Pediatric Drugs*. 2018;20,353-363.

# Vilazodone for Pediatric (7-17) Major Depression Double-Blind Placebo Controlled Comparison Trial



Findling, R. L., et al of *Journal of Child and Adolescent Psychopharmacology*. 2020. 30(6), 355-365.

# Treatment Resistant Depression Algorithm



\* Add CBT

Wagner KD, 2019



# Efficacy vs. Suicidal Risk of Antidepressants in Pediatric Patients

- Meta-analysis of 27 trials of pediatric major depression

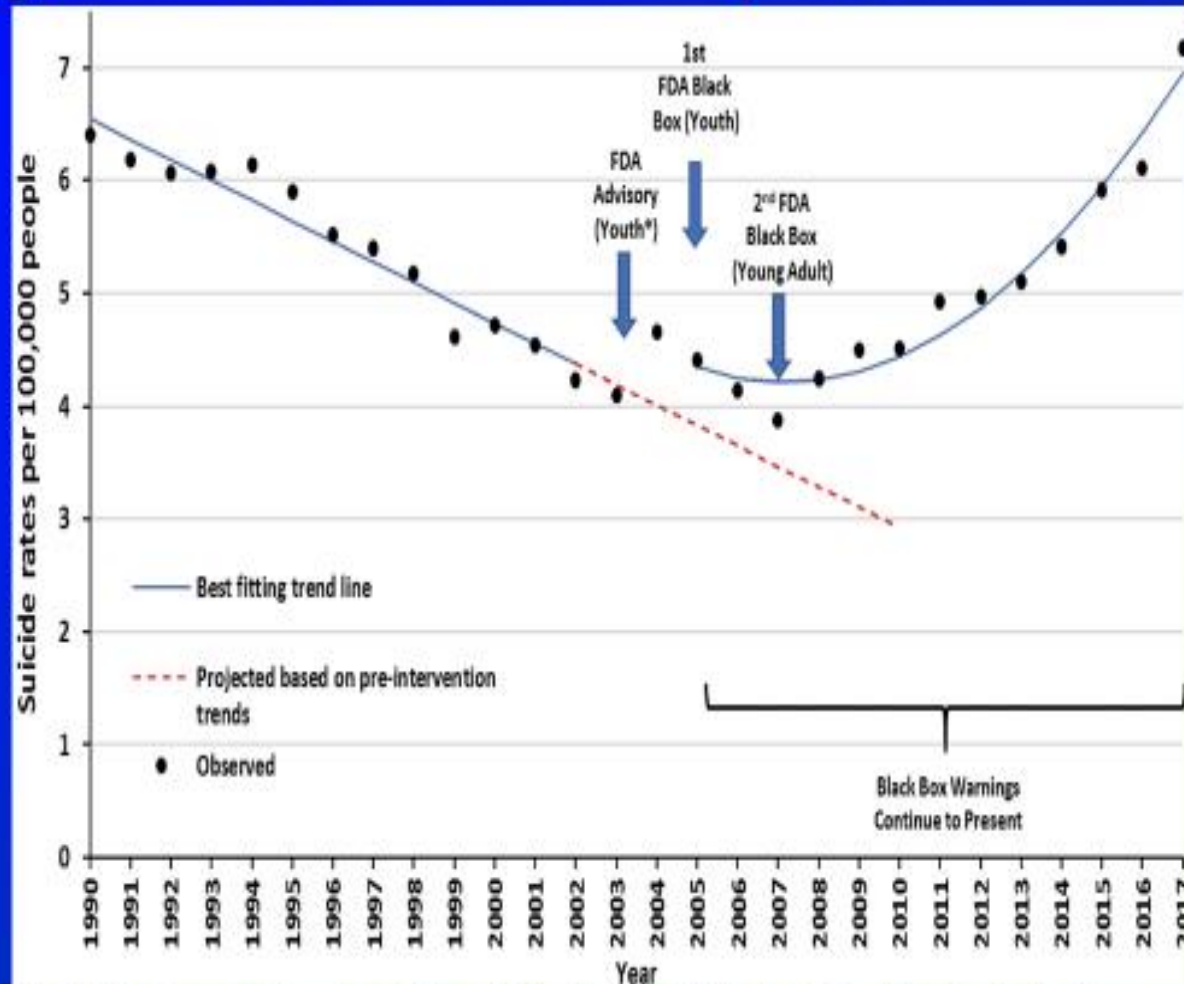
|                        |     |
|------------------------|-----|
| Number Needed to Treat | 10  |
| Number Needed to Harm  | 112 |

|                 | <u>Suicidal Ideation/attempts</u> |
|-----------------|-----------------------------------|
| Antidepressants | 3%                                |
| Placebo         | 2%                                |

Bridge et al, *JAMA*. 2007;297:1683-1696.



# Suicide Rates Following Antidepressant Box Warning and Decline with Depression Treatment



Lu, Christine Y. et al. Increases in Suicide Deaths Among Adolescents and Young Adults Following US Food and Drug Administration Antidepressant Boxed Warnings and Declines in Depression Care. *Psych Res Clin Pract.* 2020; xx:1–10; doi: 10.1176/appl.prcp.20200012

# Intravenous Ketamine for Adolescent Treatment Resistant Depression (TRD)

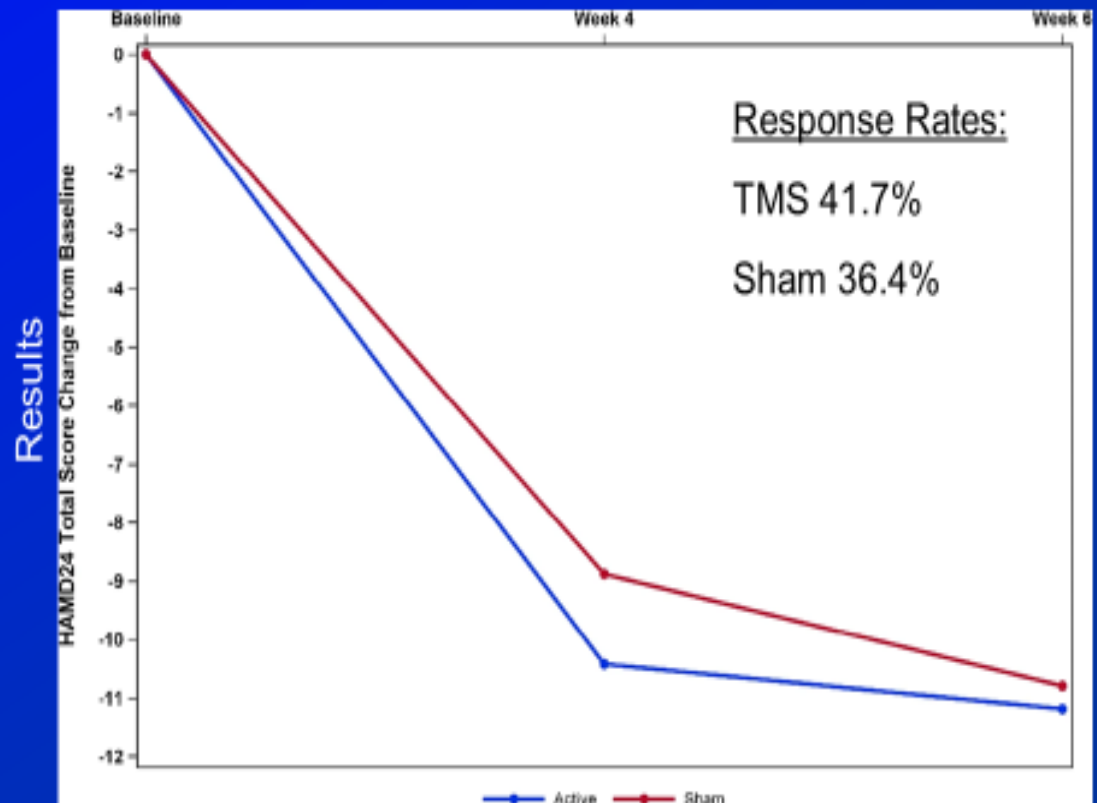
- 13 adolescents, ages 12-18, with TRD (failed  $\geq 2$  antidepressant trials)
- 6 ketamine (0.5mg/kg) infusion over 2 weeks
- Results
  - Response rate 38% ( $\geq 50\%$  decrease in CDRS-R)
  - Of 5 adolescent responders
    - 3 sustained remission at 6 week follow-up
    - 2 relapsed within 2 weeks

Cullen KR. *JCAP*. 2018;28(7),1-8.

# Transcranial Magnetic Stimulation (rTMS) for Treatment Resistant Depression

- 103 adolescents (ages 12-21) with treatment resistant depression
- Double-blind randomized, sham-controlled
- 10-Hz left frontal TMS 30 daily treatments for 6 weeks

Week 4 and Week 6 primary efficacy outcomes (HAMD24) in depressed adolescents treated with active 10 Hz TMS or sham treatment.



Croarkin PE, et al., Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial. *Neuropsychopharmacology*. 2021 Jan;46(2):462-469. doi: 10.1038/s41386-020-00829-y. Epub 2020 Sep 12. PMID: 32919400.

# Electroconvulsive Therapy (ECT) in Adolescents with Treatment Resistant Depression

- Case series
  - 13 adolescents (ages 15-18) who had ECT for treatment of depression
  - Mean of 14 ECT sessions per patient
- Results
  - 10 (77%) adolescents had clinically significant improvement in depression
  - Adverse Events: headache, muscle pain, nausea/vomiting

Zhand N, Courtney DB, Flament MF. Use of Electroconvulsive Therapy in Adolescents With Treatment-Resistant Depressive Disorders: A Case Series. J ECT. 2015 Dec;31(4):238-45. doi: 10.1097/YCT.0000000000000236. PMID: 25830809.



# Omega-3 Fatty Acids in Prepubertal Depression

- 28 children (ages 6 to 12 years) with first episode major depression randomized to Omega-3 (1000 mg/day; contained 400 mg EPA and 200 mg DHA) or placebo for 16 weeks

| Groups  | Response Rate, %<br>(>50% Reduction<br>in CDRS) | Remission, %<br>(CDRS <29) |
|---------|---|----------------------------|
| Omega-3 | 70  | 40                         |
| Placebo | 0   | 0                          |

DHA, docosahexaenoic acid

Nemets H et al. *Am J Psychiatry*. 2006;163(6):1098-1100.

# Omega-3 Fatty Acids in Adolescent Depression

- 51 adolescents with major depression randomized to omega-3 fatty acids 1.2 g/d – 3.6 g/d (combined EPA+DHA, 2:1 ratio) or placebo for 10 weeks
- Results
  - No significant difference between groups
  - Response Rates
    - Omega-3 fatty acids 43%
    - Placebo 50%

Gabbay V et al. *J Clin Psychiatry*. 2018;79(4):e1-e8.

# Psychotherapy for Depression Across Age Groups

|                            | <b>Children</b>          | <b>Adolescents</b>  | <b>Young Adults</b>     |
|----------------------------|--------------------------|---------------------|-------------------------|
|                            | (<13 years)              | (≥13-18 years)      | (≥18-24 years)          |
| Effect Size for Depression | 0.35                     | 0.55                | 0.98                    |
|                            | <b>Middle Age Adults</b> | <b>Older Adults</b> | <b>Older Old Adults</b> |
|                            | (≥24-55 years)           | (≥55-75 years)      | (≥75 years)             |
| Effect Size for Depression | 0.77                     | 0.66                | 0.97                    |

- Systematic review and meta-analysis of 366 randomized psychotherapy trials for depression with control conditions

Cuijpers, P., et al. of JAMA psychiatry. 2020. 77(7):694-702.



# SPARX (Smart, Positive, Active, Realistic, X-factor thoughts)

- Interactive fantasy game delivers CBT for depression
- Adolescent chooses an avatar and tries to restore balance in a fantasy world dominated by GNATS (Gloomy Negative Automatic Thoughts)
- Seven Modules
  - Level 1: Cave Province – Finding Hope
  - Level 2: Ice Province – Being Active
  - Level 3: Volcano Province – Dealing with Emotions
  - Level 4: Mountain Province – Overcoming Problems
  - Level 5: Swamp Province – Recognizing Unhelpful thoughts
  - Level 6: Bridgeland Province – Challenging Unhelpful Thoughts
  - Level 7: Canyon Province – Bringing it All Together

Merry SN et al. *BMJ*. 2012;344:e2598. doi: 10.1136/bmj.e2598.



# SPARK™



# Computerized CBT for Depressed Adolescents

- 187 adolescents with depressive symptoms randomized to computerized CBT (SPARX) or counseling (treatment as usual)
- Results
  - Similar reduction in CDRS-R scores between SPARX (10.3) and TAU (7.6)
  - Similar response rates (SPARX:66%; TAU:58%)

Merry SN et al. *BMJ*. 2012, 344:e2598. doi: 10.1136/bmj.e2598.

# American Academy of Child and Adolescent Psychiatry Presidential Initiative

- AACAP Depression Resource Center
  - [www.aacap.org](http://www.aacap.org)



## Depression Resource Center

- > Depression Resource Center
- > Resources for Parents
- > Resources for Youth
- > Resources for Clinicians
- > FAQs
- > Getting Help
- > Resource Centers



Resources  
for Parents



Resources  
for Youth



Resources  
for Clinicians

## Depression Resource Center

Last updated October 2019

### About

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Many children have times when they are sad or down. Occasional sadness is a normal part of growing up. However, if children are sad, irritable, or no longer enjoy things, and this occurs day after day, it may be a sign that they are suffering from major depressive disorder, commonly known as depression.

Some people think that only adults become depressed. However, approximately 2% of children and at least 4% of adolescents suffer from depression at any given time. By the end of high school, approximately one young person in five will have had at least one episode of depression.

Children and adolescents who are under stress, who experience loss, or who have attentional, learning, conduct, or anxiety disorders are at a higher risk for depression. Depression also tends to run in families. The good news is that depression is a treatable illness.