Major Depressive Disorder: Responding to Suboptimal Treatment Response

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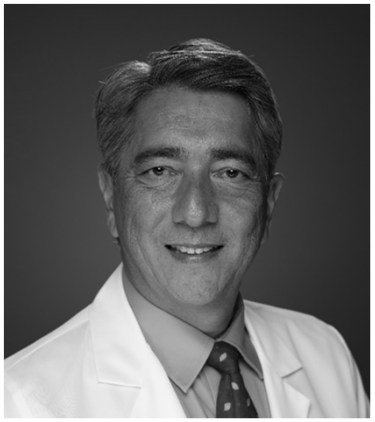

BayCare

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Learning Objectives

1. Learners will renew their understanding of the DSM-5 diagnostic criteria for Major Depressive Disorder (MDD) its differentials and comorbidities.
2. Learners will be able to list common measurement resources to diagnose MDD and to assess treatment outcome.
3. Learners will be able to choose among various treatment options for MDD with emphasis on pharmacological options.
4. Learners will be able to describe approaches to suboptimal outcomes with initial pharmacological choices.

Disclosures

- No financial relationships to disclose
- Off label use of medications
- Adult psychopathology
- EBM……..as much as possible

DSM-5 Criteria
Major Depressive Disorder

- ≥ 5/9 symptoms, 2-week duration, change from baseline and at least depressed mood or anhedonia·
- "The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning."
- No hypomania or mania
- Not a direct effect of a medical condition or substances
- Cannot be better explained by another psychiatric condition or bereavement

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

“SIGECAPS”

S	**S**leeping problems
I	Loss of **I**nterest in pleasurable activities (Anhedonia)
G	Feelings of **G**uilt, worthlessness, hopelessness
E	Decreased **E**nergy; fatigue
C	**C**oncentration difficulties
A	**A**ppetite/Weight changes
P	**P**sychomotor changes
S	**S**uicidal thoughts

DSM-5 Criteria
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American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

Differentials and Comorbidities

- Medical
  - Autoimmune
  - Endocrine
  - Infectious
- Psychiatric
  - Adjustment Disorders
  - Bereavement
  - Psychotic Disorders
- Substances
  - Recreational drugs
  - Iatrogenic

- Neurologic
- Malignancies
- CAD

- Anxiety Disorders
- Personality Disorders

Medications that can cause depressed mood

Antivirals	efavirenz
Cardiovascular Agents	beta blockers, CCB, clonidine
Retinoic Acid Derivatives	isotretinoin
Antidepressants	
Anticonvulsants	levetiracetam, phenobarbital, primidone, phenytoin, topiramate
Parkinson's Agents	rasagiline, pramipexole, carbidopa/levodopa, amantadine
Antimigraine Agents	triptans
Antipsychotics	aripiprazole, quetiapine
Hormonal Agents	corticosteroids, OCPs, GnRH agonists, tamoxifen
Prokinetic Agents	metoclopramide
Anticholinergics	dicyclomine
Smoking Cessation Agents	varenicline
Immunologic Agents	interferon α, interferon β

Adapted from: Botts, S., et. al. (2010). *Drug-induced diseases: prevention, detection, and management*. ASHP.

Measurement-Based Care

- Primary Care Assessment Approach
  - Screen Patients ≥ 18 yo
  - DSM-5 clinical criteria
  - Rating scales (Measurement-Based Care)

Siu, et al. (2016). JAMA, 315(4), 380-387.

Measurement Tools

- Beck Depression Inventory (BDI II)
- Hamilton Depression Rating Scale (HAM-D, HDRS)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Hospital Anxiety and Depression Scale (HADS)
- Edinburgh Postnatal Depression Scale (EPDS)
- Geriatric Depression Scale (GDS)
- Patient Health Questionnaire (PHQ-2, PHQ-9)

Hospital Anxiety and Depression Scale (HADS)

Zigmond, A. S., & Snaith, R. P. (1983) Acta Psychiatr Scand, 67, 361-37o.

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Edinburgh Postnatal Depression Scale (EPDS)

Cox. J. L, Holden, J. M., Sagovsky, R. (1987)
Br J Psychiat. 150, 782-786.

Life with a new baby is not always what you expect.

Please underline the answer that most accurately describes your feelings in the last 7 days.

1. **I have been able to laugh and see the funny side of things.**
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all

2. **I have looked forward with enjoyment to things.**
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

3. **I have blamed myself unnecessarily when things went wrong*.**
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never

4. **I have been anxious or worried for no good reason.**
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often

5. **I have felt scared or panicky for no very good reason*.**
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all

6. **Things have been getting on top of me*.**
   - Yes, most of the time I haven't been able to cope at all
   - Yes, sometimes I haven't been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever

7. **I have been so unhappy that I have had difficulty sleeping*.**
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all

8. **I have felt sad or miserable*.**
   - Yes, most of the time
   - Yes, quite often
   - Not very often
   - No, not at all

9. **I have been so unhappy that I have been crying*.**
   - Yes, most of the time
   - Yes, quite often
   - Only occasionally
   - No, never

10. **The thought of harming myself has occurred to me*.**
    - Yes, quite often
    - Sometimes
    - Hardly ever
    - Never

2006

Geriatric Depression Scale (GDS)

Sheikh, J.I., & Yesavage, J.A. (1986). Clin Gerontologist 5(1-2): 165-173, 1986.

Geriatric Depression Scale (GDS) Short Form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life?	Yes	No
2. Have you dropped many of your activities and interests?	Yes	No
3. Do you feel that your life is empty?	Yes	No
4. Do you often get bored?	Yes	No
5. Are you in good spirits most of the time?	Yes	No
6. Are you afraid that something bad is going to happen to you?	Yes	No
7. Do you feel happy most of the time?	Yes	No
8. Do you often feel helpless?	Yes	No
9. Do you prefer to stay at home rather than going out and doing new things?	Yes	No
10. Do you feel you have more problems with memory than most?	Yes	No
11. Do you think it is wonderful to be alive now?	Yes	No
12. Do you feel pretty worthless the way you are now?	Yes	No
13. Do you feel full of energy?	Yes	No
14. Do you feel that your situation is hopeless?	Yes	No
15. Do you think that most people are better off than you are?	Yes	No

Source: Sheikh, J.I., and Yesavage, J.A. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist* 5(1-2): 165-173, 1986.

Patient Health Questionnaire (PHQ -2)

The Patient Health Questionnaire-2 (PHQ-2)

Patient Name _____ Date of Visit _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3

Kroenke, K, Spitzer, R. L., Williams, J. B. (2003). *Medi Care,* 41, 1284-92.

Patient Health Questionnaire (PHQ-9)

Kroenke, K, Spitzer, R. L., & Williams, J. B. (2001). *J Gen Int Med*, 16(9), 606-613.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

Name: _____ **Date:** _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems? *(use "√" to indicate your answer)*

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	**0**	**1**	**2**	**3**
2. Feeling down, depressed, or hopeless	**0**	**1**	**2**	**3**
3. Trouble falling/staying asleep, sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way.	0	1	2	3
Add Columns:		_____ +	_____ +	_____
TOTAL:	_____			

If you checked off <u>any</u> problem on this questionnaire so far, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

Mood Disorder Questionnaire (MDQ)

Mood Disorder Questionnaire

Patient Name _____ Date of Visit _____

Please answer each question to the best of your ability

1. Has there ever been a period of time when you were not your usual self and...	**YES**	**NO**
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	☐	☐
...you were so irritable that you shouted at people or started fights or arguments?	☐	☐
...you felt much more self-confident than usual?	☐	☐
...you got much less sleep than usual and found that you didn't really miss it?	☐	☐
...you were more talkative or spoke much faster than usual?	☐	☐
...thoughts raced through your head or you couldn't slow your mind down?	☐	☐
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
...you had more energy than usual?	☐	☐
...you were much more active or did many more things than usual?	☐	☐
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
...you were much more interested in sex than usual?	☐	☐
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
...spending money got you or your family in trouble?	☐	☐
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	☐	☐

3. How much of a problem did any of these cause you - like being unable to work; having family, money or legal troubles; getting into arguments or fights?

☐ No problems ☐ Minor problem ☐ Moderate problem ☐ Serious problem

Hirschfeld, R. M. (2002). *J Clin Psychia*t, 4, 9–11.

Measurement-Based Care

- Primary Care Assessment Approach
  - Screen Patients ≥ 18 yo
  - DSM-5 clinical criteria
  - Rating scales (Measurement-Based Care)
  - R/O differentials and comorbidities
  - Safety evaluation

MDD Treatment

Treatment Options

Severity	Rx	"Psychotherapy"	Combination	ECT
Mild to Moderate	Yes	Yes	Maybe	Yes (certain pts)
Severe w/o Psychotic Features	Yes	Not alone	Yes	Yes
Severe w/ Psychotic Features	Yes	Not alone	Yes (psychotherapy and antidepressant + antipsychotic)	Yes

APA Treatment Guidelines [Gelenberg, A. J., et al.(2010). *Am J Psychiat*, 167(10), 1.]

“Psychotherapy”
Cognitive Behavioral Interventions (CBI)

- Identifying maladaptive thoughts, beliefs, expectations, assumptions
- Challenging these faulty cognitions

Cognitive

- Identify environmental or external factors/triggers that precipitate, perpetuate depression
- Learning new habits and skills

Behavioral

Treatment Options

Severity	Rx	"Psychotherapy"	Combination	ECT	
Mild to Moderate	Yes	Yes	Maybe	Yes (certain pts)	
Severe w/o Psychotic Features	Yes	Not alone	Yes	Yes	**Refer**
Severe w/ Psychotic Features	Yes	Not alone	Yes (psychotherapy and antidepressant + antipsychotic)	Yes	**Refer**

APA Treatment Guidelines [Gelenberg, A. J., et al.(2010). *Am J Psychiat*, 167(10), 1.]

Rx Treatment Options – 1st Line

SSRI*	Fluoxetine	Prozac, Prozac Weekly, Sarafem
	Paroxetine	Paxil, Paxil XR, Pexeva
	Sertraline	Zoloft
	Citalopram	Celexa
	Escitalopram	Lexapro
SNRI*	Venlafaxine	Effexor, Effexor XR
	Desvenlafaxine	Pristiq
	Duloxetine	Cymbalta
	Levomilnacipran	Fetzima
NDRI*	Bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Budeprion SR, Budeprion XL, Aplenzin, Forfivo XL
Serotonin antagonist*	Mirtazapine	Remeron, Remeron SolTab
Mixed serotonin activity (5HT modulators)*	Nefazodone	Serzone (not often used as 1st line)
	Trazodone	Desyrel, Oleptro (not often used as 1st line)
	Vilazodone	Viibryd
	Vortioxetine	~~Brintellix~~ renamed: Trintelix

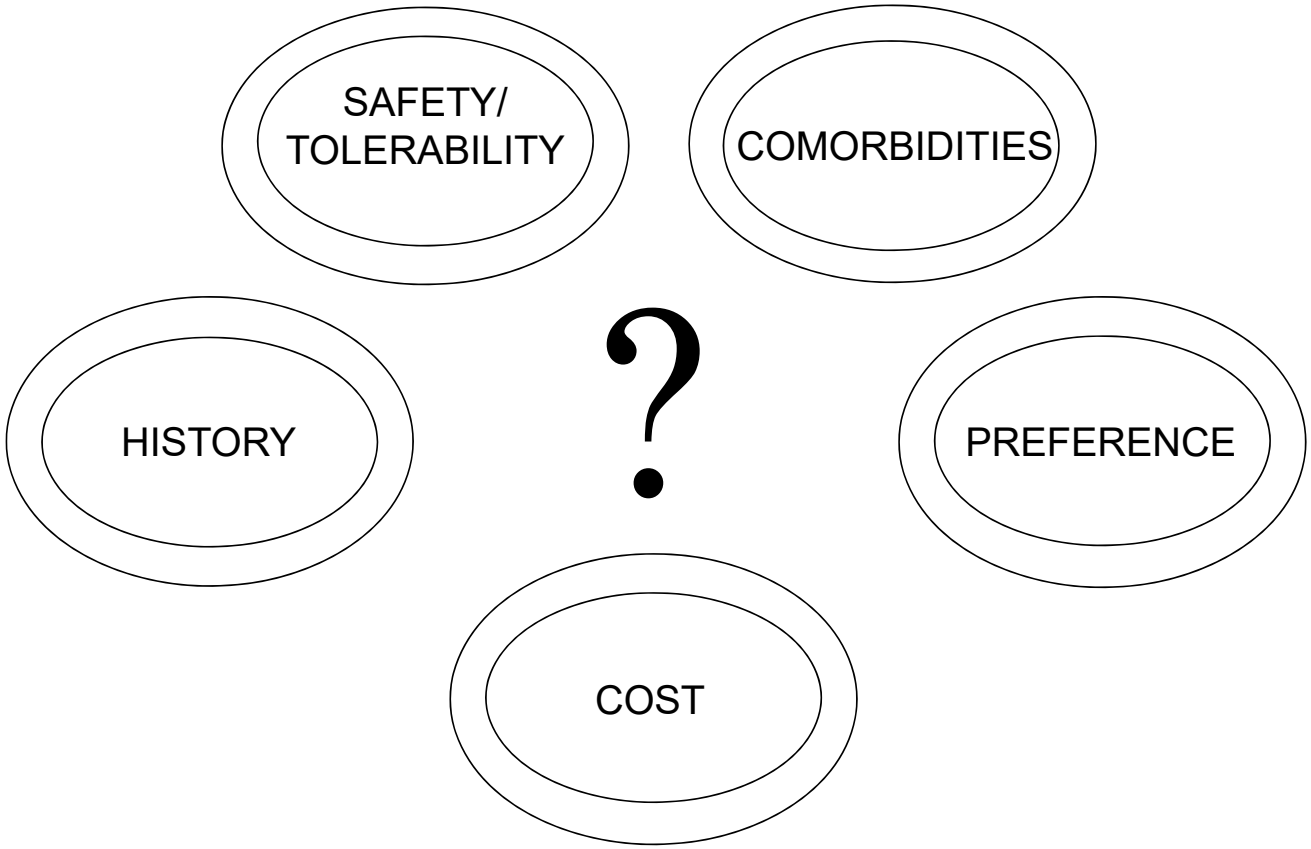
* FDA Approved for Major Depressive Disorder or Depression

Rx Treatment Options – 2nd Line

TCA (SNRI)*	Amitriptyline	Elavil
	Amoxapine	Generic only
	Chlordiazepoxide/Amitriptyline	Generic only
	Desipramine	Norpramin
	Doxepin	Generic only
	Imipramine	Tofranil
	Maprotiline	Generic only
	Nortriptyline	Pamelor
	Perphenazine/Amitriptyline	Generic only
	Protriptyline	Vivactil
	Trimipramine	Surmontil
MAOI*	Isocarboxazid	Marplan
	Phenelzine	Nardil
	Selegiline	Emsam (transdermal)
	Tranylcypromine	Parnate

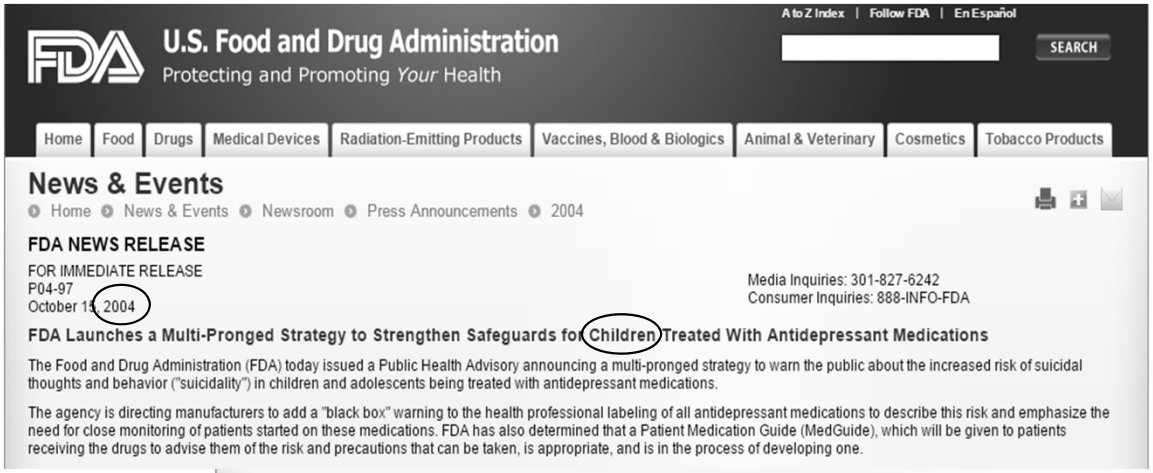
* FDA Approved for Major Depressive Disorder or Depression (w/ or w/o anxiety)

Antidepressant Selection



Suicidality - All Antidepressants

Black Boxed Warning: Increased risk of suicidal thinking or behavior in children, adolescents, and adults



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FDA NEWS RELEASE

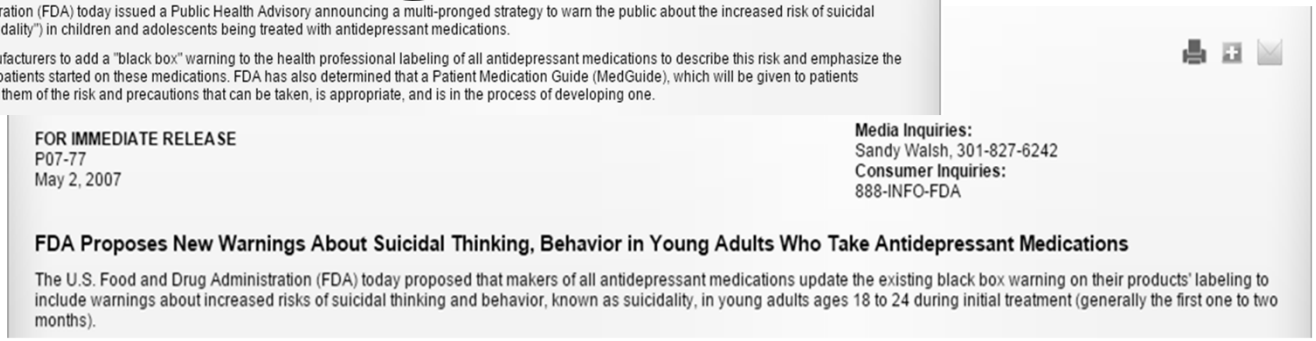
FOR IMMEDIATE RELEASE
P04-97
October 15, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated With Antidepressant Medications

The Food and Drug Administration (FDA) today issued a Public Health Advisory announcing a multi-pronged strategy to warn the public about the increased risk of suicidal thoughts and behavior ("suicidality") in children and adolescents being treated with antidepressant medications.

The agency is directing manufacturers to add a "black box" warning to the health professional labeling of all antidepressant medications to describe this risk and emphasize the need for close monitoring of patients started on these medications. FDA has also determined that a Patient Medication Guide (MedGuide), which will be given to patients receiving the drugs to advise them of the risk and precautions that can be taken, is appropriate, and is in the process of developing one.



FOR IMMEDIATE RELEASE
P07-77
May 2, 2007

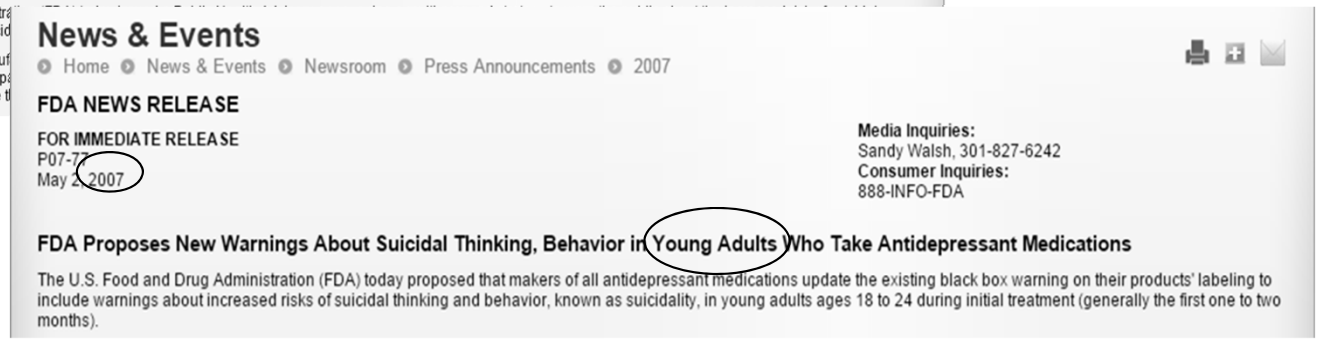
Media Inquiries:
Sandy Walsh, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications

The U.S. Food and Drug Administration (FDA) today proposed that makers of all antidepressant medications update the existing black box warning on their products' labeling to include warnings about increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months).

Suicidality - All Antidepressants

Black Boxed Warning: Increased risk of suicidal thinking or behavior in children, adolescents, and adults



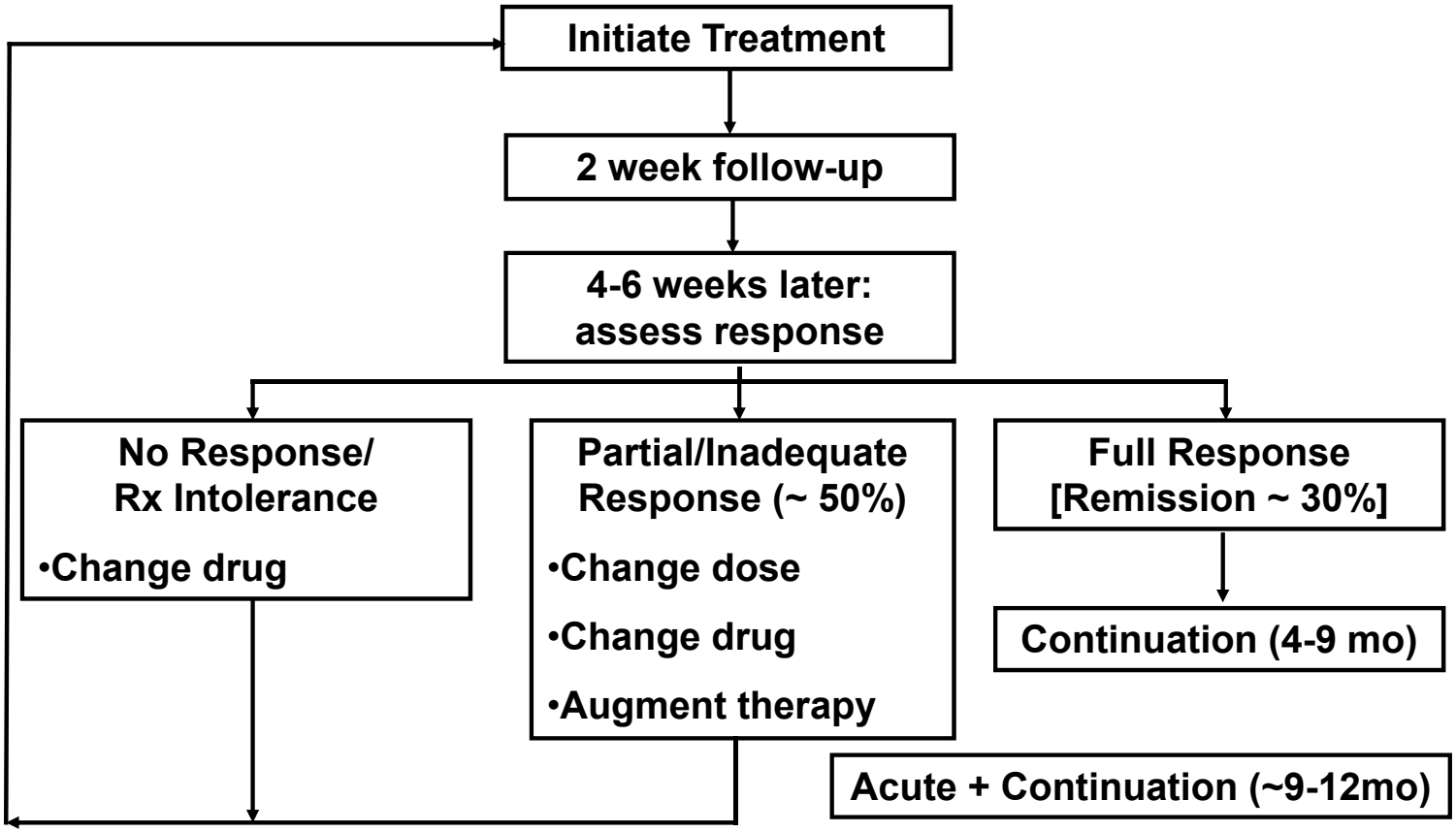
Safety, Tolerability, Adverse Effects

Class	Safety, Tolerability, Adverse Effects
SSRI	• QT prolongation (citalopram, escitalopram) • Increased risk of bleeding, glaucoma • Nausea, diarrhea, headache, fatigue, activating • Weight gain, insomnia, sexual SE, activating (fluoxetine)
TCA	• Orthostatic hypotension, arrhythmia, seizure • Anticholinergic • Weight gain, sexual SE, somnolence
SNRI	• Incr. BP, Incr. QT interval (venlafaxine) • Drug:Drug interactions (less with desvenlafaxine) • Nausea, headache, sweating, tachycardia, urinary retention • Insomnia, sexual SE, activating • Hyperhidrosis, ↑ HR, ED, palpitations (levomilnacipran)
Mixed 5-HT	• Orthostatic hypotension, liver failure (nefazodone), priapism (trazodone) • Nausea, diarrhea, headache, dizziness, somnolence (trazodone) • Weight gain and sexual SE (vilazodone)
Bupropion	• Seizure • Nausea, dry mouth, tremor, insomnia, activating
Mirtazapine	• Dry mouth, constipation, weight gain, somnolence
MAOI	• Serotonin syndrome, hypertensive crisis, postural hypotension • Sexual dysfunction

Matching Antidepressants to the Pt
Tips from Clinical Practice

- fluoxetine, bupropion: stimulating
- mirtazapine, trazodone, paroxetine, TCAs: sedating
- SSRIs: insomnia, sexual SE, weight gain
- SNRIs: ↑ blood pressure (esp. venlafaxine)
- TCAs: avoid w/ HTN, ↑ age, orthostatic hypotension, seizure, arrhythmia, suicidal
- mirtazapine: most weight gain
- bupropion: least weight gain, least sexual SEs, lowers seizure threshold
- citalopram/escitalopram, TCAs, SNRIs: Incr QTc interval
- citalopram, desvenlafaxine: less Rx-Rx SE
- paroxetine, venlafaxine: short half-life
- fluoxetine: long half-life
- MAOIs: questionable use in primary care

Drug Treatment Algorithm



Common Residual Symptoms

- Low mood
- Anhedonia
- Insomnia
- Guilt
- Reduced libido
- Decreased energy, fatigue
- Cognitive impairment
- Weight gain
- Somatic or physical symptoms
- Irritability
- Anxiety

Israel, J.A. (2006). J. Psychopharmacol. 2006, 20, 5–10

Causes of Suboptimal Tx Response

- Correct diagnosis?
- Optimal treatment choice, dose, type, frequency duration?
- Treatment adherence?
- Side effect(s) of treatment selected?
- Severity of illness?
- Complicating co-occurring conditions?
- New environmental factors/events?
- Quality of the therapeutic alliance?

Adapted from: Gelenberg, A. J., et al.(2010). *Am J Psychiat*, 167(10), 1.

Suboptimal Treatment Outcome
Causes/Risks and Responses

• Risk Factors	• Responses
– Comorbid general medical disorders	⋯▸ Diagnose and treat medical comorbidities
– Chronic pain	⋯▸ Manage chronic pain
– Medications (sub therapeutic 20%)	⋯▸ Adherence (40%), AEs (20-30%)?
– Comorbid psychiatric disorders	⋯▸ Diagnose and treat comorbidities
– Severe depressive symptoms	⋯▸ Change/augment treatment, Refer
– Suicidal thought and behavior	⋯▸ Assess and treat/refer appropriately
– Adverse life events	⋯▸ Stay the course
– Longer or recurrent depressive episodes	⋯▸ Change/augment treatment, Refer
– Enzyme inducers, rapid metabolizers?	⋯▸ Pharmacokinetics, Laboratory testing

CBI (for all of these risk factors)
Refer to psychiatry/psychology for any of the above

Lynch, T., Price, A. (2007). Am Fam Physician.76(3):391-396.
Thase, M., & Connolly, K. R. (2015). UpToDate, Waltham, MA, 2016

Approaches to Suboptimal Treatment Outcome

- Maximize the initial treatment
- Change to another treatment

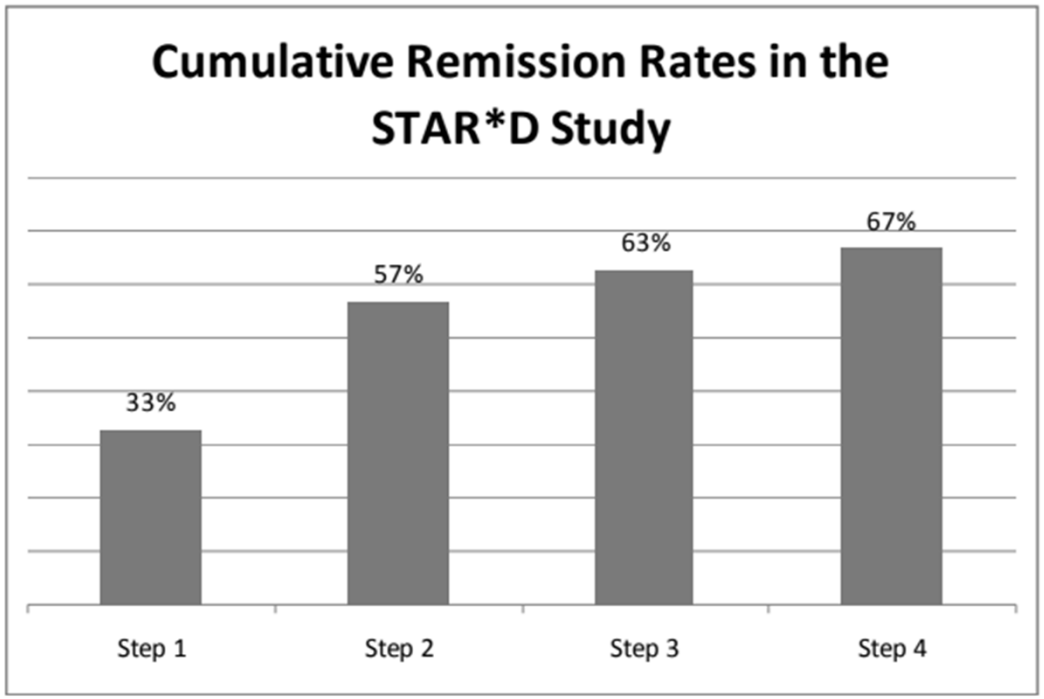
American Psychiatric Association. (2015). Treating major depressive disorder: a quick reference guide. 2010.

Changing to another Antidepressant

- Direct switch
  - Within same class or between SSRI/SNRI (dose dependent)
- Cross taper
  - Dose of ineffective medication slowly reduced over 3-7 days while titrating new antidepressant

Soreide, K. K., Ward, K. M., Bostwick, J. R., (2017). Psychiatric Times, Vol 34 No 12, Volume 34, Issue 12.

Evidence for Changing to another Antidepressant



Ruhe H. G., et.al., (2006). *J Clin Psychiat*, 67(12): 1836-1855
Rush, A. J., et.al., (2006). *Am J Psychiat*, 163(11), 1905-1917.

Approaches to Suboptimal Treatment Outcome

- Maximize the initial treatment
- Change to another treatment
- Augment or combine treatments

American Psychiatric Association. (2015). Treating major depressive disorder: a quick reference guide. 2010.

Approaches to Suboptimal Treatment Outcome

- Augment with another antidepressant
  - another non-MAOI from the same class
  - another non-MAOI from a different class
- Augment with a non-antidepressant

Other Rx Augmentation Options

Second Generation· Antipsychotic*♦	Aripiprazole, Brexpiprazole, Olanzapine, Quetiapine	Abilify, Rexulti, Seroquel XR, Zyprexa
Novel†	Lithium♦	Lithobid
	Stimulants	Methylphenidate Amphetamine mixes
	Modafinil & Armodafanil	Provigil, Nuvigil
	Triiodothyronine, Liothyronine (T3)♦	Cytomel, Triostat
	Anticonvulsants	Carbamazepine, Lamotrigine, Valproate
Other†	St. John's Wort	Drug interactions, photosensitivity
	S-adenosylmethionine (SAM-e)	Some evidence
	L-methylfolate	Some evidence
	Omega-3 fatty acid	Prolongs bleeding time
	Celecoxib	Small – Mod effects, w/ & w/o other Rx
	♦Anxiolytic, Sedative Hypnotic, GABA agonist	If anxiety or insomnia prominent
Newest*	Esketamine	Spravato
	Brexanolone	Zulresso

* FDA Approved for MDD adjunctive treatment, acute treatment resistant Major Depressive Disorder, or postpartum depression
† Used but not FDA approved
♦ APA Practice Guideline recommendation

2nd Gen Antipsychotics

Table 3. Some Relative Adverse Effects of Second-Generation Antipsychotics

Drug	Diabetes	Weight Gain	Extrapyramidal Symptoms	QTc Interval Prolongation	Elevated Prolactin
Aripiprazole	+/-	+	++	+/−	−
Asenapine	+	++	++	+	++
Brexpiprazole*	+	++	+	−	+/−
Cariprazine*	+/−	+	+++	−	−
Clozapine	++++	++++	+/−	+	+/−
Iloperidone	++	++	+/−	++	+/−
Lumateperone*	+	+	+/−	+	+
Lurasidone	+/−	+/−	++	+/−	+/−
Olanzapine	+++	++++	+	+	+
Paliperidone	++	+++	+++	+	+++
Quetiapine	++	+++	+/−	+/++	+/−
Risperidone	++	+++	+++	+	+++
Ziprasidone	+/−	+/−	+/−	++	+

* Limited experience; long-term data not available

Gerhard, T., et. al., (2020). PloS one, 15(9), e0239206
Med Lett Drugs Ther. 2020;62(1603):114.
Mulder, R., et. al., (2018). *Bipolar Disord*, *20*, 17-24.
Zhou, X., et. al., (2015). *J Clin Psychiat*, 76(4), 487-498.

Other Rx Augmentation Options

Second Generation· Antipsychotic*♦	Aripiprazole, Brexpiprazole, Olanzapine, Quetiapine	Abilify, Rexulti, Seroquel XR, Zyprexa
Novel†	Lithium♦	Lithobid
	Stimulants	Methylphenidate Amphetamine mixes
	Modafinil & Armodafanil	Provigil, Nuvigil
	Triiodothyronine, Liothyronine (T3)♦	Cytomel, Triostat
	Anticonvulsants	Carbamazepine, Lamotrigine, Valproate
Other†	St. John's Wort	Drug interactions, photosensitivity
	S-adenosylmethionine (SAM-e)	Some evidence
	L-methylfolate	Some evidence
	Omega-3 fatty acid	Prolongs bleeding time
	Celecoxib	Small – Mod effects, w/ & w/o other Rx
	♦Anxiolytic, Sedative Hypnotic, GABA agonist	If anxiety or insomnia prominent
Newest*	Esketamine	Spravato
	Brexanolone	Zulresso

* FDA Approved for MDD adjunctive treatment, acute treatment resistant Major Depressive Disorder, or postpartum depression
† Used but not FDA approved
♦ APA Practice Guideline recommendation

Approaches to Suboptimal Treatment Outcome

- Maximize the initial treatment
- Change to another treatment
- Augment and combine treatments
- Refer to subspecialty psychiatry/psychology (Treatment Resistant Depression)
  - “Psychotherapy”
  - Electroconvulsive Treatment (ECT)
  - Transcranial Magnetic Stimulation (TMS)
  - Vagus Nerve Stimulation (VNS)
  - Esketamine

Adapted from: American Psychiatric Association. (2015). Treating major depressive disorder: a quick reference guide. 2010.

Prescribing Tips and Tricks

- Frequency of follow-up
- Formally monitor tx response (measurement-based care)
- Dual Rx therapy
- Length of treatment
- Serotonin Syndrome

	Serotonin Syndrome	**Neuroleptic Malignant Syndrome**
Inciting Agent	Serotonin Agonist SSRI SNRI TCA buspirone mirtazapine anticonvulsants cyclobenzaprine dextromethorphan linezolid meperidine odansetron trazodone tramadol others (MAOIs)	Dopamine antagonists (or w/drawal of dopamine agonist antipsychotics chlorpromazine metoclopramide bromocriptine (ag) pramiprexole (ag) ropinirole (ag)
Onset	Abrupt (hours)	Days to weeks
Neuromuscular Sx	Hyperreflexia, tremor, myoclonus	Bradyreflexia, led-pipe rigidity
GI symptoms	Nausea, vomiting, diarrhea	Not common
Pupils	Dilated	Normal
Treatment	BZD, cyproheptadine	bromocriptine
Course	Rapid (w/in 24 hours) *fluoxetine – longer 2^o > t(1/2)	Days to weeks

Prescribing Tips and Tricks

- Frequency of follow-up
- Formally monitor tx response (measurement-based care)
- Switching antidepressants
- Dual Rx therapy
- Length of treatment
- Serotonin Syndrome
- Discontinuing treatment

Serotonin **Discontinuation** Syndrome - FINISH

Flu-like symptoms

Insomnia

Nausea

Imbalance

Sensory disturbances

Hyperarousal

Berber, M. J. (1998). J Clin Psychiat, 59(5), 255..

Prescribing Tips and Tricks

- Frequency of follow-up
- Formally monitor tx response (measurement-based care)
- Dual Rx therapy
- Length of treatment
- Serotonin Syndrome·
- Discontinuing treatment
- MDD recurrence

Fava, M., et. al. (2006). *Am J Psych*, *163*(7), 1161-1172.
Shelton, R. C., Osuntokun, O., Heinloth, A. N., & Corya, S. A. (2010). CNS Drugs, 24(2), 131-161.

Depression Treatment Outcomes

Key Statistics on the Treatment of Depression	Definition of Improvement	Source
54% show improvement after antidepressant medication	50% reduction of symptoms	Meta-analysis (165 PCT)
35-40% show improvement after pill placebo	50% reduction of symptoms	Meta-analysis (252 PCT)
53% of untreated depression show improvements in 12 months	Study defined remission rates	Meta-analysis (19 waitlist control groups & observational studies)
62% show improvement after psychotherapy (66% in CBT)	Did not meet MDD criteria in diagnostic interview	Meta-analysis (35 RCT)
50% of those with depression will have depression only once in their lives	Diagnostic Interview Schedule, Life Cart Interview	Prospective population-based cohort study w/ 23 year follow-up
25-40% recurrence in 2 years, 60% after 5 years, 85% after 15 years.	New episodes of MDD	Narrative review

PCT – Placebo Controlled Trials
RCT – Randomized Controlled Trials

Cuijpers, P., Stringaris, A., & Wolpert, M. (2020). Lancet Psychiat, 7(11), 925-927.

Take Home Points

- Major Depression is a common problem
- Screen yearly using Measurement-Based Care (MBC)
- Rely on the DSM5 to make the formal diagnosis
- Choose from among non-Rx and Rx treatments
- Target full response and remission
- Regularly asses for treatment response (MBC)
- Optimize dosing/tx, change or augment drug/tx for suboptimal treatment response
- Refer to specialty psychiatry/psychology as necessary

Thanks for Listening

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