

## Prescribing Antidepressants in Primary and Integrated Care

**Elena Volfson, MD, MPH**

General and Addiction Psychiatrist  
 Medical Director of the Behavioral Health Lab (Integrated Care Program) at the Philadelphia VAMC  
 Clinical Assistant Professor of Psychiatry  
 Perelman School of Medicine  
 University of Pennsylvania

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Elena Volfson, MD, MPH

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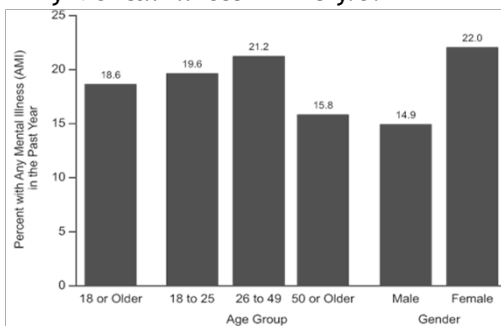
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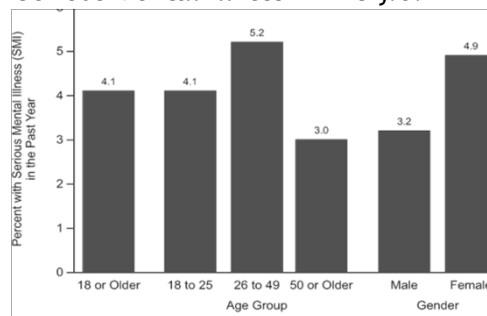
## Outline of the presentation

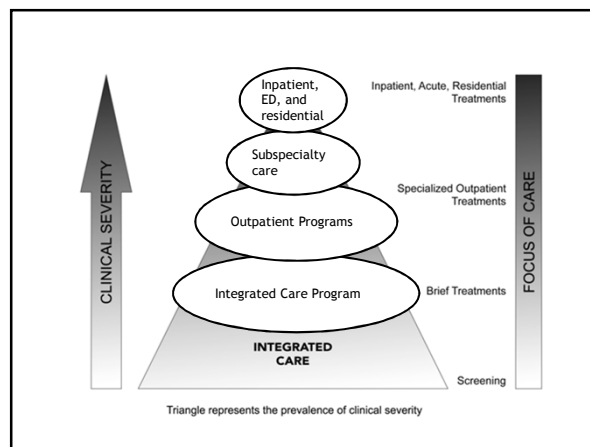
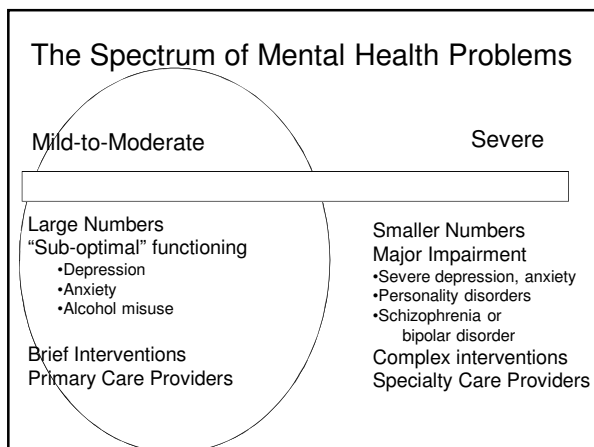
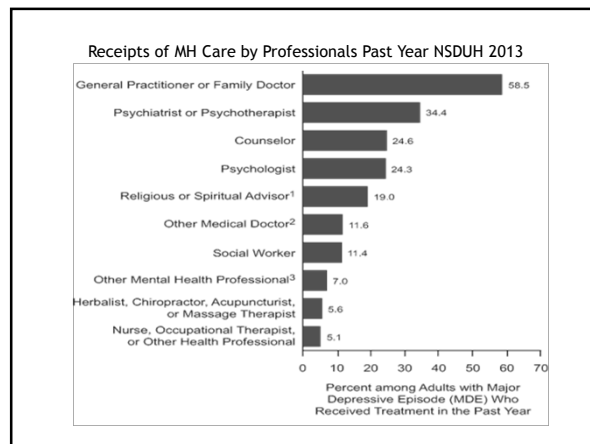
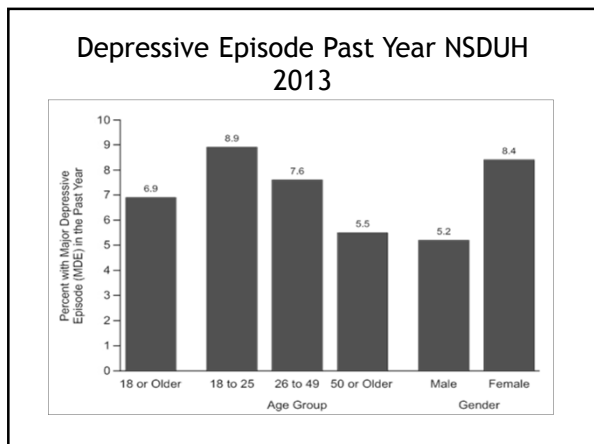
1. Epidemiology of Mental Health Disorders in the US
2. Challenges of screening, diagnosis and management of depression and anxiety disorders in primary care
3. Collaborative/Integrated Care
4. DSM-V criteria for depression
5. Screening
6. Review of antidepressants
7. Anxiety management
8. Considerations in treatment of older patients
9. STAR\*D and COMED studies

**NSDUH SAMHSA 2012 Results  
 Any Mental Illness in >18 y.o.**



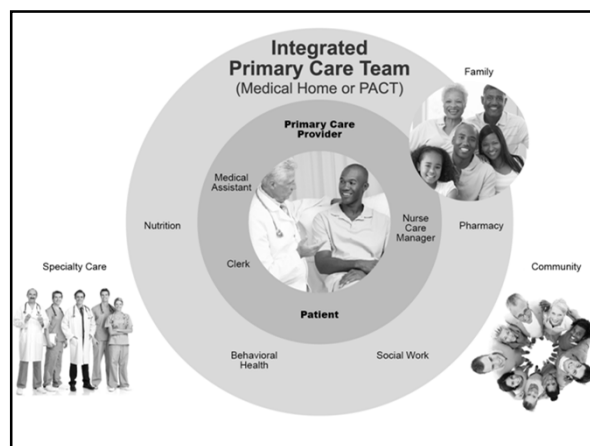
**NSDUH SAMHSA 2012 Results  
 Serious Mental Illness in >18 y.o.**





### ACP: Patient-Centered Medical Home

- A Patient-Centered Medical Home is a team-based model of care led by a personal physician who provides continuous and coordinated care throughout a patient’s lifetime to maximize health outcomes.
- The PCMH practice is responsible for providing for all of a patient’s health care needs or appropriately arranging care with other qualified professionals. This includes the provision of preventive services, treatment of acute and chronic illness, and assistance with end-of-life issues



### Why Use New Paradigm of Care

- Suboptimal outcomes and high cost of current system of care
- Not enough providers
- Evolved technology (soft-and hardware, computers, smart phones, tele-medicine)
- Evolved patients needs and expectations ( desire to be informed of progress and maintain frequent contact, to be involved in decision-making, desire to monitor own symptoms, easy access to providers)
- Ever-increasing amount of information and communication

### Major Depressive Disorder (MDD)

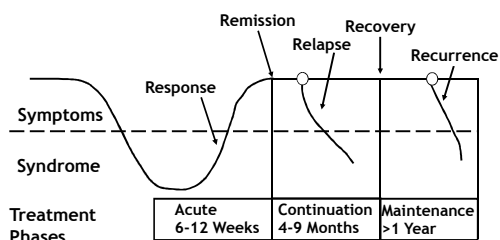
- Lifetime prevalence of MDD in adults: 7 -16.5%
  - Women are 70% more likely to experience MDD than men
- Caused by a combination of genetic, biological, environmental, and psychological factors
- Highly comorbid with anxiety disorders, eating disorders, substance use disorders, and medical illnesses
- Associated with an estimated \$70 billion in medical expenditures, lost productivity, and other costs per year
- Leading cause of disability in the US in individuals 15 to 44 years of age

- Unhappiness is not a psychiatric diagnosis
- Not in DSM-IV or DSM-V
- Unhappiness does not equal depression

### DSM-V Criteria for MDD

- Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning
  - Depressed mood most of the day, nearly every day
  - Loss of interest or pleasure in activities
  - Significant weight loss or gain or change in appetite
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive or inappropriate guilt
  - Decreased ability to think/ concentrate or indecisiveness
  - Recurrent thoughts of death; suicidal ideation
- At least one of the symptoms is either depressed mood or loss of interest or pleasure

### Stages of Treated Depression



Kupfer DJ. J Clin Psychiatry;1991;52(suppl 5):28-34.

### Screening for Depression

- PHQ-2 (Patient Health Questionnaire)
- PHQ-9
- QIDS (Quick Inventory for Depressive Symptomatology)
- HAM-D (Hamilton Depression Scale)
- Geriatric Depression Scale
- Cornell Scale for Depression in Dementia
- Center for Epidemiologic Studies Depression Scale

## PHQ-9

Over the last 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
3. Trouble falling or staying asleep, or 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

## Screening for Depression

- Little evidence recommending one screening method over another
- All positive screens should trigger full diagnostic interviews that use standard diagnostic criteria
- USPSTF: Screen adults *when staff-assisted depression care supports are in place* to assure accurate diagnosis, effective treatment, and follow-up

## Follow-up Care of Depression

- Treatment of depression requires follow-up to monitor response, adjust medication dose, and manage side effects
- There are no established guidelines
- Two proposals:
  - FDA guideline for depression management
    - Weekly visits 1<sup>st</sup> month, 2 visits 2<sup>nd</sup> month, 1 visit 3<sup>rd</sup> month
  - NCQA HEDIS metric for quality of care
    - At least 3 visits during 1<sup>st</sup> 3 months
- In reality, <20% of cases seen in primary care have one follow-up visit

National Committee for Quality Assurance: HEDIS Volume 2: Technical Specifications for Physician Measurement, Washington, DC, 2004  
Morris EH, et al. Am J Psychiatry. 2008;165(1):42-50.

## Treatment of Depression

- No treatment: 23% of cases remit in 3 months, 32% within 6 months, 53% within 12 month and 73% within 24 months (Whiteford, 2013; Grilo, 2005)
- Education/Exercise/Support
- Psychotherapy
- Pharmacotherapy
- Combinations

## Proprietary Recipe of Treatment of Any Mental Disorder by Dr. Elena Volfson

- Brain Transplant
- Re-parenting
- Administration of common sense and perspective (PO, IM, IV, sublingually etc.)

Psychotherapy is the best treatment, unless the patient is actively psychotic, demented or mentally retarded. Functional frontal lobes are required for therapy.

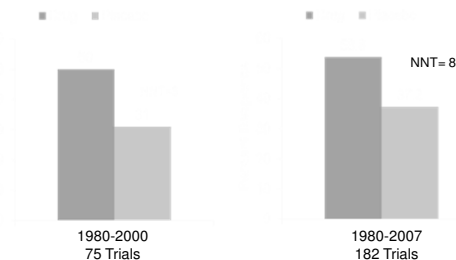
## When to Refer to Psychiatry

- Dangerousness to self and/or others
- Failure to respond to initial treatment
- Need for psychotherapy, light therapy, electroconvulsive therapy (ECT), etc.
- Psychotic depression, bipolar disorder, schizoaffective disorder, severe anxiety, or other major psychiatric illness
- Concomitant/associated substance use
- If the diagnosis is uncertain

## Antidepressants

- Comparable efficacies (Gartlehner, 2011; Mead, 2012; Castren, 2013)
- Second generation are better tolerated and safer
- Poor compliance is common (Olsson, 2006; Mitchell, 2006, Lin, 1998)
- Patient education alone does not improve compliance
- Collaborative care improves adherence - multiple studies

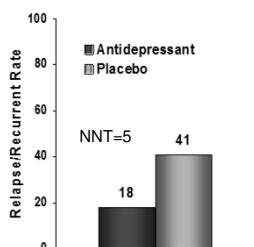
## How Effective Are Antidepressants? Antidepressant vs Placebo Response Rates



Walsh BT, et al. *JAMA*. 2002;287(14):1840-1847.  
Papakostas GI, Fava M. *Eur Neuropsychopharmacol*. 2009;19(1):34-40.  
Gartlehner G, et al. *Ann Intern Med*. 2011;155(11):772-785.

## Relapse/Recurrence Prevention Studies in MDD

- Meta-analysis of 31 RCTs with 4410 patients
- Findings consistently positive
- Antidepressants reduce odds of relapse by 70%
- Most studies were 12 months in duration, but treatment effect persisted for up to 36 months in some trials



RCTs = randomized controlled trials  
Geddes JR, et al. *Lancet*. 2003;361(9358):653-651.

## APA Guidelines on Antidepressant Selection

First line - SSRIs, SNRIs, mirtazapine, or bupropion (second generation)  
Second line - TCAs, MAOIs (first generation)

- Antidepressant choice depends on:

- Side effects and safety issues
- History of response or lack of response
- Drug interactions
- Mechanism of action
- Indication for comorbid disorder
- Cost
- Patient preference

ACP 2008 Guidelines list 2<sup>nd</sup> generation agents in alphabetical order

APA. *Am J Psychiatry*. 2010.  
<http://psychiatryonline.org/content.aspx?bookID=28&sectionID=1667485464274>

## Suicidality Data on Antidepressants

2006 meta analysis of >100,000 patients from 372 randomized controlled studies...

- Risk of suicide with antidepressant is strongly related to age
- Young adults 18-24 during the first two months of treatment: OR 1.62 (2007 black box warning by FDA)
- Adults 25-64: OR 0.79
- Elderly 65 and older: OR 0.37

Changes to antidepressant black box on suicide recommended by FDA panel. "The Pink Sheet" 2006;68(5):3.

## Tenets of Pharmacotherapy

- Evaluate every 1-2 weeks for the first 2 months (by phone or in-person)
- Initial response occurs in about 4 weeks, improvement within two weeks; early improvement might be predictive of remission (Ciudad A. et al, 2012; Posternak, 2005; Nierenberg, 1995; McIntyre, 2010)
- Goal of treatment is remission; partial response at 8 weeks should prompt change or augmentation
- Treat for 6-9 months and then taper (first episode)
- Consider chronic treatment if >3 episodes

Date /Indications	Name	Dose	Pearls
1987 MDD, OCD, bulimia, PMDD	Fluoxetine (Prozac)	10-40 mg	T1/2 4-5 days, for metabolite 7-15 days; +drug interactions
1991 MDD, GAD, PTSD	Sertraline (Zoloft)	50-250 mg	T1/2 26 hrs; dopaminergic at 100 mg ; + drug interactions; multiple titrations
1993 MDD, GAD, PTSD 2002 Paxil CR	Paroxetine (Paxil)	10-40 mg	T ½ 24 hrs; +drug interactions; anticholinergic (muscarinic)
1993 OCD, social anxiety, not MDD (!) 2008 Luvox CR	Fluvoxamine (Luvox)	25-300 mg	T1/2 16 hrs; many interactions, side effects
1989 MDD, social anxiety, panic and OCD Mixture of S (active) and D (inhibitor?) enantiomers	Citalopram (Celexa)	10-40 mg	T1/2 35 hrs; few drug interactions; well-tolerated; dose-dependent QTC prolongation (FDA warning)
2002 MDD, GAD, social anxiety and panic Isolated S-enantiomer	Escitalopram (Lexapro)	10-20 mg	T1/2 35 hrs; few drug interactions; well-tolerated
2014 MDD	Vortioxetine (Brintellix)	10-20 mg	T1/2 66 hrs, very few interactions, well-tolerated, not generic

### Effects of Serotonin Reuptake Inhibition

- Jitteriness, headaches, fatigue, emotional blunting
- Sleep disturbance (no sleep benefit)
- Sexual side effects: anorgasmia, diminished libido; delayed ejaculation, decreased sperm count (infertility)
- Bones: osteoporosis, which is also due to hyperprolactinemia -> increased risk of fragility fractures
- GI: Nausea, vomiting, diarrhea
- Platelets: platelet dysfunction and increased/prolonged bleeding

### SSRI-Induced Bleeding

- Platelet aggregation problems: bruising, petechiae, purpura, epistaxis, hematomas, heavy menstrual bleeding, GI bleeding, hemorrhagic strokes, surgical bleeding
- Tests: decreased platelet aggregability and activity and prolongation of bleeding time
- Degree of serotonin reuptake inhibition varies among SSRIs (highest in fluoxetine, paroxetine and sertraline)
- Patients with hx of platelet disorders, coagulation disorders and von Willebrand disease should be monitored – non-SSRIs should be preferred

Hassan et al, 2005; Scharf et al, 2011; Halperin et al, 2007

### SSRI-Induced Bleeding

- Increase risk of upper GI bleeding (OR 3), particularly for those taking NSAIDs (OR15.6) – synergistic effect
- Coumadine + SSRIs non-GI bleeding (OR 1.7), but risk for GI bleeding is not
- SSRIs increase need for RBC transfusions with surgery (SSRIs OR 3.71, non-SSRIs OR 0.74) and post-partum hemorrhage (Seitz DP, 2013; van Haelst IM, 2010)
- Surgical procedures: urgent and elective – no increase of post-op morbidity and mortality. Discontinuation is unwarranted in most cases.

Li et al. *Blood Coagul Fibrinolysis* 1997;8:517-23; de Abajo et al. *BMJ* 1999;319:1106-9; de Abajo et al. *Arch Gen Psychiatry* 2008;65:795-803; Schalekamp et al. *Arch Intern Med* 2008;168:180-5; Movig et al. *Arch Intern Med* 2003;163:2354-8.

### Other Effects Associated with Serotonin Reuptake Inhibition

- Movement disorders: akathisia, dyskinesia, dystonia, Parkinsonism, tremor, and tardive dyskinesia, bruxism
- Dose-dependent QTC prolongation (especially Citalopram and Escitalopram) (Castro et al., 2013)
- Weight gain (increased carbohydrate craving, 2C receptor) 0.5-6%of body weight per year (Psychiatryonline.org, APA Guidelines for Management of Depression)
- Diabetes mellitus (2 years of taking SSRIs doubles the risk) (Anderson et al, 2009; Rotella F, 2013)

### Serotonin-Norepinephrine Reuptake Inhibitors

Drug	Dose	Side effects / pearls
Venlafaxine (Effexor) 1994 Venlafaxine XR 1997 Mixture of two enantiomers (D and S)	37.5 mg-300 mg NE effects only at 150 mg and above	Side effects problematic; HTN, cardiac toxicity risks; T1/2 5 hrs, metabolite 11 hrs Sometimes used for pain (NNT 3); highly toxic in overdose (like tricyclics); severe discontinuation syndrome
Desvenlafaxine (Pristiq) 2008	50-400 mg	T1/2 11hrs, same side effects
Duloxetine (Cymbalta) 2004	20-90 mg True SNRI	Used for diabetic neuropathy and other pain syndromes (NNT 3); T1/2 12 hrs; severe discontinuation syndrome
Milnacipran (Sevella) 2011	12.5 -200 mg	T1/2 12 hrs Fibromyalgia treatment only, not MDD
Levomilnacipran (Fetzima) 2013 S-enantiomer	20 - 120 mg	T1/2 12 hrs Two-fold potency for NE over 5HT. 10-fold higher selectivity for NE vs. 5HT as compared to venlafaxine and duloxetine.

### Other Noradrenergic Antidepressants

1997 Mirtazapine (Remeron)  S (active)&D enantiomers	15-45 mg	T1/2 40 hrs Does not block serotonin reuptake!!! Noradrenergic Alpha 1-2, 5HT2 and 5HT-3 (anti-nausea), H1, cholinergic, DA. Sleep-promoting at lower doses, more activating with higher doses. Appetite stimulation and weight gain in some patients. No significant interactions. Useful for pain.
1982, 1989 Bupropion (Wellbutrin) IR 1982; SR 1996, XL 2003  Fortivo XL 2014	150-450 mg  DNRI	P450: 2D6, 2B6 T1/2: IR 14 hrs, SR 20 hrs, XL 21-50 hrs Non-addictive amphetamine. Weight loss, improves concentration, energy level, sexual function. Stimulates nicotinic receptors – useful for tobacco dependence. Seizure risk in XL is comparable to SSRIs and SNRIs (0.1%). Useful for pain. Reduces anxiety. No dose-dependent QTC prolongation.

### SARI- Serotonin Antagonists/Reuptake Inhibitors

Name	Dose	Pearls
Trazodone 1981  Oletpro XL 2009	25-400 mg nightly	T1/2 7-10 hrs Good soporific. Priapism.
Nefazodone (Serzone) 1991	200-600 mg divided BID	T1/2 2-5 for parent compound, 33 hrs for metabolites. P450 interactions. Hepatic failure; discontinued in 2004, but still available
Vilazodone (Viibryd) 2011	10-40 mg daily	T1/2 25 hrs no interactions

### MAOI (First Generation) Antidepressants

Generic Name	Trade Name
Selegiline	EmSam* *old medicine that is newly available in a transdermal patch
Tranylcypromine	Parnate
Phenelzine	Nardil

- Complicated to prescribe
- Dietary restrictions

### Tricyclic (First Generation) Antidepressants

Generic Name	Trade Name
Desipramine	Norpramin
Nortriptyline	Pamelor
Amitriptyline	Elavil
Imipramine	Tofranil
Clomipramine	Anafranil

\*Highly toxic in overdose, narrow therapeutic window

- ### Additional Treatment Modalities
- Psychotherapy
  - Exercise/Yoga
  - Neuromodulation/neurostimulation: ECT, rTMS, DBS, VNS
  - Bright light therapy
  - Family support and psychoeducation
  - Interactive computer programs (e.g “Beating the Blues”)

- ### Antidepressant Enhancers
- L-methylfolate
  - Antipsychotics
  - Lithium
  - Thyroid hormone
  - Beta-blockers (e.g.Pindolol)
  - Omega 3, vitamin D 3
  - St. Johns Wort
  - New agents: sarcosine and ketamine (NMDA), nociceptin (OFQ/N); triple reuptake inhibitors

## Anxiety Management

- Screening: GAD-7 or GAD-2
- Anxiety has two components: mental (ruminations, obsessions, fear, panic) and somatic (palpitations, sweating, hyperventilation etc.)
- Antidepressants DO NOT alleviate somatic symptoms !!!
- For somatic symptoms: antihistamines (hydroxyzine), benzodiazepines, beta-blockers or anticonvulsants

## Antidepressants in Elderly Patients

- Elders may require longer maintenance therapy due to higher risk of relapse
- SSRIs - first line, but may exacerbate Parkinsonism, cause akathisia, anorexia, sinus bradycardia and hyponatremia
- Monotherapy is preferred
- Start low, but go to the full dose
- Citalopram < 20 mg daily due to cardiotoxicity
- Bupropion and mirtazapine are very useful
- SNRIs - diastolic hypertension, poorly tolerated as compared with SSRIs

## Two Major Antidepressant Studies: STAR\*D (2006) and CO-MED (Feb 2010)

- Head-to-head comparison of antidepressants and their combinations
- Both include men and women ages 18-75
- Both done at primary and specialty care sites
- STAR\*D: citalopram, bupropion, sertraline, mirtazapine, venlafaxine, tricyclics, nortriptyline, Li, T3 and CBT
- CO-MED: escitalopram alone, bupropion SR with escitalopram, venlafaxine XR with mirtazapine

## Sequenced Treatment Alternatives to Relieve Depression (STAR\*D)

- Multisite (41 clinics nationwide)
  - 18 primary care
  - 23 specialty care
- Multistep, prospective, randomized clinical trial of outpatients with non-psychotic MDD
- 6 years, 1999-2006, \$ 35 million
- Sponsored by NIH and NIMH

## Sequenced Treatment Alternatives to Relieve Depression (STAR\*D)

### Inclusion criteria:

- 18-75 years of age
- Clinician deems antidepressant medication is indicated
- Baseline HAM-D > 14
- Most concurrent Axis I, II, III disorders allowed

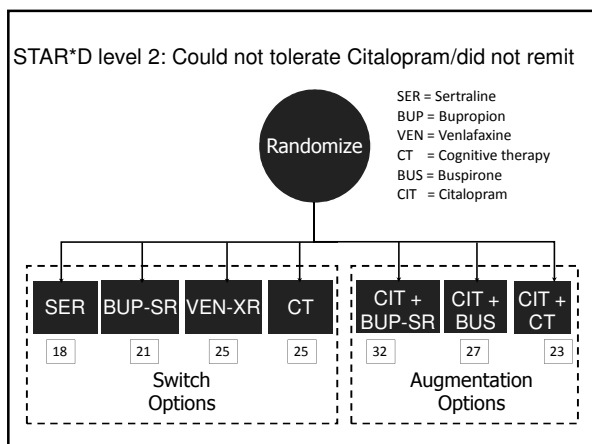
### Exclusion criteria:

- Bulimia, anorexia, OCD, need for detox

## Sequenced Treatment Alternatives to Relieve Depression (STAR\*D)

- All subjects (n=2876) started on Citalopram for up to 14 weeks with 28% remission rate and 47% response rate
- Those who could not tolerate Citalopram (9%) or did not remit (68%) progressed to level 2





### STAR\*D Pharmacologic Therapy Follow-Up

- 5-6 visits every 2-3 weeks
- Clinician rated and patient rated scales
- Completed in-person or by phone
- Treatment manual with medication guidelines

### STAR\*D Remission Rates by Levels

Level 1 (2876)	<b>32.9</b>
Level 2 (1439)	<b>30.6</b>
Switch (789)	27.0
Augment (650)	35.0
Level 3 (377)	<b>13.6</b>
Switch (235)	10.3
Augment (142)	19.1
Level 4 (109)	<b>14.7</b>

### Average Doses Used in STAR\*D

- Level 1:
  - Citalopram 41.8 mg
- Level 2:
  - Sertraline 135 mg, bupropion SR 282.7 mg (267 mg for augmentation), venlafaxine ER 193 mg, buspirone 41 mg
  - 16 CBT treatments over 12 weeks

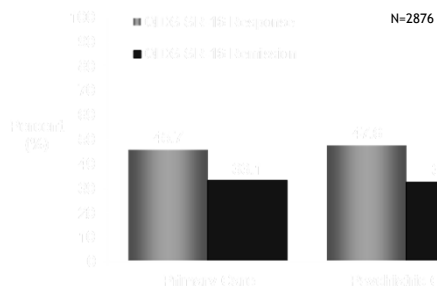
### STAR\*D Follow-Up

- 12 months naturalistic follow-up with continued medications
- Those who achieved remission had better outcomes
- Rates of relapse were greater for those who required more levels of treatment

### STAR\*D Remission and Relapse Factors

- Being white, female and married with higher educational attainment, higher economic status, private insurance, fewer concurrent medical and psychiatric conditions, greater life satisfaction, and shorter index episode  
 HAM-D <7; QIDS-SR <5; PHQ <5
- Being unmarried, living alone, having longer index episodes, greater number of GMC and psychiatric disorders, lower baseline function, lower quality of life, presence of residual depressive symptoms  
 HAM-D >14 ; QIDS-SR >11; PHQ >10

## Similar Outcomes in Primary Care and Psychiatric Care Settings



## Comparable Results in Primary Care and Specialty Care

- Similar remission and response rates
- MDD is more similar than different in two settings
- Equivalent degrees of severity and presentation, differences with rates of medical comorbidities and prior suicidal hx
- Psych comorbidities: social anxiety, GAD, PTSD
- Gender differences in depression

## Conclusions in STAR\*D

- 30 % of patients will achieve remission following initial tx with an SSRI
- Switching or augmenting adds 20-25%
- Both within-class and out-of-class switches are equally effective
- Timely changes, optimal doses and duration of tx can improve outcomes
- **Measurement-based care is essential for chronic disease management**

## COMED Study

1. Outpatients with chronic or recurrent major depression (MDD) were randomized to initial treatment with:
    - escitalopram+placebo 38.8%
    - bupropion-SR + escitalopram 38.9%
    - venlafaxine-XR + mirtazapine 37.7%
  2. Response rates were 51.6%-52.4 %
  3. At 7 months, remission rates (41.8%-46.6%), response rates (57.4%-59.4%), and most secondary outcomes were not significantly different
- Conclusions: Neither medication combination outperformed monotherapy with escitalopram

Am J Psychiatry. 2011 May 2; Combining Medications to Enhance Depression Outcomes (COMED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study. Rush AJ, et al.

## Conclusions

- Depression is a relapsing chronic disease that requires measurement-based care
- Medications and psychotherapy may not be sufficient
- Collaborative/Integrated Care with assisted technologies may be helpful to primary care providers and to patients in management of depression, anxiety and substance-use problems
- Collaborative/Integrated Care implementation requires a paradigm shift and additional training for all team members
- Patients appreciate this new way of care delivery