Treatment Resistant Depression in Youth

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Learning Goals/Objectives

- Familiarity with the prevalence and impact of depression in children and adolescents
- Familiarity with psychoeducation and evidence based treatments for pediatric depressive disorders
- Develop a management approach for pediatric depressive disorders that prove resistant to initial treatment

Pediatric Depressive Disorders Prevalence

- ~2% of children
- ~4 to 8% of adolescents
- Cumulative incidence 10-20% age 18
- Gender ratio
  - Equal before puberty
  - Females predominate after puberty

Pediatric Depressive Disorders Public Health Relevance

- Often unrecognized
  - By patients and families
  - By clinicians
- Functional impairment
  - Interpersonal and social impairment
  - Poor school attendance/performance
- Risk of persistence/recurrence
Pediatric Depressive Disorders
Public Health Relevance (cont.)

• Psychiatric Comorbidity
  ✓ ~ 1/3 to 2/3 of patients
  ✓ Greater impairment and service use
  ✓ Associated with treatment resistance

• Physical Comorbidity
  ✓ Functional somatic symptoms
  ✓ Minor physical illness
  ✓ Chronic physical illness

Pediatric Depressive Disorders
Common Presentations – Signs

• Declining school performance
• Social withdrawal
• Temper outbursts/arguing
• Alcohol/substance abuse
• School absenteeism
• Functional somatic symptoms

Pediatric Depressive Disorders
Public Health Relevance (cont.)

• Physical health risks
  ✓ Suicide, violence, accidental injury
  ✓ Alcohol/drug/tobacco use
  ✓ Health risk behaviors/unhealthy lifestyle
  ✓ Exacerbation of existing physical disease
    • Nonadherence
    • Physiologic effects on disease process

Major Depressive Disorder (MDD) Features in Youth

• Clinical picture similar to adults
• Median duration
  ✓ 7 - 9 months - clinical samples
  ✓ 1 - 2 months - community samples
  ✓ ~ 90% remit by 1 to 2 years
• Recurrence ~ 70% within 5 years
**Major Depressive Disorder (MDD)**

**Features in Youth (cont.)**

- Bipolar disorder in 10 to 20%
- Predictors of bipolar disorder
  - Psychosis
  - FH of bipolar disorder
  - Rapid onset/offset
  - Mania/hypomania with Rx

**Risk for Recurrence**

- Greater initial severity
- Subsyndromal depression
- Parent-child conflict
- Abuse history

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**Major Depressive Disorder (MDD)**

**Risk for Prolonged Episode**

- Greater initial severity
- Psychiatric comorbidity
  - Dysthymic disorder
  - Other psychiatric disorder
    - Anxiety, ADHD, Substance abuse
- Parental depression
- Parent-child conflict

**Building Foundation for Intervention**

**Establishing Credibility**

- Clear and frank diagnosis
  - Reassurance and education
  - Address uncertainties
- Treatment as a partnership
  - Delineate responsibilities
  - Facilitate communication
  - Honest collaboration
- Instill hope and positive expectations
Treatment of Pediatric Depression

**What is known?**

- Psychotherapeutic treatment
  - Cognitive Behavioral Therapy
  - Interpersonal Therapy
- Psychopharmacologic treatment
  - SSRIs
- Combination treatment
  - CBT + SSRI

**SSRIs**

*Selective Serotonin Reuptake Inhibitors*

- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)

- FDA approved pediatric MDD, OCD
- FDA approved pediatric OCD

**Self-Care**

SSRI Efficacy

*Major Depressive Disorder (MDD)*

- Several positive RCTs
  - Best data for fluoxetine
  - Less data for other individual SSRIs
  - > 2 positive trials needed for FDA approval
  - Often 4-5 trials needed for adult Rx approval
  - High placebo response rates (33-59%)
- SSRI continuation may ↓ depression relapse
- Combination CBT + SSRI > SSRI alone
TADS
Treatment for Adolescents w/ Depression Study

- 12-week multisite study of youth aged 12 to 17 years with MDD (N=439)
- Clinical Global Improvement
  - CBT + fluoxetine 71%*
  - Fluoxetine 61%*
  - CBT 43%
  - Placebo 35%
  * significantly different from placebo
  - CBT did not differentiate from placebo
- Suicidality ↓ from 29% to 10% by week 12

SSRI Safety
Practical Considerations

- Pharmacokinetic drug-drug interactions
  - Cytochrome P-450 system
    - Citalopram, escitalopram, sertraline least problematic
- Lack of long-term safety data

SSRI Safety
Practical Considerations

- Relatively HIGH therapeutic index (TI)
  - Low short term toxicity
- Risk of suicidality
- Risk of precipitating mania
- Pharmacodynamic interactions
  - Serotonin syndrome, bruising/bleeding

SSRI Tolerability
Common AEs (Side Effects)

- Usually mild and dose dependent
  - GI symptoms (e.g., nausea, diarrhea)
  - Headache
  - Anxiety, nervousness, panic
  - Sleep disturbance
  - Restlessness, irritability, and agitation
  - Sedation, fatigue
  - Dizziness or lightheadedness
  - Sexual dysfunction
  - Other (e.g., tremor, dry mouth, sweating)
- No well demonstrated long-term AEs in youth
SSRI Safety
FDA “Black Box” Warning

- To all antidepressant medications in U.S.
  ✓ “increase the risk of suicidal thinking and behavior in children and adolescents…”
- Based on FDA review of 24 RCTs (N ~ 4400)
  ✓ **SSRIs** (Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
  ✓ **Non-SSRIs** (Bupropion, mirtazapine, nefazodone, venlafaxine)
- 95 AEs reclassified from raw data
  - “Suicidality” = attempt, SI, preparatory acts
- Suicidality in ~ 4% drug vs. 2% placebo
  ✓ No completed suicides
  ✓ Only significant for venlafaxine alone

SSRI Safety
A Public Health Perspective

- Coincident ↓ pediatric suicide rates with ↑ SSRI prescribing since late 1990s
  ✓ Similar findings in US and Europe
  ✓ Geographic trends for ↓ suicide with ↑ Rx
- Longer Rx may reduce suicide risk
  ✓ Rx > 180 days vs. Rx < 55 days
- Studies of completed suicide
  ✓ < 10% completed suicides who had been prescribed antidepressants + at autopsy

Reanalysis of FDA Data
Antidepressant Efficacy for Youth

<table>
<thead>
<tr>
<th>Dx</th>
<th># of RCTs</th>
<th>N = 5,310</th>
<th>% Response Drug vs. Placebo</th>
<th>% Risk Difference (95% CI)</th>
<th>P-Value</th>
<th>NNT (95% CI)</th>
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<tbody>
<tr>
<td>MDD</td>
<td>15</td>
<td>3,430</td>
<td>61 vs. 50</td>
<td>11 (8-15)</td>
<td>&lt;.001</td>
<td>10 (7-15)</td>
</tr>
<tr>
<td>OCD</td>
<td>6</td>
<td>718</td>
<td>52 vs. 32</td>
<td>20 (13-27)</td>
<td>&lt;.001</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>1,162</td>
<td>69 vs. 39</td>
<td>37 (22-52)</td>
<td>&lt;.001</td>
<td>3 (2-5)</td>
</tr>
</tbody>
</table>

CI = Confidence Interval
RCTs = Randomized Controlled Trials

Reanalysis of FDA Data
Rate of Emergent Suicidality

<table>
<thead>
<tr>
<th>Dx</th>
<th># of RCTs</th>
<th>N = 5,310</th>
<th>Emergent Suicidality (%) Drug vs. Placebo</th>
<th>% Risk Difference (95% CI)</th>
<th>P-Value</th>
<th>NHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>15</td>
<td>3,430</td>
<td>3 vs. 2</td>
<td>1(-0.1-2)</td>
<td>NS</td>
<td>125</td>
</tr>
<tr>
<td>OCD</td>
<td>6</td>
<td>718</td>
<td>1 vs. 0.5</td>
<td>0.5(-1-2)</td>
<td>NS</td>
<td>200</td>
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<tr>
<td>Anxiety</td>
<td>6</td>
<td>1,162</td>
<td>1vs. 0.2</td>
<td>0.7(-4-2)</td>
<td>NS</td>
<td>143</td>
</tr>
</tbody>
</table>

CI = Confidence Interval
NS = Not significant
RCTs = Randomized Controlled Trials
**SSRI Dosing**

- “Start low and go slow”
  - Starting dose over first 3 to 7 days
  - If tolerated, increase to target dose
  - Reevaluate dose within 2 – 3 weeks

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Starting doses</th>
<th>Target</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>10 mg</td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5 mg</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10 mg</td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>50 mg</td>
<td>100 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25 mg</td>
<td>50 mg</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

**TORDIA**

**Treatment of Resistant Depression in Adolescents**

- 12-week multisite study of youth aged 12 to 18 years with MDD who failed to respond to SSRI (N=334)

- Clinical Response
  - SSRI 47.0%
  - Venlafaxine 48.2%
  - No CBT 40.5%
  - CBT 54.8%

**Conclusion**

- CBT + Medication change > Medication change alone
- Switch to another SSRI just as efficacious as switch to Venlafaxine and with fewer adverse events
SSRI Failure for Depression
What to do with limited evidence?

- Encourage psychotherapy – especially CBT
- Medication option 1 – Switch to a different SSRI
  - Switch to different antidepressant class
    - Novel agents (bupropion)
    - SNRIs (venlafaxine, mirtazapine, duloxetine)
    - Older agents (TCAs, MAOIs)
- Medication option 2 – Switch to a different agent
- Medication option 3 – Augmentation strategies
  - Bupropion
  - Busiprone
  - Lithium
  - Atypical antipsychotics (e.g., aripiprazole)

Treatment-Refractory Depression
Lessons from
Sir Arthur Conan Doyle & Sherlock Holmes
Stephen F. Pariser, M.D.
Professor OSU Department of Psychiatry
Director Mood Disorders Clinic
Associate Chairman, CME
Ohio State University
College of Medicine & Public Health

Sir Arthur Conan Doyle
1859-1930

- Son of Charles Altamont Doyle, a civil servant in the Edinburgh Office of Works, and Mary (Foley) Doyle. His father suffered from epilepsy and alcoholism and died in an asylum in 1893—mother kept a boarding house
- Educated in Jesuit schools; later studied at Edinburgh University, qualifying as a doctor in 1885. After graduation practiced medicine until 1891, when he became a full time writer
- Based Sherlock Holmes* on Doctor Joseph Bell, a surgeon and teacher**

*As far as Holmes' name, his last name may have been based on American jurist and fellow doctor Oliver Wendell Holmes and his first name from a young boy named Harry Gratch, a patient of Dr. Bell's who often spoke in a particular way about his doctor.

**Dr. Bell had the uncanny ability to reveal a patient's symptoms, diagnose patients and report on their origins before they would speak a word to him about their afflictions.

Dr. Joseph Bell (1837-1911)
The Inspiration for Sherlock Holmes*

- "In teaching the treatment of disease and accident," Dr. Bell stated, all careful teachers have first to show the student how to recognize accurately the case."
- "The recognition depends in great measure on the accurate and rapid appreciation of small points in which the diseased differs from the healthy state…"

Sherlock Holmes
"...It Is a Capital Mistake to Theorize Before One Has Data…"

**W: What do you imagine that it means?**
**SH: I have no data yet. It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts…’

*From a Scandal in Bohemia
Sir Arthur Conan Doyle

<table>
<thead>
<tr>
<th>Treatment-Resistant Depression</th>
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<tbody>
<tr>
<td><strong>Introduction/Definitions</strong></td>
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<tr>
<td>Epidemiology</td>
</tr>
<tr>
<td>Medical comorbidity</td>
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<tr>
<td>Psychiatric comorbidity</td>
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<tr>
<td>Treatment issues</td>
</tr>
<tr>
<td>Summary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Depressive Disorder</th>
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</thead>
<tbody>
<tr>
<td>Typically Chronic Or Recurrent</td>
</tr>
</tbody>
</table>

- 10%-30% have MDD episodes that last longer than two years
- 20%-30% have MDD superimposed on dysthymia (double depression)
- 60% of psychiatric hospitalizations
- Worsens morbidity and mortality of: CAD and MI, Chronic Pain, Diabetes, Asthma

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Conan Doyle met Dr. Bell in 1877 at the University of Edinburgh Medical School

HAM-D17 Scores

Efficacy – 50% Reduction/Remission ≤ 7

- Depressed
- Response, but symptoms
- Remission (HAM-D17)
  (Virtually symptom free)

MDD: Earlier Age of Onset
(STAR*D) Can Mean:

- More lifetime depressive episodes and suicide attempts
- Greater symptom severity and suicidal ideation in the index episode compared to those with later ages at onset of major depressive disorder

Questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels and weight loss. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.


MDD: Earlier Age of Onset
(STAR*D) Can Mean:

- Never being married
- More impaired social and occupational function
- Poorer quality of life
- Greater medical and psychiatric comorbidity
- More negative view of life and the self

Bipolar Depression

- Bipolar depression is the predominant abnormal affective pole and causes greater disability and economic burden than mania
- Bipolar patients spend 33% of their time in a state of depression compared to 11% of time spent in a manic state.
- Duration of time depressed and severity of depression are associated with increased risk for suicide, which occurs in 10% to 20% of bipolar patients


Bipolar Depression
### Delayed Diagnosis of Bipolar Disorder Common

- For misdiagnosed bipolar patients, when mood stabilizer initiation is delayed, outcomes appear to be poorer
- Exposure to antidepressants, particularly in the absence of mood stabilizers, can precipitate switching into manic or mixed states or cycle acceleration in a subset of bipolar patients
- Patients with MDD exposed to mood stabilizers unnecessarily would be expected to suffer poorer outcomes because of side effects or lesser likelihood of treatment response

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### Depression: Bipolar/Unipolar

<table>
<thead>
<tr>
<th></th>
<th>Bipolar</th>
<th>Unipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of Mania</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sex Ratio</td>
<td>Equal</td>
<td>Women &gt; Men</td>
</tr>
<tr>
<td>Age At Onset</td>
<td>Teens, 20s-30s</td>
<td>30s-50s</td>
</tr>
<tr>
<td>Postpartum</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Episode Onset</td>
<td>Often abrupt</td>
<td>More insidious</td>
</tr>
<tr>
<td>Episodes</td>
<td>Numerous</td>
<td>Fewer</td>
</tr>
<tr>
<td>Duration</td>
<td>3-6 months</td>
<td>3-12 months</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Retardation</td>
<td>Agitation</td>
</tr>
<tr>
<td>Sleep</td>
<td>Hypersomnia</td>
<td>Insomnia</td>
</tr>
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### Risk for Bipolar Illness in Patients Initially Hospitalized for Unipolar Depression

- Cumulative proportion (45%) manifested signs of one or more manic or hypomanic periods at some point during these 15 years.
- May underestimate the magnitude of polarity switches, since ratings were based on systematic assessments of affective syndromes for the 1 year preceding each follow-up assessment combined with data on course of illness, treatments, and narrative clinical material.

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### Treatment-Resistant Depression

- Introduction/Definitions
- Epidemiology
- Medical comorbidity
- Psychiatric comorbidity
- Treatment issues
- Summary

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Mood Disorders Lifetime Prevalences

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Dep Episodes</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>Manic Episode</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Remission is Challenge

- 30-45% of patients show partial response or no response at all
- About 1/3 of patients achieve remission (HAM-D17 ≤7) on single-drug therapies\(^1\-^3\)

Major Depression

12-month Cases Receiving Adequate Treatment

Most lifetime (72.1%) and 12-month (78.5%) cases had comorbid CIDI/DSM-IV disorders, with MDD only rarely primary.

Treatment-Resistant Depression

- Introduction/Definitions
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Thoughtful Consideration

"Problems may be solved in the study which have baffled all those who have sought a solution by the aid of their senses."

The Five Orange Pips

Medical Comorbidity and Treatment Outcome

- Logistic regression analysis showed that CIRS (Cumulative Illness Rating Scale) score was not associated with likelihood of remission or premature study discontinuation
- Medical comorbidity does not appear to be associated with significantly poorer outcome among patients whose major depressive disorder failed initially to respond to an initial trial of 20 mg/day of fluoxetine

Prevalence of significant general medical comorbidity in this population was 50.0% (95% CI = 48.1% to 52.0%)

Concurrent significant medical comorbidity was associated with older age, lower income, unemployment, limited education, and longer duration of index depressive episode

Logistic regression analysis showed that CIRS (Cumulative Illness Rating Scale) score was not associated with likelihood of remission or premature study discontinuation

Medical comorbidity does not appear to be associated with significantly poorer outcome among patients whose major depressive disorder failed initially to respond to an initial trial of 20 mg/day of fluoxetine

Clinical Features of Depression in Outpatients With and Without Co-Occurring General Medical Conditions in STAR*D: Confirmatory Analysis (previously unanalyzed cohort; 2541 outpatients)

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Depression and Pain Comorbidity

- The prevalence of pain in depressed cohorts and depression in pain cohorts are higher than when these conditions are individually examined
- When pain is moderate to severe, impairs function, and/or is refractory to treatment, it is associated with more depressive symptoms and worse depression outcomes

Depression and Pain Comorbidity

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- When pain is moderate to severe, impairs function, and/or is refractory to treatment, it is associated with more depressive symptoms and worse depression outcomes

References:


http://www.pain.com/frameindex.cfm

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http://www.pain.com/frameindex.cfm
Evidence suggests stress and depression result in impairment of the immune response and might promote initiation and progression of some types of cancer, mainly associated with a DNA tumour virus, retrovirus insertion near a cellular oncogene and other viruses such as EBV.

Through HPA activation, the mediators released during chronic stress suppress some non-specific and specific parts of the immune response* compromising the most important effectors of the immune response against tumours.

The temptation to form premature theories upon insufficient data is the bane of our profession—
Part I: 2. Mr. Sherlock Holmes Discourses
The Valley of Fear
Comorbid Anxiety Disorders Present In Major Depression
(255 depressed adult outpatients consecutively enrolled in MGH Depression Program)


5.16.9 14.5 10.6 6.3
50.6

0
10
20
30
40
50
60
%

Comorbid Psychiatric Diagnoses In Patients With Major Depression

• MDD (68.2%) and PTSD (50.0%) were highly prevalent on a lifetime basis in female victims of IPV
• PTSD and MDD symptoms are frequently seen in the aftermath of IPV, and often co-occur


Alcohol Abuse (AA) and Dependence (AD) By Psychiatric Group Status (3,006 women)


Major depressive and post-traumatic stress disorder comorbidity in female victims of intimate partner violence

• MDD (68.2%) and PTSD (50.0%) were highly prevalent on a lifetime basis in female victims of IPV
• PTSD and MDD symptoms are frequently seen in the aftermath of IPV, and often co-occur


Treatment-Resistant Depression

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The dysregulation of 5-HT and NE strongly associated with depression may amplify pain signals. May help explain why dual action antidepressants influence pain.

Sequenced Treatment Alternatives to Relieve Depression

- Both psychiatric and primary care settings
- Patients with non-psychotic major depression (N=2876)
- Duration: 7 years (October 1999 - September 2006)
- Stage I treatment Citalopram, 12-weeks with mean final dose of 41.8 mg/day

Sequenced Treatment Alternatives to Relieve Depression

- Determine best “next-step” treatments for depressed patients who fail to respond satisfactorily to earlier treatment attempts
- Compare relative efficacy and patients’ acceptance of different treatment strategies
- Determine longer term benefits of successful strategies
- Compare their side effect burden and economic costs
- Determine predictors of response to specific treatments

STAR*D Level 1

- In level 1, participants were given the antidepressant citalopram (Celexa) for 12 to 14 weeks
- Those who became symptom-free during this time could move on to a 12-month follow-up period during which the citalopram was continued and patients were monitored
- Those who experienced intolerable side effects or did not become symptom-free during this level could go on to level 2


Evaluation of Outcomes With Citalopram for Depression Using Measurement-based Care in STAR*D: Implications for Clinical Practice

- QIDS-SR response rates: 47%
- QIDS-SR remission rates: 33%
- Similar response/remission rates in primary care and psychiatric settings
- Of participants who responded, 56.0% did so only at or after 8 weeks of treatment—of those who achieved QIDS-SR remission, 40.3% did so only at or after 8 weeks of citalopram

*Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR)

STAR*D Level 2

- Participants had the option of switching to a different medication or adding on to their existing citalopram
- Those who joined the “switch” group were randomly assigned to either sertraline (Zoloft), bupropion-SR (Wellbutrin), or venlafaxine-XR (Effexor)
- Those who joined the “add-on” group were prescribed either the non-SSRI antidepressant bupropion-SR (Wellbutrin), or buspirone (BuSpar)
- Participants could also switch to, or add on, cognitive psychotherapy

Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression

Randomly assigned 727 adult outpatients with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram to receive one of the following drugs for up to 14 weeks: sustained-release bupropion (239 patients) at a maximal daily dose of 400 mg, sertraline (238 patients) at a maximal daily dose of 200 mg, or extended-release venlafaxine (250 patients) at a maximal daily dose of 375 mg.

After unsuccessful treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant. Any one of the medications in the study provided a reasonable second-step choice for patients with depression.
STAR*D
Prognosis better at all levels for participants who entered follow-up in remission

- No differences in remission rates or times to remission among medication switch or among medication augmentation strategies at any treatment level
- Participants who required increasing numbers of treatment steps showed greater depressive illness burden and increasingly greater relapse rates in the naturalistic follow-up period (40%-71%)

Antidepressant Tolerability

- Discontinuation rates due to inability to tolerate medication range from approximately 10 to 25% (likely a conservative estimate - most clinical trials utilize generally healthy patient samples)
- Patients intolerant of one medication may readily tolerate another one of the same class

Timing of Onset of Antidepressant Response With Fluoxetine Treatment

- The lack of onset of response at 4-6 weeks was associated with about a 73%-88% chance that patients would not have an onset of response by 8 weeks.

Maintenance Phase Antidepressant Rx
Factors Contributing to Recurrence:

- Prior history of depressive episodes
- Persistence of dysthymic symptoms after recovery from an episode of depression
- Presence of an additional, nonaffective psychiatric diagnosis
- History of severe and/or long-term depression
- Presence of a chronic general medical disorder
- Consider symptom severity and longevity

50%-80% of Patients With Single Episode Of Major Depression Will Have Another Episode
The world is full of obvious things which nobody by any chance ever observes.

Sherlock Holmes
The Hounds of Baskerville 1901