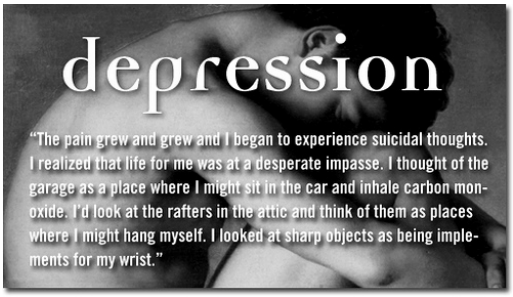


Adil Virani, BSc (Pharm), Pharm D, FCSHP

Outline


REVIEW ARTICLE

Major Depressive Disorder

- Learning Objectives
- Emily's case
- Goals of therapy
- Overview of pharmacology of antidepressants
- Treatment overview & guidelines
- Factors to consider
- Comparing antidepressants

Suggested Reading: Belmaker RH, Agam Galila. Major Depressive Disorder. N Engl J Med 2008; 358:55-68.

Epidemiology:

- Average age of onset is mid 20s
- Lifetime Risk
  - ~1 in 5 Women
  - ~1 in 10 Men
- ~1 in 50 children < 12
- ~1 in 15 adolescents

Overall:

At any given time, ~1 in 20 Canadians suffer from clinical depression!

* WHO Report 2001. Mental Health; New Understanding, New Hope.

Emily

- 25 yo woman, wt = 60kg, with low mood x 4 mo
- Dropped out of BCIT because she couldn't concentrate and didn't want to be a student any more
- Sleeps 12 hrs/night & says she "can't get out of bed"
- Chief complaint: Low mood, confused and constantly irritated. Says she "can't win" and is never hungry
- Failed 2 courses in school
- Broke up with her partner 3 months ago
- NKAs and no other medical conditions

How would you rate Emily's symptoms?

What do you think Emily should do?

- Write down what you think the Goals of Therapy are for Emily
- What treatment options would you consider?
- Please write a prescription for Emily…

Goals of Therapy

- SHORT TERM
  (e.g., 2-3 months)
  - Stabilize depressive symptoms
  - Prevent complications (e.g., suicide)
  - Minimize side effects
  - Induce remission (not only response)
  - Improve quality of life
  - Education

- LONG TERM
  (e.g.,>3 months)
- Prevent relapse and recurrence
- Maintain a stable mood
- Manage side effects
- Education

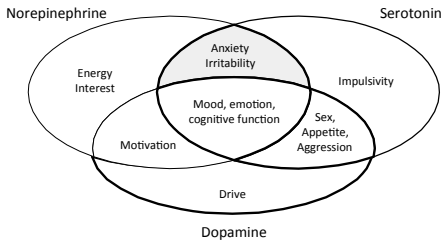
Depression Treatment Options

1. Antidepressant medication(s)
2. Psychotherapy
   - Cognitive behavioural therapy (CBT)
   - Intrapersonal therapy (IPT)
3. Electroconvulsive therapy (ECT)
4. Light therapy
5. Alternative therapies
   - St. John's wort, SAM-e, transcranial magnetic stimulation therapy, etc.

Overview of Antidepressant Pharmacology

- Acute:
  Block reuptake or degradation of monoamines (NE, 5HT, DA)
  - post-synaptic alpha-1 receptor
  - presynaptic autoreceptors
- Chronic:
  - Down regulation of the post-synaptic receptors
  - Alteration of second messenger systems
  - Alteration of protein synthesis

Neurotransmitters Involved in Regulating Mood



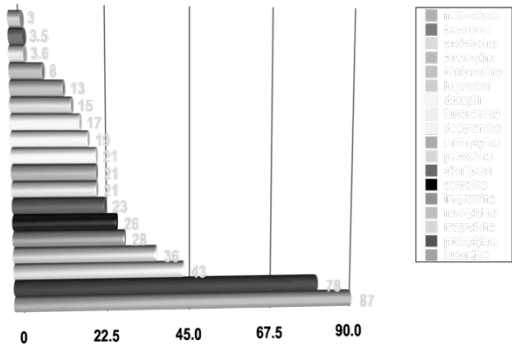
Adapted from Stahl SM. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 2nd ed. Cambridge, UK: Cambridge University Press; 2000:152.

Overview of Antidepressant Pharmacokinetics

In general:

- Absorption is rapid
- Metabolism: extensive 1st pass
- Oxidation, hydroxylation, demethylation
- 5% = "slow acetylators"
- Many have drug-drug interactions to be aware of
- Protein bound: 90 – 95%

Antidepressant half-lives (hrs)



Antidepressant MoAs

1. Inhibit the reuptake of serotonin and noradrenaline:
   - Tricyclic antidepressant (TCA) & serotonin-noradrenaline reuptake inhibitor (SNRI)
2. Decrease the metabolism of serotonin, noradrenaline, and dopamine by inhibiting monoamine oxidase:
   - Monoamine oxidase inhibitors (MAOI)
   - Riversible inhibitors of Monoamine oxidase (RIMA)
3. Inhibit the reuptake of serotonin:
   - Selective serotonin re-uptake inhibitor (SSRI)

Stahl, 1999

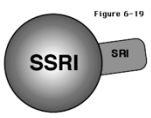
Antidepressant MoAs

4. Antagonize serotonin 5HT2 action at post-synaptic receptors and inhibit the reuptake of serotonin:
   - Serotonin antagonist/reuptake inhibitor (SARI)
5. Inhibit the reuptake of noradrenaline and dopamine:
   - Noradrenaline-dopamine reuptake inhibitor (NDRI)
6. Modulates the serotonin system to increase release of noradrenaline and serotonin
   - Noradrenergic & specific serotonergic antidepressant (NaSSA)

Overview of Antidepressant Classes

OPTIONS FOR 1ST OR 2ND CHOICE		
TCAs:	Tricyclic antidepressants	8 agents
SSRIs:	Selective serotonin reuptake inhibitors	6 agents
NaSSA:	Noradrenergic and serotonergic specific antidepressant	1 agent
RIMA	Reversible Inhibitor of Monoamine Oxidase	1 agent
NDRIs:	Noradrenaline dopamine reuptake inhibitors	1 agent
SNRIs:	Serotonin noradrenaline reuptake inhibitors	3 agent
RESERVED		
SARIs:	Serotonin antagonists/reuptake inhibitors	1 agent
MAOIs:	Monoamine oxidase inhibitors	2 agents
Heterocyclics: Maprotiline		1 agent

SSRI Similarities



- Similar MoA
- Equally effective for depressive & anxiety disorders
  - ~ 70% in adults; 50-60% in C&A
- Relatively similar rate of GI, CNS and sexual side effects
- Comparable cost
- Similar profiles on brain imaging
- Brand names have 2 syllables and an “X” or a “Z”

SSRI Differences

SSRI	Additional Receptor Activity	Potential Clinical Implication	Drug Interactions	Withdrawal Effects
Fluoxetine	5HT2c antagonist Noradrenaline RI	Bulimia; increase arousal	+++	-
Fluvoxamine	Sigma 1 receptor blockade	Psychotic depression; OCD	+++	++
Sertraline	Dopamine RI	Panic Disorder; OCD; no prolactin incr.	+	++
Paroxetine	Noradrenaline RI Muscarinic RI	Panic Disorder; OCD; anticholinergic	++	+++
Citalopram	More selective for serotonin receptors	Less drug interactions	-/+	+
Escitalopram	Most selective for serotonin receptors	Less drug interactions	+	+

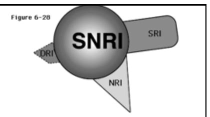
RI = Reuptake Inhibitor

SSRI Dosing

- Relatively flat dose-response curve in depression
- Higher doses used in anxiety disorders (e.g., OCD)

SSRI	Starting Dose (mg)	Target Dose (mg)	Maximum Dose (mg)	Canadian Approval
Fluoxetine	10-20	20-40	80	Nov. 1988
Fluvoxamine	50-100	100-200	300	July 1990
Sertraline	25-50	50-150	200	Jan. 1992
Paroxetine	10-20	20-40	60	May 1993
Citalopram	10-20	20-40	60	Feb. 1999
Escitalopram	10	20	20-30	Dec. 2004

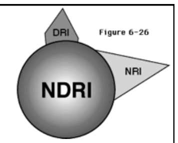
Venlafaxine & Duloxetine



The **Serotonin-Norepinephrine Reuptake Inhibitor** blocks the reuptake of norepinephrine and of serotonin

- Venlafaxine - Dual reuptake blockade of 5HT & NA at intermediate doses. At high doses DA blockade
- Drug interactions: <SSRIs; CYP2D6 inhibition; potentiates 5-HT effects
- Similar side effects to SSRIs
  - Intermediate sexual side effects
- NA side effects may be observed at higher doses
  - Insomnia, restlessness, tremor, sweating, BP increase
- Withdrawal reactions with abrupt cessations

Bupropion (NDRI):



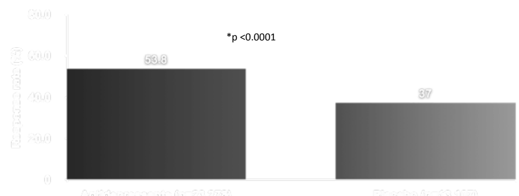
- Demonstrated equivalent to SSRIs for depression
- Blocks reuptake of NE & DA
- Drug interactions:<SSRIs; CYP2D6 inhibition
- Effective for ADHD and smoking cessation
- No documented withdrawal reactions
- Minimal sexual side effects
- Side effects/precautions:
  - Agitation, dry mouth, constipation, headache, tremor, seizure risk, hypertension
- Ask patients if they are taking "Zyban"

Mirtazapine (NaSSA):

- Enhances NA and 5HT1A effects by mediating serotonergic neurotransmission
- H1 receptor blockade
  - Sedation (especially at low doses: 15-30 mg/day)
- 5HT2C receptor blockade
  - (appetite stimulation/weight gain)
- Minimal drug interactions
- Less sexual dysfunction than SSRIs

Overall Response Rates: Antidepressants

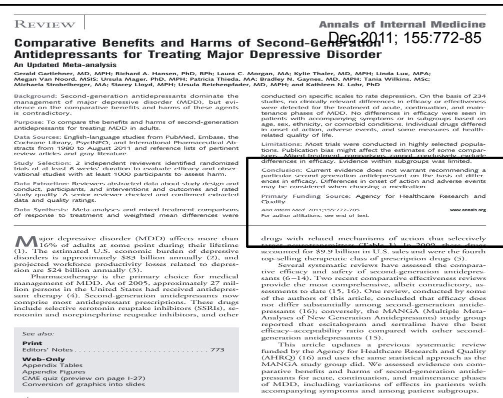
Meta-analysis including 262 drug-placebo comparisons from 182 clinical trials (n=36,385)



Papakostas, Fava. Eur Neuropsychopharmacol 2009:19:34-40

How do you pick which treatment to start?

Dec 2011; 155:772-85



conducted on specific scales to rate depression. On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. Individual drugs differed in onset of action, adverse events, and some measures of health-related quality of life.

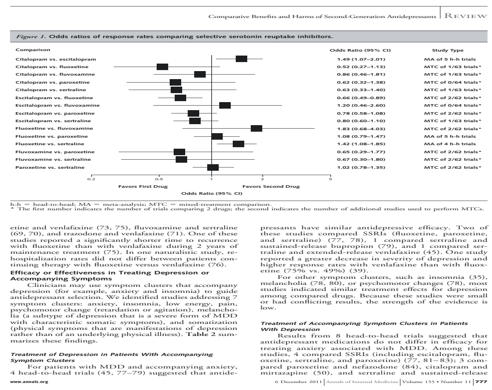

Comparative Benefits and Harms of Second-Generation Antidepressants | REVIEW

Figure 1. **Odds ratios of response rates comparing selective serotonin reuptake inhibitors.**

Comparison	Odds Ratio (95% CI)	Study Type
Citalopram vs. escitalopram	1.49 (1.07–2.01)	MA of 5 h-h trials
Citalopram vs. fluoxetine	0.52 (0.27–1.13)	MTC of 1/63 trials*
Citalopram vs. fluvoxamine	0.86 (0.46–1.81)	MTC of 1/63 trials*
Citalopram vs. paroxetine	0.62 (0.32–1.38)	MTC of 0/64 trials*
Citalopram vs. sertraline	0.63 (0.33–1.40)	MTC of 1/63 trials*
Escitalopram vs. fluoxetine	0.66 (0.49–0.89)	MTC of 2/62 trials*
Escitalopram vs. fluvoxamine	1.20 (0.46–2.60)	MTC of 0/64 trials*
Escitalopram vs. paroxetine	0.78 (0.58–1.08)	MTC of 2/62 trials*
Escitalopram vs. sertraline	0.80 (0.60–1.10)	MTC of 1/63 trials*
Fluoxetine vs. fluvoxamine	1.83 (0.68–4.03)	MTC of 2/62 trials*
Fluoxetine vs. paroxetine	1.08 (0.79–1.47)	MA of 5 h-h trials
Fluoxetine vs. sertraline	1.42 (1.08–1.85)	MA of 4 h-h trials
Fluvoxamine vs. paroxetine	0.65 (0.29–1.77)	MTC of 2/62 trials*
Fluvoxamine vs. sertraline	0.67 (0.30–1.80)	MTC of 2/62 trials*
Paroxetine vs. sertraline	1.02 (0.78–1.35)	MTC of 2/62 trials*

0.2 0.5 1 2 5
Favors First Drug — Favors Second Drug
Odds Ratio (95% CI)

h-h = head-to-head; MA = meta-analysis; MTC = mixed-treatment comparison.
* The first number indicates the number of trials comparing 2 drugs; the second indicates the number of additional studies used to perform MTCs.

etine and venlafaxine (73, 75), fluvoxamine and sertraline (69, 70), and trazodone and venlafaxine (71). One of these studies reported a significantly shorter time to recurrence with fluoxetine than with venlafaxine during 2 years of maintenance treatment (75). In one naturalistic study, rehospitalization rates did not differ between patients continuing therapy with fluoxetine versus venlafaxine (76).

Efficacy or Effectiveness in Treating Depression or Accompanying Symptoms

Clinicians may use symptom clusters that accompany depression (for example, anxiety and insomnia) to guide antidepressant selection. We identified studies addressing 7 symptom clusters: anxiety, insomnia, low energy, pain, psychomotor change (retardation or agitation), melancholia (a subtype of depression that is a severe form of MDD with characteristic somatic symptoms), and somatization (physical symptoms that are manifestations of depression rather than of an underlying physical illness). **Table 2** summarizes these findings.

Treatment of Depression in Patients With Accompanying Symptom Clusters

For patients with MDD and accompanying anxiety, 4 head-to-head trials (45, 77–79) suggested that antidepressants have similar antidepressive efficacy. Two of these studies compared SSRIs (fluoxetine, paroxetine, and sertraline) (77, 78), 1 compared sertraline and sustained-release bupropion (79), and 1 compared sertraline and extended-release venlafaxine (45). One study reported a greater decrease in severity of depression and higher response rates with venlafaxine than with fluoxetine (75% vs. 49%) (39).

For other symptom clusters, such as insomnia (35), melancholia (78, 80), or psychomotor changes (78), most studies indicated similar treatment effects for depression among compared drugs. Because these studies were small or had conflicting results, the strength of the evidence is low.

Treatment of Accompanying Symptom Clusters in Patients With Depression

Results from 8 head-to-head trials suggested that antidepressant medications do not differ in efficacy for treating anxiety associated with MDD. Among these studies, 4 compared SSRIs (including escitalopram, fluoxetine, sertraline, and paroxetine) (77, 81–83); 3 compared paroxetine and nefazodone (84), citalopram and mirtazapine (50), and sertraline and sustained-release

www.annals.org — 6 December 2011 | Annals of Internal Medicine | Volume 155 • Number 11 | 777

Factors to Consider When Starting Therapy

- Severity of episode
- Age
- Long term adherence
  - Risk of relapse increases if discontinued early (35%-60% vs. 10%-25%)
- Previous treatment response
- Comorbid psychiatric or medical disorders
- Drug interactions
- Accessibility
- Pharmacokinetics
- Potential side effects
- Suicide risk/impulsivity
- Patient preferences
- Clinician experience
- Effectiveness of treatment

Things to Review when Starting an Antidepressant

1. Address patient's concerns
2. Purpose of medication(s)
3. Expected minimum treatment duration
4. Time to benefit & relapse prevention
5. Likelihood of benefiting
6. Dosing do's and don'ts
7. Side effects
8. Reassurance (not addictive)
9. Don't stop just because you feel better
10. When its time to stop, taper slowly (where appropriate)

Prognosis: Relapse rates

# of previous episodes	Risk (in 5 yrs) of having an additional episode if not taking meds
1	35-60 %
2	70 %
3	90 %

- 5-10% of individuals with a single depressive episode have a manic episode

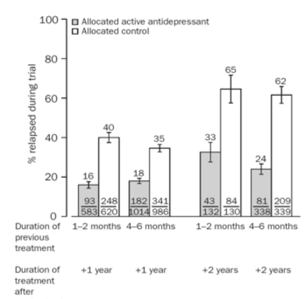
Keller MB. J Clin Psych. 1999; 60(suppl 17):41-45

Antidepressant Relapse Prevention

Relapse rates after 1 or 2 years of antidepressant treatment in patients already treated for 1–2 or 4–6 months after an acute episode of depression

Odds of relapse: ↓50-70% with continued Rx

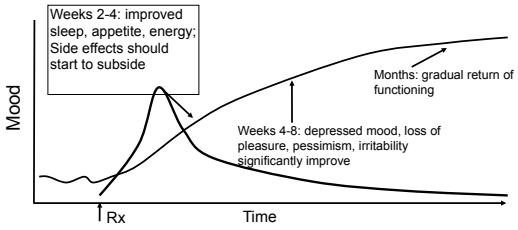
Average relapse rates:
Antidepressant: 18%
Placebo: 41%



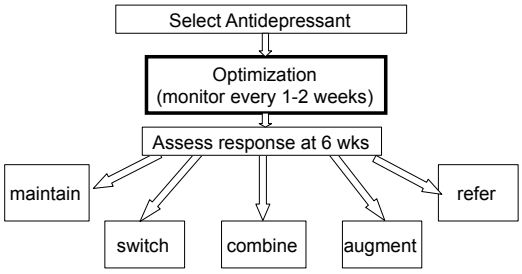
Geddes et al. Lancet 2003

Antidepressants: Onset of Effect

- Symptoms begin to improve slowly over several weeks
- 6/10 see a noticeable improvement at 4 wks
- If no improvement at 3-4 wks, 20% probability of benefiting



Strategies for Reaching Remission



Kennedy et al, 2001

Clinical Issues with Antidepressants

- Intolerability
- Persistent side effect burden
- Withdrawal syndromes
- Need for multiple medications
- Suicide/self harm controversy
- Non-adherence
- Safety during pregnancy
- Safety in overdose
- Public/self perceptions

General Antidepressant Side Effects

1. Anticholinergic
2. CNS effects
   - Activation/agitation
   - Sedation
   - Paresthesias
   - Seizures
   - Increased suicidality
3. Cognitive
4. Dermatitis
5. GI
6. Cardiovascular
7. Sexual
8. Weight Gain

Serotonin Syndrome

- Idiosyncratic drug reaction that is usually caused by a drug interaction when combining 2 or more serotonergic agents (e.g., SSRIs and MAOIs,, meperidine, amphetamines, linezolid, DM, 2nd generation antipsychotics, triptans)
- Symptoms
  - Variable reaction: mild to death (Libby Zion Death/Law)
  - Delirium, agitation, hyperpyrexia, diaphoresis, myoclonus, hyperreflexia, tremor, hypertension, diarrhea, incoordination
- Treatment
  - Stop suspected drug(s)
  - Supportive care

SSRI/SNRI Discontinuation Syndrome

- Seen with abrupt cessation of SSRI or SNRI (usually the ones with short half lives)
- Modest but clinically significant increase in favor of SSRIs vs. TCAs
- 1-2 weeks of feeling “off” or “fluish”
  - Common: dizziness, anxiety, nausea, sweating, coryza, headache, insomnia,
  - Occasionally: electric shock-like sensations, parasthesias, visual disturbances, myalgias, chills, confusion
- Can be VERY DISTRESSING and DISABLING

Michelson et al. Br J Psychiatry 2000

SSRI/SNRI Discontinuation Syndrome

- Management:
  - Prevent by advising patient not to stop SSRI/SNRI cold turkey (exception fluoxetine)
  - Taper SSRI/SNRI over 1-4 weeks
  - If mild symptoms: encourage them to try to let it pass over 1-2 weeks
  - If moderate to severe or symptoms > 2 weeks REINTRODUCE SSRI and taper more slowly or switch to fluoxetine (long $t_{1/2}$) then taper

Michelson et al. Br J Psychiatry 2000

Monitoring Parameter	Timeline
1. Target Symptoms for Depression, severity of symptoms and functioning (efficacy of antidepressant – aim for remission)	q7-14 days for 4-6 wks then q 1-3 months (to watch for relapse
2. Antidepressant adverse effects (depends on the medication selected – you should be able to identify which ones you'd be concerned with)	q7-14 days for 4 wks then q 3 months
3. Increase in obsessive, obtrusive suicidal thoughts/behaviours (especially in children, adolescents and young adults)	q7-14 days for 4-8 wks
4. Serotonin syndrome	First 2 wks of AD or new medication
5. Discontinuation syndrome	At discontinuation of therapy

Key Messages

1. All antidepressants are equally efficacious at reducing symptoms of depression.
2. Antidepressants help reduce symptoms of (moderate to severe) depression in 50-60% of adults and decrease the risk of relapse by approximately 50% (at 1 yr).
3. Benefits over placebo are greater as severity of depression increases (mostly because placebo effects decrease).

Key Messages

4. Use low doses initially
5. Despite the publication bias in adult MDD trials, antidepressants are, on average, more EFFECTIVE (than placebo) at reducing the symptoms of depression.
6. Reduce reliance on antidepressants (reserve them for moderate to severe depression)
7. Ensure adequate patient contact and monitoring

Questions?