

# Pharmacological treatment of depression

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## Overview

### Questions

1. Is an effective drug therapy available?
2. Is the effect clinically relevant?
3. Which drugs are available?
4. In which way should we treat?
5. Whom should we treat?

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## 1. Is an effective drug therapy available?

### Methodological problems

- Number and size of trials
- Generalizability
- Outcome measure
  - Scales (e.g. Ham-D; CGI)
  - Response; remission
- Study duration
- Placebo response rate; spontaneous remissions

### Overall

- Antidepressants are more effective than placebo also in elderly people

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## 2. Is the effect clinically relevant?

- Effects are modest\*
- Number needed to treat (response)†: 8
  - NNT complicated by a high placebo response rate
- Drug-placebo differences increase as a function of baseline severity ‡

\* Nelson et al., Am J Geriatr Psychiatry. 2008 May 12

† Taylor et al., Neuropsychopharmacology. 2004 Dec;29(12):2285-99

‡ Kirsch et al., PLoS Med. 2008 Feb;5(2):e45.

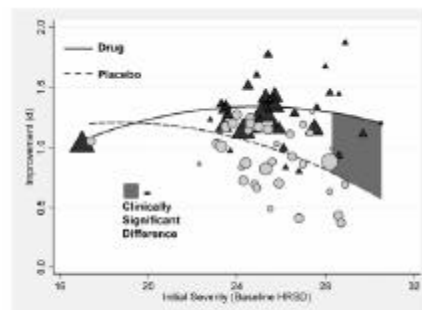


Figure 2. Mean Standardized Improvement as a Function of Initial Severity and Treatment Group

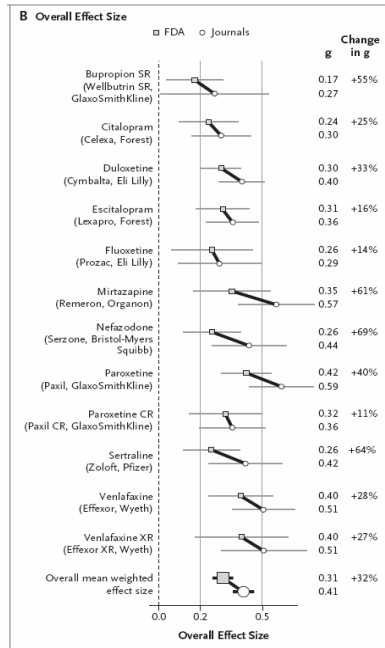
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Is the effect clinically relevant?

**Publication bias  
(trials with modern antidepressants)**

Effect size of all studies (left; FDA-Database) and of published trials (right)

Turner et al., NEJM 2008;358:252-60



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**3. Which drugs are available?**

**Tricyclic antidepressants (1. generation)**

- Amitriptyline
- Doxepine
- Imipramine
- Nortriptyline
- (Trazodone)

**SSRI (2. generation)**

- Citalopram
- Sertraline
- Paroxetine
- Fluoxetine

**New antidepressants (3. generation)**

- Mirtazapine
- Reboxetine
- Venlafaxine
- Duloxetine

**Reversible MAO A inhibitors**

- Moclobemide

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## *Side effects of TCA and SSRI*

- Tricyclic antidepressants (TCA)
  - Cardiac effects
  - Anticholinergic effects: confusion and delirium, glaucoma, urinary retention, obstipation, postural hypotension and falls
  - Fatal overdose
  
- Selective serotonin reuptake inhibitors (SSRI)
  - Nausea, diarrhea, weight loss, headache, tremor, sexual dysfunction, insomnia, hyponatremia, withdrawal symptoms
  
- SSRI have a more favourable safety and tolerability profile and should be preferred in elderly people

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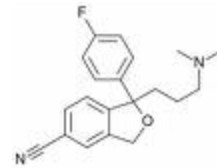
## *Falls and fractures in TCA and SSRI*

- It was hypothesized that SSRI may have a lower risk for falls than TCA and therefore also a lower risk for fractures
  
- Observational studies
  - Falls: SSRI might carry even higher risks\*
  - Fracture rate: no difference or even higher rates in persons treated with SSRI
  - Bone mass density: decreased after treatment with SSRI but not with TCA

\*Hartikainen, J Gerontol A Biol Sci Med Sci. 2007 Oct;62(10):1172-81. Review

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## Which SSRI?



	T <sub>1/2</sub>	Active metab.	Once-daily dosing	Drug interactions (CYP 450)	Beneficial also in anxiety	Sedation
Citalopram	33 h	+	+	-	+	-
Fluoxetine	1-3 d	+	+	+	+	-
Paroxetine	24 h	-	+	+	+	-
Sertraline	23 h	-	+	+	+	-

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## New antidepressants

- Noradrenergic and specific serotonergic antidepressants (NaSSA)
  - **Mirtazapine**
    - (Side) effects: sedation (evening dose), increased appetite; few interactions
- Norepinephrine reuptake inhibitors (NRI)
  - **Reboxetine**
    - (Side) effects: dry mouth, constipation, excessive sweating, insomnia; activating
- Serotonin-norepinephrine reuptake inhibitors (SNRI)
  - **Venlafaxine**
    - (Side) effects: similar than in SSRI; activating
  - **Duloxetine**
    - Also used for: stress urinary incontinence; pain in diabetic neuropathy

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## *Concomitant problems*

- Sleeplessness
  - Mirtazapine, Trazodone, (Amitryptiline, Doxepin)
- Anxiety
  - Paroxetine, other SSRI, Trazodone
- Agitation
  - Mirtazapine, Trazodone
- Apathy
  - SSRI, Reboxetine, Venlafaxine
- Psychotic symptoms
  - Combination with antipsychotics

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## 4. In which way should we treat?

- Monotherapy (no evidence that combination therapy is better; risk of a serotonin syndrom)
- Therapeutic resistance
  - No effect over 4-6 weeks with 2 different antidepressants
  - Management
    - Increase dose over standard dose
    - Increase treatment period to 12 weeks
    - Change to another substance
    - Augmentation with lithium
    - Electroconvulsive therapy
- Treatment duration
  - 6-12 months after remission, (longer if multiple prior episodes)

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## 5. Whom should we treat?

### Depressive syndromes

- Depressive episode
  - Single
  - Recurrent
  - Bipolar
  - With psychotic symptoms
- Dysthymic (Cyclothymic) disorder
- Adjustment disorder with depressed mood
- Organic mental disorder

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### *Organic mental disorders and depression*

- „Vascular“ depression, stroke
  - Review: no strong evidence that antidepressants produce remission or prevent depression after stroke\*
- Parkinson's disease
  - Optimisation of dopaminergic medication
  - SSRI (not together with Selegeline!), Mirtazapine
- Dementia
  - Acetylcholinesterase inhibitors?
- Organic mental disorders have basically no good response on pharmacologic treatment

\* Hackett et al., Stroke 2005;36:1092-7

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## Conclusion

- Antidepressants are more effective than placebo
  - Effects are modest
- SSRI and newer antidepressants should be preferred
  - Substance depends from concomitant problems
- The response on pharmacologic treatment in patients with organic mental disorders is limited
- Not only pharmacotherapy but also psychotherapy should be considered



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