How to choose an antidepressant drug

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A Lundbeck lecture

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Contrary to some skeptics and antipsychiatry viewpoints in magazines and even professional journals, **Antidepressant drugs are highly effective when chosen and used properly!**
Appearance of drugs with antidepressant properties

- Imipramine + other TCAs
  - mianserin, trazadone, bupropion, fluoxetine, mirtazapine
  - citalopram, sertraline, venlafaxine, duloxetine
  - milnacipran
  - escitalopram, agomelatine

- Lithium
  - Antipsychotics with serotonin components
  - loxapine, amoxapine, other atypical antipsychotics such as quetiapine and aripiprazole

- Timeline:
  - 1950s
  - 1970-80s
  - 1990s
  - 2000s
Many Antidepressant drugs available, but which one to choose? People commonly think of antidepressants by name or by class

**TCAs**  e.g. amitriptyline, imipramine, nortriptyline, desipramine

**MAOIs**  e.g. phenelzine, tranylcypromine, isocarboxazid, moclobemide, selegiline, rasagiline

**SSRIs**  e.g. fluoxetine, sertraline, paroxetine, fluoxamine, citalopram, escitalopram

**SNRIs**  e.g. venlafaxine, duloxetine, milnacipran

**Others**  e.g. trazodone, bupropion, agomelatine

**Metabolites and alternate formatting** (for patent extension purposes: e.g. desvenlafaxine, Levomilnacipran, solutabs, XR, etc)

**Minor tranquillizers are NOT antidepressants** (but are commonly given and mistaken by doctors and patients)
Current Antidepressant drugs induced remission in a significant % of depressed cases

Common Scenario:

1\textsuperscript{st} drug
~ 30-60 % patient responded

2\textsuperscript{nd} drug
~ 10 % patient of the remaining responded

3\textsuperscript{rd} drug
~ 2- 5 % of remaining responded

Adding another drug to existing : ~ 5 -10 %
Over-diagnosed or Rx

1. Unnecessary medications
2. Costs
3. Label/stigma
4. Placebo effect
5. ???

Under-diagnosed or Rx

1. Rotating through many specialties (costs)
2. Unnecessary medications of all kinds (e.g. pain killers, benzodiazepines)
3. Unnecessary surgeries
4. Unnecessary high Costs
5. Irreversible damages (e.g. surgeries)
6. Failures (school, job, marital, social, …..)
7. Suicide
8. ……..??????
All current antidepressant drugs & all depressed cases requiring treatment

Current antidepressants non-responsive

Augmentation required

All current antidepressant drugs responsive (~ 50-60%)

Select 1st best antidepressant drug from all current antidepressants
Selecting a proper 1st antidepressant is more important than most people believed

1. For compliance and to establish trust (dropping out from Treatment is common)
2. Second switch do not carry much significant chance of success
3. Resistant cases may need augmentation rather than switching, and drug with less drug drug interaction chance would give a safe start in augmentation
Popular Myths to be discussed & to be diffused in this talk

1. Antidepressant drugs are selected/switched on the basis of drug class/group (e.g. TCA/SSRI/SNRI/NRI/TRI/Multi-target)

2. More action is better (e.g. SNRIs are better than SSRIs)

3. 5HT drugs versus NE drugs

4. Some drugs have different non-”aminergic” mechanism of action
Understanding Ki

**Ki**: the smallest amount of drug needed to get to its “target”
The smaller the better
<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>5HT</th>
<th>NE</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milnacipran</td>
<td>151</td>
<td>68</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>3.7</td>
<td>20</td>
<td>439</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>145</td>
<td>1420</td>
<td>3070</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>67</td>
<td>63</td>
<td>7500</td>
</tr>
<tr>
<td>Citalopram</td>
<td>19</td>
<td>8690</td>
<td>&gt;100,000</td>
</tr>
</tbody>
</table>

Ki: 5HT, NE, DA reuptake
Vaishnavi et al., 2004
Class classification is erroneous and invalid when *in vivo* (inside human body)

5HT and NE  RI

NRI

Amitriptyline

Nortriptyline
Class classification is erroneous and invalid when *in vivo* (inside human body)
Efficacy superiority is not related to uptake inhibition of more neurotransmitter types, which could even be harmful or counter-productive (e.g. TCAs) but to the pharmacology of the compound itself, especially whether the additional target(s) are useful.
Therefore, Drug Classes do not correlate with efficacy!

1. Classification into TCAs, SSRI, SNRI and TRI is only an *in vitro* exercise and not applicable *in vivo*
2. Antidepressants within same class and their metabolites once in body differ tremendously in their *K* for targets and clinical efficacy
3. Differences in efficacy is related to the compound itself, NOT the class (e.g. escitalopram and SSRIs)

**Conclusion:** The proposal of switching from one class to another in some treatment guidelines is totally erroneous and is not supported by clinical pharmacological evidence.
Pyramidal neurons
Glial Supports

- Astrocyte
- Spine
- Neuron
- Cell body
- Dendrite
- Axon
- Neurotransmitters
- Synapses
- Dendrite with spines and synapses
抗抑鬱藥的標靶

5HT transporters

AXON

SPINE

5HT

5HT_2c

5HT_2a
**Current Antidepressant Drug Targets**

1. **Re-uptake Inhibitors**
   - all TCAs, SSRIs, SNRIs, NRIs, NDRI

2. **Auto-receptor Antagonist**

3. **MAOI (A & B)**
   - Pargyline, Phenelzine (Nardil)
   - Selegilene (Deprenyl)
   - Tranylcypromine (Parnate)
   - Rasageline

4. **5HT2C**
   - Agomelatine (antagonist)
   - Trazodone (agonist)

5. **1,2,3,4, plus Other receptor modulators**

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Examples:
- 1. Amitriptyline, Imipramine
- Fluoxetine (Prozac)
- Paroxetine (Paxil)
- Escitalopram (Lexapro)
- Venlafaxine and metabolites
- Duloxetine, Bupropion

- 2. Mirtazapine, Mianserin

- 3. Pargyline, Phenelzine (Nardil)
- Selegilene (Deprenyl)
- Tranylcypromine (Parnate)
- Rasageline

- 4. Other compounds on 5HT receptors (e.g. 5HT2c)
- Agomelatine (antagonist)
- Trazodone (agonist)
All current antidepressant drugs have a 5HT target.
What can you infer from the numbers?

Table 1. Affinity ($K_i$) of transporters for the 5-HT reuptake site

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>2.3</td>
</tr>
<tr>
<td>Citalopram</td>
<td>1.6</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.1</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1.1</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0.26</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Adapted from Owens et al, 2001.
Table 2. Affinity ($K_i$) of transporters for norepinephrine (NE) and dopamine (DA) reuptake sites

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_i$ (nM)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NE transporter</td>
<td>DA transporter</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>7,841</td>
<td>27,410</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>6,190</td>
<td>16,540</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1,427</td>
<td>16,790</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>714</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>599</td>
<td>3,764</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>45</td>
<td>268</td>
<td></td>
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</tbody>
</table>

Adapted from Owens et al, 2001.1
Refining the SSRI key

5HT Keys
Specificity

TCAs
Fluoxetine
Paroxetine
Sertraline
Citalopram
Escitalopram (Lexapro®)

Increasing specificity

Decreasing side effects

Serotonin re-uptake inhibitors are useful antidepressant drugs. They differ in their specificity, with Escitalopram being the most specific and purest SSRI on the market.

© Tang 2005
Axon

autoreceptor

transporter

5HT

MAO

5HT receptors

Spine

© Tang
5HT transporters in axon where all SSRIs act

© Tang
The 5HT Transporter

Chen et al. Submitted; Elfving et al. 2003
TCAs, SSRIs, SNRIs

5HT going thru transporters
5HT transporters

Escitalopram (Lexapro®)
Citalopram/escitalopram binding sites

All SSRIs binding to primary site (serotonin uptake inhibition)

Important for additional escitalopram binding to allosteric site

All SSRIs

2nd binding site for escitalopram

Chen et al. Submitted; Elfving et al. 2003
Citalopram & Escitalopram

1. Binding of active citalopram to 5HT transporter is interfered by inactive citalopram in the racemic drug
2. Binding of escitalopram to 5HT transporter is to 2 sites & also self enhancing

[dissociation and association studies of radiolabelled escitalopram : the left /right hand glove concept]
5-HT uptake site

SSRI
Figure 3. The R-enantiomer interfering with the binding of the S-enantiomer (escitalopram) to the 5-HT transporter.
Factors to consider

1. Side effects: compliance, job safety
2. Adverse effects (e.g. teratogenicity, metabolic, liver & kidney toxicity)
3. Safety (suicide, fatal dose)
4. Age (e.g. cardiac, dementia risks, polypharmacy)
5. Drug-drug interactions (CYP enzymes)
6. Polypharmacy environment
7. High dose requirement (e.g. OCD)
SSRIs: p450 profile (drug-drug interaction)

Escitalopram is an insignificant substrate for the p450 enzymes which are responsible for the metabolism of many common drugs. Therefore escitalopram has a lower chance of drug-drug interaction. This is important in polypharmacy situations, especially in geriatric patients.

<table>
<thead>
<tr>
<th>Sertraline</th>
<th>Paroxetine</th>
<th>Fluoxetine</th>
<th>Citalopram</th>
<th>Lexapro* Escitalopram</th>
<th>CYP P450</th>
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</thead>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>3A4</td>
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<td>1A2</td>
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<td>2C9</td>
</tr>
</tbody>
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Potential risk combinations:
- Buspirone
- Ca²⁺ antagonists-various
- Cancer therapies-various
- Clarithromycin
- Cyclosporin-A
- Erythromycin
- Grapefruit juice
- Ketocnazole
- Lidocaine
- Lovastatin/simvastatin
- Protease inhibitors-various
- Quinidine
- Tamoxifen
- Tefenadine
- Triazolam
- Vinblastine
- Zopiclone

Anti-arrhythmics-various
- B-blockers-various
- Codeine
- Haloperidol
- Neuroleptics-various
- TCAs

Caffeine
- Ciprofloxacin
- Desipramine
- Donepezil
- Haloperidol
- Tamoxifen
- Theophylline
- Verapamil

Clomipramine
- Dapoxetine
- Imipramine
- Nortriptyline
- Prasugrel

Losartan
- Micardis
- NSAIDs
- Phenylpropanol
- S-warfarin
- Tolbutamide

Strong Interaction
Moderate Interaction
Very Weak Interaction
Negligible Interaction

References:
- Von Molin et al. Drug Metab Dis 2001;29: 1102-1109
Polypharmacy Problems

1. Many patients (especially the elderly) are on many drugs of all classes (e.g. GI, cardiac, pain killers, tranquillizers, hypnotics…)

2. Pharmacokinetic and Pharmacodynamic interactions are many

3. **Interactions** could be catastrophic and **hard to predict**
Herbal preparations, OTC preparations

- Many Asian patients consult Chinese traditional medicine practitioners and use herbal and OTC preparations concurrently with western medicine.
Therefore, 2 important points for both clinician and patient
對醫師和病者來說，重要的有兩點：

1. Very important to choose the first drug which has few side/adverse effects, easy dosing to enable good compliance
選擇病者最容易接受而肯長期服用的抗抑郁药

2. Choose a drug which has little drug-drug interaction potentials so that augmentation with another drug comes easier
選擇和其他药物不會相沖的抗抑郁药
Escitalopram or other antidepressants as 1\textsuperscript{st} antidepressant drug choice

1. First drug brings significant response (up to 60% on average)

II. Therefore, choice would be based on:
   a. Simplicity
   b. Efficacy & fast onset
   c. Side effects and adverse effects
   d. Kinetic and dynamic drug drug interaction potential
   e. Safety when over-dose, dosage safety margin
   f. Medical literature support & long term accumulated experience