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Selecting Antidepressant Drugs for Management of Depression in Primary Care (Part 2)

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Selecting Antidepressant Drugs for management of depression in Primary Care

Amresh Srivastava,
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Declaration

• Janssen Group
• Eli Lilly
• Astra Zeneca
• Nicholas Piramal-Rosch
• Sun Pharma- India
• Consultant
• Advisor
• Drug trial coordinator
• Research Investigator
• Reviewer
• Speaker
• Educational Groups
Medications
Psychotropics

- Stimulants
- Sedative-hypnotics, antianxiety
- Cognitive enhancers
- Antipsychotics
- Antidepressants
- Mood stabilizers
Common side effects

Sedation

Hypotension

Anticholinergic

Sexual weight

Metabolic

CNS

GI

DDI
Antidepressant drugs
hypersecretion of CRF

impaired negative feedback by cortisol

adrenal hypertrophy

excess cortisol released

circulation

impaired negative feedback by cortisol

desensitisation of cortisol receptors, increased activity of macrophages and increased release of pro-inflammatory cytokines

desensitisation of cortisol receptors leads to disturbances in noradrenaline and serotonin transmission

neurotransmitters

neuropeptides

immune system

adrenal cortex

cortisol

ACTH

CRF

AVP

pituitary

hypothalamus

hippocampus + amygdala

cortex
<table>
<thead>
<tr>
<th>SSRI</th>
<th>Name</th>
<th>Starting Dose</th>
<th>Usual daily dose</th>
<th>Mean half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>20</td>
<td>20-40</td>
<td>35</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Cipralex</td>
<td>10</td>
<td>10-20</td>
<td>27-32</td>
</tr>
<tr>
<td>Fluoxeine</td>
<td>Prozac</td>
<td>20</td>
<td>20-60</td>
<td>72-216</td>
</tr>
<tr>
<td>Fluoxamine</td>
<td>Luvox</td>
<td>50</td>
<td>50-300</td>
<td>15</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil</td>
<td>25</td>
<td>25-62.5</td>
<td>15-20</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>50</td>
<td>50-200</td>
<td>26-66</td>
</tr>
</tbody>
</table>
## SNRI

<table>
<thead>
<tr>
<th>SNRI</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>Cymbalta</td>
<td>30</td>
<td>60-90</td>
<td>12</td>
</tr>
<tr>
<td>Venlafaxin</td>
<td>Effexor</td>
<td>37.5</td>
<td>75-225</td>
<td>5-11</td>
</tr>
<tr>
<td>Venelafaxin XR</td>
<td>Effexor XR</td>
<td>37.5</td>
<td>75-225</td>
<td>5-11</td>
</tr>
</tbody>
</table>
## Serotonin modulators

<table>
<thead>
<tr>
<th>SM</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nefadozzone</td>
<td>Serzone</td>
<td>50</td>
<td>150-300</td>
<td>4</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Deseryl</td>
<td>50</td>
<td>75-300</td>
<td>7</td>
</tr>
</tbody>
</table>
## Norepinephrine-serotonin modulators

<table>
<thead>
<tr>
<th>NSM</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazepine</td>
<td>Remerone</td>
<td>15</td>
<td>15-45</td>
<td>20</td>
</tr>
<tr>
<td>SM</td>
<td>name</td>
<td>Starting dose</td>
<td>Usual dose</td>
<td>Half life</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>---------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>bupropion</td>
<td>Welbutrine</td>
<td>150</td>
<td>300</td>
<td>14</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>Welbutrine sr</td>
<td>150</td>
<td>300</td>
<td>21</td>
</tr>
<tr>
<td>TCA Tertiary amines tricyclics</td>
<td>name</td>
<td>Starting dose</td>
<td>Usual dose</td>
<td>Half life</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>---------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil</td>
<td>25-50</td>
<td>100-250</td>
<td>16-27</td>
</tr>
<tr>
<td>Clomiramine</td>
<td>Anafranil</td>
<td>25</td>
<td>100-250</td>
<td>32-69</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil</td>
<td>25-50</td>
<td>100-300</td>
<td>8-17</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Surmountil</td>
<td>25-50</td>
<td>100-300</td>
<td>24</td>
</tr>
</tbody>
</table>
## TCA

<table>
<thead>
<tr>
<th>TCA Secondary amines tricyclics</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>Norpramine</td>
<td>25-50</td>
<td>100-300</td>
<td>17</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Aventryl</td>
<td>25</td>
<td>50-150</td>
<td>27</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Vivacil</td>
<td>10</td>
<td>15-60</td>
<td>79</td>
</tr>
</tbody>
</table>
## Tetra-CA

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxipine</td>
<td>Ascedin</td>
<td>50</td>
<td>100-400</td>
<td>8</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Ludiomil</td>
<td>50</td>
<td>100-225</td>
<td>43</td>
</tr>
</tbody>
</table>
## MAO-Inhibitors

<table>
<thead>
<tr>
<th>MAO-I Irreversible</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocarboxazid</td>
<td>Marplan</td>
<td>10</td>
<td>20-60</td>
<td>2</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Nardil</td>
<td>15</td>
<td>15-90</td>
<td>2</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Parnate</td>
<td>10</td>
<td>30-60</td>
<td>2</td>
</tr>
</tbody>
</table>
### MAO-Inhibitors

<table>
<thead>
<tr>
<th>MAO-I-Reversible</th>
<th>name</th>
<th>Starting dose</th>
<th>Usual dose</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meclobamide</td>
<td>Menerix</td>
<td>150</td>
<td>300-600</td>
<td>2</td>
</tr>
</tbody>
</table>
# Guideline for choosing ADD

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unipolar depression</td>
<td>Choose on the basis of previous response, side effects, &amp; co morbid medical or Psychotic disorder</td>
</tr>
<tr>
<td>Bipolar depression</td>
<td>Lithium, lamotrigine, olanzapine-fluoxetine combination, Quetiapine XR</td>
</tr>
<tr>
<td>Depression with psychotic features</td>
<td>ADD+ APD; or ECT; avoid bupropion</td>
</tr>
<tr>
<td>Depression + OCD</td>
<td>SSRI, Chlomipramine</td>
</tr>
<tr>
<td>Depression + panic disorder</td>
<td>SSRI, TCA</td>
</tr>
</tbody>
</table>
### Guideline for choosing ADD

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression + seizures</td>
<td>Avoid bupropion &amp; TCA</td>
</tr>
<tr>
<td>Depression + parkinson’s disease</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Depression with sexual dysfunction</td>
<td>Bupropion, Mirtazepine</td>
</tr>
<tr>
<td>Depression with melancholic features</td>
<td>TCA, (newer ADD)</td>
</tr>
<tr>
<td>Depression with atypical features</td>
<td>SSRI, MAOI</td>
</tr>
</tbody>
</table>
TCA

- Serotonin + NE reuptake inhibitor
- Once daily, titrated
- Sedation
- Weight gain
- Sexual dysfunction
- Anticholinergic effects, orthostatic Qunidine like effect on cardiac condition and lethal in overdose
SSRI

• Serotonin reuptake inhibitor
• Once daily, titration minimal
• Sedation-minimal
• Weight gain-rare
• Sexual dysfunction
• GI symptom, headache, insomnia
BUPROPION

• DA + NE reuptake inhibitor
• Divided, titrated some times
• Sedation-rare
• Weight gain-rare
• Sexual dysfunction-rare
• GI symptom, headache, insomnia, agitation (seizure)
VENLAFAXINE

- Serotonin + NE,>DA reuptake inhibitor
- Once daily, titrated
- Sedation-minimal
- Weight gain-rare
- Sexual dysfunction-rare
- Similar to SSRI and dose dependent hypertension
DULOXETINE

- Serotonin + NE reuptake inhibitor
- Once daily, titrated-minimal
- Sedation-minimal
- Weight gain-rare
- Sexual dysfunction-some
- Similar to SSRI
TRAZOLONE

• 5-HT\textsubscript{2} antagonism+weak Serotonin reuptake inhibitor
• Twice daily, titrated
• Sedation
• Weight gain-rare
• Sexual dysfunction-rare
• Sedation priapism, hypotension
MIRTAZEPINE

• $\alpha_2$-adrenergic + 5-HT$_2$ antagonism

• Once daily, titrated-minimal

• Sedation

• Weight gain

• Sexual dysfunction-rare

• Anticholinergic effects, increased serum lipids
MAO Inhibitors

- Inhibition of MAO
- 2-3 times daily, titrated
- Sedation-rare
- Weight gain
- Sexual dysfunction
- Orthostatis, insomnia, peripheral oedema, concern in congestive heart failure and hepatic impairment, life threatening drug interaction.
Side effects

- GI symptoms
- Sexual dysfunction
- Stimulation & Insomnia
- Bleeding
- Neurological: Sedation,
- Weight gain / loss
- Syndrome of inappropriate secretion of antidiuretic hormone
- Serotonin syndrome
- Discontinuation syndrome
- Apathy syndrome
- Vivid dreams
- Rash
Anticholinergic
- Impaired memory & judgment
- Disorientation
- Confusion

Antihistaminic
- Sedation
- Impaired Psychomotor Function,
  Increased RT

$\alpha_1$-adrenergic blockade
- Imbalance
- Impaired coordination
- Clumsiness
Exposure of antidepressants in clinical audit
McDonald, BMJ, 1996
Side effects

• Occurs only in 30-35% of patients

• Different side effects occur at different time, during first 3-4 weeks of therapy

• Most of the adverse reactions have an adaptation mechanism and get better within few days

• In a majority of patients these side effects can be treated/minimized by reducing the dose or rescheduling the dose or prescribing another molecule

• Withdrawing or stopping the psychototropic should be last option
Side effects & Caution

- Dependence
- Hypotension
- Seizure
- Sedation
- GI symptoms
- Sexual SE
- Weight gain

- Extra pyramidal reaction
- Acute &
- Chronic
- Tremors
- Dystonias
- Akathesia
- T.D.
High risk patients

- Pregnancy & lactation
- Children
- Old age
- Recent medical illness
- Medically compromised patients
- Alcoholism and substance abuse

Drug-Drug Interaction
Newly introduced antidepressants

- Meclobamide: MAO Inhibitor for atypical depression and social phobia
- Fluvoxamine: SSRI for OCD and depression
- Venelafaxin: SSRI for anxiety depression
- Paroxetine
- Citalopram
- Mirtazepine
- Welbutrine
Newer mood stabilizers

- Valproic acid
- Divalproxate sodium
- Lamotrigine
- Gabapentine
- Toperamate
- Oxcarbamezapine
# Approximate Potency of Inhibition of Biogenic Amine Uptake

<table>
<thead>
<tr>
<th>Compound</th>
<th>Serotonin</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>6</td>
<td>1,100</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>25</td>
<td>500</td>
<td>4,200</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1</td>
<td>350</td>
<td>2,000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>7</td>
<td>1,400</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td><strong>½ life</strong></td>
<td>Long</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolite</strong></td>
<td>Active</td>
<td>Inactive desmethyl (norfluoxetine) sertraline</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Interaction</strong></td>
<td>Present</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td><strong>EPS</strong></td>
<td>More</td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td><strong>Prolactin</strong></td>
<td>↑</td>
<td>↑ (Less) or nil</td>
<td></td>
</tr>
</tbody>
</table>
# Fluoxetine Vs. Sertraline

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Anxiogenic</td>
<td>Anxiolytic</td>
</tr>
<tr>
<td>Sleep</td>
<td>Breaks</td>
<td>No or little effect</td>
</tr>
<tr>
<td>Selectivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for 5-HT</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>D. mellitus</td>
<td></td>
<td>Hypoglycemia Drug of choice</td>
</tr>
<tr>
<td>Ph. kinetic profile</td>
<td></td>
<td>Nonlinear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear</td>
</tr>
</tbody>
</table>
Fluoxetine Vs. Sertraline - Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Nervousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Anorexia</td>
<td>More</td>
<td>Less</td>
</tr>
</tbody>
</table>
## Fluoxetine Vs. Sertraline - Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Abnormal ejaculation</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Weight gain</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Overdose</td>
<td>2 deaths?</td>
<td>No deaths</td>
</tr>
</tbody>
</table>
Fluoxetine ↔ Sertraline

- Trial warranted
- Low dose
- 6 - 8 weeks trial
- Watch out for withdrawal
Sertraline Vs. Other AD

- Linear pharmacokinetics
- Less cognitive impairment
- Less motor in co-ordination
- Better QOL
- Less side effects
- Less EPS
Sertraline In Elderly

✦ Better tolerance
✦ Fewer serious side - effects
✦ Polypharmacy fewer drug interactions
✦ Linear pharmacokinetics
✦ Equally efficacious
✦ Paucity of adverse cognitive effects
Effects of Antidepressants on Glucose Metabolism

Sertraline (Drug of choice in diabetes - Goodnick P.J., Psychiatric Annals 7, 1997)

- ↓ HbA1c in 75% of NIDMM
- Limited drug interaction
- Less sleep disturbance
- Less or no effect on memory function
- ↓ pain due to neuropathy (100 mg/day)