Pharmacotherapy of depression
"Can't concentrate, wake up early, no interest, low mood, suicidal...."
"Can't concentrate,
wake up early,
no interest,
low mood,
suicidal...."

"I'm sorry to hear that Doctor."

(Doctor and patient meeting at desk.)
- Stuff you already know
- Stuff you probably know
- Stuff you possibly don’t know
- Stuff you thought you knew but are mistaken about
How long does it take for antidepressants to work?

- Around 65% of improvement in the first two weeks
- Around 25% of improvement in weeks 2-4
- 10% thereafter

The theory of delayed onset of action is a fallacy based on time to statistical separation from placebo.
Delayed onset?
A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder

Rakesh Jain, Atul R. Mahableshwarkar, Paula L. Jacobsen, Yinzhong Chen, and Michael E. Thase
Antidepressant/placebo differences
How long is a fair trial?

- The complete absence of response at two weeks is a strong indicator of future non response.
- The complete absence of response at four weeks predicts eventual non response with near certainty.
- Partial response/improvement is more difficult to interpret.
Where to start?

Two options?

SSRI

Mirtazapine (trazodone)
Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

Summary
Background Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression.

Methods We systematically reviewed 117 randomised controlled trials (25 928 participants) from 1991 up to Nov 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis.

Findings Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (1.41, 1.35, 1.30, and 1.27, respectively), paroxetine (1.35, 1.30, 1.27, and 1.22, respectively), and reboxetine (2.03, 1.95, 1.89, and 1.85, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.

Interpretation Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.

Funding None.

Cipriani et al. Lancet 2009; 373: 746–758
Network of eligible comparisons for multiple-treatment meta-analysis for efficacy (response rate)

Width of lines is proportional to number of trials comparing each pair of treatments. Size of each node is proportional to number of randomised participants (sample size). Network of eligible comparisons for acceptability (dropout rate) analysis is similar.

Note: Ranking indicates the probability of the best treatment, the second best, the third best, and so on, among the 12 antidepressants Cipriani et al. *Lancet* 2009; 373: 746–758.
Probability of being among top four drugs for efficacy* and acceptability** at mean of 8 weeks of treatment

* At least 50% reduction in depression score or much/very much improved in CGI
** All-cause withdrawal

Network Meta-Analysis and Cost-Effectiveness Analysis of New Generation Antidepressants

Ai Leng Khoo¹ · Hui Jun Zhou¹ · Monica Teng¹ · Liang Lin¹ · Ying Jiao Zhao¹ · Lay Beng Soh² · Yee Ming Mok³ · Boon Peng Lim¹ · Kok Peng Gwee³
Patient self-management

• Where appropriate advise patient to adjust frequency of dosing according to tolerability
  
  • e.g. miss a day if nausea intolerable: start again at half dose

• Warn patient of possible prolonged sedative affects of mirtazapine
  
  • Advise that higher doses may be less sedating
  • Next day hangover very common in those affected by sedation
# Managing adverse effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Temporary&lt;br&gt;Sslow titration</td>
</tr>
<tr>
<td>Anxiety/agitation</td>
<td>Temporary, occasionally severe&lt;br&gt;Sslow titration</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Temporary, uncommon&lt;br&gt;Ssleep improves alongside depression</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Usually temporary, uncommon&lt;br&gt;May need to switch</td>
</tr>
<tr>
<td>Sweating</td>
<td>Idiosyncratic, cause not known&lt;br&gt;May need to switch</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>Not temporary&lt;br&gt;May need to switch</td>
</tr>
<tr>
<td>Anorgasmia</td>
<td>Not temporary&lt;br&gt;Not always adverse</td>
</tr>
</tbody>
</table>
Bleeding

- SSRI = aspirin
- Bleeding risk increased 50-100% with warfarin (vs warfarin alone)
- Bleeding risk increased 100-400% with NSAID (vs nothing)
- ‘Bleeding’ = cerebral, GI, GU.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>+++</td>
</tr>
<tr>
<td>Citalopram</td>
<td>++ (no increased risk of arrhythmia)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>+ (overdose only)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+ (overdose only)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>-</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>-</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>-</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>-</td>
</tr>
</tbody>
</table>
QT interval and antidepressant use: a cross sectional study of electronic health records

Victor M Castro team lead¹, Caitlin C Clements clinical research coordinator²,³, Shawn N Murphy associate professor of neurology⁴, Vivian S Gainer team lead¹, Maurizio Fava Slater Family professor of psychiatry⁵, Jeffrey B Weilburg assistant professor of psychiatry⁵, Jane L Erb assistant professor of psychiatry⁶, Susanne E Churchill executive director, i2b2 National Center for Biomedical Computing⁷, Isaac S Kohane director, i2b2 National Center for Biomedical Computing⁷, Dan V Iosifescu associate professor of psychiatry⁹, Jordan W Smoller associate professor of psychiatry², Roy H Perlis associate professor of psychiatry³

¹Partners Research Computing, Partners HealthCare System, One Constitution Center, Boston, MA 02129, USA; ²Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114, USA; ³Center for Experimental Drugs and Diagnostics, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114, USA; ⁴Laboratory of Computer Science and Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA; ⁵Depression Clinic and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114, USA; ⁶Department of Psychiatry, Brigham and Women’s Hospital, Boston, MA 02215, USA; ⁷Information Systems, Partners HealthCare System, New Research Building 255, Boston, MA 02215, USA; ⁸Department of Medicine, Brigham and Women’s Hospital, Boston, MA 02215, USA; ⁹Mood and Anxiety Disorders Program, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029, USA
Mean (SD) corrected QT (QTc) interval recorded on electrocardiogram 14–90 days after prescription of antidepressant or methadone, by drug dose

* Dose a significant predictor of QTc in fully adjusted linear models at α=0.05
† QTc at specified dose is significantly different from that at prior dose in fully adjusted linear models at α=0.05
Evaluation of the FDA Warning Against Prescribing Citalopram at Doses Exceeding 40 mg

Kara Zivin, Ph.D.
Paul N. Pfeiffer, M.D.
Amy S.B. Bohnert, Ph.D.
Dara Ganoczy, M.P.H.
Frederic C. Blow, Ph.D.
Brahmajee K. Nallamothu, M.D.
Helen C. Kales, M.D.

Failure to respond

- At two weeks, consider dose increase where appropriate
- At four weeks, abandon and switch if no response
- Partial response at four weeks – continue, assess at six weeks, discuss with patient

The expectation of prescriber and patient should be the same: a return to premorbid level of mood and functioning.

Partial response is an unacceptable outcome.
What to use next?

- It probably doesn’t matter

- Options include:
  - Alternative SSRI
  - SSRI to mirtazapine
  - Mirtazapine to SSRI
  - Trazodone?
  - Venlafaxine?
What to use after that?

• It probably doesn’t matter

• Options include:
  • Anything from previous slide not already done
  • Combine SSRI with mirtazapine
  • Full dose tricyclic
  • Agomelatine (not NICE)
  • Vortioxetine (NICE)
  • Quetiapine 150-300mgs
Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies

David Taylor professor of psychopharmacology¹,², Anna Sparshatt senior clinical pharmacist², Seema Varma senior clinical pharmacist², Olubanke Olofinjana senior clinical pharmacist and statistician²

¹King’s College London, Institute of Pharmaceutical Science, London SE1 9NH, UK; ²South London and Maudsley NHS Foundation Trust, Pharmacy Department, London SE5 8AZ, UK
Standardised mean differences (SMD) for agomelatine vs antidepressant in studies on antidepressant efficacy of agomelatine

<table>
<thead>
<tr>
<th>Study</th>
<th>Agomelatine (Mean, SD)</th>
<th>Antidepressant (Mean, SD)</th>
<th>SMD (95% CI)</th>
<th>Weight (%)</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAGO178A2303</td>
<td>17.1 (7.38)</td>
<td>14.0 (7.53)</td>
<td>-0.41 (-0.63 to -0.20)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>CL3-022</td>
<td>14.5 (8.2)</td>
<td>13.3 (7.6)</td>
<td>-0.15 (-0.39 to 0.09)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>CL3-023</td>
<td>13.0 (8.0)</td>
<td>12.2 (8.1)</td>
<td>-0.10 (-0.33 to 0.14)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>CL3-024</td>
<td>12.7 (8.2)</td>
<td>12.5 (7.4)</td>
<td>-0.03 (-0.22 to 0.17)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>CL3-026</td>
<td>12.3 (8.4)</td>
<td>11.8 (8.3)</td>
<td>-0.06 (-0.26 to 0.14)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>CL3-069</td>
<td>12 (7.4)</td>
<td>11.8 (8.0)</td>
<td>-0.03 (-0.18 to 0.13)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>CL3-070</td>
<td>8.0 (6.6)</td>
<td>8.3 (6.6)</td>
<td>0.05 (-0.17 to 0.26)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Subtotal: P=0.08, I²=47%</td>
<td></td>
<td></td>
<td></td>
<td>56</td>
<td>-0.10 (-0.20 to 0.01)</td>
</tr>
<tr>
<td>Published studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hale 2010</td>
<td>11.1 (7.3)</td>
<td>12.7 (8.5)</td>
<td>0.20 (0.03 to 0.38)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Kasper 2010</td>
<td>10.3 (7.0)</td>
<td>12.1 (8.3)</td>
<td>0.23 (0.01 to 0.46)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Kennedy 2008</td>
<td>10.1 (7.8)</td>
<td>9.8 (7.9)</td>
<td>-0.04 (-0.27 to 0.20)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Lemoine 2007</td>
<td>9.9 (6.6)</td>
<td>11.0 (7.4)</td>
<td>0.16 (-0.06 to 0.37)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Loo 2002</td>
<td>12.77 (8.23)</td>
<td>13.09 (8.37)</td>
<td>0.04 (-0.20 to 0.27)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Quera-Salva 2011</td>
<td>11.4 (5.9)</td>
<td>12.7 (6.7)</td>
<td>0.21 (-0.14 to 0.55)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Subtotal: P=0.52, I²=0%</td>
<td></td>
<td></td>
<td></td>
<td>44</td>
<td>0.14 (0.05 to 0.23)</td>
</tr>
<tr>
<td>Overall: P=0.003, I²=59%</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>0.00 (-0.09 to 0.10)</td>
</tr>
</tbody>
</table>

Note: weights are from random effects analysis

Favours antidepressant Favours agomelatine
Vortioxetine - effective in patients with a sub-optimal response to an SSRI or SNRI

Change from baseline in MADRS total scores by visit

**p<0.01, ***p<0.001 vs agomelatine

Vortioxetine 10–20 mg / day (n=252)
Agomelatine 25–50 mg / day (n=241)

Primary endpoint (non-inferiority to agomelatine)

doi: 10.1002/hup.2424. [Epub ahead of print]
Secondary care treatments

- Add lithium
- Add aripiprazole/olanzapine/quetiapine
- Add thyroxine
- Ketamine
- High dose tricyclic/venlafaxine
- MAOIs
How to switch

- SSRI to SSRI usually stop-start, with slow titration of second drug. Increase according to tolerability. Beware fluoxetine.

- SSRI/mirtazapine switches - usually cross taper

- Agomelatine – no problems

- MAOIs and tricyclics – too difficult to go into here
Discontinuation reactions

- Common to all antidepressants

- Well known features
  - Insomnia
  - Nausea
  - Flu-like symptoms
  - Electric shocks
  - Mood changes/anxiety

- Tapered cessation reduces symptom severity but prolongs symptom duration

- Cold turkey shortens but increases symptom severity. Rarely used option as abrupt cessation predicts depressive relapse
Pregnancy

- Depression is more dangerous than antidepressants

- Options include:
  - TCAs – amitriptyline; imipramine
  - Sertraline
  - Fluoxetine

- Maintain current antidepressant*, if effective and well tolerated

- Continue during breast feeding

* Except paroxetine
Discuss choice of drug with the patient

- Include: Potential therapeutic effects, Possible adverse effects, Likelihood of discontinuation symptoms, Likely time to respond
- (good therapeutic alliance predicts response to medication)
- Suggest SSRI as first choice; mirtazapine if sedation required

Start antidepressant

- Titrate (if necessary) to recognised therapeutic dose. Assess efficacy after 2 weeks

No effect

Assess weekly for a further 1-2 weeks
- If still no response, consider increasing dose (see notes)

Effective

Continue for 6-9-12 months at full treatment dose

- Consider longer-term treatment in recurrent depression

No effect

Switch to a different antidepressant (see notes)

- Titrate (if necessary) to therapeutic dose. Assess over 3-4 weeks, increase dose as necessary

Effective

Poorly tolerated or no effect

Switch to a different antidepressant (see notes)

- Titrate (if necessary) to therapeutic dose. Assess efficacy over 3-4 weeks

No effect

Consider third choice options

- Mirtazapine (if not already used), vortioxetine, agomelatine

No effect

Refer to suggested treatments for refractory depression
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add lithium.</td>
<td>Well established&lt;br&gt;Aim for plasma level of 0.4–0.8 mmol/L initially, increasing to up to 1.0 mmol/L if sub-optimal response</td>
<td>Sometimes poorly tolerated at higher plasma levels&lt;br&gt;Potentially toxic (NICE recommends ECG)&lt;br&gt;Usually needs specialist referral&lt;br&gt;Plasma level monitoring is essential (and TFTs; eGFR)&lt;br&gt;May not be effective in patients refractory to multiple treatments</td>
<td>15, 18–21</td>
</tr>
<tr>
<td>Electroconvulsive therapy</td>
<td>Well established&lt;br&gt;Effective&lt;br&gt;Well supported in the literature</td>
<td>Poor reputation in public domain&lt;br&gt;Necessitates general anaesthetic&lt;br&gt;Needs specialist referral&lt;br&gt;Usually reserved for last-line treatment or if rapid response needed&lt;br&gt;Best used with other treatments to prevent relapse</td>
<td>22–24</td>
</tr>
<tr>
<td>Add tri-iodothyronine (20–50 μg/day)</td>
<td>Usually well tolerated&lt;br&gt;Good literature support (including STAR*D)</td>
<td>TFT monitoring required&lt;br&gt;Usually needs specialist referral&lt;br&gt;Some negative studies&lt;br&gt;No advantage over antidepressant alone in non-refractory illness</td>
<td>15, 26–30</td>
</tr>
<tr>
<td>Higher doses have been safely used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add olanzapine and fluoxetine (12.5 mg + 50 mg daily)</td>
<td>Well researched&lt;br&gt;Usually well tolerated&lt;br&gt;Olanzapine + TCA may also be effective</td>
<td>Risk of weight gain&lt;br&gt;Limited clinical experience in UK&lt;br&gt;Most data relate to bipolar depression</td>
<td>31–35</td>
</tr>
<tr>
<td>*Add quetiapine (150 mg or 300 mg a day) to SSRI/SNRI</td>
<td>Good evidence base&lt;br&gt;Usually well tolerated&lt;br&gt;Plausible explanation for antidepressant effect&lt;br&gt;Possibly more effective than lithium</td>
<td>Dry mouth, sedation, constipation can be problematic&lt;br&gt;Weight gain risk in the longer term</td>
<td>36–41</td>
</tr>
<tr>
<td>Add risperidone (0.5–3 mg/day) to antidepressant</td>
<td>Small evidence base&lt;br&gt;Usually well tolerated</td>
<td>Hypotension&lt;br&gt;Hyperprolactinaemia</td>
<td>42–47</td>
</tr>
<tr>
<td>Add aripiprazole (2–20 mg/day) to antidepressant</td>
<td>Good evidence base&lt;br&gt;Usually well tolerated and safe&lt;br&gt;Low doses (2–10 mg/day) may be effective</td>
<td>Akathisia and restlessness common at standard doses (≥10 mg/day)</td>
<td>48–55</td>
</tr>
<tr>
<td>SSRI + bupropion up to 400 mg/day</td>
<td>Supported by STAR*D&lt;br&gt;Well tolerated</td>
<td>Not licensed for depression in the UK</td>
<td>13, 26–60</td>
</tr>
<tr>
<td>SSRI or venlafaxine + mianserin (30 mg/day) or mirtazapine (30–45 mg/day)</td>
<td>Recommended by NICE&lt;br&gt;Usually well tolerated&lt;br&gt;Excellent literature support&lt;br&gt;Widely used</td>
<td>Theoretical risk of serotonin syndrome (inform patient)&lt;br&gt;Risk of blood dyscrasia with mianserin&lt;br&gt;Weight gain with mirtazapine</td>
<td>16, 51–62</td>
</tr>
</tbody>
</table>
**Table 4.7** Second choice: less commonly used, variably supported by published evaluations  
(no preference implied by order)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Refs</th>
</tr>
</thead>
</table>
| Add ketamine (0.5 mg/kg IV over 40 minutes) | - Very rapid response (within hours)  
- Very high remission rate  
- Some evidence of maintained response if repeated doses given  
- Usually well tolerated at this sub-anaesthetic dose | - Needs to be administered in hospital  
- Cognitive effects (confusion, dissociation, etc.) do occasionally occur  
- Associated with transient increased in BP, tachycardia and arrhythmias. Pre-treatment ECG required¹  
- Repeated infusions necessary to maintain effect (beware bladder problems)  
- Not widely available | ²–⁶ |
| *Add lamotrigine (200 mg and 400 mg a day have been used) | - Reasonably well researched  
- Quite widely used | - Slow titration  
- Risk of rash  
- Appropriate dosing unclear. High doses often needed  
- Two failed RCTs | ⁷–¹¹ |
| SSRI + buspirone up to 60 mg/day | - Supported by STAR*D | - Higher doses required poorly tolerated (dizziness common)  
- Not widely used | ¹²,¹³ |
| Venlafaxine (>200 mg/day) | - Usually well tolerated  
- Can be initiated in primary care  
- Recommended by NICE¹⁴  
- Supported by STAR-D | - Limited support in literature  
- Nausea and vomiting more common  
- Discontinuation reactions common  
- Can increase BP: monitoring essential | ¹⁵–¹⁸ |
SSRI

Other SSRI or SNRI

Switch to mirtazapine or vortioxetine or agomelatine* or augment with:

Mirtazapine or Mianserin or Aripiprazole or Olanzapine or Quetiapine or Risperidone or Lithium or T₃ or Buspirone or Bupropion

Consider alternative augmentation strategy (from above list)

Consider other commonly used options, e.g.:

MAOIs, TCAs +/- lithium, Ketamine, Lamotrigine augmentation, TCA + MAOI, SSRI + TCA
Conclusion

- Antidepressants work quickly
- Some differences in efficacy
- Choice guided more by tolerability
- >90 of depression will respond to drug Tx
- Adverse effects are important
- Ketamine indicates way forward?