Depression

Paul Glue
Registrars May 2015
Objectives

• Today we will cover:
  – Overview of diagnosis and epidemiology of MDD (Bipolar d/o is next week)
  – Brain and signalling changes in depression
  – Treatment
Depression spectrum

“Doctor I’m depressed” could mean...

- Major Depressive Disorder ~5%
- Dysthymia ~3%
- Adjustment disorder 5-10%
- BP .5%
- Psychotic depression
- Melancholia

- Most treatment data for MDD and BP depression
DSM-5 Major Depressive Disorder

- 5/9 symptoms for >2 wks
- Must have either (a) **depressed mood**, or (b) **loss of interest**.
  - A considerable loss or gain of weight.
  - Insomnia or hypersomnia
  - Behaviour that is agitated or slowed down.
  - Feeling fatigued/diminished energy.
  - Thoughts of worthlessness or extreme guilt
  - Impaired ability to think, concentrate, or make decisions
  - Frequent thoughts of death or suicide (with or without a specific plan), or attempt of suicide.
And...

- The person's symptoms cause clinically significant distress or impairment in social, occupational, other areas of functioning.
- The person's symptoms are not caused by substance use (e.g., alcohol, drugs, medication), or a medical disorder.
- No better explanation of symptoms by (e.g.) schizoaffective/other psychotic disorder
- No past manic/hypomanic episodes.
Table 2.1: Lifetime, 12-month and one-month prevalences of mental disorders

<table>
<thead>
<tr>
<th>Disorder group</th>
<th>Lifetime prevalence % (95% CI)</th>
<th>Twelve-month prevalence % (95% CI)</th>
<th>One-month prevalence % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anxiety disorder</td>
<td>24.9 (23.6, 26.2)</td>
<td>14.8 (13.9, 15.7)</td>
<td>9.3 (8.6, 10.1)</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>20.2 (19.3, 21.1)</td>
<td>7.9 (7.3, 8.7)</td>
<td>2.3 (2.1, 2.7)</td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>12.3 (11.6, 13.1)</td>
<td>3.5 (3.0, 4.0)</td>
<td>1.5 (1.3, 1.8)</td>
</tr>
<tr>
<td>Any eating disorder</td>
<td>1.7 (1.5, 2.1)</td>
<td>0.5 (0.3, 0.6)</td>
<td>0.2 (0.1, 0.4)</td>
</tr>
</tbody>
</table>

Individual disorders<sup>1,2,3</sup>

| No disorder                                | 60.5 (58.8, 62.1)            | 79.3 (78.1, 80.5)                | 88.4 (87.6, 89.3)              |
| One disorder                               | 20.0 (18.8, 21.3)            | 13.0 (12.1, 14.0)                | 8.5 (7.8, 9.2)                 |
| Two disorders                              | 9.9 (9.2, 10.6)              | 4.4 (3.9, 4.8)                   | 2.0 (1.7, 2.3)                 |
| Three or more disorders                    | 9.7 (9.0, 10.4)              | 3.3 (2.9, 3.7)                   | 1.1 (0.9, 1.3)                 |
| Any disorder<sup>2</sup>                   | 39.5 (37.9, 41.2)            | 20.7 (19.5, 21.9)                | 11.6 (10.7, 12.4)              |

NZ Mental Health Survey 2006

....and it’s very common
Differential Diagnosis

- Dysthymia (now Persistent Depressive Disorder in DSM-5): chronic, mild mood disturbance
  - Daily low mood >2y.
- Adjustment disorder with depressed mood: psychological response to an identifiable event/stressor
- Bipolar disorder: low and elevated mood cycles
- Mood disorder secondary to physical illness, medications, and/or substance abuse.
- Dementia
  - (patients with prominent concentration, apathy, cognitive symptoms)
Epidemiology of MDD

Peaks in 20’s
Lifetime prevalence: ~15%
Gender ratio: F (2-3x) > M

Global burden of depression, 2010

Plot 1: World map showing age-standardised YLD rates (per 100,000) by country

Ferrari, PLoS Med 2013
Recurrence of Major Depression

• Cumulative probability of recurrence after index episode

Int J Meth Psych Res 1994, 4:211
N=359; time following index episode of unipolar major depression

• Probability of recurrence as a function of # of previous episodes

<table>
<thead>
<tr>
<th># of previous episodes</th>
<th>Probability of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>&lt;60</td>
</tr>
<tr>
<td>2</td>
<td>60-90</td>
</tr>
<tr>
<td>3</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

Arch Gen Psych 1992, 49:809

• Risk Factors For Recurrence

Previous/frequent depressive episodes
Long duration of episodes
Onset after age 60
Double depression (MDD + dysthymia)
Family history of depression
Poor symptom control while on treatment
Comorbid anxiety/substance abuse
Biggest cause of disability globally, based on years lost to disability.

Top ten causes of disability:
Depression accounts for the biggest share of the world's burden of disease, measured by years lost to disability (YLD); healthy years 'lost' because they are lived with a physical or mental disability.
Neural model of emotional regulation structures
- Circuits involving prefrontal cortex and subcortical limbic structures
- MDE associated with altered activity in some of these areas

Pathophysiology of Major Depression

- Unknown
- High genetic loading (MZ ~40%; DZ ~20%; ~15% population)
- Presumably polygenic; association with 2q polymorphism (associated with CREB gene) in recurrent early onset MDD; others.
- Changes in: regional blood flow and metabolism
  - ↑ in the amygdala, orbital cortex, and medial thalamus
  - ↓ in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex

What brain areas are working abnormally in MDD?

- Subgenual cingulate gyrus (BA 25) is metabolically overactive in treatment-resistant depression
- Functionally: involved in generation of emotional states
- ↑ activity predicts non-response to drugs, psychotherapy

Mayberg; Neuron 2005, 45:651
Immediate mood improvement with DBS

• “In general, patients described a **sudden disappearance of something negative**, which was more often than not a change in a visceral state: a **sudden sense of intense calm and relief, clearing of mental heaviness, lifting of a black cloud**, the **disappearance of a void**... Such effects, when present, were contact- and dose-specific and could be reproduced in a blinded fashion with repeated testing. Their time course was quite rapid, occurring approximately **15-20 seconds after initiating stimulation** at the specific electrode contact.

• Deep brain stimulation reduced BA25 metabolic activity
  - 6 months: 60% responders, 35% remitted
  - 36 months: 75% responders, 50% remitted  *(Int Rev Psych 2011, 23:424)*

Regional cerebral bloodflow, 3 months stimulation (difference vs baseline)
MDD Risk Factors

Frequently co-occurring with other Axis I disorders
Interactions: Relationship between life stress and onset of depression – influence of number of prior depressive episodes

- Likelihood of recent life stress precipitating depression
- Risk (OR) of depression onset per month

Female subjects only n = 2395

Initial Management for MDD

- Explain the diagnosis
- Treatment options:
  - Mild depression: no evidence base to support any treatment
  - Moderate depression: psychotherapy (CBT) or antidepressant
  - Severe depression: antidepressant + mood stabilizer + ECT
- Evaluate suicide risk – if high, refer to 2º services
- Educate the patient
  - Drug will take at least 2 weeks before improvements appear, and 4-6 weeks before maximal benefit
  - Explain adverse event profile
- Book a series of follow-up appointments (1-2 weeks initially)
- Plan on continuing antidepressant for 6 months AFTER the patient achieves remission from this episode
  - Reduces risk of relapse
My mood has improved..... Why should I take antidepressants for 6 more months when I’m feeling fine?

Euthymic

Depressed

AD’s lift pt out of depressive cycle

AD course <6mo – 40% risk of relapse

AD course >6mo – <10% risk of relapse

Depressive cycles last ~1yr

6 months
Psychological/Social Management

- **Education**
  - about the disorder/treatments
  - about stable lifestyle routines e.g. basic sleep hygiene; anticipating and managing life stress
  - about early warning signs of impending episodes, and methods for managing those impending episodes through rescue medication

- **Case management**
  - careful review of symptoms at each clinic visit
  - careful review of side effects at each clinic visit.
  - life charting of previous episodes; daily mood diary

- **Social/psychological support/therapy**
  - specific psychological therapies (IPT, CBT) as effective as antidepressants in mild-moderate depression. **Internet CBT**
  - Self-help and support groups
Antidepressants

• Misleading term
  – Also effective in anxiety disorders, bipolar depression, quitting smoking, ADD, bedwetting

• Lots of different acute pharmacologies
  – Long term pharmacology is likely to be indirect, probably common to all drugs

• All have delayed onset of action, only work in ~2/3 patients
  – Main initial differentiation is based on tolerability, safety; QD dosing; flat dose response profile
# Evolution of antidepressant treatments

<table>
<thead>
<tr>
<th>Decade</th>
<th>Uptake Blockers</th>
<th>Receptor Blockers</th>
<th>Enzyme Inhibitors</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930s</td>
<td></td>
<td></td>
<td></td>
<td>ECT</td>
</tr>
<tr>
<td>1940s</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1950s</td>
<td>TCAs</td>
<td>NA-selective</td>
<td>MAOIs</td>
<td>Li</td>
</tr>
<tr>
<td>1960s</td>
<td>TCAs</td>
<td>5HT-selective</td>
<td>mianserin</td>
<td></td>
</tr>
<tr>
<td>1970s</td>
<td>TCAs</td>
<td>SSRIs</td>
<td>trazodone</td>
<td>Subtype-selective MAOIs</td>
</tr>
<tr>
<td>1980s</td>
<td>TCAs</td>
<td>SSRIs</td>
<td>(nefazodone)</td>
<td>RIMAs</td>
</tr>
<tr>
<td>1990s</td>
<td>SNRIs</td>
<td></td>
<td>mirtazapine</td>
<td></td>
</tr>
<tr>
<td>2000s</td>
<td>NRIs</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **Uptake Blockers**: Enzyme Inhibitors - MAOIs (Subtype-selective), RIMAs
- **Receptor Blockers**: Subtype-selective - 5HT-selective, NA-selective
- **Enzyme Inhibitors**: MAOIs (Subtype-selective), RIMAs

**Others**
- ECT
- Li

**Ingredients**
- **1930s**: Maprotiline, Desipramine
- **1940s**: All SSRIs, Clomipramine
- **1950s**: Phenelzine, Tranylcypromine
- **1960s**: Venlafaxine, AMI, IMI
- **1970s**: Mirtazapine
- **1980s**: Mirtazapine, Moclobemide
- **1990s**: Mirtazapine
- **2000s**: Mirtazapine
Choice of antidepressant

- Safety
  - Newer selective drugs are significantly safer than older TCAs, esp. in overdose

- Tolerability
  - SSRIs are better tolerated than older drugs or those with NE uptake
    - Despite this, SSRIs still have significant side effect profile
  - Some SSRIs (e.g. fluoxetine) have flat dose/efficacy relationship but positive dose/side effect relationship
  - SSRIs may need less or no dose titration

- base initial selection on safety/tolerability criteria
  - e.g. SSRI, buproprion for patients with low energy, hypersomnia
  - mirtazapine, maprotiline for patients with features of anxiety, insomnia
What to do if the first antidepressant doesn’t work?

STAR-D trial (Rush, Am J Psych 2006, 163: 1905)

- Sequenced Treatment Alternatives to Relieve Depression (STAR*D)
  - US NIMH-funded study in primary and psychiatric care settings
  - Wide inclusion/few exclusion criteria to enroll “real world” patients to ensure “generalizability”
  - Well defined treatment and assessment guidelines to ensure adequate treatment delivery/assessment
  - Focus on symptomatic remission (HAMD < 8) as outcome
Design

Stage 1
All patients – open label citalopram (to 60mg/d)

Remission – remain on Rx for 12 months
<Remission/nonresponse – randomized to next stage

Stage 2
Switch within class (CIT → SERT) or
Switch between classes (CIT → BUP or VEN) or
Augment (CIT + BUP or BUSP)

Remission – remain on Rx for 12 months
<Remission/nonresponse – randomized to next stage

Stage 3
Switch to mirtazepine or NOR or
Augment antidepressant with Li or T3

Remission – remain on Rx for 12 months
<Remission/nonresponse – randomized to next stage

Stage 4
Switch to MAOI (tranylcypromine) or
VEN + mirtazepine combo

(RCT)
**Stage 1**
Open label citalopram (n=3671)
Remission – 28%

**Stage 2**
Switch within class (n=238) or
Switch between classes (n=488) or
Augment (n=565)

- Remission – 18%
- Remission – 25%
- Remission – 30%

**Switching** (within/between classes) – level of response slightly lower than Stage 1 or Stage 2-augment arms.
No differences in remission rate or time to remission between treatment arms
→ Switching from 1 failed SSRI to a second AD, including an alternative SSRI, are valid treatment options

**Augmenting:** Overall level of response similar to Stage 1
No differences in remission rate or time to remission between treatment arms

→ If patients are tolerating a failed first-line SSRI, **augmenting** may be a better second step than switching to a new drug.
→ If patients are not tolerating a first-line SSRI, **switch**.
STAR-D Overall Results

- Theoretical cumulative remission rate: 67%

- Remission rates declined after 2 failed AD trials
  - Risk factors for more failed trials
    - More severe depression
    - More concurrent medical and psychiatric illnesses

- Persistence is required in identifying what works for individual patients
  - Homogeneity of response to treatments with different MoAs do not provide guidance in this process

- Relapse rates and intolerance increase with number of failed AD trials
ECT

- Local data - ~90% complete or good response to treatment
Post ECT treatment and relapse
Sackheim, JAMA 2001, 285:1299

- ECT responders randomized to NTI+Li, NTI or placebo
- Relapse showed clear benefit for Li+AD > AD alone > placebo
ECT Relapse meta-analysis
Neuropsychopharmacology 2013, 38:2467

• By 6 months – 37.7%
• By 12 months – 51.1%
• Continuation Rx with antidepressants halves risk of relapse (RR=0.49; NNT = 3.3)
Maintenance Treatment/Depression

- Objectives:
  - to prevent recurrence of a new episode of depression after full recovery from a previous episode
  - those with ≥3 prior episodes MDD, + family history, severe episodes, comorbid dysthymia, anxiety/other Axis I disorders, etc
  - long term antidepressant or mood stabilizer
  - RCTs: recurrence rates on pbo ~2.5x the rates for active therapy
Antidepressants in Pregnancy (1)

- **Risk/benefit consideration**: potential harm to foetus vs risks of untreated depression to mother
- **Teratogenicity risk** appears to be low
  - **Exception**: increased risk of cardiac malformations on paroxetine
- **Mixed reports** on associations of SSRI use with:
  - Persistent pulmonary hypertension of newborn (very rare)
  - Prematurity
  - Withdrawal symptoms
- **No effects** of SSRIs on postnatal development
  - Cognitive development, growth etc
Antidepressants in Pregnancy (2)

• Benefits
  – improved maternal performance, bonding with baby, marital relationship
  – reduced risk due to untreated depression

ANZJPsych 2010, 44:978
...but avoid mood stabilizers

- Lithium – Ebstein’s abnormality ↑50-100x
- Valproate (>CBZ, LTG) – structural defects
  - Neural tube defects, craniofacial abnormalities
  - Reduced foetal growth
  - Shorter gestation
  - Delayed cognitive development (esp. VPA)

*ANZJPsych 2010, 44:967*
Thank you!

Any questions?