Antidepressant Prescribing: The important bits

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Why is depression THE most important disorder to know how to treat?
Depression increases morbidity and mortality from common physical disease

39% increase in mortality in cancer patients diagnosed with depression.¹

Depression associated with 60% increased risk for CHD⁶ and 2X risk of death in CHD patients with depression.⁷

COPD – depressive symptoms almost double the risk of mortality.²

Depression associated with 60% increased risk for developing diabetes³, increased mortality⁴

COPD = chronic obstructive pulmonary disease
CHD = coronary heart disease

5. Wulsin LR and Singal BM. Psychosomatic Medicine 2003;65:201-10
Impact of depression on benefit claims (2010)

Most common illnesses cited in benefit claims (top ten and selected)

- Depression: 398,700
- Back pain: 168,330
- Unknown causes: 129,450
- Other anxiety disorders: 93,880
- Pain: 61,400
- Other neurotic disorders: 56,210
- Learning disorders: 53,450
- Mental retardation: 50,420
- Schizophrenia: 49,760
- Epilepsy: 48,040
- Alcoholism: 42,360
- Drug abuse: 37,480
- Obesity: 1,830

Source: Dept for Work and Pensions, August 2010
Depression: Some key questions

• Who should be treated?
• Treatment: what and how?
• .....and then what?
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Depression

The treatment and management of depression in adults

This is a partial update of NICE clinical guideline 23
Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines

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Rules of thumb

Emphasis on issue of importance to day to day practice
Depression: Some key questions

• Who should be treated?
• Treatment: what and how?
• ...and then what?
Diagnostic Dilemmas/Issues

1. Differentiating normal human misery from depressive illness
Depression is a complex syndrome

Emotional Symptoms
- Suicidal
- Lack of Interest
- Sadness
- Obsessive Rumination
- Brooding
- Irritability
- Excessive Worry Over Physical Health

Physical Symptoms
- Lack of Energy
- Change in Appétite
- Pain
- Decreased Concentration
- Change in Psychomotor Skills
- Change in Sleep
- Tearfulness
- Feelings of Guilt
- Anxiety or Phobias

Associated Symptoms
- Anxiety or Phobias
- Lack of Interest
- Feelings of Guilt
- Sadness
- Obsessive Rumination
- Brooding
- Irritability
- Excessive Worry Over Physical Health

Diagnosis of Depression

DSM-IV Criteria – as recommended by NICE

- **5 or more** of the following over a **two week** period:
  - *depressed mood*
  - *markedly diminished interest or pleasure in all activities*
  - weight loss, decreased or increased appetite
  - insomnia or hypersomnia
  - psychomotor agitation or retardation
  - fatigue or loss of energy
  - feelings of worthlessness or inappropriate guilt
  - diminished ability to think or concentrate
  - recurrent thoughts of death or suicide

- N.B. must have one of symptoms marked with *
- **Must be associated with impairment of function**
Diagnosis – a pitfall

• NOTE – It does not matter how understandable the depression is. If it meets criteria, **then it is depression**

Big rule of thumb!!
Diagnostic Dilemmas/Issues

1. Differentiating normal human misery from depressive illness
2. Differentiating bipolar disorder from unipolar
Bipolar disorder

- Bipolar disorder often does not respond to antidepressants and may be made worse by them. It is vital to identify it.

- With every new presentation of a depressive episode, ALWAYS ask about symptoms of elevated mood — (elation, racing thoughts, lack of need for sleep, increased activity etc)

Big rule of thumb!!
Indications for antidepressants: Duration and severity of depression guides treatment choice (BAP guidelines)

• Antidepressants are a first line treatment for:
  — moderate and severe MDD in adults,
  — Sub-threshold depression that has persisted for 2 years or more.

• Antidepressants are an option for mild MDD in adults especially if:
  — there is a history of moderate to severe recurrent depression
  — the depression has persisted for more than 2–3 months

• Antidepressants are not a first line treatment for short duration sub-threshold depression in adults but consider if:
  — there is a prior history of moderate to severe recurrent depression
  — the depression persists for more than 2–3 months
Depression: Some key questions

- Who should be treated?
- Treatment: what and how?
- ......and then what?
Correlation Between Hippocampal Volume and Duration of Untreated Depression

Female Outpatients With Recurrent Depression in Remission

* Significant inverse relationship between total hippocampal volume and the length of time depression went untreated.

Effect of duration of un-treated depression on response and remission

De Diego-Adelino et al. (2010) J Affect Disorders 120:221 - 225
Algorithm (ALGO) vs treatment as usual (TAU)

HR=2.0 (p=0.004)
Survival analysis (ITT group)

TAU (N=74)
ALGO (N=74)

Principles of treatment of depression

• Don’t waste too much time before treating patients
  — If you do it damages their brains and makes them less likely to respond

• Be systematic in how you treat patients
  — Your plan should include critical decision points:
    • At a specific point in time if X then do 1; if Y do 2.
McAllister-Williams & Yates (2014) in “ABC of Anxiety and Depression” Gask and Chew-Graham, Wiley
Getting started

PHQ >10 and/or persistent symptoms despite low level non-drug interventions

Citalpram 20mg/day
Sertraline 50mg/day

START

Suicidal risk?

Follow switching guidance

Review risk and tolerability of drug after 1 week

If agitation/insomnia/nausea or sexual dysfunction:
- Mirtazapine 30mg
- If emotional blunting or lethargy:
  - Reboxetine 4mg bd
  - Lofepramine 140mg

Review risk and tolerability of drug at 2 weeks
  Up Sertraline to 100mg

Tolerating drug?

Y

N
Assessing response

1. Tolerating drug?
   - Yes: Full response? (PHQ < 5)
   - No: Review at 4-6 weeks, Re-do PHQ

2. Review at 4-6 weeks, Re-do PHQ
   - Yes: Full response? (PHQ < 5)
   - No: Non response? Minimal change (2 points or less) in PHQ

3. Non response? Minimal change (2 points or less) in PHQ
   - Yes: Partial response? PHQ decreased but ≥ 5
   - No: Tolerating drug?

4. Partial response? PHQ decreased but ≥ 5
   - Yes: Full response? (PHQ < 5)
   - No: Tolerating drug?
Lack of early response predicts failure to achieve remission

Meta-analysis of 41 studies of TCAs, mirtazapine, SSRIs, venlafaxine, etc. (6,562 patients) \(^1\)

- 6,562 patients with MDD from 41 studies
- Week 2: 35% of the patients did not achieve a 20% reduction of HAM-D\(_{17}\)
- Week 4-8: Of this 35%, only 4% had achieved remission in weeks 4–8

Conclusion:
- Lack of improvement during the first two weeks (\(\leq 20\%\) decrease in HAM-D\(_{17}\)) of treatment may indicate that changes in depression management should be considered earlier than conventionally thought

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Incomplete remission associated with chronic impairment in functioning

STAR*D: Failure to achieve remission increases the risk of relapse

Remission is defined as QIDS-SR$_{16} \leq 5$ and response is defined as $\geq 50\%$ improvement of QIDS-SR$_{16}$ after 12–14 weeks of acute treatment in level 1, 2, 3 or 4. The relapse rate was examined over 12 months of naturalistic treatment.

Assessing response

• Assess response systematically

• Review response after 4-6 weeks
  – After 2-4 weeks there should be at least some response; 4-6 weeks there should be significant response (add 1-2 weeks if elderly)

• Assess for response, partial response and no response
  – Partial response is associated with impaired social functioning and increased risk of relapse

Rule of thumb!!
Dealing with partial response

1. Partial response? PHQ decreased but ≥ 5
2. On going sleep problems?
   - Y: Consider: CBT for insomnia and/or hypnotics
   - N: Consider:
     - Increasing dose of antidepressant:
       - Citalopram 40mg
       - Sertraline 150mg
       - Mirtazapine 45mg
       - Fluoxetine 40mg
       - Reboxetine 8mg bd
     - IAPT/CBT in addition to antidepressants
3. Review after further 4-6 weeks
4. Full response?
   - N
   - Y: Consider: CBT for insomnia and/or hypnotics
Depression & sleep

- Don’t go straight for a sedative antidepressant in patients with sleep disturbance
  - The sleep disturbance usually resolves as mood improves

- However if partial response is due to ongoing sleep disturbance do something about this
  - CBT for insomnia
  - Hypnotics
  - Increase dose of antidepressant
  - Switch antidepressant (e.g. mirtazapine)
Dealing with non-response

Non response? Minimal change (2 points or less) in PHQ

Adherent to medication?

Consider switching to fluoxetine 20mg/day

Consider:
- Switching antidepressant and return to START
  Options include another SSRI, Mirtazapine, an SNRI, reboxetine or Iofepramine
- Treat as per partial response
- Getting prescribing advice/referral
Switching antidepressant vs increasing dose of current one

• If partial response and tolerability try increasing the dose
  – Probably only do this once with SSRIs

• If absolutely no response (esp. after one increase in dose)
  – Switch drug

Rule of thumb!!
How to switch antidepressants

• Abruptly from one to the other

• Exceptions
  — if on high doses reduce for a week (or 4-5 weeks in the case of fluoxetine) before making the abrupt switch
  — SSRI to a TCA: Taper and stop the SSRI and wait 4-7 days (or 4-5 weeks if switching from fluoxetine) and then introduce the TCA.
  — MAOIs – take care!

Rule of thumb!!
Beyond switching/increasing

• Lithium augmentation
  – Mainly done with SSRIs, SNRIs, TCAs and MAOIs
  – Aim for level of 0.6-0.8 mmol/l

• Antipsychotic augmentation
  – Quetiapine licensed; aripiprazole supported by data but not licensed; others less data

• Antidepressant combinations
  – Mixed evidence
  – Mostly mirtazepine plus SSRI or SNRI
  – Safest and easiest option?

• Others include:
  – T3, l-tryptophan, modafinil, lamotrigine
Depression: Some key questions

• Who should be treated?
• Treatment: what and how?
  • A comment on comorbidity
• ......and then what?
Pain and anxiety in depression

• Is very common
  – More than 50% of patients with depression will also meet criteria for a full blown anxiety disorder
  – Patients with depression are 3X more likely to be suffering pain as the general population

• Patients with depression plus pain or anxiety respond less well to medication
Comorbid anxiety leads to worse outcomes

- STAR*D study N=2,876
- Patients with MDD
- Treated with citalopram for 12 weeks
- Anxious patients defined as: ≥ 7 on anxiety/somatization
- Response and remission rated with HAMD and QIDS-SR

Baseline pain severity influences response to treatment

ARTIST – 9 month randomised open-label effectiveness trial (n=573 primary care depressed patients) comparing 3 SSRIs on HRQoL and physical symptoms.

Improvement in painful physical symptoms is associated with increased remission rate

Remission was defined as a HAM-D$_{17}$ Total Score ≤7
Painful physical symptom (PPS) improvement was measured by the Visual Analogue Scale for overall pain

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• Comorbid pain and anxiety can lead to inappropriate treatment
  – Over-sedation of anxious patients
  – Dangerous combinations of antidepressants in those with pain
Depression and pain

• Drugs do not follow sign posts to different symptoms!

• **AVOID** a patient ending up on amitriptyline for pain (or anything else) PLUS an SSRI
  
  — SSRIs can inhibit the metabolism of tricyclics leading to toxic plasma concentrations
  
  — Use amitriptyline at a full antidepressant dose (e.g. 150mg) or switch both to venlafaxine or duloxetine

Rule of thumb!!
Depression: Some key questions

• Who should be treated?
• Treatment: who, what and how?
• ......and then what?
Once in full remission......

- Presence of residual symptoms – increases the risk significantly
- Number of previous episodes – high risk if 2-3 + previous episodes
- Severity and duration – increased risk if severe or lasting more than 6 months
- Degree of treatment resistance of the most recent episode

NB – use clinical judgement
Maintenance

• Treat for 6-12 months from remission
  – if any risk factors then longer
  – If multiple risk factors then review annually
  – Residual symptoms is the biggest risk factor

Rule of thumb!!
Stopping treatment

• Be aware of symptoms of discontinuation and warn patients
  – sleep disturbance, GI symptoms, lethargy, headache, affective symptoms, paraesthesiae

• Take into account the clinical situation to determine the rate of taper
  – Serious adverse events may warrant rapid discontinuation
  – Otherwise minimum 4 weeks taper
  – Taper of some months for planned withdrawal after long-term prophylaxis

• If a discontinuation reaction does occur:
  – explanation and reassurance
  – if not sufficient restart antidepressant and tapered more slowly
Conclusions

• The management of depression is complex
  – Careful diagnosis is required
    • beware misdiagnosed bipolar disorder
    • Assess duration and severity since this influences treatment
  – Treat early and preferably follow an algorithm
  – Partial remission is not good enough
  – Comorbidities can lead to miss-treatment
    • Avoid over sedating anxious patients
    • Avoid combining an SSRI and a tricyclic
  – Once in remission treat for minimum of 6-12 months
  – For patients who are treatment refractory to a couple of antidepressants, lithium, quetiapine or aripiprazole augmentation or mirtazepine + SSRI or SNRI are options