Managing Treatment Resistant Anxiety and Depression

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Declarations of interests:

- I was Principal Investigator for (now concluded) ADD trial (AntiDepressant augmentation with metyrapone for treatment-resistant Depression)

- Previously (several years back)- have accepted honoraria and support for attending educational meetings/conferences from different pharmaceutical companies like Lilly, Pfizer, Janssen, Lundbeck, BMS, Astra Zeneca
Objectives:

By the end of this talk we will be able to –

- Recognize and evaluate Treatment Resistance in management of Anxiety and Depression (and differentiate it from some closely related conditions)

- Be more confident in using strategies for managing treatment resistance in Primary care
Outline:

- What is ‘Treatment Resistance’ in the context of management of Depression and Anxiety
- Evaluating treatment resistance (in Primary Care), Factors associated with Treatment resistance
- Choosing optimal treatments, selecting antidepressants / Augmenting agents / combinations with better evidence (and duration of Tt)
- When to get additional help (referral to secondary care)
Brexit and Antidepressants

- Recent media articles – highlighting a study showing increase in prescription of antidepressants in months after Brexit

“A study by King’s College London reveals that, relative to wider prescribing, there was a 13.4 per cent increase in antidepressant prescription in the month following the June 2016 referendum, compared to the previous year”

https://www.telegraph.co.uk/news/2018/11/20/antidepressant-use-rose-following-brexit-referendum-figures/
What is ‘Treatment Resistance’ in management of Depression and Anxiety?

- Treatment Resistant Depression (TRD) - generally held view: failure of 2 adequate (in dose and duration) trials of antidepressants

- About 1 in 2 may not fully respond to initial (1st) antidepressant
- About 1 in 3 may not fully respond to initial 2 meds
- Research - levels/grades of treatment resistance

- Similar concept can be used in Anxiety disorders
Evaluating treatment resistance:

- **Is it really Depression?** - [going back to the basics] - need to be aware of other reasons for similar presentations - adverse life events, Personality disorders, alcohol/drug misuse, prodrome of psychosis/schizophrenia, OCD, GAD (is it Depression or primarily an Anxiety disorder)?

- ICD-10 can be useful

- Use of validated diagnostic tools
Is it really Depression?

- Common issues
  - Acute Bereavement
  - Adjustment disorders
  - Substance misuse/alcohol
  - ? No MH diagnosis
  - Dysthymia
  - Unresolved grief
  - Personality disorders
  - Bipolar depression (?)
- Bipolar depression - needs a special mention

- Need to rule out Bipolar disorder / past history of mania / hypomania / mixed episode
What is NOT “Depression” (as per ICD10)

- Low mood- subsyndromal (in other contexts)
- Adjustment reactions- work, relationships, financial stressors, diagnosis of a serious physical illness
- Grief reaction
- Alcohol & Drug misuse (NOTE- it may at times MASK depression)
- Personality difficulties/ disorders
Case vignette (a):

- 55 year old male presents with “feeling depressed”. He has moved to your area recently after divorce in Spain. Some passive thoughts of “not being there” - does not have active suicidal thoughts at the time of review but says he has thought about suicide at times. He has tried self help techniques, self referral counselling but didn’t find it helpful and stopped. He has tried Citalopram in Spain but stopped as no benefit. Wants to try other antidepressants.

- Options?
ICD-10 criteria for Depression (F32)

(Note severity and Duration – 2 weeks minimum)

- Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability and diminished activity. Marked tiredness after only slight effort is common.

- Other common symptoms are:
  (a) reduced concentration and attention;
  (b) reduced self-esteem and self-confidence;
  (c) ideas of guilt and unworthiness (even in a mild type of episode);
  (d) bleak and pessimistic views of the future;
  (e) ideas or acts of self-harm or suicide;
  (f) disturbed sleep
  (g) diminished appetite
What next (good practice)?

- Schedule a routine follow up (1-2 weeks after initial)
  - Regular follow ups to monitor progress (use simple standardised tools) - IF NO RESPONSE IN 2-4 WEEKS - less likely to respond at 12 weeks (some with multiple episodes - slower response)
  - Assessment of symptom severity in each follow up, Suicidality
  - Discussion about emerging side effects (becomes more important as higher doses are used / other agents are added)
  - Improving and maintaining compliance - DOSE INCREASE (BNF)
  - Amount of alcohol, drug use (“Teesside average alcohol use”)
  - Smoking (smokers can have reduced efficacy and higher relapses)
  - DVLA & Driving / other risks
Also watch for:

- Any history or current features of bipolarity (hypomania/mania/mixed affective state); Psychotic symptoms; also family history of such features

- Depression + ongoing life events /bereavement/ separation/ financial issues, social isolation, new to area

- Medical co-morbidities, hormonal status (thyroid status), pregnancy/postnatal, peri-menopausal
Phases in treatment of Depression

Choosing optimal treatments:

Evidence base

- NICE Guidelines
- BAP guidelines - more detailed in terms of medications
- Other research
Evidence base: a good place to start-

Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines

Anthony Cleare1, CM Pariente2 and AH Young3
With expert co-authors (in alphabetical order):
IM Anderson4, D Christmas5, PJ Cowen6, C Dickens7, IN Ferrier8, J Geddes9, S Gilbody10, PM Haddad11, C Katona12, G Lewis12, A Malizia13, RH McAllister-Williams14, P Ramchandani15, J Scott16, D Taylor17, R Uher18 and the members of the Consensus Meeting19
Endorsed by the British Association for Psychopharmacology

making a difference together
General principles- managing treatment resistance:

- If NO RESPONSE in 2-4 weeks OR limiting side effects – consider changing / using another strategy
- If partial response- increase to maximal tolerated (or BNF max) dose for up to 6 - 12 weeks
- Consider addition of Psychological interventions / CBT
- Can try another SSRI initially (same class switching)
- Use another antidepressant with some evidence of higher efficacy (like Venlafaxine>150mg, Escitalopram 20mg, Sertraline, Mirtazapine)
Consider adding another agent if:

- Partial response with well tolerated antidepressant at full dose
- Switching antidepressant has been unsuccessful

**What to add?** *(Augmentation vs Combination therapy)*

- Small dose of Trazodone (50mg) for sleep (added to SSRIs- Serotonin syndrome awareness)
- **Quetiapine, Lithium**- good evidence, Aripiprazole (Note: BNF does not list Depression as an indication for Aripiprazole though it is mentioned* in NICE CG90 and has evidence for augmentation in depression)
- Also- Risperidone, Olanzapine, Tri-iodothyronine, (Mirtazapine + Venlafaxine)
- Secondary/Tertiary care/Research- high doses, ECT, VNS, rTMS, tDCS, etc.
Choosing optimal treatments:

- Guidelines and evidence base
- Past response to same medication
- **Side effect profile**—past history of side effects
- Relative safety in overdose (DO NOT START DOSULEPIN)
- Co-morbid conditions—eg. Obsessive features—SSRIs
- Interactions with other medications
- Possibility of making other medical conditions worse (eg. cardiac)
- Patient preference—improves outcomes by increasing compliance
- Doctor preference and experience

- ? The profile of symptoms of Depression in a given case (?)
### Side effect profile (BAP, 2015)

Table 5. Side-effect profiles and lethality in overdose of commonly used antidepressant drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Side effect</th>
<th>Inhibition of hepatic enzymes</th>
<th>Lethality in overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clomipramine</td>
<td>SRI+NRI</td>
<td>++ ++ + ++  + ++</td>
<td>-</td>
<td>moderate</td>
</tr>
<tr>
<td>amitriptyline, dosulepin</td>
<td>NRI-SRI</td>
<td>++ ++ - ++  - +</td>
<td>-</td>
<td>high</td>
</tr>
<tr>
<td>imipramine</td>
<td>NRI-SRI</td>
<td>++ ++ + ++  - +</td>
<td>-</td>
<td>high</td>
</tr>
<tr>
<td>desipramine, nortriptyline</td>
<td>NRI</td>
<td>+ + + + -    - +</td>
<td>-</td>
<td>high</td>
</tr>
<tr>
<td>lofepramine</td>
<td>NRI</td>
<td>+ - + + -    - +</td>
<td>-</td>
<td>sweating</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>citalopram, sertraline</td>
<td>SRI</td>
<td>- - + ++  ++ +</td>
<td>-</td>
<td>low</td>
</tr>
<tr>
<td>fluoxetine, fluvoxamine, paroxetine</td>
<td>SRI</td>
<td>- - + ++  ++ +</td>
<td>-</td>
<td>low</td>
</tr>
<tr>
<td><strong>Other reuptake inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>maprotiline</td>
<td>NRI</td>
<td>++ ++ - -    - +</td>
<td>+</td>
<td>increased seizure potential</td>
</tr>
<tr>
<td>reboxetine</td>
<td>NRI</td>
<td>+ - + + -    - +</td>
<td>-</td>
<td>hypertension, sweating</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>SRI&gt;NRI</td>
<td>- - + ++  ++ +</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>duloxetine</td>
<td>SRI+NRI</td>
<td>- + + -    ++ ++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>bupropion</td>
<td>5-DRI+NRI</td>
<td>- + + -    ++ ++</td>
<td>-</td>
<td>increased seizure potential</td>
</tr>
<tr>
<td><strong>Receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trazodone</td>
<td>5-HT₂ + α₂ &gt; SRI</td>
<td>- ++ - ++ ++ - - +</td>
<td>+</td>
<td>priapism</td>
</tr>
<tr>
<td>nefazodone</td>
<td>5-HT₂ &gt; SRI</td>
<td>+ + - + ++ - - +</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>mianserin</td>
<td>5-HT₂ + α₁ + α₂</td>
<td>+ ++ - - - - -</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>5-HT₁ + 5-HT₂ + α₂</td>
<td>- ++ - - - - -</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: ++ indicates a high risk, + indicates a moderate risk, and - indicates a low risk.
Managing specific side effects:

Important to discuss and manage to improve outcomes

- General principles - reduce dose and re-titrante/change
- Nausea/headache with SSRIs - usually time limited
- Adding short term (<2 weeks) benzodiazepines for early agitation/anxiety/insomnia (NOT ROUTINE)
- Anticholinergic effects of TCAs - more long lasting
- Dryness of mouth with Clomipramine – common
- Sexual side effects with Venlafaxine - evaluate IF it is indeed a side effect; consider Trazodone/Agomelatine; add Sildenafil/Tadalafil if indicated and safe
Choice of medications:

- Role of diagnostic clarification - helps with some choices and doses. Eg.
  - Obsessive features generally need higher doses of SSRIs, Clomipramine
  - GAD - Pregabalin is an option (sometimes after trying Venlafaxine)
  - PTSD related nightmares – some evidence for Prazosin (Kung et al, 2012) (NOTE: BNF does not list this as an indication for Prazosin)
  - Sleep difficulties: common practice to add Trazodone in small dose or Mirtazapine to Sertraline/Venlafaxine
Some issues with polypharmacy:

- Diminishing returns in efficacy/full remission
- Increased side effects with combinations
- Antipsychotics (like Quetiapine) - monitor bloods, etc.
- QTc elevation risks with certain combinations (eg. Citalopram and Quetiapine - not my favourite)
- Potentially fatal **Serotonergic syndrome** with high doses/combination antidepressants (also other agents like opioids, cocaine, metoclopramide, etc.) - acute confusion, autonomic changes, tremor, myoclonus, etc. - **Management - help of 999**
Special patient groups:

- Younger adults (under 25 years) - higher risk of suicidal thinking
- Planning pregnancy
- Unplanned pregnancy detected in otherwise stable lady/ in partial remission
- Co-morbid medical issues
  - Post MI
- Elderly age range
How long to treat:

No clear answers yet - but some information

- 6-9 months in remission in ‘uncomplicated’ cases
- 1 year or more in those with higher risks of relapse
- 2 years in GAD
How to stop antidepressants:

- After a few weeks of treatment, those with shorter half life (like Paroxetine, Venlafaxine) need to be tapered over at least 4 weeks (sometimes longer).

- Fluoxetine has very long half life - less need to taper.

- Serotonergic withdrawal features - restlessness, anxiety, flu like symptoms, insomnia, nausea.
Some special considerations:

- Antidepressant Tachyphylaxis
- Pregnancy/planning pregnancy
- Lactating mothers
- Antidepressant use in elderly population
- Antidepressant use in under 18s
- Serotonin syndrome
Management of Serotonin withdrawal

- Reassurance and psycho-education - symptoms usually last for about 1 week

- Restarting at low dose and slowly reducing again

- Changing over antidepressant to Fluoxetine
When to consider seeking help/ referral

- Increasing risks/ significant risk of suicidality
- Psychotic features/ Bipolarity (history or current)
- When further diagnostic clarification is needed
- Special subgroups with certain risks/complex meds
- Specific modalities of psychological treatments not commonly available in primary care
- Child/adolescent with major depression

Secondary/Tertiary care- other combinations, ECT, rTMS, VNS, etc. tDCS?

When to accept referral back from secondary care?
Questions?