Antidepressants – Tolerance, Dependence and Addiction

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Overview

- Revision of types of antidepressants and modes of action
- Addiction, tolerance and dependance
- Discontinuation symptoms for antidepressants.
Revision of antidepressants

- Classes of antidepressants;
- **TCA**…(Amitriptylline, Imipramine, Dosulepin)
- **TCA. 2nd Generation**…(Trazodone)
- **SSRI**…(Fluoxetine, Paroxetine, citalopram)
- **SNRI**…(Venlafaxine, Duloxetine)
- **NARI**…(Reboxetine) (noradrenaline reuptake inhibitor)
- **NASSA**…(Mirtazepine) (presynaptic alpha2 antagonist which increases central NA and 5HT transmission)
- **MAOI**…(Phenelzine, Tranylcypromine)
- **RIMA**…(Moclobemide)
What’s New?

Agomelatine – Licensed in Ireland in 2009
A new antidepressant which is particularly suitable for people who have disturbed sleep patterns (this is common in depression).

- Agomelatine causes the release of both NA and D in the prefrontal cortex, an area of the brain involved in mood, anxiety and cognition. It also has agonist action at MT1 and MT2 receptors and antagonistic action at its 5HT2c receptor and it is through these actions that agomelatine is thought to restore disturbed circadian rhythms such as the sleep wake cycle.
Discuss choice of drug with the patient
Include:
- Therapeutic effects
- Adverse effects
- Discontinuation effect
- Likely time to respond
Suggest SSRI as first choice; mirtazapine if sedation required

Start antidepressant
Titrates (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 6-9-3 months at full treatment dose
Consider longer-term treatment in recurrent depression

Poorly tolerated
Switch to a different antidepressant (see notes)
Titrates to therapeutic dose
Assess efficacy over 3-4 weeks

No effect

Effective

Switch to a different antidepressant (see notes)
Titrates (if necessary) to therapeutic dose. Assess over 3-4 weeks, increase dose as necessary

No effect
Refer to suggested treatments for resistant depression
Acknowledgement

The following slides, on addiction and tolerance, are based on a medicines education programme written by Professor Steven Bazire, Norfolk and Norwich NHS Trust, UK

http://www.ukppg.org.uk/meded-06e98.html
Tolerance, dependence and addiction

Common fear among patients that antidepressants are “addictive”
Could be related to confusion between benzodiazepines (such as Valium) and antidepressants.

The World Health Organisation states that for a substance to be addictive it must cause;

- **Desire or craving** i.e. the person must crave another dose when the previous one is wearing off, or has worn off.
- **Withdrawal symptoms** i.e. a set of symptoms which start when the drug wears off and which disappear when the next dose is taken.
- **Tolerance** i.e. where the same dose gives less effect after a while.
- **An immediate effect** or reward. It is very hard to be addicted to a drug if you don't know if you've taken it or not!
Tolerance

Tolerance means "Get used to the effects"

For example:
- can't hear a clock tick after a while
- live near a busy road and not notice the noise from the busy traffic
- can't smell the perfume/aftershave you have put on.
Tolerance to medication

As regards medication you can become TOLERANT to:

- **A: adverse effects** e.g. anticholinergic side effects such as dry mouth and constipation. These side effects gradually wear off. Some side effects gradually appear to wear off e.g. the drowsiness of antidepressants. Care is needed as you can become used to the level of drowsiness and think you're OK for driving when in fact your reaction times are slowed still.

- **B: therapeutic tolerance**: this means you may need to increase the dose of the medication in order for it to keep working e.g. benzodiazepines. These drugs may only work for a short period of time and you may need to use larger doses to get the same effect. There is evidence that a few people (around 5% perhaps) may get some tolerance to antidepressants.
Dependence

- Dependence is the need for the body to have a chemical so that it can function normally. This can be physiologically normal e.g. the body is dependent of insulin. If insulin is not produced by the body it needs to be administered in order for the body to function normally. You can become dependent on chemicals which are not needed by the body e.g. alcohol or heroin.

- If you suddenly stop a chemical which you have become dependent on you will precipitate a withdrawal reaction. The body gets used to the chemical being there and hasn't got the systems set up to cope with it not being there.

- Dependence can lead to ADDICTION.
Addiction

What is addiction? Quite often patients can't describe it. So, ask what they associate with addiction?
- Gambling, illicit drugs, football, chocolate etc.

- It becomes a social thing - an addicted person lives their life to obtain the substance or behaviour.
- They lose interest in everything else and everyone else
- They may go around with others who share their addiction
- Everything revolves around the addiction
- Are any psychiatric medicines addictive?
**Fill in the chart in groups**

Consider each item on the list for:

- Craving/desire
- Withdrawal symptoms
- Tolerance
- Reward/immediate effect
<table>
<thead>
<tr>
<th></th>
<th>Does it produce craving or desire?</th>
<th>Can you get withdrawal symptoms?</th>
<th>Does the effect wear off? (tolerance)</th>
<th>Is there a reward or an immediate effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Yes</td>
<td>Yes e.g. &quot;DTs&quot;</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Yes</td>
<td>Yes e.g. headaches</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Smoking/nicotine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heroin etc.</td>
<td>Yes</td>
<td>Yes e.g. &quot;cold turkey&quot;</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Yes</td>
<td>Yes, but usually only from high doses taken for a long time</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>Sometimes, but only for the sleep</td>
<td>Sometimes e.g. &quot;rebound&quot; insomnia</td>
<td>Sometimes</td>
<td>Yes</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Sometimes but usually not with appropriate use</td>
<td>Sometimes</td>
<td>Sometimes to the sedative effect</td>
<td>There can be</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>No</td>
<td>Not usually ‡</td>
<td>In about 5% people</td>
<td>No</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>No</td>
<td>No, if done gradually ‡</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lithium</td>
<td>No</td>
<td>No, if done slowly over 4 or more weeks ‡</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tablets for high blood pressure</td>
<td>No</td>
<td>Yes. Can produce rebound hypertension</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gambling</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes, when you win</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

† A few antidepressants, lithium, antipsychotics/neuroleptics and benzodiazepines may produce some "discontinuation" or "adjustment" effects if stopped suddenly. Gradual stopping usually solves the problem.
Steven Bazire says;

- The known drugs of abuse can produce craving, withdrawal symptoms and tolerance to their actions and are taken for their immediate effect. Most prescribed drugs do not cause craving, have no significant withdrawal symptoms and no tolerance to the beneficial effects are seen. Furthermore, all are helping to correct a known chemical imbalance in the brain.

- If you took someone’s iphone, playstation etc away, they might feel odd. listless, irritable etc. In my (SB) opinion, what the withdrawal/discontinuation symptoms show is that these are potent drugs and withdrawing them abruptly is a bit like stopping a car suddenly without a seat belt on. You can do it, but it hurts. It’s more comfortable to do it slowly (this analogy came from a patient on a forensic ward who knew more about illegal drugs than I will ever know).

- * A few antidepressants and antipsychotic drugs may produce some discontinuation or withdrawal effects if stopped abruptly. They are not strictly withdrawal effects. An "adjustment" reaction is also a way of describing them. Gradual stopping usually solves the problem. Do you live life for the drugs, or do drugs help you live your life?
Discontinuation symptoms

- Used to describe the symptoms experienced when patient stops antidepressant treatment. It does not mean patient was addicted to the drug.
- Onset is usually within 5 days of stopping treatment. Usually effects are mild and self limiting and advice to patient will help the patient to cope with any effects. Occasionally the patient experiences severe and prolonged symptoms.
- Discontinuation of antidepressants over a 4 week period reduces the risk, especially with drugs with a short half life (note fluoxetine has long half life so can be stopped over shorter period of time).
- **MAOIs, amitriptylline, imipramine, paroxetine and venlafaxine** are most associated with discontinuation syndrome.
<table>
<thead>
<tr>
<th>Antidepressants &amp; Discontinuation Syndrome</th>
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<tbody>
<tr>
<td><strong>SSRIs</strong></td>
</tr>
<tr>
<td>Dizziness, lightheadedness,</td>
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<tr>
<td>Vertigo, ataxia</td>
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<tr>
<td>GI disturbance</td>
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<tr>
<td>Lethargy, headache, tremor, sweating</td>
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<tr>
<td>Paraesthesia, numbness, “electric shock”-like sensations</td>
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<tr>
<td>Irritability, anxiety, low mood.</td>
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</table>
Discontinuation Symptoms for SSRIs

Rates of discontinuation events have been reported as:
- Paroxetine 20%
- Fluvoxamine 14%
- Sertraline 2%
- Fluoxetine 0%

Reports of similar discontinuation symptoms with venlafaxine are becoming more frequent.

Discontinuation effects can be partially explained by receptor rebound.
Antidepressants are not addictive
They are beneficial for many patients with moderate to severe depression, as part of a complete package of care.
Some patients will experience discontinuation symptoms if treatment is stopped suddenly.
References

Be nice to your pharmacist.

We get paid to know lethal combinations of drugs.
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