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Beyond psychoanaleptics – can we improve antidepressant drug nomenclature?

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One of the great advances in psychiatry treatment over the past 50 years has been the growth in safe and effective pharmacological treatments. There are now many different antidepressants and antipsychotics, which have specific pharmacology even if this means overlapping between drug classes. However, the terminology used to describe this pharmacology has grown in a random way with little consistency and often internal inconsistencies.

I wonder whether any of you have ever come across the preferred term used by the Anatomical Therapeutic Chemical (ATC) drug classification system of the WHO for the class of drugs that antidepressants fall into – psychoanaleptics? Closer to home is the confusion caused by using the term SNRI; many people in psychiatry and related occupations extrapolate from the meaning of selective serotonin reuptake inhibitor (SSRI) to assume that SNRI means selective noradrenaline reuptake inhibitor (rather than serotonin noradrenaline reuptake inhibitor as originally conceived). Such confusion could have quite significant clinical implications if it leads to inappropriate drug prescribing; for example, noradrenaline reuptake blockers may be used with monoamine oxidase inhibitors (MAOIs), whereas drugs with SSRI activity are much more dangerous because of the risk of the serotonin syndrome. Because the acronym SNRI was taken, the term NARI or NRI (noradrenaline reuptake inhibitor) has come into use for selective noradrenaline reuptake inhibitors, which misses the point of selectivity.

There are many other inconsistencies, for example, some drugs are named based on chemical structure (e.g., the tricyclic antidepressants or TCAs), whereas others have names based on their mode of action (e.g., SSRIs, MAOIs). Some have acronyms that are not intuitive, for example, noradrenaline and selective serotonin antagonist (NaSSA) for mirtazapine, which has been misquoted by at least one expert as noradrenaline antihistamine and selective serotonin antagonist! A further challenge are new antidepressant drugs with different modes of action, for example, agomelatine, a melatonin receptor agonist and 5HT_{2C} receptor antagonist, which has yet to have an agreed name.

From the above, it is clear that it is possible to classify antidepressants according to a variety of criteria, so which is the best? The WHO ATC classification system, which was primar-

ily designed for drug utilisation research divides drugs into different classes according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The current WHO nomenclature is shown in Figure 1. For antidepressants, it starts with an attempt at pharmacology but, as newer drugs with more complicated pharmacology have become available, it unfortunately puts most of them into the 'Other' category – one which conveys no therapeutic information and has no educational value.

In this editorial, I suggest another logical approach – to segregate according to pharmacology – target molecules and neurotransmitter or other outputs. This is shown in Table 1, where the key elements of antidepressant efficacy are detailed in relation to neurotransmitter targets and mode of action.

Although this approach has some merits, because it is in the form of a table, it has limitations if one requires a simple linear form of classification that international drug classification systems, such as the ATC, currently use. Another approach that is being actively discussed in other areas of brain therapeutics is to use more generic classification based on whether the drugs have single or multiple sites of action (unimodal–v– multimodal acting). If we apply this to the antidepressants, then we have a series of categories, fewer than the cells in the table above, and with possibly more generic heuristic value.

These are shown in Figure 2. Here, you can see that the prime delineator is mode of action with subgroupings based on the number of neurotransmitter systems involved in the action of a particular drug. The first three classes of antidepressants are well described as reuptake blockers, receptor blockers and enzyme blockers.

Reuptake blockers are well known as the TCAs, SSRIs and others. They can be considered as single (selective) agents (e.g., the SSRIs) or mixed agents (e.g., the SNRIs and some TCAs).

Receptor blocking agents can work in one of two ways. Some block inhibitory receptors and increase the neurotransmitter function; the best example is mirtazapine that blocks inhibitory α_2 adrenoreceptors and increases both noradrenaline and 5HT release. Other forms of receptor antagonist work to reduce neurotransmitter activity. Although none of these have yet reached the market, the NK1 (substance P) and NK2

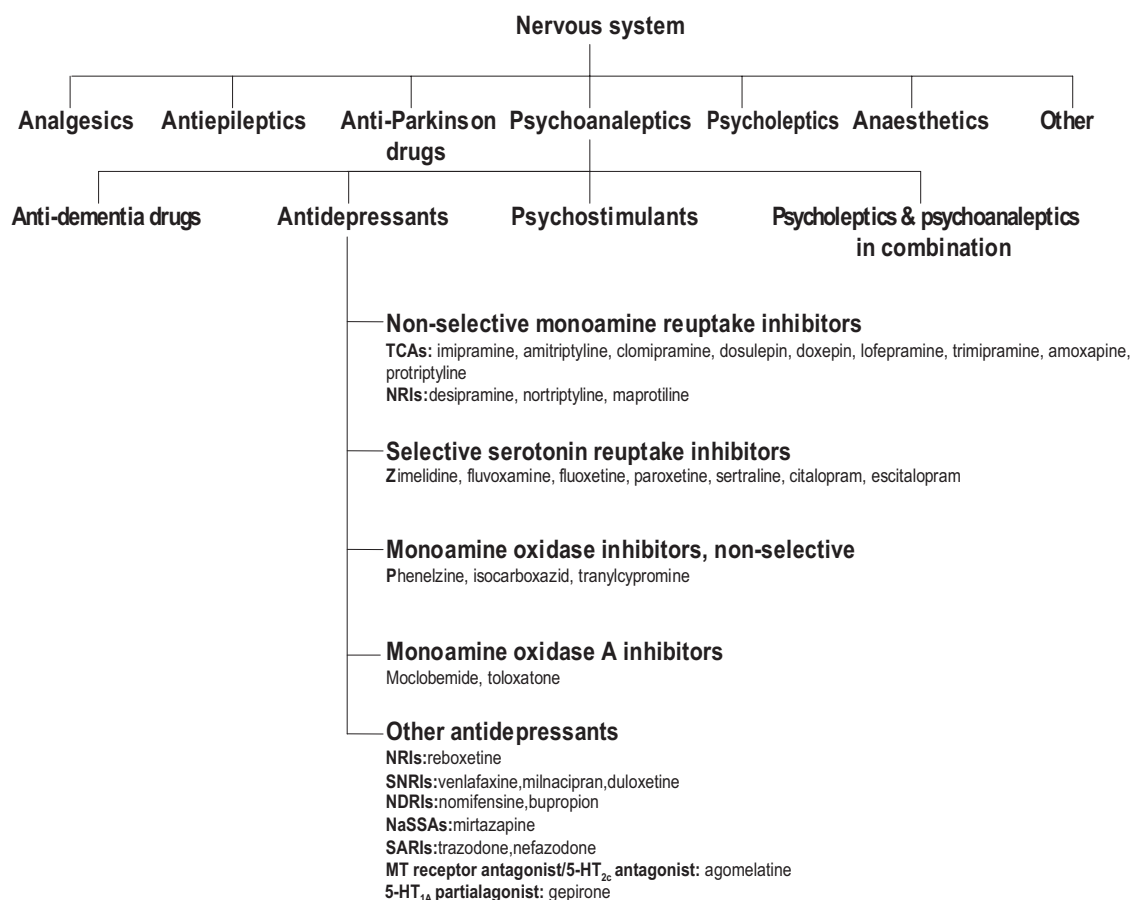


Figure 1 Current antidepressant nomenclature under the WHO system.

receptor antagonists did show early promise as antidepressants. Both CRF and glucocorticoid receptor (GR) antagonists are in clinical trials for reducing excess cortisol activity in depression.

Enzyme inhibitors are currently of the MAOI class with the A inhibitors being of proven efficacy, whereas the B inhibitors have

lesser, though still some, clinical efficacy in depression. MAOIs can be subdivided into reversible (e.g., moclobemide) and irreversible (phenelzine) inhibitors. Drugs that block other enzymes that metabolise amines are used in other brain disorders, especially catechol-o-methyl transferase (COMT) inhibitors for Parkinson's

Table 1 One possible way to classify antidepressants

Neurotransmitter targets	5HT	Noradrenaline	Dopamine	Others
Reuptake sites	SRI, SSRI, TCAs	NARIs, TCAs, NDRIs	NDRIs	?
Receptors	Trazodone, Mirtazapine, Agomelatine (TCAs)	Mirtazapine (TCAs)	Atypicals antipsychotics when used in depression?	? NK1 NK2, ? GR, ? CRF
Enzymes	MAOI A	MAOI A	MAOI B	

SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; NARI, noradrenaline reuptake inhibitor; NDRI, noradrenaline dopamine reuptake inhibitor (nomifensine and bupropion); NK, neurokinin; GR, glucocorticoid receptor; CRF, corticotropin releasing factor; MAOI, monoamine oxidase inhibitors.

SRI, drugs that block 5HT/serotonin reuptake such as certain TCAs (clomipramine, imipramine, amitriptyline) and the SSRIs.

NARI, includes both TCAs such as desipramine and nortriptyline and the non-TCA reboxetine.

TCAs refer to the fact that they do have receptor-blocking actions, but these are generally deleterious (especially in overdose) rather than adding to the therapeutic benefit.

Enzyme inhibitors

- single target
 - o MAOI A
 - o MAOI B
- multi targeted
 - o non selective MAOIs

Reuptake blockers

- single target
 - o SSRI
 - o NARI
- Multi-target
 - o SNRIs
 - o NDRIs
 - o TCAs

Receptor acting drugs

- single target
 - o substance P antagonists
- multi-target
 - o NaSSAs
 - o MT receptor agonist/5HT_{2C} antagonist

Multi-modal drugs

- o Reuptake and receptor antagonists
- o 5HT reuptake and 5HT receptor blockers

disease, and it may be that they will be shown to have utility in depression at some stage.

The fourth is a class that has not been much discussed before – the multimodal agents. These act on more than one of the molecular targets thought to be critical to antidepressants mode of action. Early examples of these are trazodone and nefazodone that are both 5HT (and possibly noradrenaline) receptor antagonists as well as having some 5HT reuptake blocking properties. Newer agents of this class are drugs currently under investigation including vilazodone (a 5HT reuptake inhibitor with a 5HT_{1A} agonist) and LuAA21004 (a 5HT reuptake inhibitor with a 5HT₃ antagonist and 5HT_{1A} agonist). The potential advantages of multimodal agents are that the multiple actions support each other in terms of either efficacy or safety/tolerability. For this reason, I have not included the TCAs in this class, although many of these also have receptor antagonist as well as reuptake blocking properties, as their receptor actions (especially at cholinergic, noradrenaline and histamine receptors) tend to be deleterious rather than provide therapeutic benefit.

One possible advantage of this new system is that it can be applied to other classes of drugs used in psychiatry (e.g., neuroleptics/antipsychotics), where these can be construed as unimodal or multimodal inhibitors of dopamine and other neurotransmitter function.

I think everyone will agree that the present system is less than ideal and would be interested to get feedback on the alternative ideas as set out above.

Figure 2 A possible new approach to antidepressant classification.

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In Figure 1, agomelatine is referred to as an MT receptor antagonist/5HT_{2c} antagonist. This should be MT receptor agonist/5HT_{2c} antagonist.