



A RATIONAL MODEL FOR ANTIDEPRESSANT DRUG PRESCRIPTION

Why the need?

It is commonly argued that all antidepressant drugs are similarly efficacious, an argument supported by results in randomized controlled trials. Clinicians are commonly encouraged to select an antidepressant on the basis of its side-effect profile rather than by any evidence of differential efficacy.

However, when we survey clinicians who have extensive experience in managing mood disorders, we find considerable variation in the judged ‘real world effectiveness’ or perceived ‘powerfulness’ of the differing antidepressants. Their experience shows that the powerfulness of the differing antidepressants could be illustrated as follows:

MORE POWERFUL	Tricyclic and monoamine oxidase inhibitors
↓	Dual action drugs
↓	SSRIs
LESS POWERFUL	Narrow action drugs

Such experience does suggest a difference between the published knowledge base and clinical experience.

Research at the Institute (and its predecessor, the Mood Disorders Unit) over the last ten years has allowed a model to be developed that suggests a more rational approach to choice of antidepressant drugs.

The model

In the figure below we present (left-hand side) a ‘structural model’ of the principal depressive classes:

- non-melancholic depression
- melancholic depression and
- psychotic depression.

Key distinguishing features of the principal depressive classes

- Each has a central and shared ‘depressed mood’ component which becomes more severe (in general terms) as the classes are ascended.
- **Melancholia** is distinguished from the **non-melancholic** disorders by observable psychomotor disturbance (defined on this website in our research section by the CORE measure).
- **Psychotic depression** is distinguished from melancholic depression by the greater severity (generally) of the psychomotor disturbance but, specifically, by the presence of psychotic features (delusions and/or hallucinations).

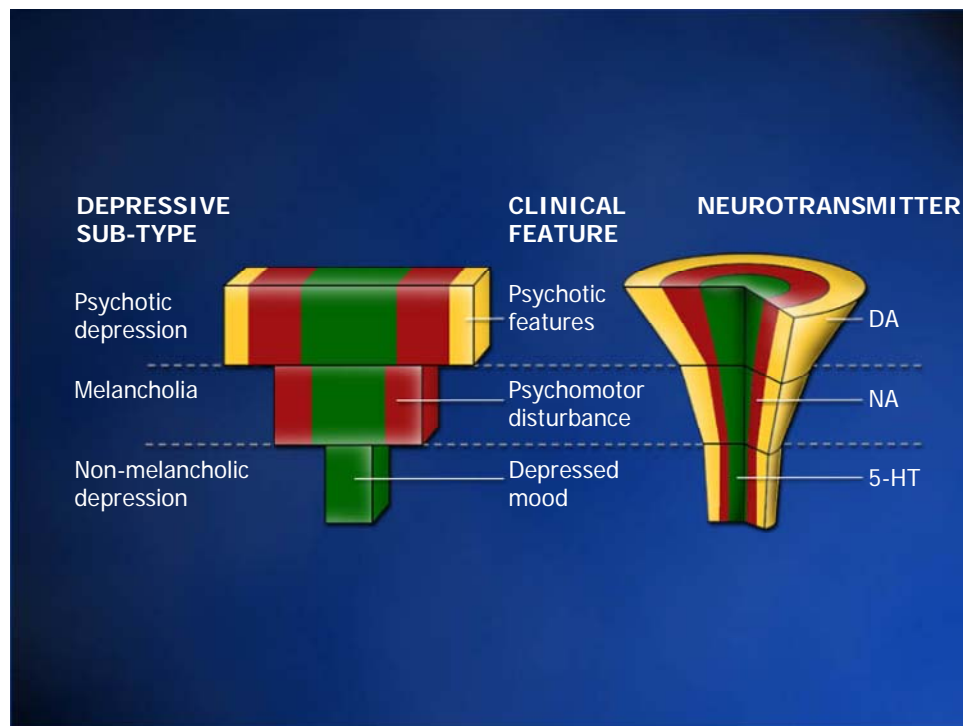


Figure 1

Differing aetiology

We assume that each of the three differing classes reflect differing aetiological processes – particularly reflected in neurobiological underpinnings.

On the right-hand side of the figure we offer our ‘functional model’, which captures the role of differing neurotransmitters. We are not arguing that each class is underpinned by one neurotransmitter only – but more arguing that the classes are distinguished by quite differing neurotransmitter ratios. In essence, we suggest:

- that the non-melancholic disorders are largely underpinned (when there is a neurotransmitter contribution) by a serotonergic contribution.
- for melancholic depression, we argue for a greater noradrenergic contribution.
- for psychotic depression, we argue for a greater dopaminergic contribution.

Implications for selecting treatments

To the extent that this model is valid, it allows antidepressants to be considered and prescribed as ‘narrow-action’ or ‘broad-action’, much in the same way antibiotics might be considered both as a treatment strategy and in relation to the underlying pathology.

- ***Non-melancholic depression***

Empirical research suggests that all antidepressant drug classes are similarly effective for non-melancholic depressive disorders. Our model would explain why. In essence, to the extent that these are serotonergically underpinned, then most antidepressant drug classes would be expected to be able to correct such disorders (as they have a serotonergic profile) and therefore most classes would have an equal chance of helping.

However, there would not be any great advantage to prescribing a broad-action antidepressant as this risks ‘over-kill’, in that there is no need to go beyond a serotonergic contribution. Thus, we would

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suggest that the SSRI drugs are the most appropriate antidepressant for non-melancholic depression in that they are as likely as any other drug class to be effective, while their side-effect profile is likely to be the least concerning.

- ***Melancholic depression***

Turning to melancholic depression, where a noradrenergic contribution is more prominent, then while an SSRI might be effective, overall, the dual-action drugs (that effect serotonergic and noradrenergic function) are more likely to be effective. Once again, very broad-action drugs might also be effective, but there may be no need to go beyond dual-action drugs in light of the neurobiological underpinnings.

- ***Psychotic depression***

Turning to psychotic depression, and where there is a much greater dopaminergic contribution, there is a need for a broad-action antidepressant strategy, which is most generally achieved by the prescription of an antidepressant plus an antipsychotic drug.

Augmentation with atypical antipsychotics

In addition to the different antidepressants having their own range of action, each of the antidepressants can have their profile ‘broadened’ by augmentation with an atypical antipsychotic – and the flow-on effect of this strategy can be understood in light of the model outlined here.

In essence, if a patient needs a broad-action antidepressant and is merely given a narrow-action antidepressant, and if there is no improvement, then the addition of an augmenting antipsychotic drug may induce a response. However, there may be no need to so proceed when the prescription of a dual-action or a broad-action antidepressant alone had not been trialled.

The use of an augmenting atypical antipsychotic drug should probably be restricted to situations when narrow-action, dual-action and broad-action antidepressants have failed or when there is a need to increase the rate of response allowed by antidepressant alone.

Effectiveness studies

The model is clearly speculative, and has been detailed in a 2005 publication (Malhi, Parker and Greenwood. Structural and Functional Models of Depression: from Sub-Types to Substrates. Acta Psychiatrica Scandinavica, 111:94-105), but has been supported by a number of effectiveness studies. For example, we have shown that those with melancholic depression are more likely to respond to a broad-action antidepressant than a narrow-action SSRI. This does not argue that one must necessarily trial a broad-action antidepressant first. If, however, a narrow-action antidepressant was trialled for an individual with melancholic depression, and it failed, then we would argue that it would be wise not to trial another narrow-action antidepressant but to move to a dual-action drug and, if that failed, to move to an even more broad-action antidepressant.

We hope this model is of some assistance to your clinical prescribing.

We also attach a single page, larger diagram of the model that you may like to print out and use in dealing with your patients.



DEPRESSIVE SUB-TYPE

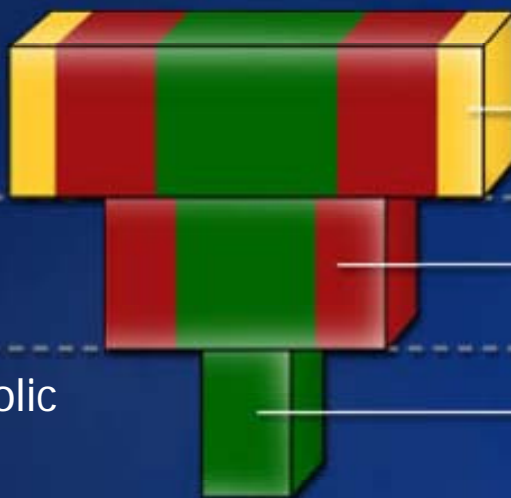
CLINICAL FEATURE

NEUROTRANSMITTER

Psychotic depression

Melancholia

Non-melancholic depression



Psychotic features

Psychomotor disturbance

Depressed mood



DA

NA

5-HT

DA = Dopamine NA= Noradrenaline 5-HT = Serotonin