Venlafaxine: an enduring SNRI myth

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Venlafaxine (Effexor, now out of patent) and its 'badge-engineered' metabolite off-spring (desvenlafaxine, Pristiq- in patent, which is even weaker than venlafaxine as an NRI) are examples of drugs whose attribution as 'SNRIs' relates to marketing imperatives, but not pharmacology.

Promoting these two drugs as beneficial and superior for severe or TR depression is a deceitful charade: the theory behind it is poor and the evidence so weak you could not hang a festive paper hat on it.

When I wrote my first note about this drug, the best part of 20 years ago, I was sceptical, but more cautiously so. Now that another decade's worth of evidence is available I am confident in stating the above: that as an 'SNRI' it is a deceitful imposter.

Its' claim to be an SNRI has been gullibly and naïvely accepted by psychiatrists. It has no clinically significant effect on noradrenalin *in vivo* even at doses of 300 mg per day. I quote Blier himself: "These data indicate that venlafaxine, even at a dose that is four times higher than its minimal effective dose in depression (i.e. 75 mg/d), didnot appear to inhibit the NE reuptake process in the present study in healthy volunteers (1).

Note that I quote Blier because that group of researchers were the ones who claimed in 1998 (2) that, "This dual action, combined with the differential potency of venlafaxine, might constitute the biological substratum responsible for its apparent unique clinical efficacy in major depression". And that at a time when any evidence for superior effect was so slight as to exist only in the mind of a fevered over-optimistic ingénue.

Blier advanced this fanciful notion further, in a paper entitled'Possible neurobiological mechanisms underlying faster onset of antidepressant action' (3). The old chestnut of faster onset of antidepressant action has been used to flog most new ADs from the year dot.

I suppose he could defend him-self by saying he did include the weasel-words 'apparent' & 'possible'.

Venlafaxine is extremely weak as an NRI, and desvenlafaxine is weaker still. It is one thousand times weaker than desipramine as an NRI in 'test tube' assays (i.e. '*in vitro*') and more than 100 times less potent than amitriptyline or nortriptyline. This clearly indicates that it is meaningless to classify it as an SNRI.

Two findings go against the dual action notion:

1. Its' *in vitro* potency as an NRI is so weak that 'on paper' we would not expect it to have any relevant noradrenergic activity.
2. It has a no effect in reducing the hypertensive response to tyramine, indicating it does not act as an NRI *in vivo* in humans.

3. Also, incubation of human fibroblasts with desipramine or reboxetine, but not with venlafaxine, caused a highly significant reduction in nuclear CREB-P; which suggests desipramine and reboxetine (NRIs), may exert direct noradrenergic effects beyond beta adrenoceptors, but not venlafaxine .
   All this indicates that neither venlafaxine, nor desvenlafaxine (Pristiq) are clinically significant noradrenalin reuptake inhibitors (NRI) in humans.
   As I have commented previously the ratio of venlafaxine's potencies for 5-HT vs NA is much more unequal than is, for instance, the ratio of sertraline's potency for 5-HT vs DA. What that means is that it is far more justified to regard sertraline as a serotonin and dopamine reuptake inhibitor (SDRI) than it is to regard venlafaxine as an SNRI. So, for sertraline, increasing the dose to several hundred milligrams *might* be justified because it could achieve a significant degree of dopamine reuptake inhibition.
   Once one has achieved a therapeutic level of SRI (75 mg for venlafaxine), increasing the dose further is only likely to give rise to more side effects in other systems, like the GI & GU tracts, for instance, or even more severe adverse effects. That is one of the reasons why it is now generally held that increasing the dose of any of the SSRIs above the proven clinically effective dose for 80+% inhibition of SERT is not only pointless, but likely to be counter-productive.
   We know already that Venlafaxine is an SRI that has greater side-effects, withdrawal effects, and toxicity and any of the other SRIs. Therefore, to increase its dose to 4 times the recommended level for its SRI effect, whilst still failing to achieve an NRI effect, is just plain stupid.
   I would be prepared to make a large wager that says that the pharmacologists in the drug company who developed this drug would have thought it was a complete waste of time pushing it as a supposed SNRI. I can only suppose it was a marketing decision driven by desperation, perhaps they had no other new drug candidates that the marketing dept. thought were goers.
   The truth would be interesting, but a wise man said (I cannot recall who) "If my hands were full of truths I should be careful of opening them."
   Now I recall, partly. It was in French, so something like 'Si les mains sont repliens de verite, je me garderais de les ouvrir'. I still cannot recall who said it. Rochefoucault perhaps? Does anyone know?

NRI potency (Affinity Ki nmol)

Desipramine 1 most potent
Nortriptyline 10
Amitriptyline 50
Fluoxetine 240
Venlafaxine >1000
Desvenlafaxine >1000
Explanation of the above numbers is hardly needed.

And it is more toxic

Venlafaxine has greater toxicity in over-dose (and more severe withdrawal effects) than any other new antidepressant, as well as some of the 'old' TCAs (5-7). The slow release formulation may cause even more problems and toxicity following over-dose, even after activated charcoal and whole-bowel irrigation.

Venlafaxine in overdose is pro-convulsant and cardiotoxic, more than TCAs (whereas SSRIs are much less so) and more likely to cause serotonin toxicity (serotonin syndrome) than either TCAs or SSRIs (6, 8).

The (sometimes) severe withdrawal effects seem to be characterised by: headache, nausea, fatigue, dizziness and dysphoria. In some cases, even slow tapering has not helped; it is not likely that the slow release preparation will make much difference to withdrawal effects. As with serotonin reuptake inhibitors it is probable that dose and duration of treatment will be relevant factors, i.e. high doses and longer time on treatment leads to greater likelihood of withdrawal symptoms.

Venlafaxine's toxicity in over-dose and its similarities to the narcotic analgesic tramadol warrant monitoring and caution; although data suggests Venlafaxine does not have significant affinity at opiate receptors (9).

I see no point in wasting any more space or time discussing this drug: it is one of many examples of how researchers and doctors have deceived themselves, and then deceived others, with naïve optimism and wild over-extrapolation from minimal data (see this commentary).

References

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