PsychoTropical Commentaries 2021:4;1-11

Vortioxetine: Hope or hype

Abstract

Vortioxetine is another in a series of 'new' anti-depressants with serotonin-related mechanisms and 'faster-better' AD action. In this instance it is promoted with the new catchphrase 'multi-modal'. Evidence for usefully novel action or efficacy via these 'multi-modal' actions remains speculative, though the drug has now been in use for 10 years. Even the (lesser) potency of its 'principal' pharmacological action — of serotonin reuptake inhibition — remains inadequately verified and replicated; and its SRI potency relative to other drugs is uncertain.

The quality of the clinical trials assessing its actions have been judged as poor by most commentators. Its efficacy, and its place in a rational treatment algorithm, remains inadequately defined. Claims and opinions presently rest on unreplicated and insubstantive evidence, even a decade after its approval.

Multi-modal or multi-muddle?

> 'A triumph of hope over experience' Samuel Johnson

Vortioxetine (Lu AA21004) was FDA approved in Sept. 2013 for MDD.

The brand name Brintellix was changed to Trintellix in June 2016 in some countries. Also remember, if doing searches for pharmacological data on this drug to include this code name for it, Lu AA21004, in the search; otherwise, you will miss the early literature that does not mention the name vortioxetine.

Is it commonly regarded as an 'SRI'? Those marketing it are emphasising its putative action as a 'multi-modal' anti-depressant: I expect the representatives of the company are coached to emphasise the 'multi-modal' point of difference, rather than the fact that it is an SRI.

Boswell reports Dr Samuel Johnson to have said, after an acquaintance rushed into a second marriage:

> 'A second marriage is a triumph of hope over experience'.
> Statistically, second, third, and subsequent marriages are shorter.

Well, this is something like the 10th SRI-type drug; what would Samuel Johnson say about the magnitude of the 'hope dimension' in this situation!

It is difficult to know what impression doctors are getting of this drug: the way it has been presented will lead some to assume that it is not an SRI. One paper is titled 'Vortioxetine versus SSRIs…' which infers that it is different and not an SRI. I have already seen it being co-prescribed with an MAOI. I suspect the promotion and advertising is downplaying that aspect of its action because the selling-point is 'multi-modal' action on other receptors: that practice creates a risky confusion.

One of the early 'Lundbeck' papers [1] states — one can almost feel the wide-eyed and breathless excitement — I hesitate to label it as naïve, however, it is certainly optimistic:

> 'Recently, the term multimodal was coined for compounds that combine at least two separate pharmacological modes of action that complement each other in terms of efficacy … 5-HT3 receptors … blockade i) increases pyramidal neuron activity by removing 5-HT3 receptor-mediated excitation of GABA interneurons, and ii) augments SSRI effects on extracellular 5-HT.'

Most 'Lundbeck' writings say 'Vortioxetine **is** a multimodal antidepressant': when that statement was first made the evidence was, how might one put it?

Address for correspondence. Dr Ken Gillman: kg@matilda.net.au

not well-established? even speculative? The evidence is even now less than convincing. Different receptors have been put forward as candidates for the special properties at various times (1A, 1B, 2A, 2C, 3, and 7). After 10 years there are still remarkably few substantive studies on this drug and none that I can find trialling it in melancholic depression, which is really the acid test of whether it is a 'proper' antidepressant.

'Multi-modal'

There are certainly plenty of serotonin receptors to choose from, indeed a veritable smorgasbord, various of which have been postulated to be of relevance for Vortioxetine, beyond its (weak) hSERT antagonism — viz. 5HT1A, 5HT1B, 5HT1D, 5HT2A, 5HT2C, 5HT3, and 5HT7 receptors [2, 3].

The definition of multi-modal is given as affecting 'two or more mechanisms', and by this definition both the TCAs and mirtazapine would be considered 'multimodal', and they were introduced 50 years ago, at a time when I was busier enjoying the company of nurses than doing psychopharmacology! As Shakespeare said, 'there is nothing new under the sun'.

Different receptors, especially those feedback receptors adjacent to the synapse, have different sensitivities to different concentrations of the neurotransmitter, and also change their sensitivity (receptor sub-sensitivity or super-sensitivity) following constant stimulation, to different extents, and over different time-frames.

That means the interpretation of a 'multi-modal' drug's relative potencies at different receptors, and the net effect it may have after chronic administration, is hard to fathom, and currently impossible to predict.

Until there is some technique to give definite indications of what the longer-term effects of such drugs are on neuro-physiology and neuro-transmission, all notions concerning their final effects are still firmly in the realm of speculation.

Those who are interested in a detailed analysis with a more positive spin, from a Lundbeck team member, should look at the detailed data in Sanchez et al. [4].

Wearing why my well-worn cynics hat, I would immediately say that; 1) it is not well established that vortioxetine is an effective AD, and 2) it is certainly not established, if it does work, that these 'multimodal mechanisms' are relevant to that action — a devil's advocate might say instead, 'this is another dirty drug with multiple receptor affinities, the effect of which is unknown'.

Incidentally, some readers may appreciate that I have pointed out elsewhere that the trend for selective or specific drugs, over the last few decades, has got more to do with marketing than pharmacology. The most effective drugs are dirty drugs with multiple mechanisms of action.

Similar drugs (that have putative effects on various feedback and modulatory receptors) have been developed previously and they have mostly disappeared into the abyss, usually without any papers about their clinical use being published; or if they have got into clinical use, they have fallen out of use quickly. That is because they generally failed to show sufficient useful effects. I have discussed this aspect of the failure of drugs that are supposed to act at 'modulatory' presynaptic receptors in another commentary which outlines the (fairy) story of mianserin, mirtazapine and the 'serenics'.

Dr Ken Gillman: ken.psychotropical@gmail.com

The 5-HT receptor family: A glimpse

The 5-HT1 receptors: five types; 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F receptors.

The 5-HT2: three types; 5-HT2A, 5-HT2B and 5-HT2C receptors.

And then there are the **5-HT3, 5-HT4, 5-HT5, 5-HT6, 5-HT7**.

That is 13 in all.

If you can feel a headache coming on you are not alone.

They are all G-protein-coupled, except for 5-HT3, which is a ligand-gated ion channel.

This complex system has been reviewed recently [5, 6]. It is complicated and complex and well beyond the scope of this commentary (or this author), however I will give a taste of the Okaty review with a series of excerpts from it [5]:

> Glutamate, the recent application of optogenetics has yielded *in vivo* evidence suggesting that subsets of 5-HT neurons co-release glutamate. Co-expression of various neuropeptides and 5-HT has been suggested by many studies.
> It has also been proposed that cytosolic 5-HT may directly diffuse across the cell membrane under certain conditions, an unusual non-exocytotic mode of release potentially relevant to 5-HT neuron auto-inhibition, or that 5-HT may be released from dendrites in an action-potential-independent manner.
> The differential distribution of SERT regionally and by axon type also raises the possibility that the extent to which 5-HT diffuses through the extracellular space may be region-dependent, varying with the relative abundance of SERT.
> Although here we focus on studies that have assayed exploration and coping behaviours, territorial aggression, and respiratory control as illustrative examples, many other cognitive, behavioural and physiological processes broadly associated with the 5-HT system — such as sociability, memory, reward (recently reviewed by, sleep and feeding — are also probably supported by discrete 5-HT neuron subtypes, as suggested by several recent studies not discussed here.
> Conclusion: the 5-HTergic neuronal system probably operates as a conglomeration of subsystems rather than as a homogeneous entity … the 5-HT neuronal system is modular and speaks to a complex organization that extends well beyond anatomical subdivisions.
> By identifying the key 5-HT neuron subtypes related to a given functional deficit and the set of druggable targets expressed by these cells and their downstream partners, we will be better positioned to develop compounds that modify the activity of functionally specialized 5-HTergic brain circuits rather than targeting the multifunctional 5-HT neuron system as a whole.

That is what I call complex. But there is a chink of light coming through the door which suggests it is theoretically reasonable to postulate that something, such as activity at 5-HT1B receptors, might have some special effect, like enhancing cognitive function. A 'precedent' is that it is established that ondansetron antagonises 5HT2C receptors and attenuates the feeling of nausea. If we had comparable replicated receptor affinity data that might enable an inference about vortioxetine — perhaps it is capable of increasing nausea? I am not dismissing notions that these various receptors may be of functional relevance, but I do require solid (replicated) evidence that they have functional relevance, in the long term, not just in the short term.

The 5-HT1B receptors are widely distributed throughout the brain and predominantly located on axon terminals where they serve as auto-receptors on serotonergic neurons, and hetero-receptors on non-serotonergic neurons. There is probably consequential drug occupancy of 5-HT1B receptors at the therapeutically administered doses of vortioxetine.

Dr Ken Gillman: ken.psychotropical@gmail.com

There is a paucity of sufficiently selective ligands to identify the relative contribution of these multiple serotonin receptors to putative physiological or clinical effects.

And here is something you really need to know: Vortioxetine reduces marble-burying behavior in mice [7]. If you want to get 'one up' on some smart-arse at a conference, ask what they think the significance of that finding might be!

Vortioxetine: *in vitro* hSERT potency

SRI potency (hSERT) is given as 1.6 nm [1], but this appears to be the only value in the literature: it definitely requires replication and direct comparison with a range of other SRIs.

The Bang-Andersen paper references, for this hSERT value: 'External data obtained from MDS Pharmaservices.' No details about the assay are given, that is not usual practice in such scientific papers — this means the only value we have is 'semi-anonymous'. They did the 1B values 'in house'.

We need to remind ourselves that such *in vitro* data shows around tenfold variability between different laboratories (sometimes more) — that makes comparison of these values (hSERT and 5HT1B) of uncertain meaning because the values were done by different laboratories — neither are they usefully comparable with values for other drugs.

There are no independent assays I can find replicating these values, which means one must exercise even more caution when comparing them with other SSRIs or SNRIs.

For those not conversant with this sort of data, what this really means is that the affinity data for this drug is of little value and not able to be compared with anything else.

> NB. Various sources use the equivalent terms **hSERT** (human serotonin transporter) which is the re-uptake mechanism, and **5HTT**, which stands for the 5HT transporter, which is the same thing. The small 'h' proceeding it denotes it is the human transporter, rather than the one in rats or monkeys. Many papers and other sources use these two terms interchangeably and inconsistently (mea culpa), you will just have to get used to that.

Human platelet 5-HT depletion

Younger readers may have forgotten that the human platelet 5HT level model of SRI potency was the only one available in the last millennium, prior to *in vitro* HCR receptor assays. Potent serotonin reuptake inhibitors cause considerable depletion of platelet 5HT [8]; e.g., paroxetine decreased platelet serotonin concentrations by -83% [9] — direct comparisons would be necessary for a more accurate picture. Nevertheless, it looks like vortioxetine produces a smaller decrease [10-12]. That is in keeping with its lower brain SERT occupancy revealed by PET studies, below.

PET studies

Stenkrona et al. was a study in humans that was independent, but it did receive a little funding from Lundbeck.

Yang's study involved five female rhesus monkeys and looked at hSERT and 5HT2A & 1B binding.

Areberg's early Lundbeck study [13] (subjects, 46 healthy males, no females) appears not to be given much prominence in subsequent papers.

I expect most drug companies do not encourage or ask too many research questions once they have got FDA/EMA approval. That risks producing 'inconvenient' data that may damage credibility and sales. It is the equivalent of the legal maxim that you do not ask a question to which you do not already know the answer.

Dr Ken Gillman: ken.psychotropical@gmail.com

PET: post-synaptic receptors

The observations by Yang (in monkeys) suggest that vortioxetine binds to the 5-HT1B receptor at clinically relevant doses [14]; whether it has relevant actions and other subtypes remains uncertain or doubtful. **They failed to show significant occupancy at the 2A receptor**.

PET: serotonin transporter (hSERT)

As might be expected from its weak effect from the above measurements of platelets, and human *in vitro* transporter potency, its effect on the transporter in PET studies appears also to be weak.

Areberg: this early Lundbeck study in healthy humans (2012) — published using its codename Lu AA21004, not the name vortioxetine*, therefore will be missed by a lot of people when they search — had some four dozen subjects [13]: it showed a plasma level of 20-40 ng/ml was needed for 80% 5-HTT occupancy. A 5 mg dose produced around 50% occupancy.

> *It is relevant to note that the paper the previous year, announcing the discovery of the compound (using its complete chemical name), had the name vortioxetine in brackets. This name was obviously attached to the compound before the Areberg paper, yet they choose not to use it anywhere in the paper. You might conclude that they were deliberately trying to reduce the visibility of these (unconvincing) results in the databases; but I would not dream of suggesting that.

Stenkrona concluded (human study): 'A dose of 20–30 mg per day [approx. plasma levels 20-30 ng/mL, see below] is suggested to give 'clinically relevant' occupancy [only 50%] at the 5-HTT'. Note, this was measured at the time of peak plasma levels — 5-HTT occupancy ranged from only 2% (2.5 mg day 1) to 97% with 60 mg day — which is three times the max recommended dose [15].

NB. 20 mg per day produces a mean plasma level of ~30ng/mL, or, from Matsuno's data [16] 7 ng/ml.

Yang, likewise, found the occupancy of SERT with 5 or 10 mg/kg/day was only ~50% [14] — other SSRIs are typically 85 to 90% at usual therapeutic doses. However, these were monkeys, and the anaesthetic agent was ketamine, hardly a felicitous choice one might think.

Bang-Andersen (Lundbeck) [1] 'Vortioxetine is a new multi-modal drug against major depressive disorder with **high affinity** for a range of different serotonergic targets in the CNS'. Presenting findings of animal studies of uncertain validity when extrapolated to humans, they speculate freely concerning the possible effects on receptor subtypes such as 5-HT1B and 5-HT7 in relation to how it might affect synaptic serotonin compared to SSRIs — however whether any changes remain relevant under chronic treatment in humans is unknown.

I have highlighted the term '**high affinity'** above, because it is frequently used, one presumes to give the impression that it must be clinically relevant. **Clinical relevance has not been established**. Indeed, extrapolating from other sources and data, I consider clinical relevance to be doubtful — many drugs require single figure nanomolar potency, or less, to have a clinical effect. Indeed, one could argue that every word in that title is misleading — it is inappropriate to announce the results in the title; we were always taught that that was presumptive and wrong.

Add to that the variation in plasma levels related to 2D6 status etc. and it is clear that neither functional inhibition of 5-HTT, nor any receptor, can be expected to have been achieved in a significant proportion of patients included in the published antidepressant trials.

Dr Ken Gillman: ken.psychotropical@gmail.com

Cytochrome P4502D6 metabolism

It is said to be metabolised largely by P4502D6 and is subject to considerable variation in its rate of inactivation (it has no active metabolite) and therefore the half-life varies (depending on 2D6 genetic status, or inhibition by other drugs), but is around 60 hours. It will take at least seven days to approximate steady state.

The plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolizers than in extensive metabolizers (as stated in SPC). I cannot see the data indicating what the extreme range of plasma level and half-life was in patients who were extensive vs. slow metabolisers [17], one would expect it to be greater (see Matsuno below).

It may well be that the optimal therapeutic window for vortioxetine's effects (which may involve partial or inverse agonism at particular concentrations) is narrow, therefore it is going to be difficult to steer that narrow path through to discovering what the ideal dosage level is in each individual patient when there are such variations in metabolism. Since we do not have any clinical index of the effect of the drug on 5HTIB receptors, or any other receptors, that is going to be possible only via clairvoyance.

Plasma levels

Plasma levels, C max (ng/mL), showed linear pharmacokinetics at doses of 5-60 mg, they were, at 5 mg 9 ng/mL, at 10 mg 18 ng/mL, and at 20 mg 33 ng/mL [18]. The SPC does not suggest routine CYP2D6 genotyping before starting vortioxetine treatment, but says a dose adjustment may be considered, **with a maximum recommended dose of 10 mg for known CYP2D6 PMs**. The differences in levels between slow and fast metabolisers appear to be only around two-fold, but the data showing the full range of distribution is not presented [17]: two-fold is less than I would expect and may suggest that other P450 enzymes play a significant part in its breakdown, thus minimising the effect of 2D6 variation.

Matsuno's study had >100 subjects; in steady state **10 mg gave a mean level of ~20ng/ml** [16]. **Half-life varied from 34-113 hrs**.

The concentration is given as 100 nM which is equal 30 ng/ml of Vortioxetine (well 29.8 to be precise — but since we're dealing in units which are not accurate to that number of decimal places we might as well call it 30).

Bupropion (a 2D6 inhibitor) approximately doubled vortioxetine exposure with AUC x 2.3, which is in step with the above data.

Clinical efficacy

Anxiety (GAD)

I am on record as describing the last few decades of development of depressant drugs as 'the anodyne era', meaning drugs that cause little harm, but do little good either — as far as anxiety is concerned; this drug seems to have taken this concept to a new level, where this meta-analysis [19, 20] seems to show neither detectable good, nor any detectable harm. It is a pharmacological mantra that 'a drug with no side-effects has no effects at all': even if that is not quite exact, it is useful to remember.

Anyone at all familiar with my writing will appreciate that we all take it as a given that there is, or there will soon be, a meta-analysis that shows it has some (slight) benefit.

Dr Ken Gillman: ken.psychotropical@gmail.com

Depression

The Cochrane review of 2017 [21] concluded: 'The place of vortioxetine in the treatment of acute depression is unclear. Our analyses showed vortioxetine may be more effective than placebo in terms of response, remission and depressive symptoms, but the clinical relevance of these effects is uncertain.' De Giorgi's comment was equally negative [22].

The Inoue study [23] illustrates why: in this large RCT in depression MADRS score was 3 pts less than placebo, after 8 weeks. The authors describe this as a 'robust response'. That comment cannot be considered as well grounded. If you wish to see for yourself how a clinically unimpressive change in symptoms will alter the score by three points just look at this link below and do an imaginary rating scale yourself.

https://psychology-tools.com/test/montgomery-asberg-depression-rating-scale

I would put it this way; if you were paying $400 a month for this treatment (plus consultation fees to see a doctor) you would not consider it value for money — indeed you might even consider taking action against the company under consumer protection legislation for a defective product.

Cognitive effect

There seems to be evidence of some benefit in cognitive effect [24-26], but, as always, consolidation and replication of this putative effect is required.

Medicines agencies (EMA/FDA)

Their 'summary of product characteristics' (**SPCs**) often referred to as the product information (**PI**) and are gathered and published, e.g., the 'FDA' version as the physicians' desk reference, the e-versions as 'Prescriber's Digital Reference (PDR)' or the UK version as 'MIMS'. These are written by the company personnel (including lawyers and marketing personnel), but not by a clinical pharmacologist. They contain content influenced by medico-legal, and other, considerations; they do contain some useful information.

They are not clinical pharmacology documents.

Therefore, it is important for practising clinicians to appreciate the actions taken based on the information in these documents may produce poor outcomes for individual patients; for instance, drug interaction warnings are unnecessarily cautious, or even totally inappropriate.

The SPC states: 'In humans, **two positron emission tomography (PET) studies** have been conducted using 5-HT transporter ligands (11C-MADAM or 11C-DASB) to quantify the 5-HT transporter occupancy in the brain across different dose levels [NB they provide no references] cf. Areberg study. The mean 5-HT transporter occupancy in the raphe nuclei was approximately 50% at 5 mg/day, 65% at 10 mg/day and increased to above 80% at 20 mg/day.'

That is putting a positive spin on the data. I suggest the following information adds usefully to the picture:

Stenkrona et al. stated [15]: '**A dose of 20-30 mg per day is suggested to give clinically relevant occupancy at the 5-HTT'**… doses of 20–30mg are recommended, to reach a 5-HTT occupancy of about 70-80%' — and that is marginal occupancy to justify being considered as 'clinically relevant' when it is usually considered something closer to 90% is required [27]. Indeed, Meyer suggests in that paper; 'Previous work has shown 80% serotonin transporter (5-HTT) occupancy to be a consistent finding at the

Dr Ken Gillman: ken.psychotropical@gmail.com

minimum therapeutic dose during selective serotonin reuptake inhibitor (SSRI) treatment.'

Thus, by these criteria, vortioxetine may not achieve clinically effective action at the 5-HTT, unless doses higher than the maximum recommended dose of 20 mg daily are used.

In their 2020 update: the EMA say: a causal relationship between vortioxetine and insomnia is at least a reasonable possibility, … a causal relationship between vortioxetine and aggression and agitation is at least a reasonable possibility, … a causal relationship between vortioxetine and glaucoma is at least a reasonable possibility.

Reviews: the dreaded plague of meta-analyses

I commented previously that the eminent Harvard professor John Ioannidis had made the observation that there were more meta-analyses of antidepressants than actual original studies of them [28]; this sentiment was repeated by De Giorgi from Oxford [22] in his comment on the Cochrane review of vortioxetine. He stated: 'the clinical significance of these findings is difficult to interpret because of the very poor quality of the evidence supporting them'. Not just 'poor', de Giorgi says, but 'very poor'.

Also 'comparing vortioxetine with…SNRIs the quality of the evidence was extremely low'. And he is a Cochrane centre reviewer not just anybody.

That is representative of similar statements made by other commentators.

When one considers that this RCT lark has been going on for 50 years and this is the best statement that can be made about the latest rash of trials of this latest antidepressant, that might be interpreted as reflecting poorly indeed on academic psychiatry, which is failing to guide clinicians in relation to what might be the most reasonable treatments to employ.

Competent and experienced physicians may make better decisions about what is best for **individual patients** because of their bedside clinical experience — they are well advised to exhibit caution when extrapolating the measly meagre results of these trials.

Remember that RCTs are inevitably made up of an aetiologically heterogenous group whose responses cannot be extrapolated to individuals who suffer biological depression, nor to the general population of 'patients'. That is the great, even fatal, inadequacy of RCT methodology.

If I was an academic professor who had played a role in these sorts of trials, I would be hanging my head in shame. Although I suppose a riposte to that might be that academic psychiatrists no longer participate in trials; they merely sacrifice their departments' patients to CROs which conduct the trials; they have little direct involvement, except putting their names at the top of the resultant papers, after scanning the ghost-written text.

It is time that the hegemony of RCTs was ended.

Inferences and interpretations

Vortioxetine has weak, possibly sub-therapeutic, serotonin-related effects in the platelet model, in the *in vitro* hSERT assays, and in PET hSERT studies.

Its effectiveness via the mechanism of 5HTT inhibition is uncertain and appears to be weaker than the existing SSRIs, unless doses well beyond the recommended maximum of 20 mg are used, which makes it expensive.

It probably has an effect on the 5HT1B receptor; whether that is sustained in the medium to long term is unknown. Whether other receptors are engaged to a clinically meaningful extent remains uncertain and in the realm of speculation.

Dr Ken Gillman: ken.psychotropical@gmail.com

I am surprised — and concerned — that after all this time there is not an extensive body of data comparing the affinities of this drug, at the full array of receptors, to a range of other drugs.

By now there should be extensive data replicated by independent laboratories. I am unable to explain why this is the case for almost all drugs that I have previously reviewed and yet it is not the case for this drug. I was so surprised that I contacted the staff at the PDSP database, which maintains extensive documentation of this kind of data, to check whether they were aware of any other data: they are not — they have undertaken to look into this. They do independent receptor affinity assays, so perhaps they can add to the data themselves before too long.

It does appear to have greater serotonin elevating effects in micro-dialysis studies than do SSRIs, at least in short-term studies, in rats. Whether such effects are sustained during long-term treatment in humans is an uncertain extrapolation and a moot point. Such studies need to be strengthened and replicated.

The clinical trial evidence of its effectiveness in depression remains 'under exploration' and its usefulness in relation to other existing antidepressants is undefined. There are no useful studies of its effects in serious melancholic depression, which is the acid test of a truly effective antidepressant.

There is near-universal agreement that it is **ineffective** in GAD.

It is hard to see what its place might be in a treatment algorithm. I suggest it should only be used with careful documentation of the outcomes by specialists.

I have always been of the opinion that drugs such as this should only be available to specialists, at least until the benefit in particular groups, in longer-term treatment, can be more critically assessed in a real-world environment.

In the brief and dismissive note that I wrote about this drug five years ago (not in menu any more, but available here) **I concluded with a yawn, and suggested it was just another SRI** — *plus ça change, plus c'est la même chose.* Five years on and we can say the verdict may be even less favourable than that, because it is an unproven SRI that may be less effective than existing drugs, not more effective.

Perhaps the relative paucity of pharmacological and PET data is because Lundbeck are being shrewd and avoiding the 'sunk cost fallacy', because they have concluded this drug is never going to be a 'blockbuster'; therefore, there is no purpose in funding further work and pouring good money after bad.

It is difficult to find much convincingly positive to say about this drug, I will conclude by mentioning that one or two people I have spoken to feel it can be a useful combined with an SRI.

Caveat Utilitor.

References

1. Bang-Andersen, B., et al., *Discovery of (Vortioxetine) 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder.* J Med Chem, 2011. **54**(9): p. 3206-21.

2. Stahl, S.M., *Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): blocking 5HT3 receptors enhances release of serotonin, norepinephrine, and acetylcholine.* CNS Spectr, 2015. **20**(5): p. 455-9.

3. Mork, A., et al., *Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder.* J Pharmacol Exp Ther, 2012. **340**(3): p. 666-75.

Dr Ken Gillman: ken.psychotropical@gmail.com

4. Sanchez, C., K.E. Asin, and F. Artigas, *Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data.* Pharmacol Ther, 2015. **145**: p. 43-57.

5. Okaty, B.W., K.G. Commons, and S.M. Dymecki, *Embracing diversity in the 5-HT neuronal system.* Nat Rev Neurosci, 2019. **20**(7): p. 397-424.

6. Hoyer, D., *Serotonin receptors nomenclature*, in *The Serotonin System*. 2019, Elsevier. p. 63-93.

7. Witt, N.A., et al., *Vortioxetine Reduces Marble Burying but Only Transiently Enhances Social Interaction Preference in Adult Male BTBR T(+)Itpr3(tf)/J Mice.* ACS Chem Neurosci, 2019. **10**(10): p. 4319-4327.

8. Lingjaerde, O., *From clomipramine to mianserin: therapeutic relevance of interactions with serotonin uptake and storage, as studied in the blood platelet model.* Acta Psychiatr Scand Suppl, 1985. **320**: p. 10-9.

9. Hergovich, N., et al., *Paroxetine decreases platelet serotonin storage and platelet function in human beings.* Clin Pharmacol Ther, 2000. **68**(4): p. 435-42.

10. Dvojkovic, A., et al., *Effect of vortioxetine vs. escitalopram on plasma BDNF and platelet serotonin in depressed patients.* Prog Neuropsychopharmacol Biol Psychiatry, 2021. **105**: p. 110016.

11. Sagud, M., et al., *A prospective, longitudinal study of platelet serotonin and plasma brain-derived neurotrophic factor concentrations in major depression: effects of vortioxetine treatment.* Psychopharmacology (Berl), 2016. **233**(17): p. 3259-67.

12. Zhuang, X., et al., *Platelet serotonin and serotonin transporter as peripheral surrogates in depression and anxiety patients.* Eur J Pharmacol, 2018. **834**: p. 213-220.

13. Areberg, J., et al., *Occupancy of the serotonin transporter after administration of Lu AA21004 and its relation to plasma concentration in healthy subjects.* Basic Clin Pharmacol Toxicol, 2012. **110**(4): p. 401-4.

14. Yang, K.C., et al., *Effect of clinically relevant doses of vortioxetine and citalopram on serotonergic PET markers in the nonhuman primate brain.* Neuropsychopharmacology, 2019. **44**(10): p. 1706-1713.

15. Stenkrona, P., C. Halldin, and J. Lundberg, *5-HTT and 5-HT1A receptor occupancy of the novel substance vortioxetine (Lu AA21004). A PET study in control subjects.* European Neuropsychopharmacology, 2013. **23**(10): p. 1190-1198.

16. Matsuno, K., et al., *Pharmacokinetics, Safety, and Tolerability of Vortioxetine Following Single- and Multiple-Dose Administration in Healthy Japanese Adults.* Clin Pharmacol Drug Dev, 2018. **7**(3): p. 319-331.

17. Areberg, J., et al., *Population pharmacokinetic meta-analysis of vortioxetine in healthy individuals.* Basic Clin Pharmacol Toxicol, 2014. **115**(6): p. 552-9.

18. Chen, G., et al., *Vortioxetine: Clinical Pharmacokinetics and Drug Interactions.* Clin Pharmacokinet, 2018. **57**(6): p. 673-686.

19. Qin, B., et al., *Vortioxetine treatment for generalised anxiety disorder: a meta-analysis of anxiety, quality of life and safety outcomes.* BMJ Open, 2019. **9**(11): p. e033161.

20. Kong, W., et al., *Comparative Remission Rates and Tolerability of Drugs for Generalised Anxiety Disorder: A Systematic Review and Network Meta-analysis of Double-Blind Randomized Controlled Trials.* Front Pharmacol, 2020. **11**: p. 580858.

21. Koesters, M., et al., *Vortioxetine for depression in adults.* Cochrane Database Syst Rev, 2017. **7**: p. CD011520.

22. De Giorgi, R., *Vortioxetine for depression: the evidence for its current use in the UK: COMMENTARY ON... COCHRANE CORNER.* BJPsych Advances, 2019. **25**(1): p. 3-6.

23. Inoue, T., et al., *Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of vortioxetine in Japanese patients with major depressive disorder.* Psychiatry Clin Neurosci, 2020. **74**(2): p. 140-148.

Dr Ken Gillman: ken.psychotropical@gmail.com

24. Cumbo, E., et al., *Treatment Effects of Vortioxetine on Cognitive Functions in Mild Alzheimer's Disease Patients with Depressive Symptoms: A 12 Month, Open-Label, Observational Study.* J Prev Alzheimers Dis, 2019. **6**(3): p. 192-197.

25. Bennabi, D., E. Haffen, and V. Van Waes, *Vortioxetine for Cognitive Enhancement in Major Depression: From Animal Models to Clinical Research.* Front Psychiatry, 2019. **10**: p. 771.

26. Nierenberg, A.A., H. Loft, and C.K. Olsen, *Treatment effects on residual cognitive symptoms among partially or fully remitted patients with major depressive disorder: A randomized, double-blinded, exploratory study with vortioxetine.* J Affect Disord, 2019. **250**: p. 35-42.

27. Voineskos, A.N., et al., *Serotonin transporter occupancy of high-dose selective serotonin reuptake inhibitors during major depressive disorder measured with [11C]DASB positron emission tomography.* Psychopharmacology (Berl), 2007. **193**(4): p. 539-45.

28. Ioannidis, J.P., *The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses.* Milbank Q, 2016. **94**(3): p. 485-514.

Dr Ken Gillman: ken.psychotropical@gmail.com

Filename: 1 Vortioxetine- hope or hype.docx
Directory: /Users/kengillman1/Library/Containers/com.microsoft.Word/Data/Documents
Template: /Users/kengillman1/Library/Group Containers/UBF8T346G9.Office/User Content.localized/Templates.localized/Commentary_template.dotx
Title: Serotonin toxicity (serotonin syndrome)
Subject:
Author: Ken Gillman
Keywords:
Comments:
Creation Date: 24/04/2021 18:51:00
Change Number: 2
Last Saved On: 24/04/2021 18:51:00
Last Saved By: Ken Gillman
Total Editing Time: 0 Minutes
Last Printed On: 24/04/2021 18:51:00
As of Last Complete Printing
Number of Pages: 11
Number of Words: 8,680 (approx.)
Number of Characters: 49,478 (approx.)