

Vortioxetine Retrospective Study in MDD: A Proposal for Outcome Analysis by the Treating Psychiatrist

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To cite this article:

Mohammed Allam. Vortioxetine Retrospective Study in MDD: A Proposal for Outcome Analysis by the Treating Psychiatrist. *American Journal of Psychiatry and Neuroscience*. Vol. 10, No. 4, 2022, pp. 182-187. doi: 10.11648/j.ajpn.20221004.14

Received: October 17, 2022; **Accepted:** November 2, 2022; **Published:** November 16, 2022

Abstract: Methodology of clinical trials is a major determinant to their level of evidenced based medicine. Prospective longitudinal trials such as randomized controlled trials (RCT) have significant position in the hierarchy of evidenced based practice. One of the shortcomings of the RCT could be in the inclusion and exclusion criteria unlike real life settings with clinical decisions made by a psychiatrist due to clinical necessity and not for a protocol necessity or earlier deadlines for data collection. Retrospective analysis gives time to see consistent response over time in real life settings not only six to eight weeks' response to an antidepressant. Multicenter retrospective analyses by different research groups involving the same antidepressant have the shortcomings of including different cut off points, different inclusion and exclusion criteria or different statistical tools causing challenges in the extrapolation of data. Retrospective interpretation of notes or tools used by different colleagues could be challenging due to interrater reliability issues even with same tool used by different colleagues with different levels of training on/agreement on score allocations for particular patients' responses. Interpreting what others meant by their notes is another challenge. Questionnaires filled by patients alone in waiting rooms to save time are liable to mistakes and misinterpretations. The aim of this paper is to propose a retrospective naturalistic study to be conducted by the same treating psychiatrist for patients treated with Vortioxetine as a mono/combination therapy for at least a year trying to reduce the interrater errors with the suggested aid in appendixes included.

Keywords: Vortioxetine, Retrospective Analysis, Naturalistic Retrospective Analysis, Antidepressant Therapy

1. Introduction

1.1. Issues with Randomized Controlled Trials RCT

Antidepressants effectiveness in major depressive disorder (MDD) is still questioned because the extrapolation of randomized controlled trial (RCT) results to "real life" settings is problematic [1]. Mood disorder fits a bio-psychosocial model, where therapeutic benefits could result from the context in which the study is performed [2, 15, 16, 17]. The National Institute for Clinical Excellence (NICE) guidelines on the treatment and management of depression in adults (NICE, 2020) advise caution when considering the application of RCTs results in routine practice, and suggests that better ways of assessing effectiveness have yet to be developed [1]. RCTs typically last 6–8 weeks whereas it is recommended that an antidepressant treatment be continued for at least six months after remission of the episode of depression [3].

We cannot expect antidepressants to perform like penicillin where we can count the bacilli and know if it is working [4].

1.2. Issues with the Depression Measurement Tools

The assumption that depression rating scales measure one underlying depression construct and therefore patients who score similarly on the composite have a similar 'severity' of depression and are comparable to one another, this assumption is unfounded [5]. This may suggest that whilst different classes of antidepressants might, overall, be equally effective at achieving remission, they do so by improving different symptoms [6].

1.3. Issues with Retrospective Studies

Disadvantages of retrospective studies

Inferior level of evidence compared with prospective studies.

Controls are often recruited by convenience sampling. Convenience sampling involves using respondents who are “convenient” to the researcher, a convenience sample has an extremely high degree of bias, and are thus not representative of the general population and prone to selection bias. Despite the enormous disadvantage of convenience sampling that stems from an inability to draw statistically significant conclusions from findings obtained, convenience sampling does still have some uses. For example, it can be helpful in obtaining a range of “attitudes” and “opinions” and in identifying tentative hypotheses that can be tested more rigorously in further research.

Prone to recall bias or misclassification bias. Recall bias is a systematic error that occurs when participants do not remember previous events or experiences accurately or omit details [7].

Misclassification bias: wrong classification at baseline and at follow-up are both misclassification biases, in the former the bias resulting from misclassification could be considered a selection bias, as the wrong (diseased) subjects are included in the cohort while in the latter, it would be commonly defined as misclassification bias [7, 8].

Recall bias occurs most often in case-control studies, but it can also occur in retrospective cohort studies. For example, those who have been exposed to a potentially harmful agent in the past may remember their subsequent outcomes with a different degree of completeness or accuracy [7, 8].

Advantages of retrospective studies

A relatively inexpensive ability to research the rich readily accessible existing data; easier access to conditions where there is a long latency and the generation of hypotheses that then would be tested prospectively. They can be performed immediately because they are retrospective. Less time consuming [9].

1.4. Issues with Statistical Models Used – Dealing with Missing Data as an Example

Five studies on venlafaxine versus placebo had extractable data. Meta-analyses of response rates using a random effect model were performed under different hypotheses about missing data. Five situations were considered:

- 1) Optimistic bias analysis: non-assessed patients are recorded as in remission if they belong to the antidepressant group and as having not responded if they belong to the placebo group;
- 2) ITT (intention to treat) LOCF (last observation carried forward): patient status is derived from the LOCF method on continuous outcomes;
- 3) OC: observed case analysis;
- 4) Attrition = failure: non-assessed patients are recorded as not having responded in both groups;
- 5) Maximum bias: non-assessed patients are recorded as in remission if they belong to the placebo group and as not having responded if they belong to the antidepressant group.

This example illustrates the uncertainty that arises from missing data when assessing antidepressant effect, which can

vary from a marked superiority of antidepressants over placebo to a superiority of placebo over antidepressants, depending on the imputation method used for missing data [1].

2. Vortioxetine Overview

Vortioxetine was licensed for the treatment of depression by the Food and Drugs Administration (FDA) in September 2013 in the USA (FDA 2014) and by the European Medicines Agency (EMA) in December 2013 for the EU (EMA 2014). According to the WHO Anatomical Therapeutic Chemical Classification System (ATC), a classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties), Vortioxetine is placed in the category of "Other" antidepressants (WHO 2016) [9].

The mechanism of action of Vortioxetine as a multimodal antidepressant:

- 1) Partial agonist to postsynaptic 5-HT_{1B} post synaptic heteroreceptor located in the GABAergic interneuron may increase the release of glutamate in the hippocampus and prefrontal cortex (PFC) which may further contribute to an antidepressant effect. Same mechanism of action may also increase clinical efficacy in treating cognitive symptoms.
- 2) Serotonin transporter SERT reuptake inhibitor, enhancing central serotonin transmission.
- 3) Serotonin receptor antagonist (5HT₇- 5HT_{1D}).
- 4) Full agonist to 5HT_{1A}.
- 5) Vortioxetine may inhibit GABAergic neurotransmission in some brain regions via a 5-HT₃ receptor antagonism-dependent mechanism and thereby disinhibit pyramidal neurons and enhance glutamatergic signaling.
- 6) There is accreting mechanistic evidence that vortioxetine can also indirectly modulate dopaminergic, noradrenergic, histaminergic, and cholinergic systems.

These actions could improve the efficiency of information processing in malfunctioning brain circuits by facilitating long-term potentiation, neuroplasticity and increased firing of pyramidal neurons [10, 11-14].

3. Conclusion

It is clear we are trying to get benefit from static data already available in treating psychiatrists' notes, so analysis of the notes written by the same treating psychiatrist is expected to eliminate the error/bias that could happen if the analysis is done by an independent researcher due to the difference in interpretations of what is meant by what is written.

This retrospective study might show the keen interest of psychiatrists for testing Vortioxetine in a certain group of patients or to manage a particular symptoms' profile which is on its own a good reason to test this concept in further studies. This could be a good reason to have the same treating psychiatrists' views about what they think about the

symptoms that improve the most and what combinations work to further collect more specific retrospective data or to further plan for another retrospective analysis at a bigger multinational level.

Despite discussing here a retrospective study analysis, still there is a room for a prospective study that needs to focus on what the treating psychiatrists found worthy of longer follow up when it comes to particular benefits from the Vortioxetine and to hopefully replicate the findings of the retrospective study findings. The proposed prospective study could be a head to head comparison with other antidepressants. The proposed assessment is expected to focus on the symptoms that improve the most with the Vortioxetine and to have an idea about the patient profile that benefits the most from Vortioxetine. We are also expected to comment on specific and consistent functional recovery in response to the interventions used in the Vortioxetine arm and the comparator arm and not to just describing a score reduction in an antidepressant efficacy assessment tool.

There should be transparency and awareness with the statistical tool used and the full range of the all possible alternative outcomes with the used tool.

Disclosure

Last consultancy provided to Lundbeck was in 2003-Last consultancy provided to Sanofi-Synthelabo was in 2002.

Appendix

Appendix I – Data Required in the Retrospective Analysis

- 1) Initial diagnosis of patients studied: Unipolar depression only (mandatory inclusion criterion), and personal history of Bipolar disorder is an exclusion criterion. Specify severity of current depressive episode (mild-moderate-severe), and without psychotic features is a must inclusion criterion.
- 2) Comorbid illicit substance use and Alcohol dependence are exclusion criteria.
- 3) Specify the number of the current major depressive episode (specific if it is first - and if recurrent what is the number of the episode but you still can use terms like recurrent and possibly the 5th for instance or just mentioning being a recurrent depressive episode).
- 4) Has been there a major Bio-psycho-socio-cultural life stressor that could have served as a precipitating factor for the “current” depressive episode irrespective of being first or recurrent depressive episode. If yes, what was the nature of the possible precipitating factor and was it short living precipitating factor so, if ceased we might think of its cessation role in improvement or if it is a precipitating with long lasting consequences such as loss of job, money status or physical injuries and in this case the possible attribution of improved depression will be most probably a consequence to the antidepressant used (if you think there might be other different reasons for improved

depressive symptoms with the used antidepressant please specify).

- 5) If the current depressive episode is recurrent, does this patient tend to relapse in a particular pattern “due to a particular stressor” for instance exams, studying or working overseas in unfavorable conditions, breakups, and does the patient tend to improve following the cessation of the possible stressor irrespective of the antidepressant use. Try to find a pattern for relapse and a pattern for improvement with or without the antidepressant to evaluate the possible role of the antidepressant in a Bio-psycho-socio-cultural model.
- 6) Family history for Unipolar and Bipolar depression, how many blood relatives are/were affected and degree of closeness. This will help to have an idea about the genetic load/biological burden to develop depression.
- 7) Other antidepressants used for management of prior depressive episodes:

Names – dosages – durations of management – particular responses (if particular symptoms have improved what are they – if particular symptoms did not improve specify them – if existing symptoms worsened with a particular antidepressant used, try to specify these symptoms – new symptoms developed and were not there (possible psychological side effects to the antidepressant) to be mentioned. Physical side effects, to also specify them. Try to find comments about a specific symptom improved with the particular anti-depressant used with main focus of the antidepressant of your choice in the retrospective study analysis.

- 8) Reason for choosing the antidepressant (Vortioxetine) in this particular patient. (if the reason is symptoms’ profile, mention these symptoms) – (if you tried most of antidepressants and the outcome was unsatisfactory and it was a random choice specify that) – (a patient blood relative/s responded to Vortioxetine) – (the patient read about it and asked me to try it) – (if Vortioxetine was combined with another antidepressant - see appendix III).
- 9) Symptoms on first patient review that were documented by the treating psychiatrist.....

Indicators of dysfunction on first psychiatric review to be documented and to be followed up in successive visits (patient is still dysfunctional – slowly improving functionality at work – or back to previous level of functioning). Indicators of my previous choices for work related dysfunction (absenteeism from work / poor work performance / comments from colleagues and managers / evaluation at work verbally or in writing / given a warning letter, others.....) Also academic dysfunction to be described. Comment on improved functionality and give examples (such as passing exams following failing exams, meeting deadlines after not meeting deadline, GPA improving, and good comment on stability of the improvement etc.....)

- 10) Symptoms on second review: that showed improvement and to what extent they improved according to my notes compared with first review and whether:
- I am using a score from zero to 10
 - I am documenting Patient's own words
 - My own words from my understanding to the patients' improvements + or – comments from a spouse or a family member.....
 - New symptoms: Medication side effects – others
 - Changes associating dose escalation:
 - Particular symptoms improvements
 - Particular worsening.....
 - Important information the treating psychiatrist wants to add in particular to this patient and believes that will help this retrospective study.....
- 11) Discontinuation of an antidepressant is an opportunity to analyze specific symptoms that improved whilst on medication:

Processing of *negative information* / processing of same information while on the antidepressant in a different way following the discontinuation of the same antidepressant. For instance, during compliance with the antidepressant a patient can describe a situation of a family member saying.

He has a good job (1), his employer likes the way he works (2), because of his current job he can support his family overseas (3), he lives in a nice accommodation and in good situation generally (4) and he is really lucky to hold down a job in these difficult times (5) and same patient following discontinuation of the antidepressant for whatever reason his processing for the same information could be different “negative processing of information” for instance describing the same relative saying: he works hard and goes home really tired (1), yes he has been with same employer, so what (2), he sends money like a cash machine to his family overseas and he is lonely here (3) he lives alone and he could die unnoticed (4) I think he is miserable (5).

Specific symptoms improving with the same antidepressant and same symptoms relapsing on discontinuing same antidepressant for whatever reason and if the patient is reinstated on the same antidepressant we need to check if the same symptoms improved again in a consistent way indicating *specificity of particular symptom/s improvement with Vortioxetine*. There could be a trend and causal relationship could be elicited if is found statistically significant. We are looking here for (improvement – relapsed – improvement again with same antidepressant commencement – cessation/discontinuation – recommencement of the antidepressant). In other words, discontinuation of the antidepressant is also an opportunity to try to find trends to be followed up more closely in prospective studies or other retrospective studies.

Appendix II – Pattern Analysis from the Collected Data

Has there been any of the following links to the antidepressant use.

- 1) What is the reported functional improvement in the last visit as evidenced by patient's actual regain of functional capacity? Is it evidenced academically or at work place and if possible try to find comments from family to detect an evidence of functional improvement.
- 2) We can try to detect consistent improvement on the antidepressant of your choice (specific duration of continuous improvement whilst on the same antidepressant) specially with a retrospective analysis study which is longer than prospective studies that report improvements in 6 to 8 weeks' trials.
- 3) Can you attribute improvement in the patient's depressive symptoms to possible significant psycho-socio-cultural changes (attributions that would mean the psycho-socio-cultural changes together with the antidepressant) possibly explain the resultant improvement and the psychiatrist opinion is very much encouraged if the impression for instance is that, the psycho-socio-cultural intervention that managed a particular perpetuating psycho-socio-cultural stressor or in other words the psycho-socio-cultural changes helped the biological intervention (the antidepressant) resulting in a significant improvement after a period of plateaued improvement with the antidepressant only which might make the treating psychiatrist almost believe that, the reason for the improvement is most probably the “cessation of the perpetuating stressor”. In saying that I do acknowledge the references that indicate that psycho-socio-cultural interventions in a patient with depression have different effects on brain chemistry.
- 4) Has any of your patients developed Bipolar disorder whilst on Vortioxetine. Yes, we are talking about treating unipolar depression but as many bipolar depression patients start as unipolar depression patients before becoming bipolar patients (genetic overlap), has the antidepressant of your choice resulted in hypomanic or mania.
- 5) Has psychotherapy been used for treatment and was it done by a clinical psychologist and how many sessions were done. Patient's opinion about the psychotherapy intervention used and patient's opinion about symptoms improvement with the antidepressant used (try to match onset of improvement with a particular intervention commenced or a particular intervention combined to a first one to see if that added intervention added significant improvement in depressive symptoms for instance after a period of plateaued response). Quote [psychotherapy is a special type of enriched learning environment — particularly for social learning. All learning is reflected in "neural plasticity," that is, in the excitability, growth, connection, and reorganization of connections between neurons] also [A good therapist encourages change by keeping stress and psychological

arousal at mild to moderate levels, which is known to activate growth hormones and best support learning at the neural level] 15 - 16.

6) We need to analyze if there are medical comorbidities in our retrospective study in real life attempt to treat depression and to check if associated medications/or the medical comorbidity in the course of the management in each particular patient might had a negative impact on the mood and served as either a precipitating factor or maintaining factor for depression. So we need to check if medical comorbidities in the opinion of the treating psychiatrist played role in the outcome of management meaning the presence of the medical comorbidities was a maintaining factor for depression and the successful management of the same medical comorbidities made the antidepressant outcome more favourable Also we need to comment if possible if cessation / end of course of treatment of a particular medication used to manage a medical comorbidity possibly resulted in mood improvement. [quote: pain and depression are closely correlated from the perspectives of both brain regions and the neurological function system, whereby chronic pain may lead to depression. One of the important causes for chronic pain leading to depression appears to be the crucial

effect of common neuroplasticity changes on the occurrence and development of the two disorders in question, neuroplasticity crucially affects the occurrence and development of chronic pain and depression and may involve the same brain structures, neurotransmitters, and signaling pathways.] 17. [quote: inflammatory response has been shown to cause pain and depression; thus, inflammatory response-mediated pain may be more strongly associated with depression] 17. [quote: By affecting depression-related pathophysiological functional areas via the blood-brain barrier, inflammatory signals can induce changes in neurotransmitter metabolism, neuroendocrine function, and neuroplasticity] 17. [quote: Additionally, the depressive symptoms of affected patients receiving systemic treatment for malignant melanoma or hepatitis C virus infection with INF- α have been found to be aggravated in several studies, where major depressive disorder (MDD) was clinically diagnosed in up to 45% of sufferers. Furthermore, a high ratio of plasma kynurenine (a pathway redirects tryptophan away from the production of serotonin) and tryptophan in patients undergoing IFN- α therapy has been shown to predict depression severity [18].

Appendix III – Judging the Possible Therapeutic Effect of a Combination of VORTIOXETINE and Another Antidepressant

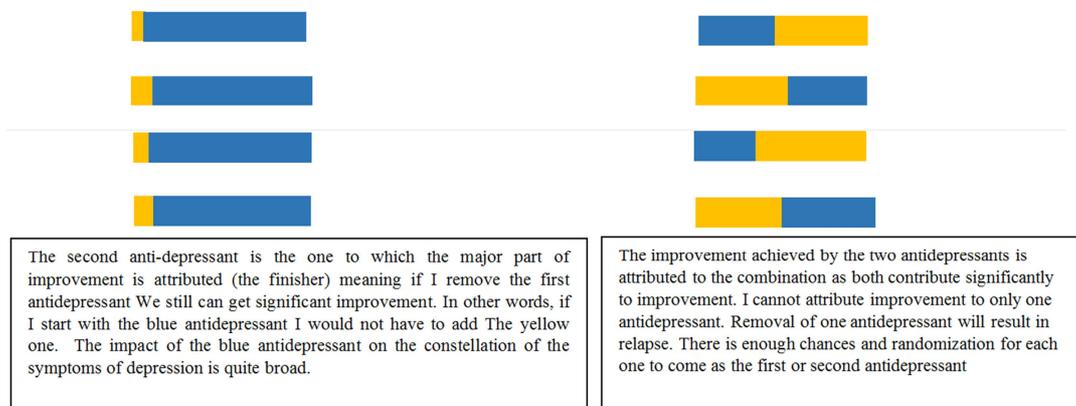


Figure 1. The possible bias in interpreting the outcome of the combination of 2 antidepressants if one is always used as a finisher or to bring about the main final improvement. Diagram has copy rights; no prior approval is required for reusing.

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