Our comments to the reviewer are in italics.

I have been asked to review the background and objectives (page 1-3) of the proposed protocol 'Interventions to help patients withdraw from antidepressants'.

I judge the current manuscript to be unacceptable in its current form. The manuscript is not logically organized, lacks balance in the concepts it addresses and makes numerous unreferenced statements some of which are expressed in language which appears to be 'emotive' rather than dispassionately scientific.

We have changed the language, see our comments to editors. Our protocol has been carefully referenced.

Although not explicitly stated, the authors appear to be painting a picture that antidepressant prescription is so undesirable that any reasonable reader would infer that it should avoided be possible. This view does not in any way represent the scientific consensus, although the casual reader would certainly take the idea from the present manuscript that the authors' views were the current consensus.

Our review is not about scientific consensus or the benefits of antidepressants. It aims at helping patients and doctors withdraw the drugs when this is desired, safely. There is a huge need for such a review.

In various places I find the language used quite questionable and unnecessarily emotive. A good example is the sentence (page 3) 'some patients refer to the myth about a chemical imbalance in their brain being the cause of the disorder'.

We have changed the wording, see our comments to editors.

If the authors wish to argue that neurochemical theories of depression are incorrect they should make the case scientifically but not with dismissive or 'emotional language' which suggests, with no evidence, that prescribers are somehow perpetuating untruths in order to justify drug prescription. To describe theories of chemical changes in the brain as being a 'myth' is to refute many decades of evidence relating to neurochemical changes observed in depression and anxiety (such as those established by neurotransmitter manipulation methods, and receptor abnormalities identified on neuroimaging). If the authors wish to describe such evidence as 'mythical' they need to produce evidence to refute this work, or else this emotive language should be removed.

The hypothesis of a lack of serotonin as the cause of depression has been discredited, by many convincing studies, e.g. mice that genetically completely lack serotonin, are as happy as other mice. We are not aware of "many decades of evidence" that, with reliable research, has found the serotonin hypothesis being correct. But our review is not the place for these interesting discussions.

Similarly, on page 3 'how the intervention might work' the authors state 'the vast majority of patients who have managed to come off psychiatric drugs report that it has resulted in a better life…'.

We have changed "psychiatric drugs" into "antidepressants" and "the vast majority" to "many." We have explained to the editors why "many" is correct.

First, the proposed review is about antidepressants and not 'psychiatric drugs' in general – here, and in many other places in this proposal the authors are introducing the problems with certain other drug classes and trying to imply that they apply equally to antidepressants (which is unreasonable and outside the parameters of proper scientific argument).

The problems with stopping psychiatric drugs are similar for different drug types because quite many patients experience withdrawal symptoms. And it is also relevant to mention that withdrawal symptoms are very much the same with antidepressants as with benzodiazepines.

Second, no evidence to support this questionable statement is presented, and this argument lacks sophistication as it ignores the trade-off that prescribers and patients must make between offering treatment or prophylaxis against dangerous and disabling diseases and the risk associated with continuing or stopping medications.

Our review is not about such deliberations. It is about helping people when the decision has been made to withdraw a drug.

Third, to some extent this argument is circular – prescribers are fully aware that ALL drugs have potential side effects, therefore which prescriber would want a patient to be taking ANY drug if coming off it gave them a better life?

It has been documented that, unfortunately, many doctors advise continued drug treatment, sometimes for life, with antidepressants, and that many patients, going against their doctor's advice, find out that their life has become much better after they came off the drugs. This is well-known, and we are therefore very surprised by the reviewer's comment.

The statement refers only to the patients who stopped the drug and found that the benefits of stopping outweighed those of continuing – otherwise they would likely go back to taking the drug and would not appear in this sample – thus a sample of people who did better after successfully stopping is very unrepresentative of the full population of people taking antidepressants.

This comment is misleading. We include randomised trials of withdrawal, which will include all patients, whether they succeed or not. And it is not a matter of presenting an unrepresentative sample by noting in the background section that many patients have benefitted from coming off their drugs, when the review is about coming off drugs. In Cochrane reviews of antidepressants and other psychiatric drugs, we are constantly told how beneficial these drugs are in the background section. Following the reviewer's logic, this is unrepresentative and should be changed.

In my opinion the manuscript needs to be changed in the following ways.

1) Start with a statement as to why antidepressants are considered by the scientific community to be beneficial, in that they are effective (in almost every published meta-analysis) in treating a broad range of highly disabling and debilitating mental health problems including depression, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder and PTSD.

Our review is not an advertisement for antidepressant drugs. As we noted to the editors, it is not relevant to discuss the effect of these drugs in a review about stopping using them.

2) Explain the concept of ongoing prophylactic antidepressant treatment, a well-accepted clinical strategy. Thereby acknowledge that for any individual there is both a potential value and a potential cost to continuing (or stopping) antidepressants. This is a much more reasonable and balanced approach to take then the current statement I have highlighted above in 'How the intervention might work'.

Again, this is not the focus of our review.

3) Remove ambiguous references to other drug classes such as benzodiazepines and antipsychotics (e.g. much of the first full paragraph on page 2). I estimate that over 75% of the 'problems with psychotropic drugs' discussed in this manuscript are actually references to these or other classes.

Our references to other drug classes are highly relevant. And it is wrong that 75% of all drug problems relate to other drugs than antidepressants. Since they are by far the most widely used psychotropics, most problems are due to these drugs.

They are therefore an obfuscation to the point of this manuscript. It is not acceptable to talk of problems with benzos and/or antipsychotics and argue that this is evidence to either encourage people to stop antidepressants or that antidepressants must by necessity have the same problems when their pharmacology is entirely different. I also believe that in paragraph 4 on page 2 where the Nielsen paper is discussed, and SSRIs are likened to benzodiazepines, from the discussion provided by the authors the evidence presented is extremely weak. Indeed 37 of 42 symptoms are 'the same' but if all potential bodily symptoms were divided into 42 categories we would find that most pairs of drugs, or drug withdrawals, were capable of inducing some reports of a majority of symptom categories. The important issue is not which symptom groups have ever been reported, but which occur commonly or frequently on stopping the drugs. The current statement could be misinterpreted as implying that benzo withdrawal and SSRI withdrawal are similar phenomena (which would require the symptoms to appear with similar frequencies which is not what the authors have stated that the Nielsen paper describes). This statement should therefore be qualified or removed.

The reviewer does not seem to be familiar with the research literature. About half of patients complain of difficulties with coming off antidepressants. There are no major differences to benzodiazepines.

4) In talking about the potential impact of stopping antidepressants, please set out earlier in the introduction the distinction between 'Rebound symptoms' [i.e. the illness the drug was treating returning] and 'withdrawal symptoms' – [i.e. symptoms not part of the illness occurring de novo]. At present the manuscript conflates these two repeatedly.

We do not conflate the two, but many psychiatrists do, unfortunately.

I understand that the authors may argue that some symptoms of depression or anxiety could co-occur with a true withdrawal syndrome, if so they can make this third possibility clear, which at present they have not (see my comments on the Rosembaum paper below). In one place (page 2, 5th paragraph) this issue is discussed but there is no clarity – they talk of 'withdrawal symptoms' overlapping with the symptoms that occur in diagnoses treated with antidepressants but include agitation and aggression on this list. The only reasonably common scenario in which antidepressants are used for aggression is as a fourth or fifth line treatment for aggression in dementia, although this is an unlicensed indication. The presence of agitation and aggression on this list is an obfuscation, the overwhelming majority of antidepressant prescriptions for mental health diagnoses are for depression and anxiety disorders.

We did not discuss usage of antidepressants but withdrawal symptoms, and Rosenbaum's study shows that abrupt withdrawal can cause one-third of the patients who are well to develop an immediate withdrawal depression, which is not a relapse of a depression but an adverse effect of being drugged.

It is especially unacceptable to argue that all cases of people having depressive or anxiety relapses constitute 'withdrawal syndromes' or 'dependence'.

This is a strawman argument, as we have never said this.

For example, the statement on page 3 ' about half of the hundreds of millions of people who take antidepressants have become 'dependent' on them is not acceptable. This assumes that 'taking a drug which provides efficacy but might cease to provided efficacy if it was stopped' is dependence. This is not in any way an acceptable definition.

This is how patients tell their doctors they perceive it, which we have documented. It is not about ceasing to provide efficacy; it is more similar to taking the alcohol away from an alcoholic whose brain has become used to a constant supply of alcohol.

This would be the same as arguing that most people taking thyroid replacement medication are 'dependent' because hypothyroidism would return if they stopped taking it (which it clearly would), or that all people taking statins for hypercholesterolemia are dependent because their cholesterol concentrations would go back up if they stopped taking them (which again they would). Do the authors believe we should be critical of thyroid or lipid-lowering medications in this way (or antihypertensives, insulin or anti-epileptic medication for that matter)?

This is another strawman argument. For antidepressants, it is not the disease returning but abstinence symptoms similar to those after other non-specific brain-acting substances, e.g. alcohol and opioids.

With people taking antidepressants for extended periods, we have a) a proportion who could stop safely without either rebound or withdrawal, b) a proportion who would get a rebound of their treated illness, c) a proportion who would experience unpleasant withdrawal symptoms, and d) a number who might get both rebound of their mental health symptoms and withdrawal symptoms together. In my opinion, (a) and (b) are large groups (most likely the largest groups except perhaps for paroxetine), just as they would be for many of the non-psychotropic medications like thyroid hormone, statins etc. mentioned above and neither imply 'dependence'.

We prefer evidence for the reviewer's opinions, which, moreover, are clearly wrong. Most people who suddenly stop with antidepressants suffer from withdrawal symptoms.

However, the authors have written their argument in many places in a way which appears to imply that (b), (c) and (d) are essentially all the same problem – thereby leaving the erroneous impression that (b) ['rebound'] is another example of the 'withdrawal syndrome' seen in (c) and co-occurring in (d).

There is no value in continuing to refute the reviewer's strawmen. We have not implied what the reviewer has fabricated.

This would imply to any reader that compared to thyroid medication, statins, antihypertensives, insulin and anti-epileptics, antidepressants are somehow 'bad medications' that prescribers and patients should avoid.

These drug types cannot be compared this way. People with myxoedema clearly need thyroid hormones and they are highly specific, directed against the disease, which is a lack of the hormones they are prescribed, in contrast to antidepressants.

Even if this interpretation in not expressly stated in the manuscript, the implication in the text is very clear (especially as there is no mention whatsoever of the beneficial effects of antidepressants). I find this argument to be unscientific, and unacceptable in the context of the current evidence base.

The strawman argument again.

5) Following on from point 4, remove the sentence (page 3) 'the patients' condition is best described as drug dependence'. This is incorrect, changing the definition of 'dependence' in this way is an unreasonable misappropriation of a term which has an existing and more complex definition (see for example the DSM-IV drug dependence definition which has 6 distinct criteria). I also find it rather judgemental; if we are to say that people successfully treated with antidepressants who continue taking them as prophylaxis are 'dependent' then we must apply the same terminology to people with hypothyroidism, hypercholesterolemia, hypertension, diabetes or epilepsy which is being treated by the appropriate medication.

The official definitions of dependence are ridiculous and self-serving, in addition to serving the drug companies that have benefitted hugely from the false perception that only benzodiazepines cause dependence, not the SSRIs. Craving larger and larger doses as a criterion for dependence is absurd, as it means that no one who smokes 20 cigarettes every day is dependent on smoking cigarettes!

6) Please clarify the argument on page 2 paragraph 6 relating to the Rosenbaum study. The authors state that patients were switched from open therapy with an antidepressant to double blind placebo and complained of a range of 'withdrawal symptoms' with one of the three most common withdrawal symptoms being 'worsened mood' and Hamilton Depression scores increasing by 8 points. They then state that the worsened mood was not a relapse of depression. But this seems to be debatable … People who had depression stop their antidepressant, their mood gets worse and their Hamilton Depression scores gets worse, yet the inference is that this is strictly part of 'withdrawal' as opposed to it being a rebound of depressive symptoms occurring alongside any withdrawal symptoms ?

All patients had been well for a very long time, 4 to 24 months, and then had their drug withdrawn for 5-8 days, and one-third of those on short-acting drugs had a Hamilton score increase of 8 or more. How many patients would experience this, in a random week, after having been well for so long? One percent? Two percent? Obviously, not 33%.

This study was not designed to allow exploration of the aetiology of symptoms reported. Further I am concerned to see the authors are to attribute blame in their interpretation of this study, i.e. 'This study shows why doctors and patients may get it wrong …. '. I would argue it shows merely that the interplay of rebound and withdrawal is complex but there is no clear 'right and wrong' in this situation. Please therefore remove the sentence which suggests there is blame to be attributed, the case for this has not been made.

We try to explain why so many doctors get it wrong, which is very important for our review.

7) As well as addressing the use of the word 'myth' as requested earlier, please remove other non-specific but potentially emotive terms such as 'terrible withdrawal' (page 2, para 6) and 'irreversible brain damage' (page 3. Para 7).

We have changed "terrible" into "severe" and "irreversible" into "long-lasting" as this is what the science tells us. Some of the brain damage seems to be permanent, e.g. sexual dysfunction, but we no longer use that word.

This reviewer is anonymous, in contrast to all other comments we have received. We wonder why and find this unfair, particularly as we find that the reviewer's main mission is to protect psychiatrists' guild interests by denying a long array of scientific facts.