Commentary

Ceteris Paribus? – An epistemological error with ethical consequences

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Abstract

Herein I call into question a common epistemological justification for placebo controls, and thereby problematize the use of placebo in many modern clinical trials. I demonstrate both the ethical harm and epistemic inferiority of placebo controls in certain knowledge contexts, arguing the standard of care should be the more acceptable comparator for novel treatments in such contexts.

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Placebo is a treatment with no therapeutic effect used as a control in many clinical trials, and research ethics boards (REBs) must ensure its use is justified (1,2). Placebo can provide us with special knowledge about studied treatments, but carries risks because it can undertreat patients. I will argue a recent study – Croft *et al.* 2014 (3) – makes unjustified use of placebos. I will then argue that an epistemological error – belief that placebo always yields more useful knowledge than other controls by isolating pharmacologic effect – can cause unjustified use of placebos. This exposes study participants to unnecessary risk and limits usefulness of study results.

Vilazodone is a novel antidepressant with selective serotonin reuptake inhibitor activity and partial 5-HT_{1A} receptor agonism (4). Croft *et al*. 2014 is a randomized, double-anonymized (conventionally "double-blind", but see Tremain (5,6)), placebo-controlled stage IV clinical trial of vilazodone. I use this example because in December 2019, I attended a continuing medical education talk about vilazodone during a clerkship elective in Ontario. This study was discussed there as evidence that vilazodone may be effective treatment for some major depressive disorder (MDD) cases, so it is a recent study having current impact on clinical practice in Canada. The study selects participants who have moderate to severe MDD, have not failed more than one treatment, and do not have significant medical or psychiatric confounds. In other words, they are suffering from MDD, have not had adequate trials of first-line medications in this episode of illness, and are uncomplicated cases.

These patients are ideal candidates for first-line antidepressants by current clinical practice guidelines (7,8). Instead of giving the participants recommended treatments, however, the study gives them either vilazodone or placebo. Being an under-characterized medication at the time, vilazodone's effects on MDD are uncertain and potentially effective, which is why it is being studied. In research ethics terms, vilazodone is in equipoise: "Clinical equipoise means a genuine uncertainty exists on the part of the relevant expert community about what interventions are most effective for a given condition." (1)

Vilazodone is in equipoise during this trial, but placebo is not – it is known to be inferior to first-line antidepressants (7,8). This study selected patients who *should*, in the clinical and ethical senses, be treated with certain medications, and instead gave some placebo, known to be less effective. This knowingly risks harming this study's placebo-control group by giving them treatment not in equipoise with the standard of care (undertreatment), resulting in higher risk of persistent and worsening MDD.

Some argue that placebo control is not as harmful as it seems because of various safeguards (which mitigate but do not eliminate harms), and because the study participants might receive no treatment if not for their participation in the study (9). Although a study's potential benefits to participants who would otherwise receive no treatment may justify a study (but see (1,2) on justice), it cannot justify choosing placebo over a different comparator. Potential benefits to those who would otherwise receive nothing cannot justify choosing placebo because researchers are not choosing between giving participants placebo versus not having a study at all – they are choosing between giving participants placebo versus giving them the standard of care. Placebo is undertreatment compared to what the participants could receive had researchers

chosen a different study design, so researchers have chosen undertreatment, a potential harm. Patients making informed consent to these risks might mitigate the harm to autonomy of being deceived, but not the harm to body/mind of being undertreated.

How do we justify this? The Declaration of Helsinki, which many REB guidelines including Canada's TCPS2 mirror, has specific criteria. Croft *et al*. 2014 state their study "… was conducted… in full compliance with… the ethical principles of the Declaration of Helsinki" (3). The Declaration's Article 33 elaborates two criteria by which placebo controls may be appropriate. The first is that "…no proven intervention exists" (2), which is not the case with MDD, as we have evidence of many placebo-superior options.

To have passed REB review, it must then meet the second criterion. To do so it must satisfy two conditions:

1. There is "compelling and scientifically sound methodological reason" (2) to use placebo AND
2. Patients receiving placebo "will not be subject to additional risks of serious or irreversible harm" (2) by not receiving the standard of care.

It further states "Extreme care must be taken to avoid abuse of this option" (2). Whether the "serious or irreversible" clause of condition 2 is satisfied is beyond my scope. Condition 1 is our focus because it asks why placebo is needed in the first place.

Placebo controls are used because they provide special knowledge about the studied treatment. In this study, using placebo control addresses whether vilazodone has more effect than the placebo effect, i.e. whether it is having effect *ceteris paribus* (all else held equal). It does so by measuring the effect of placebo (which any treatment including vilazodone will have) to subtract from vilazodone's measured effect. If vilazodone performs better than placebo, it has another effect in addition to the placebo effect – it has pharmacologic effect. Placebo control is a part of the epistemology of holding all other factors equal to determine treatment effect in isolation, like randomization and double-anonymizing. It tells us something special about the drug itself by isolating its effect from other potential effects on the measured outcomes. Thus, there is epistemic value to the placebo control group – it shows whether vilazodone has pharmacologic effect.

For conditions without effective treatments placebo is in equipoise, and so can be used without knowingly depriving patients of a better treatment option. In such contexts, placebo will also give useful information about the studied treatment – whether it has some pharmacologic effect. Having pharmacologic effect would make it the most effective known treatment, as no placebo-superior treatments are yet known. In a context where known placebo-superior treatments exist, however, this is not true because placebo is no longer in equipoise. Vilazodone is in this latter context, where both epistemic and ethical considerations change. Ethically, we have superior options for these patients (e.g. citalopram (7,8)) and yet are knowingly depriving them of these which is potentially harmful. Epistemically, a placebo-controlled trial will tell us whether vilazodone is better than placebo but will not tell us how it performs compared to the standard of care.

Why does this matter? When no known effective treatments exist any effect greater than placebo (given an acceptable safety profile) demonstrates clinical usefulness, but this is not the case when effective treatments are known. The ground under us has shifted – *ceteris paribus* is no longer placebo, but the standard of care, because this is what the normal patient should receive as treatment. New treatments do not need to be safer and more effective than placebo to be clinically useful now – they need to be safer and more effective, or at least comparable to, existing treatments. When there are known placebo-superior treatment options we must contextualize efficacy relative to these treatments because it shows us when to use the study treatment instead of another established one. Placebo only tells us that there is some amount of pharmacologic effect, which is less clinically useful knowledge.

Croft *et al*. 2014 asks whether vilazodone is superior and its safety profile noninferior to placebo, but the clinician and patient ask whether it is as effective and safe as other options. The study asks whether there is a mechanism of action apart from placebo, but the patient and clinician ask when they should prefer it over other treatments. The study cannot answer our questions, telling us only that there is some pharmacologic effect. This is clinically inferior knowledge, and it comes at the additional cost of knowingly exposing patients to undertreatment.

One could object MDD has a high rate of non-responders to existing therapies, so we should explore novel options. Here placebo returns to equipoise as there are, by definition, no known effective therapies. But this study is explicitly not a study of treatment-resistant depression – it sheds no light on what we could expect for non-responders were we to prescribe them vilazodone, because it excludes that population.

Another objection is that the highly variable treatment response of MDD requires a placebo comparator in addition to a standard of care comparator to ensure the standard of care is placebo-superior in the study population (10,11). This may be a justification for a trial like Mathews *et al.* 2015 where vilazodone is compared to both placebo and citalopram (12). Croft *et al.* 2014, however, fails to use both comparators, thereby failing to contextualize its placebo control relative to the standard of care. Thus, it is not using placebo in this way.

Compared to a study using the standard of care, Croft *et al*. 2014's use of placebo provides less clinically useful information and risks doing more harm to study participants by undertreating them. This is unjustifiable by accepted research ethics guidelines. I do not have scope to demonstrate how common this is, but I invite the reader to review whichever clinical literatures they are engaged with and ask the same questions posed herein.

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