We re-analysed Cristea *et al*'s[3] effect sizes to demonstrate that, when procedures intended to modify cognitive bias elicit the process of cognitive bias modification, there is consistent impact on emotional disposition. Kruijt & Carlbring contend that Cristea *et al*'s method of computing effect sizes compromises sensitivity to emotional disposition, which would represent a further limitation of this meta-analysis. However, compelling evidence that when procedures intended to evoke the process of cognitive bias modification do so successfully then so too do they alter emotional disposition, is not restricted to our re-analysis, and has been reported elsewhere.[4]

We advocate adherence to the experimental medicine framework, by clearly distinguishing two questions: one asks whether successfully modifying cognitive bias yields therapeutic benefit, and the other asks whether procedures intended to modify cognitive bias successfully induce this process of cognitive change.

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Author's reply: Kruijt & Carlbring judiciously uncover significant methodological problems of the narrative re-analysis by Grafton and colleagues[1] on our previous meta-analysis on the effectiveness of cognitive bias modification (CBM) interventions in anxiety and depression.[2] The letter reinforces what we had previously noted in our invited comment,[3] namely that our approach had been grossly misconstrued. In the meta-analysis, we had pooled *all* anxiety outcomes measured on validated instruments at post-intervention, whether these measured clinical symptoms, state or trait anxiety. We specifically excluded measures applied after a stressor induction task. If multiple measures in the same outcome category (for example general anxiety) were reported, we averaged them at study level. Grafton and colleagues claim to have re-analysed the anxiety data so as to reflect 'change in emotional vulnerability' (p. 268). Not only is this construct vague and its application susceptible to bias, but, as Kruijt & Carlbring justly note, Grafton *et al* simply selected some of the already computed effect sizes and pooled them again. Essentially, this approach reflects the same mix comprising all anxiety outcomes, measured in the absence of a stressor induction task, and averaged at study level, just stemming from a more restricted pool of studies. To implement their new set of criteria, Grafton and colleagues should have recalculated effect sizes from study-level data, excluding measures and time points they did not deem appropriate for the elusive construct of emotional vulnerability. As it is, their re-analysis remains an arbitrary *post hoc* selection of study effects.

Yet a larger and more crucial problem relies in the central claim of Grafton *et al*, echoed by many leading CBM advocates: the effectiveness of these interventions should only be weighed *if* they successfully modified bias. Kruijt & Carlbring adeptly liken this to familiar arguments for homeopathy. However, it also reflects a fundamental misunderstanding of how causal inferences and confounding function in a randomised design. Identifying the trials in which both bias and outcomes were successfully changed is only possible *post hoc*, as these are both outcomes measured after randomisation; reverse engineering the connection between the two is subject to confounding. Bias and symptom outcomes are usually measured at the same time points in the trial, thus making it impossible to establish temporal precedence.[4] Circularity of effects, reverse causality (i.e. bias change causes symptom change or vice versa) and the distinct possibility of third variable effects (i.e. another variable causing both symptom and bias changes) further confound this relationship.[4] For instance, trials where both bias and symptom outcomes were successfully modified could also be the ones with higher risk of bias, conducted by allegiant investigators, maximising demand characteristics or different in other, not immediately obvious, ways from trials where neither bias nor symptoms changed. Randomised controlled studies can only show whether an intervention to which participants were randomised has any effects on outcomes measured post-randomisation.[5] Disentangling the precise components causally responsible for such effects is speculative and subject to confounding. To this point, randomised studies show CBM has a minute, unstable and mostly inexistent impact of any clinically relevant outcomes.

1 Grafton B, MacLeod C, Rudaizky D, Holmes EA, Salemink E, Fox E, et al. Confusing procedures with process when appraising the impact of cognitive bias modification on emotional vulnerability *Br J Psychiatry* 2017; **211**: 266–71.

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Towards a definition of unbearable suffering and the incongruence of psychiatric euthanasia

In the article by Verhofstadt *et al*, the authors rightly observe that the concept of 'unbearable suffering' in relation to euthanasia remains poorly defined in the medical literature.[1] We wish to make three observations which may contribute to a better understanding of 'unbearable suffering' and highlight the incongruence of considering euthanasia as psychotherapeutic.

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First, suffering in one form or another is part and parcel of being human. It is the time-tested signal that something is going wrong. It is also the moment to test the limits of character and affective maturity. This is not to say that suffering is always welcome. Indeed, a sign of human progress is the alleviation of many forms of suffering, and medicine certainly plays a key part in this. Nevertheless, medicine alone cannot be expected to shoulder the burden of relieving all forms of human suffering. Verhofstadt and colleagues identify five categories of unbearable suffering in psychiatric patients: medically related, intrapersonal, interpersonal, societal and existential. It is a fact that modern psychiatry is able to treat many psychiatric disorders, but asking psychiatrists to treat all forms of suffering including existential doubts may be actually leading the profession away from medicine.

Second, suffering is a normal human affective-emotional reaction to a perceived or real threat to the integrity of personhood, following the classic definition by Cassell[2] adapted by Dees *et al* in their proposal for defining 'unbearable suffering'.[3] We would argue that suffering is bearable when a person is able to rationalise the perceived threat to integrity in view of a higher end or good. Indeed, many of the greatest figures in history are admired precisely for having suffered for a cause. On the other hand, suffering is unbearable when a person is unable to rationalise the suffering. In other words, it is a suffering that has no meaning for that person. It is unreasonable. The humanisation of suffering is about restoring meaning to suffering, not annihilating the person.[4]

Third, adding euthanasia to the therapeutic repertoire of psychiatry is in truth an alteration of psychiatry and not an advancement of science. Twenty-five centuries ago, Hippocrates finally managed to separate science from hocus pocus, the doctor from the sorcerer, curing from killing.[5] Readmitting this vanquished foe to the fold is to change the very character and goals of medicine. Psychiatrists should shun euthanasia as a 'treatment' for suffering-in-want-of-a-reason and instead concentrate on what they do best – treating psychiatric disorders and helping patients find meaning for their suffering.

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Authors' reply: Kioko and Requena propose a primary therapeutic focus on assisting patients in finding a meaning in their suffering and life itself.[1] They also propose that euthanasia is incompatible with psychotherapeutic care, referring to psychiatrist Frankl's example of self-endured suffering once one's attitude towards suffering has been modified and the meaning of life itself has been found, despite being confronted with the most extreme manifestations of dehumanisation.[2] The rationale of his coping mechanism is that hurtful situations in themselves might indeed be beyond one's control, but that attitudes toward these situations – and, as a consequence, suffering experiences – can be mastered. There are many religious and philosophical tendencies supporting this point of view, in contrast to the many counterpoints. One can find many different stances in many more areas of expertise which express opposing – though inconclusive – positions. To the best of our knowledge, there is no evidence that the abovementioned meaning-of-life approach can be effective to alleviate unbearable suffering or prevent/revoke psychiatric patients from requesting euthanasia.

The authors evoke anecdotal evidence of great deeds done by (responding to) suffering. In this vein, many artists have created unique art, perhaps because of that suffering, perhaps not. Contrarily, there are also many examples of artists who committed suicide. Such anecdotes confirm the subjective nature of suffering, determined by a patient's environment, context, current and future perspectives, physical and mental capacity, and personality.[3]

Concerning the role of psychotherapists, their aim to alleviate human suffering indeed stretches back to antiquity. Nevertheless, a deeper understanding of suffering and ways to alleviate it remain elusive. Physicians denying that there are limits to treatment and holding an absolute stance on life protection, not fully fathoming patients' total suffering that leads to suicidal ideations, attempts or euthanasia requests, paradoxically might steer the therapeutic relationship to a standstill as patients might feel unheard, misunderstood and strengthened in their conviction of being unworthy and, as a consequence, in their death wish.[4]

In acknowledging unbearable suffering and the limits of medical treatment to alleviate suffering in an adequate way, the psychotherapeutic key focus on protection of life only seems to be undermined. However, the scarce available evidence from Belgian clinical euthanasia practice shows that following a two-track approach, with a focus on psychotherapeutic treatment while also acknowledging euthanasia as a plausible emergency break, paradoxically might offer psychiatric patients sufficient peace of mind to continue their lives and give further or alternative treatment options a fair chance for success.[5] Hence, more research into the nature of suffering and meaning of a death request is needed in order to develop highly needed clinical interventions that might both relieve patients of their death wish and enforce new or alternative life perspectives. We hope our qualitative study can contribute to paving the way for further research endeavours that are tolerant and respectful to patients' subjective notions of unbearable suffering and death wish, as well as directly addressing their cry for extended life aid and thus assisting the patient to continue living, without polarising these into irreconcilable opposites.

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