Are personalized treatments of adult depression finally within reach?

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COMMENTARY TO SPECIAL ARTICLE

Are personalised treatments of adult depression finally within reach?

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Personalised treatments for depression are very much needed, because all psychological and pharmacological treatments seem to be equally effective in the aggregate even though we know that treatment effectiveness varies substantially at the level of the individual patient. We are presently, unable to predict which patients will benefit from which treatments, making it necessary to use a trial and error approach to the treatment that is almost certainly implicated in the high rates of treatment drop-out found among patients in treatment for depression and delays recovery for those patients who persist with treatment until a helpful modality is found for them. Personalised treatments hold out the promise of solving this problem by predicting which patients will benefit the most from which treatments. Accurate prediction of this sort would bring us a step closer to more effective treatments, which is very much needed because treatments are effective but by far not effective enough. Unfortunately, despite the attempts from several research areas, not much success has been made in the development of personalised treatment and until now very little personalised advice has been incorporated in treatment guidelines. Kessler and colleagues suggest that we may have finally come a step closer to developing true personalised treatments that can be used in clinical practice (Kessler *et al.* 2016). Will we finally be able to take this important step in developing better treatment for depressive disorders?

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The need for personalised treatment of depression

There is no doubt that personalised therapies are very much needed in the treatment of adult depression. Several types of antidepressant medication have been found to be effective compared with placebo, and several hundreds of trials directly comparing different types of medication have shown that all these medications are most likely about equally effective. Furthermore, several types of psychotherapy have also been shown to be effective, such as cognitive behaviour therapy and interpersonal psychotherapy. Trials directly comparing different types of psychotherapy have also shown that there are no or only small differences between the effects of these therapies compared with control groups, and several dozens of studies have shown that psychotherapies and antidepressant medication are also about equally effective. So all available treatments, psychological and pharmacological seem to be equally or about equally effective, while hardly anything is known about who benefits from which treatment (Cuijpers, 2014), and a trial and error approach is the only approach that remains.

At the same time the effects of these treatments are not impressive, as they cannot reduce more than 33% of the disease burden of depression and that only in optimal conditions (Andrews *et al.* 2004). Furthermore, 40% of patients do not or only partially respond to treatment, less than one-third are completely recovered after treatment, and relapse rates are considerable.

Earlier approaches

Several research disciplines have attempted to develop personalised treatments of depression. Pharmacogenetics, where expectations were high, was thought to improve pharmacotherapies by knowledge of genotyping (Holsboer, 2008) as about 50% of the response to antidepressants can be attributed to genetic factors. Unfortunately, the regulation of gene transcription and the interactions of these with environmental factors have been found to be extremely complicated. Therefore, it is

also very complicated to translate that individual genetic information into personalised treatments for depression.

Another attempt to develop personalised approaches to the treatment of depression has been to identify subtypes of depression that may respond differentially to different treatments, such as melancholic, atypical, anxious and psychotic depression, early and late-onset depression, and chronic depression (Baumeister & Gordon, 2012). Unfortunately, there is no evidence that these subtypes are either absolutely distinct from one other or stable (van Loo *et al.* 2012), and there is substantial overlap across symptoms, aetiologies and time of onset. Furthermore, as of now there is very little evidence that specific subtypes respond better to one treatment above the other (Baumeister & Gordon, 2012), so also this road to personalised treatment of depression has not succeeded.

A third approach is based on the concept of clinical staging. In clinical staging models, a treatment is specified for each stage. For depression, the stages include: subthreshold depression, a first episode, a new episode after having had several earlier ones and chronic depression. Although this approach is clinically appealing, there is at this moment insufficient evidence that clinical staging results in better outcomes.

Comparative trials and moderators

Another approach to personalised treatments comes from the field of randomised trials. Trials in which two types of treatment are directly compared with each other in a specific target population can also identify patients that benefit more from one treatment than the other. A considerable number of such comparative outcome trials in specific patient samples have been conducted. In a meta-analysis of trials among the specific target groups comparing antidepressant medication, psychotherapy and combined treatment we found that medication is probably the best treatment for dysthymia and combined treatments are more effective in depressed older adults (Cuijpers *et al.* 2012). However, the number of trials that is needed for this approach is huge. In our meta-analysis, we found that in order to examine the comparative effectiveness of psychotherapy, pharmacotherapy or combined treatment among 20 specific target groups we required 254 trials for sufficient statistical power, whereas only 20% of these studies presently have been conducted.

The last approach to develop personalised therapies has focused on research on outcome moderators. When two treatments are compared with each other in an unselected group of participants such moderators of outcome can be examined. Is one of the two treatments more effective than the other in men or women, older or younger patients, patients with comorbid anxiety disorders? The problem with this approach is that most of these trials are designed to find (differential) effects of the intervention, not to find moderators. Therefore, the power is typically insufficient to identify moderators and significant findings have a considerable risk of being chance findings. Furthermore, moderators identified in such trials can only be considered as indirect evidence. If for example, it would be found that one treatment is better in women and another in men, this finding would still be confirmed in a new randomised trial in which women are randomised to these treatments. So this approach is also not very promising for the development of personalised treatments.

Will personalised treatment be possible after all?

The paper by Kessler and colleagues (Kraemer, 2013; DeRubeis *et al.* 2014) describes a whole new approach to personalised treatments. The approaches described by Kraemer already showed that it is possible to personalise treatments based on clinical observations and patient reports obtained prior to beginning treatment. The approach proposed by Kessler has the promise to further improve and enhance these earlier approaches. We are not there yet, because none of these approaches has been tested in a new randomised trial, showing that patients who receive the personalised treatment do indeed have a bigger chance for a positive outcome than patients who receive the standard care. Moreover, the nature of the predictors may be less than optimal given that these characteristics may have been measured only once, at the baseline. Other variables that predict changes in personal characteristics might themselves be needed. In short, the approach may be limited by the quality and sensitivity of the personal characteristics. Nevertheless, after other attempts that did not progress this field, it is encouraging to see one potential route that holds alive the promise of personalised treatments for psychiatry; and this is a good news for patients with depression.

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