Redefining Therapeutic Outcomes of Depression Treatment

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Abstract: Responses to evidence-based interventions for depression are divergent: Some patients benefit more than others during treatment and some do not benefit at all or even deteriorate. Tailoring interventions to the individual may improve outcomes. However, such personalization of evidence-based treatment in depression requires investigation of individual outcomes and the individual trajectories towards these outcomes. This theoretical paper provides a critical reflection on individual outcomes of depression treatment. First, it is argued that outcomes should be broadened, from a focus on mainly depressive symptomatology to recovery in different domains. It is acknowledged that recovery from depression reflects a personal journey that differs from person to person. Second, outcome measures should be lengthened beyond the acute treatment phase, taking a lifetime perspective on depression. The challenge then is to discover which trajectories of what measures during what interventions result in personalized sustainable recovery and for whom. Routine outcome monitoring systems may be used to inform this quest towards assessment of personalized sustainable therapeutic outcomes. Adaptations to broaden and lengthen measurements in routine outcome monitoring systems are proposed to identify predictors of personalized sustainable recovery. Routine outcome monitoring systems may eventually be used to implement personalized treatments for depression that result in personalized sustainable recovery.

Keywords: Depression, Routine Outcome Monitoring, Personalized sustainable recovery, Personalized treatment, Therapeutic outcomes

"Personalized treatment of depression is one of the most important challenges for mental health researchers in the next decades" (Cuijpers et al., 2016. p. 977)

The outcomes in depression research are traditionally compared between groups. If reduction of symptomatology is larger in an intervention condition than in a control group, the intervention is deemed effective. There are various evidence-based treatments for depression, including psychotherapeutic interventions (Cuijpers, Karyotaki, Reijnders, & Ebert, 2019), pharmacological interventions (Cipriani et al., 2018), or the combination of both (Cuijpers, De Wit, Weitz, Andersson, & Huibers, 2015). However, an intervention that improves average outcomes in a group does not necessarily result in improved outcomes for each individual patient in that group.

Results from an individual patient data meta-analysis (N = 1700; Vittengl et al., 2016) demonstrated that some patients benefit more than others, while negative outcomes (deterioration during treatment or very high depression scores after treatment) were observed in around 13% of

depressed patients receiving cognitive behavioural therapy or pharmacotherapy. In a large trial investigating the treatment steps required to achieve remission (N = 3,671; STAR*D; Rush et al., 2006), 37 percent of patients achieved remission after the first phase of (pharmacological) treatment, while approximately 30 percent of patients did not achieve remission even after four consecutive phases of various types of treatment. Thus, group-based outcomes fail to represent the large heterogeneity of treatment effects in depression.

Assessment of individual outcomes of depression treatment is needed to predict which intervention works best for whom. Personalizing interventions by matching patient characteristics to potential treatments is one avenue towards improving outcomes of depression treatment. Many studies have examined clinical moderators of treatment effects, such as pharmacogenetics, subtypes of depression or clinical stages. To date, these efforts to identify subgroups of patients that respond particularly well to a certain treatment have been disappointingly unproductive (Cuijpers & Christensen, 2017; Cuijpers, Ebert, Acarturk, Andersson, & Cristea, 2016). Combining several baseline variables, such as socio-demographics, childhood adversity and comorbid symptomatology, does hold promise for development of clinical decision tools, given that many of these characteristics predict differential treatment outcomes to some extent (Kessler et al., 2017).

Outcomes assessed at the individual level are also required for another manner in which interventions may be tailored to the individual depressed patient, namely using feedback tools. Based on repeated assessments of patient reported outcome measures during treatment, feedback tools are being developed that inform patients and clinicians on the trajectories during treatment, so that interventions for patients who are "not on track" can be adjusted (Kendrick et al., 2016; Shimokawa, Lambert, & Smart, 2010). To date, however, there is a lack of understanding of trajectories that are predictive of outcomes and the effects of these feedback tools are mixed (Kendrick et al., 2016).

In sum, identifying the patient characteristics at the start of treatment and change trajectories during treatment that predict individual outcomes of depression treatment has proven to be a great challenge. Crucially, predicting individual treatment outcomes requires assessment of these outcomes per individual. In the efforts described above, the same instruments used to assess outcomes in groups – typically a measure of depressive symptomatology – have been applied to the individual patient. This method of assessing individual outcomes may have hampered the quest for personalizing interventions. In this paper, we will argue that assessment of personalized sustainable recovery is needed. Possibilities for assessing these outcomes using routine outcome monitoring systems will be discussed.

Assessment of personalized sustainable recovery

Broader than symptomatic remission

The optimal treatment outcome for depression has long been symptomatic remission, defined as the (virtual) absence of depressive symptomatology for over eight weeks (Judd et al., 2016; Keller, 2003). Accordingly, depressive symptomatology is commonly used as outcome measure in the scientific literature (e.g. Cuijpers et al., 2016). However, how symptomatic remission should be defined is currently being debated (de Zwart, Jeronimus, & De Jonge, 2018). Moreover, as others have argued (e.g., Greer, Kurian, & Trivedi, 2010; Rush, Aaronson, & Demyttenaere, 2019), recovery entails more than the absence of depressive symptomatology.

During a depressive episode, the vast majority of individuals experience severe impairments in other domains besides their depressive symptomology (Kessler et al., 2003), including work functioning (Lagerveld et al., 2010; Lerner & Henke, 2008), social functioning (Hirschfeld et al., 2000; Kupferberg, Bicks, & Hasler, 2016), and reductions in quality of life (IsHak et al., 2011). Many patients consider improvements in these other domains to be at least as important as symptomatic remission (Zimmerman et al., 2006). When asked about what entails being cured from depression, patients place high importance on enjoying life, finding meaning in life and being satisfied with themselves. When comparing what patients and clinicians define as most important aspects of recovery from depression, patients focus more on improving the quality of life and increasing positive affect, whereas clinicians place relatively more emphasis on reductions of symptomatology and improvement of functioning (Demyttenaere et al., 2015, 2016).

Although symptomatic remission in depression is associated with improvements in other domains (Zimmerman et al., 2008), it appears to be neither sufficient nor necessary for recovery in other domains. Even after symptomatic remission, patients often experience impairments in diverse forms of functioning (de Vries, Koeter, Nieuwenhuijsen, Hees, & Schene, 2015; IsHak et al., 2016; Lerner & Henke, 2008; McKnight & Kashdan, 2009; Sarfati et al., 2017; Trivedi et al., 2013) and quality of life (IsHak et al., 2011). Improvements in other domains can lag behind compared to symptomatic recovery (McKnight & Kashdan, 2009) and vice versa (Solomon et al., 2008). Therefore, therapeutic outcome measures in the treatment of depression should be broadened to include other aspects of recovery than symptomatic remission alone (Romera et al., 2014).

This broadened view of recovery in depression (Demyttenaere et al., 2015) fits well within recent efforts of mental health organisations and policy makers to shift the focus from reducing mental illness to increasing mental health. Mental health or positive health should not be seen as the

absence of mental illness, but rather as the ability to adapt and self-manage, and it can occur in the presence of mental illness (Huber et al., 2011). The road to recovery in depression can be described as a complex personal journey (Richardson & Barkham, 2017) and how recovery can best be defined may be an individual matter (Demyttenaere, 2016). Individual outcomes of depression treatment may thus be viewed as both reducing mental illness and increasing mental health.

Beyond post-treatment

It is increasingly recognized that depression should be viewed in a lifetime perspective (Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015). Depression is characterized by a highly recurring course (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010; Richards, 2011). Studies of recurrence in individuals who have been in psychiatric care for their problems reported a recurrence rate of 25% over 1 year up to 85% over 15 years (Holma, Holma, Melartin, Rytsala, & Isometsa, 2008; Mueller et al., 1999; Solomon et al., 2000). Therefore, treatment outcomes (at the end of treatment) should not only be reflective of recovery at that moment, but also predictive of sustainable recovery (after treatment).

How to evaluate the likelihood of personalized sustainable recovery during treatment is not yet known. There are several end-of-treatment factors that contribute to the prediction of depressive relapse, indicating symptomatic recovery was not sustainable. A first important predictor is the level of residual symptoms at the end of treatment: As the number of residual symptoms increases, so does the likelihood of relapse (e.g. Judd et al., 2016; Sakurai, Suzuki, Yoshimura, Mimura, & Uchida, 2017). Including other clinical information (e.g., symptoms from other domains of psychopathology, childhood adversity and abuse, and the number of previous episodes) adds to the prediction of relapse (van Loo, Aggen, Gardner, & Kendler, 2015; Wang et al., 2014). However, many of these variables are not modifiable during treatment and are therefore unsuitable as predictors of sustainable therapeutic recovery. Moreover, even the latest clinical prediction tool, based on the most consistent findings and taking several differences between previously depressed patients into account, only modestly predicts individual relapse (Klein, Holtman, Bockting, Heymans, & Burger, 2018). In sum, overall sustainability of therapeutic outcomes of depression treatment seems limited and individual assessment of this sustainability is poor.

Taking a lifetime perspective on depression further highlights the importance of a broadened view on recovery in depression, because the importance patients place on improving positive affect increases after treatment and is higher in patients with recurring depression (Demyttenaere et al., 2015). The literature to date has almost exclusively examined symptomatic relapse after treatment; how formerly depressed individuals fare in other domains of recovery is very much unclear (Rhebergen et al., 2010). Sustainable symptomatic recovery may not reflect recovery in all domains, given that the trajectories of recovery for the different domains may be largely independent, as described above. Therefore, it is important to evaluate sustainability of therapeutic outcomes in other domains longitudinally as well.

Furthermore, the sustainability of outcomes may benefit from a broader look on outcome measures in depression (Johnson & Wood, 2017; Rottenberg, Devendorf, Kashdan, & Disabato, 2018). For example, a lower risk of symptomatic relapse was found in individuals with higher psychosocial functioning (Solomon et al., 2004) and quality of life (IsHak, Greenberg, & Cohen, 2013). Moreover, early improvements in psychosocial functioning during treatment are predictive of long-term symptomatic remission (Jha et al., 2016), demonstrating that change in different recovery domains during treatment may be indicative of sustainable therapeutic recovery. Possibly, broader recovery posttreatment contributes to sustainability of therapeutic outcomes. However, this is a hypothesis that needs to be empirically tested.

Towards prediction of personalized sustainable recovery using routine outcome monitoring systems

To summarize, outcome measures in depression need to be broadened to include recovery in different domains and lengthened to include sustainability of recovery. Furthermore, individual characteristics and change trajectories during treatment need to be identified which are predictive of personalized sustainable recovery. In other words: For whom do which trajectories of which measures result in personalized sustainable recovery, and which interventions may be used to achieve these outcomes?

Identifying predictors of personalized sustainable recovery requires large datasets including information about individual differences at baseline, the treatment (or components thereof; Cuijpers, Cristea, Karyotaki, Reijnders, & Hollon, 2019), individual trajectories during treatment, and outcomes as assessed on different domains over a longer period of time (Kessler, 2017; 2018). These datasets could be generated in clinical practice (Kessler, 2018). Here, routine outcome monitoring systems are in place, in which patient-reported outcome measures are administered repeatedly: at the start, during, and at the end of treatment. These assessments differ between health care settings, but typically include measures of symptoms, patient satisfaction, functioning, and quality of life (Delespaul, 2015).

A broadening of measurements in routine outcome monitoring systems is needed. Outcome measures may for example be broadened by including measures of quality of life or positive mental health. A critical review of the outcome measures is needed to take the depressed patient's perspective on recovery from depression into account

(Demyttenaere, 2016). Assessments may be personalized using patient-defined outcomes measures or adaptive questionnaires to combine the strengths of validated questionnaires with personalized preferences.

Experience sampling methodology (Csikszentmihalyi & Larson, 2014) may be integrated in routine outcome monitoring systems to contribute to personalizing interventions in depression (Verhagen, Hasmi, Drukker, van Os, & Delespaul, 2016). This methodology has high ecological validity and provides a unique opportunity to assess potentially highly relevant processes, such as resilience when confronted with stressors (Waugh & Koster, 2015). Furthermore, trajectories of change during treatment can be assessed using experience sampling methodology, which may differ from person to person (Slofstra et al., 2018), and may be predictive of symptomatic relapse (Verhoeven, Wardenaar, Ruhé, Conradi, & de Jonge, 2018). Indeed, experience sampling tools with integrated feedback are already being developed and evaluated (Bastiaansen et al., 2018).

Most importantly, the lengthening of routine outcome monitoring systems is essential. Current routine outcome monitoring systems are almost always limited to measurements before, during, and at the end of treatment. However, investigating whether changes during treatment are predictive of sustainable recovery requires assessments of recovery after treatment, over a longer period of time. By relating between-individual differences and within-individual trajectories during treatment to these long-term outcomes, predictors of personalized sustainable recovery can be identified. It is the combination of between-individual differences and within-individual change that may improve the prediction of long-term depression treatment outcomes (e.g. Monden, Stegeman, Conradi, de Jonge, & Wardenaar, 2016) and, ultimately, the treatment outcomes themselves (Holmes et al., 2018). As long as these have not been identified and the prediction of sustainable recovery remains poor, such long-term follow-ups allow for monitoring of the course of recovery of all patients after treatment and, if necessary, application of timely interventions.

Potential for identifying working mechanisms and tailoring interventions

The understanding of working mechanisms is crucial for tailoring interventions to individuals and optimization of therapeutic outcomes (Kazdin, 2007). To date, the working mechanisms of treatments for depression are poorly understood (Kazdin, 2016; Lemmens, Müller, Arntz, & Huibers, 2016). It has been argued before (e.g. Slofstra et al., 2017) that trajectories during treatment as assessed using experience sampling methodology may provide new insights on working mechanisms, for example by uncovering differential effects of treatments (Bakker et al., 2016). No two individuals are the same, and the same mechanisms of treatment may not hold for every depressed individual. In sum,

identifying individual trajectories of change during treatment that are predictive of personalized sustainable recovery hopefully contributes to personalizing interventions by elucidating how treatments work and for whom.

It is expected that some of these working mechanisms may be transdiagnostic, such as emotion regulation (e.g. Gratz, Weiss, & Tull, 2015), mental imagery (Holmes & Mathews, 2010), repetitive negative thinking (Ehring & Watkins, 2008), and generating hope (Schrank, Stanghellini, & Slade, 2008). The proposed broader outcome measures are perfectly suited to explore such potentially transdiagnostic processes. Targeting these mechanisms with transdiagnostic treatments is another potential avenue towards personalizing treatments and improving outcomes (Craske, 2012).

Eventually, treatment selection models and feedback systems may be integrated in the routine outcome monitoring systems to inform clinicians and patients on the best course of treatment (Kendrick et al., 2016; Shimokawa et al., 2010). Routine outcome monitoring systems have been implemented in clinical practice worldwide over the last decades (Roe, Drake, & Slade, 2015) to optimize treatment, to provide data for scientific research, and to compare mental health care institutions (i.e. benchmarking) (Boswell, Kraus, Miller, & Lambert, 2015; de Beurs et al., 2011; Delespaul, 2015). Most clinicians and researchers agree that it provides valuable data for evaluating and optimizing individual treatments, although there are debates on the validity and reliability of benchmarking using routine outcome monitoring data (e.g. Hoenders et al., 2014). From a patient's perspective, routine outcome monitoring is valued as a tool to facilitate shared decision making and regular evaluation of the goals (Groeneweg, 2019). In our opinion, routine outcome monitoring may be an ideal vehicle for moving towards assessment of personalized sustainable recovery and implementation of personalized interventions in depression (Hallgren, Bauer, & Atkins, 2017).

Conclusion

Measures of individual therapeutic outcomes in depression are needed that take into account the long-term effects of treatment on different domains of recovery. Adaptations to broaden and lengthen measurements in routine outcome monitoring systems are proposed to identify which trajectories of what measures result in sustainable recovery and for whom. Investigation is needed into which (components of) interventions result in such personalized sustainable recovery and for whom. Finally, routine outcome monitoring systems may be used to implement personalized treatments for depression based on the assessment of personalized sustainable recovery.

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The authors declare that there is no conflict of interest.

Author contribution

All authors contributed to the ideas presented in this paper. CS and SB drafted the first version of the manuscript and SC and RH were actively involved in revising the manuscript. All authors read and approved the final manuscript.

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