

Personalized treatment strategies for depression

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Valorization addendum

In the present thesis, both traditional and more innovative ways to personalize treatment strategies for major depressive disorder (MDD) are studied. In this chapter, the valorization addendum, the usefulness of this research to society will be reviewed. First, the social and economic relevance of the findings will be addressed, and an overview of potential target groups for whom the research results might be of interest will be given. After that, possible activities and products as well as innovative aspects of the findings will be discussed. Finally, planning and implementation of the results and future projects will be outlined.

1. Relevance

MDD is a health care problem affecting over 300 million people annually and leading to over 50 million of Years Lived with Disability (YLD) worldwide. On a global level, MDD is the largest contributor to non-fatal health loss (7.5% of all YLD; WHO, 2017). Additionally, economic costs are large; total costs in the Netherlands are about 3 billion Euros each year (de Graaf, Tuithof, van Dorsselaer, & ten Have, 2011; Slobbe, Smit, Groen, Poos, & Kommer, 2011). Efficacious treatments for MDD are available, showing comparable effect-sizes (Cipriani et al., 2009; Cuijpers, Andersson, Donker, & van Straten, 2011; Gartlehner et al., 2008). However, individual responses to these treatments vary widely and are largely unpredictable (Kravitz, Duan, & Braslow, 2004; Simon & Perlis, 2010). In clinical practice, this results in a trial and error approach (most typical for secondary and tertiary care settings) in which consecutive treatments are being offered to determine what works best for the given individual (Rush et al., 2006). This trial and error method has many negative consequences including long treatment trajectories, chronicity, demoralization, decreased psychosocial functioning, high societal costs and treatment dropout. In other words, this approach and its consequences all add to the known over- and under treatment of MDD (Lorenzo-Luaces, 2015; Thornicroft et al., 2017).

Considering the impact of over- and under treatment of MDD on an individual and societal level, it is of high importance to improve treatment strategies, finding the optimal depression treatment for a specific individual at a specific point in time (Cohen & DeRubeis, 2018). To this end, we investigated both traditional and innovative methods. Findings indicated that traditional approaches are supported by limited and non-robust evidence, and that innovative approaches (prediction models) are promising, however still in development. These findings contribute to the growing knowledge on possibilities and limitations of personalized medicine in MDD, and provide future directions on how to improve treatment strategies, leading to higher (cost) effectiveness.

2. Target groups

The research findings of this thesis could be of interest for a broader public outside the academic circles as well. First of all, these results might be relevant for individuals with an MDD diagnosis, and their friends and family members. The current trial and error approach in MDD treatment leads to potentially long treatment trajectories, chronicity, demoralization, and decreased psychosocial functioning, that are all affecting this group directly. In addition, the application of prediction models as an alternative to clinical judgment to guide treatment selection might improve shared decision making. Although shared decision is considered key in patient-centered care (Weston, 2001), it has not yet been widely implemented in clinical practice (Couët et al., 2015). Information provided by prediction models could facilitate patient involvement by changing the dynamic between patient and clinician, moving from paternalism to a dialogue between two more equally engaged and informed partners. Secondly, since the results suggest various directions for improvement in clinical decision making (e.g., less focus on comorbidity and clinical judgment), they might be of interest to mental health care professionals. In addition, investigating ways to reduce the negative consequences of the trial and error approach can be beneficial for professionals as well, since these consequences can potentially lead to demoralization and professional dissatisfaction. Finally, since the results of this thesis contribute to future development of more efficient treatment strategies for MDD, they might be relevant to policy makers and health insurance companies as well.

3. Activities & products

The results of this dissertation could contribute to the development of various activities and products. First, findings of this thesis point towards potential adjustment of multidisciplinary guidelines for MDD. Results indicated that the traditional focus on comorbidity and clinical judgment to guide treatment strategies for MDD is supported by inconsistent, non-robust and limited evidence (**Chapter 2, 3, 4, 10**). However, this focus has not been abandoned in clinical practice. In particular, personality pathology and clinical judgment are still important pillars in treatment selection for MDD. This is illustrated by **Chapter 5**, where we found that, in contrast to clinical practice guidelines, individuals with personality pathology received significantly more psychotherapy sessions as compared to individuals without personality pathology. Although multidisciplinary guidelines for MDD do not support the more traditional approaches, the potential negative effects of relying on these approaches could be emphasized more strongly. In addition, future research is needed to better understand how current clinical decision making is impacting individual treatment outcomes. Once we gain this understanding, directions on how to relate to the current state of practice could be added to the multidisciplinary guidelines. In addition to the results on traditional methods, findings regarding long-

term effects of cognitive therapy (CT) and interpersonal psychotherapy (IPT), and findings on the role of psychotherapy in treatment resistant depression (TRD) could contribute to potential adjustment of guidelines. In the current multidisciplinary guidelines for MDD, CT and IPT are the two time-limited psychotherapies of choice for MDD. The finding that CT and IPT are equally effective in the long run (**Chapter 6**), should strengthen the guideline's stance that these are both valid treatment options. A final potential contribution of this thesis's findings to guidelines is the meta-analytic evidence that the addition of psychotherapy to treatment as usual can be beneficial for individuals with TRD (**Chapter 9**).

Second, findings of this thesis could contribute to the potential adjustment of clinical training programs of mental health care professionals. As mentioned in **Chapter 10** and **Chapter 13**, despite the evidence of the superiority of statistical prediction over clinical judgement, the role of clinical judgement in decision making is still strong in daily practice. To change this, mental health care professionals should receive ongoing clinical training and feedback on known errors in clinical judgement. In addition, education on statistics and probability theory should be a significant part of the curriculum, to better understand and evaluate new technological advances in mental health. Furthermore, the finding that different individuals could benefit differently from CT and IPT (**Chapter 8**), highlights the importance of a varied range of psychotherapeutic modalities in treatment programs for MDD. In current clinical programs the emphasis on CT is strong, while IPT is often not a required part of training (Markowitz & Weissman, 2012). To preserve a varied range of psychotherapeutic options, clinical programs should offer training of different types of time-limited psychotherapy for MDD.

Third, findings of this thesis could provide future directions on the development of prediction models and decision tools that can guide treatment strategies for MDD. As illustrated in **Chapter 7** and **Chapter 8**, prediction models show promising results in optimizing treatment planning and selection. However, current studies are predominantly "proof of concepts", since prediction models have mainly been applied in research contexts rather than being tested and implemented in real-world settings. Important next steps involve improvement of statistical techniques (**Chapter 12**), external validation (**Chapter 11**) and prospective testing. In addition, models that optimize both treatment selection and adaptation need to be explored to maximize the effectiveness for personalized treatment strategies (**Chapter 13**). Once prediction models are proven effective based on prospective testing, efforts should be made to develop decision tools that translate predictions and recommendations of these models in an evident and engaging way. In order to achieve this, involvement of end-users (patients and mental health care professionals) should be a central part to bridge the gap between clinical practice and research (**Chapter 13**).

4. Innovation

The studies in this thesis have various innovative aspects. First of all, the overall aim of this thesis is innovative, by moving from the “one size fits all” approach towards a more personalized perspective on treatment. This perspective is in line with the personalized or precision medicine movement, that has attracted a great deal of attention in the field of medicine (Katsnelson, 2013). Second, both traditional and innovative methods to personalize treatment strategies for MDD have been investigated. Examining the “status quo” of treatment strategies enables understanding of potential opportunities for innovation. Since we found that the more traditional treatment strategies are problematic, the need for more innovative solutions, such as prediction models, becomes more apparent. Third, the statistical techniques that were used in the chapters of this dissertation may be considered scientifically innovative. In **Chapter 7, 8, and 11** supervised machine learning techniques were applied to build prediction models, and in **Chapter 12** a recently developed Bayesian methodology was introduced to model subgroups of depression treatment response. Fourth, the designs and results of the studies have innovative aspects as well. In **Chapter 3 and 4**, no impact of personality pathology on MDD treatment outcome was found, which is contrary to previous meta-analyses. In **Chapter 6** enduring effects of acute phase CT and IPT were studied head-to-head for the first time. In **Chapter 11**, efforts to externally validate the Personalized Advantage Index (prediction model) are presented, which has not been done before in the context of two randomized trials. Fifth, findings reported in **Chapter 7, 8, 11, 12 and 13** of this dissertation highlight the challenges associated with the development of prediction models and decision tools and could therefore potentially serve as starting points for future innovation. Finally, findings of this dissertation include interdisciplinary research that could lead to surprising and innovate insights. In **Chapter 12**, joint efforts of researchers and clinicians from the fields of psychiatry, clinical psychology and econometrics are presented, resulting in valuable insights on subgroups of treatment response in MDD. Given the methodological challenges associated with the development of prediction models (**Chapter 13**), one could argue that these joint forces are crucial to solve complex clinical and statistical problems.

5. Planning & implementation

The chapters of this thesis were published in or submitted to international peer-reviewed journals, and are therefore accessible to researchers and mental health care professionals. To maximize the accessibility of the findings, part of the studies were published Open Access, and results of the STEPd study were published in clinical journals that specifically targets mental health care professionals who are not working in a research setting (*Tijdschrift voor Psychiatrie / Tijdschrift voor Psychotherapie*). In addition, findings have been presented to researchers and clinicians on various (inter)

national conferences (e.g., conferences of VGCT, NVvP, ISIPT, ABCT, SPR and NedKad) and at mental health care centers (e.g., Zuiderland GGZ Sittard, METggz Roermond, MUMC+). Efforts to disseminate these results to a broader audience have been undertaken as well, by discussing findings in public debates (i.e., P.C. Kuiperdebat, Studium Generale), and by outlining the need for personalized treatment strategies in a publication on an online platform (i.e., dejongepsychiater.nl). In addition, we are planning to report the results of the STEPd study in an article of *Dagblad de Limburger*. Furthermore, this thesis represents a solid infrastructure for knowledge dissemination, since it is a result of an interfaculty collaboration, and based on an (inter)national network of other research groups (e.g., VU Amsterdam, PsyQ, Radboud University, University of Pennsylvania).

In addition to the knowledge dissemination efforts for the findings of this thesis, plans for further valorization of innovative methods to personalize treatment strategies are being put in place. In the next years, we plan to develop easy-to-use decision tools to guide treatment strategies for MDD using complex statistics based on interdisciplinary teamwork. During this process, the methods and techniques that are developed will be presented and made available continuously, by means of (inter)national publications and presentations. In addition, we intend to make statistical models available to researchers, mental health care professionals and their organizations by offering free CRAN (Comprehensive R Archive Network) packages for the models using open source software. If successful, this project will result in improvement of the effectiveness of treatments for MDD in secondary and tertiary mental health settings leading to a reduction of disease burden and related costs. The new models developed in this interdisciplinary context might have potential application areas in other academic fields as well, such as social sciences, medicine, and economics. We plan to facilitate this with inter-disciplinary seminars. In the development of prediction models and decision tools we aim to 1) extend our global network, and 2) intensify end-user involvement (patients and mental health care professionals), that will contribute to the knowledge utilization. As mentioned in **Chapter 13**, a strong global network of “academic workplaces” is key to the development and validation of prediction models. Efforts to broaden our international network have been undertaken, including plans of work visits and joint grant applications. End-user involvement will be a central part of the development of prediction models and decision tools. For the prediction model development, “expert elicitation methods” will be investigated, in which expert opinion (and its uncertainty) of mental health care professionals and patients can be translated to prediction models. Part of this plan has been recently awarded with the Data Science Research Competition 2020 award of Maastricht University. In addition to model development, we will involve end-users in the creation of user-friendly interfaces of the decision tools.

6. References

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