Going beyond cost-effectiveness: analyzing routine mental healthcare data and stakeholders' perspectives to improve depression care

Kan, Kaying

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CHAPTER 1

General introduction

Major Depressive Disorder (MDD) is a highly prevalent disorder, affecting more than 264 million people globally[1]. Experiencing feelings of loss, grief, depressed mood, not sleeping well, loss of pleasure in activities that are normally enjoyed to a certain extend are part of the human condition. They are usually related to things people experience, and can be seen as an adequate reaction that may also help us cope with adversities in life. However, if such symptoms and feelings persist for longer periods, affecting functioning and wellbeing, those feelings may transform into a (clinical) depression. An episode of MDD generally takes between 3-12 months[2,3], and has a large impact on the quality of life of both patients and their families. Having an MDD is associated with limitations in both physical, social and role functioning[4]. Globally, depressive disorders are among the top three leading causes of years lived with disability according to the most recent Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2017)[5].

In this thesis, the term (clinical/unipolar) depression is used interchangeably with major depressive disorder according the definition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV/V) of the American Psychiatric Association[6].

Definition, epidemiology and etiology of MDD

A description of the diagnostic criteria of an MDD is presented in Box 1.

In the Netherlands, the lifetime prevalence of MDD is estimated at around 18.7% with a 12-month prevalence of 5.2%[7]. This means that almost one in five individuals will experience an MDD during their life. Comparable rates are found in other high-income countries (14.6% and 5.5% respectively)[8].

There is no single cause for the development of depression. A depression may arise from both social, psychological and biological/genetic factors, often catalyzed by life stresses and events. Although most people recover from their primary episode, a part will suffer from a long-lasting episode or chronic depression, whereas a significant proportion suffers from recurrences after initial recovery [9]. The percentage of recurrence of MDD in the general population is 35% after 15 years. In patients with more severe depression who are treated in specialist mental healthcare, however MDD may reoccur up to 85% (60% after 5 years, 67% after 10 years)[10].

Although a diagnosis of MDD helps guiding clinicians in the selection of treatment, heterogeneity in MDD exists. All patients satisfying the DSM-criteria for the diagnosis of an MDD might share some core symptoms, but at the same time may have considerable variation in etiology, pathogenesis, and symptoms[11,12]. The heterogeneity in manifestations and etiology makes it difficult to treat depression effectively.

The economic burden of depression

Apart from the impact on patients' lives, depressions are also associated with a substantial economic burden. In the Netherlands, depressive disorders are one of the most expensive diseases with healthcare expenditures of nearly €1.1 billion annually[13]. This

Box 1. Diagnostic criteria of major depressive disorders

According to DSM criteria, persons are diagnosed with a major depressive disorder if an individual is experiencing ≥5 symptoms during the same 2-week period. These symptoms must cause the individual impairment in important areas of functioning in comparison with previous functioning. At least depressed mood (1) or loss of interest/ pleasure (2) must be present in combination with at least four other depressive symptoms:

1. Depressed mood - most of the day, nearly every day.
2. Loss of interest / pleasure - markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
4. Sleep disturbance (insomnia or hypersomnia)
5. Psychomotor agitation or retardation - a slowing down of thought and a reduction of physical movement and observable by others (not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. In addition, the symptoms must not be due to the direct physiological effects of substance use or another medical condition.

means 4.5% of total mental healthcare expenditure and at least 1.3% of total healthcare expenditure in the Netherlands[13]. Of the depression related health expenditures, the majority of costs (87%) are spent on mental healthcare and drugs and devices (5%). Next to the direct medical costs, the indirect societal costs of presenteeism and absenteeism are considerable[14,15], as well as the costs associated with mortality due to suicides[16].

The total costs of depression in European countries are substantial and correspond to 1% of the total economy of Europe (GDP). The annual direct and indirect costs of depression in Europe were estimated at € 118 billion (direct: 42 billion, indirect costs due to morbidity and mortality € 76 billion), which corresponds to a cost of € 253 per inhabitant in 2004[17]. Results from several cost-of-illness studies performed all over the world consistently demonstrated that depression is associated with a considerable increase in both direct and indirect costs[18,19]. Differences in methodologies and the type of costs included hinders comparison between studies. Nevertheless, a review of published cost-of-illness studies of depression worldwide demonstrated that the annual average direct excess costs for a depressed individual ranged from $1000 to $2500 (when ignoring outliers)[18]. The average annual costs per individual with depression ranged from $2000 to $3700 for morbidity costs (indirect costs) and from $200 to $400 for mortality costs.

Evidence-based treatment and personalized care for MDD

Different psychological and pharmacological treatments exist for MDD. Meta-analyses have demonstrated the efficacy of these different types of treatments and treatment combinations in the treatment of MDD in adults[20-22]. Unfortunately, these meta-analyses also show that on average most treatments for MDD are only moderately effective. Although the efficacy of psychiatric treatments is comparable to that of medical treatments overall[23], around 30% of patients do not respond to treatment[24]. In addition, there is large individual variation in treatment outcomes [23]. No single treatment suits everyone, and treatment response varies substantially between individuals[25]. Therefore, in the past decades research has focused on trying to answer the famously stated question of Gordon Paul (1967)[26]: *What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?*

Indeed, the latter question may prelude precision medicine, which only today seems to become an emerging approach for treatment and prevention taking into account each person's variability in genetic makeup, environment and lifestyle[27]. Specific for precision psychiatry, the goal is to achieve better lives for those suffering from mental illness by the development of tools capable of providing more accurate diagnosis, of ascertaining prognosis, guiding treatment and predicting treatment response[28,29]. Research into precision psychiatry is ongoing and among others includes identifying predictors of the course of depression[30], of treatment response[31] and ideally also factors that would help select optimal treatment for each individual patient[32]. An example of the latter is the development of the Personalized Advantage Index (PAI), a measure of the predicted advantage in one treatment compared to another treatment for a unique individual[33].

Precision medicine [defined as: the tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment[34]] aims to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease. It is often interchangeably used with the term *personalized* medicine [individualized treatments and preventions developed for every unique patient[35]], that aims to find the most appropriate treatment for a particular patient. Personalized medicine focuses on a personal approach for every patient, by taking the patient's preferences and values into consideration, enhancing treatment outcomes. Examples are the effect that the treating clinician has on the treatment of depression, the incorporation of the patient's preferences regarding treatment or focusing on patient-relevant outcomes of treatment. When patients have positive treatment expectations prior to treatment initiation, they are more likely to recover from treatment[36].

Personalized treatment requires systematic use of knowledge regarding: (1) variables that influence the development, course and effects of specific treatment options for

depression, (2) clinical experience with similar patients in similar circumstances, and (3) the patient's experiences and preferences regarding the meaning of the disease or symptoms[37]. In addition, it requires an environment in which relevant data for clinical decision making are systematically used and can be shared with patients[37]. At the same time, it requires a supportive clinical culture that facilitates patient engagement and shared decision making regarding treatment[38].

Knowledge regarding the identification of variables that are predictive of treatment response in patients with MDD is growing rapidly. However, to date the question of *what works for whom* for the greater part remains unanswered. If it would be possible to predict which treatments are effective for what patients, thus limiting the use of a specific treatment to patients for whom treatment is effective, and meanwhile preventing patients to undergo treatment that for them are ineffective, overall treatment effectiveness would greatly increase. Knowledge about all kinds of moderating variables for the objective to help to predict whether a patient will most likely benefit from one treatment over another, and especially the translation of research data into clinical practice recommendations with relevance for an individual patient, is still limited.

Shared decision making (SDM)

Over the last decade the patient empowerment movement has resulted in shared decision making (SDM) gaining attention. SDM is an approach where patients and clinicians reach joint decisions using the best available evidence[38]. Although the majority of patients (88%) considers shared decisions regarding care important, apparently 46% has never explicitly discussed this with their clinician[39]. More attention should be paid to SDM within the treatment selection process to arrive at an informed and value-based treatment choice[40,41]. The use of data driven decision aids in clinical practice may facilitate SDM, as such tools provide personalized treatment options according to the patient's characteristics and preferences[42].

Strategies to improve effectiveness and efficiency of depression care on different levels of healthcare

Most countries only invest limited public resources in mental healthcare[43,44]. Therefore, countries must make decisions regarding which treatments to include in the basic benefit package. This requires sometimes difficult choices to maintain a comprehensive and affordable healthcare package of high quality to ensure sustainability of health systems. Accordingly, numerous frameworks exist to guide healthcare decision making[45,46]. To substantiate reimbursement decisions, developed countries may deploy formal health technology assessments (HTAs). HTA refers to the systematic evaluation of the properties and effects of a health technology, addressing the direct and indirect effects, as well as the intended and unintended effects. It is a multidisciplinary process that summarizes information about medical, social, economic and ethical issues related

to the use of a health technology while balancing these against the (extra) costs incurred to inform policy decision making[47].

National reimbursement and policy decisions influence care on both regional and individual patient level, and vice versa. For example, reimbursement decisions on a national level regarding effective care can protect patients against ineffective treatments on an individual patient-level, while at the same time influencing the availability of treatments on an organizational level. The use of HTA facilitates optimizing care on a national level as well as healthcare system level. This may be achieved through assessing the cost-effectiveness of interventions included in a healthcare package and by examining the budget impact when new interventions are added or when scaling up or scaling down certain interventions. However, HTA assumes that treatments offered may be identified as optimal and, while it is clear that treatments for depression are not optimal for each individual patient. Therefore, precision treatment strategies to optimize treatment are needed. One way to improve treatment strategies in the care of patients with MDD is by using treatment algorithms. Some examples of these studies include the German Algorithm Project (GAP), the Texas Medication Algorithm Project (TMAP), and the Sequences Treatment Alternatives to Relieve Depression (STAR*D) study. The GAP study evaluated the effectiveness, feasibility and acceptance of an algorithm-guided standard stepwise drug treatment regimen targeting inpatients with depressive disorders[48,49]. One of the studies of TMAP was the evaluation of an algorithm-guided treatment program for patients with MDD[50]. STAR*D aimed to prospectively identify which of several treatment options would be most effective for outpatients with MDD in whom initial and sometimes subsequent treatments appeared unsatisfactorily [51]. These algorithms mainly focused on treatment with antidepressant medication.

Conversely, improving the efficiency of depression care at an individual patient level impacts care and care strategies on a national level. If care is tailored and provided according to patients' needs, treatment outcomes are enhanced and actual effectiveness is improved. The demand of treatment types meeting patients' needs has implications for healthcare professionals both on an organizational level and the resources required on a national level.

Next to coverage, also the health system organization impacts choices open to care providers and patients, and on the efficiency of care. To maintain a sustainable health system, improving the efficiency of different levels of healthcare is required, while keeping in mind the social, organizational and ethical issues. This requires data regarding patient characteristics and patient demographics, data regarding treatments and diagnoses, and data regarding treatment outcomes, and obviously patient-relevant outcomes. At the same time, it also requires the identification of gaps, concerns and aspects that matter to stakeholders, as well as their values and preferences.

IMPROVE - Improving Mental Healthcare using Personalized treatment based on analyses of Routine data for Optimal Value and Effectiveness

In September 2015 the IMPROVE-project (acronym for Improving Mental Healthcare using Personalized treatment based on analyses of Routine data for Optimal Value and Effectiveness) was initiated. The IMPROVE-project pursues research, innovation and implementation by collaboration between mental healthcare organizations (Rob Giel Research *center,* RGOc), payers (De Friesland Zorgverzekeraar, an insurer), patients (MIND, an umbrella organization in mental health) and scientists (UMCG: HTA-unit, Psychiatry-unit, Netherlands Institute of Mental Health and Addiction (Trimbos Instituut)).

The collaboration between several mental healthcare organizations in the northern region of the Netherlands is unique. The Rob Giel Research *center* is a joint venture of several mental health organizations (University Center Psychiatry of the University Medical Center Groningen, GGZ Friesland, GGZ Drenthe, Lentis, Dimence Group and Mediant). As part of this collaboration, administrative data regarding mental health service use and treatment outcomes have been systematically gathered and stored in databases. Within the IMPROVE-project, these routinely collected data sources are made available for research in a data-infrastructure that respects safety and privacy issues. Once combined and enriched with new data sources, such as insurer data and qualitative data, the effectiveness and cost-effectiveness of mental healthcare in the Northern-Netherlands is analyzed to support optimal treatment choices.

Data used in this thesis

The studies described in this thesis are part of the IMPROVE-project. All quantitative studies in this thesis have mainly used observational data. We did so in spite of the notion that randomized controlled trials (RCTs) are generally considered the "gold standard" for the evaluation of treatment effectiveness, because there are also inherent limitations of using experimental data. An advantage of randomization is that it protects against several types of bias (e.g. selection bias and confounding) thus increasing internal validity. In addition, the controlled setting prevents outcome bias and observer bias. On the other hand, observational data may address the limitations of RCTs: it can improve the generalizability (external validity) and the evaluation of longer-term follow-up is less burdensome. In observational studies, treatments are not randomly assigned, as observations occur in a natural setting, i.e. without specifically selecting participants for an experiment. The assignment of subjects to groups is observed and not manipulated. A further advantage may be that data accrues naturally reaching considerable numbers and follow-up thus allowing efficient comparisons of treatment strategies or different groups of patients. Finally, observational data resembles real world decisions and circumstances (e.g. waiting lists, wrong or late referrals, professionals not adhering to guidelines).

The observational data sources used in this thesis are described in Table 1. Using observational data for evaluating the organization of care, mental health systems and treatments and costs, typically requires four types of data: (1) Patient identification data including diagnosis and basic demographic information, (2) treatment data, (3) outcome data, and (4) covariates to address selection and potential confounding such as comorbidities, and demographic information. The quantitative studies described in this thesis required linkage of these data sources, and thus allowed us to investigate costs and effectiveness of treatment, healthcare utilization in patients with depression and the impact of a mental health system change for depression care. The linkage of the data sources required a trusted third party (TTP), which facilitates the data linkage between the different data sources of several parties and care organizations while meeting the General Data Protection Regulation (GDPR)[52].

Qualitative data

Several chapters described in this thesis used qualitative research methods, as experiences, values and perspectives are difficult to obtain from quantitative data. Qualitative research methods are appropriate to answer questions about experiences, attitudes and meaning from the perspective of the participant. The method can also be used to reveal potential problems or consequences of a certain health technology, or to identify gaps in clinical practice. To strengthen each other, the outcomes of the qualitative and the quantitative studies are combined (mixed methods) in two chapters in this thesis.

Aim and outline of this thesis

The aim of the research presented in this thesis is to make use of systematically available routine mental healthcare data and stakeholders' perspectives to learn about past and current practice, and to use the outcomes of our research to improve the efficiency of depression care at both the micro-level (patient-level) and macro-level (national policy decision making level). Our assessments where enriched by using qualitative data sources. The knowledge that we obtain with this thesis provides an answer to the following question: *How can we optimize the quality and efficiency of care for depression in Northern Netherlands, by making use of existing linked administrative data sources in combination with stakeholders' perspectives?* The overall aim is to facilitate personalized treatment and to support and enhance (shared) decision-making. The knowledge obtained allows to continue developing tools to further personalize treatment for depression and to provide clinical practice recommendations.

Chapter 2 examines the clinical effectiveness of an algorithm-guided treatment program for depression, consisting of both psychotherapeutic and pharmacological interventions, in a naturalistic setting. In this study, we used administrative treatment data of GGZ Friesland (over a 3-year period) combined with routine outcome monitoring data. The effectiveness of the different treatments within the algorithm-guided

Table 1. Sources of data in this thesis.

Data source	Covered regions/ organizations and period	Content
Specialist mental healthcare treatment pathway data	Friesland: GGZ Friesland 2012-2014	Treatment pathways defined by the type of treatment, (b) the frequency of treatment and (c) the maximum number of treatment sessions. The available treatment information consisted of treatment type, starting and ending dates of treatment, number of treatment sessions recommended and completed, and treatment duration.
Psychiatric Case Register North Netherlands (PCRNN)	Friesland Groningen Drenthe 2000-2012	An administrative mental healthcare database, containing patient level specialist mental health service use and clinical diagnosis data for patients in the northern region of the Netherlands (1.7 million inhabitants). The PCRNN-data contains patient demographics, main and secondary diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders and the date and type of mental health service use.
Treatment data- DBC Informatie-ysteem (DIS) data	Friesland: GGZ Friesland, Synaeda Drenthe: GGZ Drenthe Groningen: University Center Psychiatry 2011-2020	Administrative data regarding treatment derived from Diagnosis-Treatment Combinations (in Dutch: Diagnose-BehandelCombinatie (DBC), comparable to the internationally used Diagnosis-Related Groups or Healthcare Resource Groups) data. Mental healthcare organizations are required to provide this data to the Dutch Healthcare Authority (in Dutch: de Nederlandse Zorgautoriteit)
Outcome data: Routine Outcome Monitoring (ROM) data	Friesland Drenthe Groningen 2011-2020	ROM questionnaires to evaluate treatment and to measure patients' progress. For example, the Inventory of Depressive Symptomatology – Self-Report and the Outcome Questionnaire [53,54]
Qualitative data		Data obtained from participants regarding beliefs, attitudes and experiences by conduct of focus group discussions and interviews

treatment program are compared to the efficacy reported in randomized controlled trials. In addition, this study assesses the relation between treatment continuity and remission and response rates. The outcomes of this study provide us with insights whether the effects of treatments within an algorithm guided treatment program can approach the efficacy reported in randomized controlled trials, and whether a fixed number of treatment sessions suits all patients.

As most patients with MDD have psychiatric comorbidities the majority of cost-of-illness studies correct for comorbidities. Therefore, we compared specialist mental healthcare utilization and treatment costs in patients diagnosed with MDD with and without psychiatric comorbidities in **Chapter 3**. In addition, we investigate which patient characteristics and clinical variables drive costs of treatment. For this study we use administrative data of the Psychiatric Case Register North Netherlands containing patient level specialist mental health service use covering a 13-year period. Knowledge of cost drivers may help in the development of future stratified disease management programs.

Importantly, the Dutch mental health system underwent a transformation in 2014 with the aim to realize efficient and appropriate mental healthcare. **Chapter 4** investigates

the impact of this system change on average treatment costs and inpatients stays in patients diagnosed with MDD. In this study, administrative data regarding mental care utilization are obtained from DIS treatment data from three different mental healthcare organizations in the northern region of the Netherlands from 2011-2017. The results of the study will provide insights regarding the feasibility and practicality of the goals of the system change on a regional level.

Apart from cost-effectiveness, considerations like feasibility, acceptability and equity may affect priority setting in healthcare. Therefore a priority setting procedure, that combines evidence evaluation with an explicit and transparent appraisal procedure to weigh these considerations, is preferred. **Chapter 5** describes efficiency of depression care on a regional policy decision-making level. We demonstrate a structured approach for eliciting and evaluating a broad range of assessment criteria, incorporating the results of cost-effectiveness analyses and key stakeholders' values. For a set of cost-effective substitute interventions for depression care, this study makes use of qualitative research and aims to support decision makers in priority setting in a different way than having a deliberative commission. The outcomes of this study demonstrate which concerns may hinder successful implementation prior to adoption of policies.

Moving towards personalized treatment in patients with depression requires knowledge regarding patient-relevant outcomes and ways to empower patient involvement in treatment and treatment decisions. In Chapter 6 and Chapter 7 we aim to personalize depression treatment using routinely collected intake and outcome data in combination with qualitative research. Although symptomatic remission is considered the optimal outcome in depression, symptom indicators may not fully capture patients' and clinicians' perspectives on remission. In **Chapter 6,** we use focus group discussions and semi-structured interviews to examine relevant outcomes of depression treatment in specialist mental healthcare from patients' and clinicians' perspectives. Next, we investigate whether these perspectives differ from each other. We use the outcomes of this qualitative study to develop a decision-aid for patients with depression who consider taking treatment. In **Chapter 7**, we describe the development of the decision-aid I-SHARED, which aims to provide patients and clinicians with thorough and orderly information regarding symptoms, medical history and situational factors in a digital report. Subsequently, depression treatment decisions may be guided and informed, thus enhancing shared decision-making in clinical practice. Next to the outcomes of our qualitative research, this study uses routinely collected data to provide patients and clinicians with an overview of treatment options of similar patients that recovered in the past applying a statistical learning algorithm.

Finally, **Chapter 8** summarizes the main findings of this thesis, and discusses the most important limitations. In addition, the clinical implications, as well as recommendations for future studies will be discussed.

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