Things change: The early identification of patients with an unfavourable prognosis

Boer, S.

Chapter 7

General discussion;
including a summary.

OVERALL THESIS AIM

Most health care costs for chronic conditions are used by a small subgroup of patients with an unfavourable prognosis. The main objective of this thesis was to improve identification of patients with an unfavourable prognosis of chronic disease early in their treatment course, which may facilitate proactive approaches to improve clinical outcomes. In this final chapter, we first recapture the main findings of the thesis; secondly, we discuss two conceptually distinct constructs of predictors of prognosis that can be applied in different chronic conditions: the level of control of the chronic condition, and information on early treatment response. Thirdly, we discuss the clinical implications and future perspectives. Finally, we present our main conclusions based on this thesis.

SUMMARY OF MAIN FINDINGS

In **chapter 2** we described and quantified the impact of treatment duration on mental healthcare utilization in patients with depressive and anxiety disorders. This study serves to demonstrate the relevance of early identification of patients with an unfavourable prognosis. Patients with a longer treatment course have a high impact on use of mental healthcare resources, with 60% of all contacts dedicated to 25% of patients. Thereby, treatment density is highest for patients with a prolonged treatment course (>2 years) over the entire course of treatment, with no decrease over time.

In **chapter 3** we aimed to improve clinical prediction of a prolonged treatment course based on baseline characteristics, and explored the additional predictive value of early treatment response (after 2-6 months of treatment) in symptoms, in patients with depressive and anxiety disorders. In this setting, we especially aimed to assess the role of a composite symptom severity score as an indicator for a prolonged treatment course. Results showed that number and severity of symptoms (symptom rating) at 2-6 months after treatment initiation is a strong predictor for prolonged treatment course. Other clinical predictors were outperformed by the inclusion of this indicator and therefore not included in the final risk prediction model. This allows for easy clinical risk profiling relatively early in the course of treatment; classifying patients as having a low or a high predicted risk of a prolonged treatment course. For depressive disorders, for patients with the highest scores, the positive predictive value for a prolonged treatment course was 60% (sensitivity 0.38, specificity 0.81). For anxiety disorders, for patients with the highest scores, the positive predictive value for a prolonged treatment course was 52%

(sensitivity 0.55, specificity 0.75). Although the sensitivity of the score is not very high, the positive predictive value is sufficient to consider patients with a high-risk score for evaluation and monitoring of rational medication switches, add-on psychotherapy, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances. No formal external validation study was performed.[1] We consider it likely that the prediction will improve with repeated measurement over time.

In **chapter 4** we explored whether we could identify patients with a high probability of persistent uncontrolled hypertension (systolic blood pressure > 140 mmHg) after approximately two months of (anti-hypertensive) treatment, based on patient characteristics and early treatment responses assessed by self-monitored blood pressure measurements. We showed that higher levels of systolic blood pressure at approximately two months, in addition to baseline systolic blood pressure, predicts persistent uncontrolled hypertension after one year of treatment. Other (patient characteristic) predictors did not contribute to the prediction.

In **chapter 5** we aimed to assess the risk of future adverse outcomes in patients with asthma, such as (severe) exacerbations, fixed airflow limitation and/or side-effect of medication. We considered patient characteristics and clinical variables at baseline, and information on early treatment response as potential predictors. Performance of the risk prediction improved when including information on early treatment response in terms of level of asthma control, compared to a model with only baseline characteristics (respectively an Area Under the Receiver Operating Characteristics (AUROC) of 0.84 and 0.79). The risk prediction model includes six easy to obtain predictors; sex, Asthma Control Questionnaire (ACQ)-score and exacerbations in the previous year at baseline and at 1st follow-up ACQ, smoking status and exacerbations in the previous three months (indicating early treatment response). The risk prediction model classifies 57.7% of the patients as having a low risk (absolute risk 11.7%) for future adverse outcomes. These patients could be assessed less frequent or, for example, could safely be reviewed by the practice nurse.[2]

In **chapter 6** we tried to identify those patients, based on prespecified subgroups on different levels of Fractional exhaled Nitric Oxide (FeNO), who benefit most from FeNO-driven stepped-care asthma management in primary care, compared to conventional symptom-based asthma management. FeNO-measurement is a quick and easy way to assess airway inflammation. Our results showed FeNO-driven asthma management is effective in patients with a low FeNO level, where it is possible to down-titrate

medication (such as inhaled corticosteroids) while preserving asthma control and quality of life. In primary care approximately 70% of FeNO measurements is low, and therefore, using FeNO-driven asthma management could be of enormous aid in reducing inhaled corticosteroids use without a reduction in control of asthma symptoms.

PREDICTING AN UNFAVORABLE PROGNOSIS

In this thesis we explored four chronic medical conditions (depressive disorders, anxiety disorder, hypertension and asthma) with the aim to identify patients with an unfavourable prognosis early in their treatment course. We considered variables at initiation of the treatment, as well as variables early in the treatment course. Our approach revealed two conceptually distinct constructs of predictors of an unfavourable prognosis.

The first construct of predictor of an unfavourable prognosis identified, was the **level of control** of the chronic condition; the level of symptoms in depressive and anxiety disorders, systolic blood pressure in individuals with hypertension and the level of asthma control for asthma patients. One might consider the level of control of the chronic condition to be a resultant of a broad range of underlying risk factors, as several studies in depressive and anxiety disorders, hypertension and asthma have shown: for example comorbid conditions, medication adherence and other patient characteristics as coping strategy, body mass index, inactivity or age.[3-11] By using one single variable, the level of control of the chronic condition, as proxy for a broader range of variables, the prediction of an unfavourable prognosis is clearly simplified.

The second construct of predictor of an unfavourable prognosis identified in this thesis, was information on **early treatment response**. This early treatment response, i.e. after 2-6 months, had additional predictive ability for unfavourable prognosis, compared to baseline measurements of condition severity only. In patients with hypertension and asthma the final prediction model included both a measure of baseline condition control, as well as a measure of early treatment response: in patients with depressive and anxiety disorders baseline condition control was not included, however, early treatment response was.

In the following paragraphs we will elaborate in more detail on both constructs of predictors.

Level of control: a possible reflection of a multitude of predictors

We found the level of control of the chronic conditions to be a prominent predictor for an unfavourable prognosis, which we observed for all conditions studied. The level of control of the chronic conditions could be the resultant of commonly known predictors and/or risk factors, which largely lose their predictive ability if the level of control is included in the prediction model. The level of control of a chronic condition captures not only condition specific characteristics as for example the number of symptoms experienced by the patient, but the level of control of a chronic condition is also determined by e.g. comorbid conditions, medication adherence and other patient characteristics as coping strategy, body mass index, inactivity or age.[3-14]

In patients with depressive and anxiety disorders, data were limited to administrative variables that were available for this study and we had no exhaustive set of variables with for example family history and personality traits such as neuroticism. However, with the level of symptom severity in the prediction model, a proxy of a multitude of predictors was included as it for example captures not only disorder specific, but also comorbid symptoms. This finding is in line with many previous studies, where the level of symptom severity also tends to outperform other predictors, also predictors not measured in this thesis.[3-7]

In patients with hypertension, a model containing only systolic blood pressure was capable of predicting persistent uncontrolled hypertension, without contribution of any additional predictors (e.g. age and medication adherence). In other words, systolic blood pressure possibly serves as a proxy of other common risk factors of hypertension.[8] For example, age was not included, but systolic blood pressure rises with age, or another example, the presence of a family history of hypertension increases the risk of an elevated systolic blood pressure. In patients with asthma we included two variables as proxies, with the Asthma Control Questionnaire-score and the occurrence of severe exacerbations.[15,16]

Information on early treatment response

The addition of early treatment response increased the predictive performance of risk prediction for an unfavourable prognosis. For this thesis, we defined early treatment response, measured after 2-6 months of treatment, relative to the same measurement at baseline. Therefore, change over time was included in our risk prediction model, in addition to baseline variables. Note that we do not state that the baseline assessment on itself is without meaning; at baseline the level of control of the chronic condition still predicts an unfavourable prognosis, albeit less discriminating.

Early treatment response is a proxy of different aspects concerning treatment effectiveness, e.g. adequateness of initial treatment and/or drugs, the mutual trust between clinician and patient and behavioral aspects such as treatment adherence.[17-26] Detailed data on the type of treatment and/or drugs could perhaps add to our prediction, but these data were not at our disposal in this thesis.[27,28] Treatment response adds an insight that can be acted upon; guiding decisions in the treatment plan. This will be discussed under the heading *long treatment trajectories: challenges in clinical practice*.

In **chapter 3**, in patients with depressive and anxiety disorders, the observation that addition of the 1st follow-up assessment to the prediction model outperforms the baseline level of symptom severity, and thereby the rate of change deserves some further elaboration. This finding is consistent with the assumption that patients with high symptom severity at 1st follow-up were likely to score high at the baseline level of symptoms, or even higher. These might be the patients with poor initial recovery, which in turn might be predictive of an unfavourable prognosis. Patients with a low(er) level of symptom severity at the 1st follow-up could consist of a mix of patients improving from a higher level of symptom severity at baseline or remaining low which heralds' better outcome overall.[29] Consistent with these assumptions and our findings, the rate of change, and thereby the baseline assessment no longer added information at the moment of first follow-up. It is the level of symptom severity at the moment of assessment, 2-6 months after the initiation of treatment, that determines risk of an unfavourable prognosis in patients with a depressive or an anxiety disorder. Presumably, the prediction will further improve when repeated, for example, after 9-12 months.

In patients with hypertension, and in patients with asthma, both baseline variables and early treatment response were included in our risk prediction model and thereby we included the rate of change. In patients with hypertension treatment response was assessed after approximately two months of treatment, in patients with asthma information on early treatment response was assessed after approximately three months, which is comparable to findings of earlier studies.[24,25,30,31]

PREDICTING UNFAVOURABLE PROGNOSIS: A NOTE OF CAUTION

In this thesis we developed risk prediction models for four medical conditions. Our findings should be interpreted with some considerations.

- The developed risk prediction models in this thesis show that in different chronic conditions the introduction of early treatment response in risk estimation seems a valuable opportunity to improve clinical practice; the use of measurements of early treatment response after approximately three months after initiation of treatment based on assessment at baseline. From patient and regulatory perspective, predicting prognosis at baseline has some advantages, especially for clinical decision making about the nature of the presenting problem and deciding which treatments will be most appropriate.[32,33] However, the initiated treatment does not always improve health outcomes as expected, or could be substantially reduced without adverse effects.[34] The inclusion of early treatment response supports medical decision making *after* the initiation of treatment.[35], thereby taking the effect of this treatment into account.[54]

- Data were limited to what was available and we had no exhaustive set of variables. We cannot exclude the possibility that other factors such as patient and/or family history, childhood trauma, specific co-morbidity, or personality characteristics (e.g. neuroticism) may add to the prediction.[36-41] as Also, detailed information on the type of treatment and/or drugs could perhaps add to our prediction, but these data were not at our disposal in this thesis.[27,28]

- For the four conditions in this thesis, we robustly found that early treatment response predicted an unfavourable prognosis. It should however be kept in mind that we did not study treatment effects; it thus still could be that a marginal early treatment response is a reflection of a somewhat effective treatment. A predicted unfavourable course based on a limited early treatment effect should thus not automatically lead to a termination of that treatment (see further).

- Generally, prediction models are in need of external validation to avoid overfitting, and it is known that many prediction models fail the validation test when applied to an external cohort.[42,43] For asthma, we did apply our risk prediction model to an external validation dataset and calculated the AUROC, which yielded an AUROC of 0.77; compared to an AUROC of 0.84 in the derivation dataset, suggesting reasonable generalizability of our findings. For depressive disorders, anxiety disorders and hypertension we were not able to perform an external validation.

- In this thesis we studied four chronic conditions, and whether the general

conclusions apply to a broader range of chronic conditions needs further research, as for example diabetes or chronic obstructive pulmonary disease (COPD).

LONG TREATMENT TRAJECTORIES: CHALLENGES IN CLINICAL PRACTICE

With the identification of patients at risk of an unfavourable prognosis in an early stage of treatment we offer a momentum to reconsider treatment, contributing to the development of personalized medicine and potentially leading to a more efficient use of healthcare resources by optimizing treatment.[44] This perfectly fits the adoption of value-based healthcare where the aim is to increase the value that is derived from the resources available e.g. the Choosing Wisely campaign: an initiative that seeks to advance a dialogue on avoiding unnecessary medical tests, treatment and procedures.[34,45]

For the developed risk prediction models, we considered it crucial to use data that is readily applicable in a clinical setting. For the models this means the use of variables that are easy to obtain or to measure.[46] In clinical practice risk prediction is most useful when people are stratified into clearly distinct categories of high or low risk; such categories can be used to inform treatment decisions. Thereby, the developed risk prediction models could be integrated in everyday practice, as for example in routine outcome monitoring or as (online) decision support tools. The ultimate goal is of course to influence the disease course in such way that the risk of an unfavourable prognosis is reduced; however, identification of such a patient group does not automatically translate into a better prognosis. That would require a strategy to influence such prognosis, for example by altering or intensifying treatment.[47]

In **Chapter 3, Chapter 4** and **Chapter 5** we provide clinicians with an early and clear estimate of unfavourable prognosis; patients can be easily classified as having a low or a high predicted risk. The inclusion of early treatment response allows for personalized clinical risk profiling relatively early in the course of treatment and identifies patients with high risk score for evaluation and monitoring of rational medication switches, add-on treatment, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances.

For depressive disorders and anxiety disorders, for patients with the highest scores, the positive predictive values for a prolonged treatment course were respectively 60% and

52%, the positive predictive values are sufficient to consider patients with a high-risk score for evaluation.[1]

For patients with hypertension, we derived an easy to calculate score which ranged from -1 to 12. For 57% of patients with a risk score of 5 to 12 points, the positive predictive value of prolonged treatment course was 65%, compared to 5% for patients with a score of -1 to 4 points. At this cut-off level sensitivity was 0.96 and specificity 0.64. For a risk score of 5-12 points either baseline systolic self-monitored blood pressure was ≥ 150 mmHg or after approximately two months of treatment systolic self-monitored blood pressure was ≥ 130 mmHg. Patients without or with minimal decrease of systolic blood pressure (high risk patients) for evaluation should thus be specifically considered.

In patients with asthma, after 3 months of treatment, 16.1% of the asthma patients was classified as having a high risk for an unfavourable prognosis, on the other hand the risk prediction model classifies 57.7% of the patients as having a low risk. For patients with a low risk, and although treatment could be continued, other options might be considered as well, such as a reduction in dose, by also a less frequent treatment control, or a shift in control from general practitioner to practice nurse are options. In **chapter 6** we provided an example of stepped-care asthma management is effective in patients with a low FeNO level, where it is possible to down-titrate medication while preserving asthma control and quality of life. This allows the clinician more time for an extensive review in the smaller subgroup of patients in the highest risk category.

The patient's perspective

One of the most important aspects of having a chronic medical condition regards the chances of getting and maintaining the medical condition controlled, with minimal adverse events and good health related quality of life. With the developed risk predictions, we support medical decision making on continuing, altering or even terminating treatment.[48] Even if the initiated treatment will be continued, it could be a moment to inform about the future course and to guide clinicians and patients in shared decision making on further treatment, if any. Thereby, the communication between clinicians and patients may improve, and patients tend to feel safer when they participate in their own treatment plan; which creates individualisation of treatment.[49] Furthermore, for this thesis we aimed our predictors to be easily accessible, followed by a clear and easy understandable risk prediction score, it is easier for a patient to visualise their own risk and end goal, and possible feel more urge to change some things (*see the supplement for examples, appendix 1*) .

ROUTINE HEALTH CARE DATA

Standard management of chronic medical conditions, depending on the specific condition, generally consists of frequent (routine) patients visits involving the assessment of symptoms, health related quality of life, medication adherence, laboratory measurements and additional clinical parameters.[50,51] Resulting in *routine healthcare data*, and providing a unique opportunity to improve clinical practice in facilitating continuous tailoring of treatment; and data that is increasingly used for research purposes.[46]

The potential of routine healthcare data gains a growing awareness for research purposes as it is perceived as highly representative for daily practice, the sample sizes are large, and routine healthcare data consist of a continuously input of information on the state of condition control of the patient, with a potential linkage to other databases.[52] If gathered validly, routine health care data can support clinicians in personalized medicine, as a continuously input leads to an ongoing way to support medical decision making on continuing, altering or even terminating treatment.[44,48] Thereby, it is likely that large databases will provide the base for studies on predictors of health outcomes with more power for statistical modeling, while minimizing costs and effort.[53] Increasingly, routinely healthcare data are used to study the effectiveness of treatment. Demonstrating the effectiveness of treatment is difficult, as confounding by indication is difficult to disentangle.[54] It should be kept in mind that routine healthcare data are mostly not collected for research purposes, but healthcare driven. This could imply that data is not complete, the level of details is less than desired, or the information is not uniformly coded. Therefore, the researcher always has to ensure the completeness, validity, and applicability of the data for the question of interest.[55-57] Other challenges to be considered are for example standardized collection of data within and across providers and/or institutions, or privacy-issues; who has access to patient data and how this information will be acted upon.

CONCLUSIONS

The fact that most healthcare resources are spend on a small subgroup of patients with an unfavourable prognosis has long been recognized, and is also supported by **chapter 2** of this thesis. Therefore, we emphasize, change is needed in terms of an improved identification of patients with an unfavourable prognosis, early in their treatment course, which may facilitate proactive approaches to improve outcomes. We discussed two conceptually distinct constructs of predictors of prognosis in order to improve

the identification of patients with an unfavourable prognosis. First, the level of control of the chronic condition as a predictor could reflect to some extent the presence of a multitude of other risk factors, which largely lose their significance if the level of control is included in the prediction model. Second, information on early treatment response had better predictive ability for long-term outcomes and so acts as a proxy for treatment effectiveness. Treatment effectiveness depends on different aspects e.g.adequateness of initial treatment and/or drugs, the mutual trust between clinician and patient and behavioral aspects such as treatment adherence. Treatment response adds an insight that can be acted upon; guiding personalized decisions in the treatment plan. Consider patients with high risk scores for evaluation and monitoring of rational medication switches, add-on treatment, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances. For patients with a low risk, treatment could be continued, or treatment could be safely assessed less frequent or, for example, in primary care, could be reviewed by the practice nurse. This allows the clinician more time for an extensive review and medication changes, in the smaller subgroup of patients in the highest risk category. We want to emphasize that with the risk prediction score we classify patients, it is ultimately up to the clinician to decide on treatment approach.

In conclusion, this thesis leads to improvement of personalized medicine and thereby could increase the efficient use of healthcare resources, with the early identification of patients at risk of an unfavourable prognosis.

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