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Beyond Treatment of Depressive Symptoms

Kolovos, S.

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Chapter 1 is a general introduction to this PhD thesis. Depression is a debilitating condition that influences a large number of individuals. The economic burden of depression comprises healthcare utilization expenditures and productivity losses. Patients experiencing depressive symptoms suffer also from impairments in their quality-of-life (QoL). Clinical and cost-effective treatments are therefore necessary to reduce the burden caused from depression. Internet-based treatment is an emerging form of psychological treatment for depression that can potentially reduce the cost of depression because of the reduced time therapists spend to treat patients. Therefore, the aim of this thesis is, firstly, to go beyond the depressive symptoms and examine the QoL of patients with depression, and, secondly, to provide evidence on the cost-effectiveness of Internet-based treatments.

Chapter 2 regards a systematic review of model-based studies evaluating the cost-effectiveness of treatments for depression. Data related to various methodological characteristics were extracted from the included studies and the available modelling techniques were evaluated. This methodological review included 41 model-based studies of which 21 used decision trees (DTs), 15 used cohort-based state-transition Markov models (CMM), two used individual-based state-transition models (ISM), and three used discrete event simulation (DES) models. A wide variation between the included studies in the number of health states/events, data sources, time horizon, cycle length, and adopted perspective was detected. Since the individual history of each patient is important for the prognosis of depression, DES and ISM simulation methods may be more appropriate for a pragmatic representation of the course of depression.

Chapter 3 describes a meta-analysis examining positive and negative outcomes of major depression for patients receiving treatment as usual (TAU). Four separate meta-analyses were performed to estimate remission, response, reliable change and deterioration rates at short-term (≤ 6 months from baseline). Thirty-eight studies including 2,099 patients in the TAU were identified. After adjusting for publication bias, the first meta-analysis ($n=33$) showed that 33% of the patients remitted from depression. The second meta-analysis ($n=13$) demonstrated that 27% of the patients responded to treatment. The third meta-analysis

(n= 7) indicated that 31% of the patients showed a reliable change. Finally, 12% of the patients deteriorated, meaning that their depressive symptoms became more severe. The treatments labelled as TAU for depression were clinically and statistically heterogeneous.

In *Chapter 4* the relationship between different health states related to depression severity and utility scores was explored. Individual participant data from ten randomized controlled trials evaluating depression treatments was gathered. The UK EQ-5D and SF-6D tariffs were used to generate utility scores. The average EQ-5D utility scores for five depression-related health states were 0.70 (95%CI 0.67 to 0.73) for remission, 0.62 (95%CI 0.58 to 0.65) for minor depression, 0.57 (95%CI 0.54 to 0.61) for mild depression, 0.52 (95%CI 0.49 to 0.56) for moderate depression, and 0.39 (95%CI 0.35 to 0.43) for severe depression. In comparison with the EQ-5D, the utility scores based on the SF-6D were similar for remission (EQ-5D= 0.70 vs SF-6D= 0.69), but higher for severe depression (EQ-5D= 0.39 vs SF-6D= 0.55). Individuals with less severe depressive symptoms had on average statistically significant higher utility scores than individuals suffering from more severe depressive symptomatology.

Chapter 5 presents a meta-analysis investigating the effectiveness of psychotherapy for depression on global QoL and on the mental health and physical health components of QoL. 44 randomized controlled trials comparing psychotherapy for adults to a control group were included. The results demonstrated small to moderate effect size (Hedges' $g = 0.33$, 95% CI 0.24–0.42) for global QoL, moderate effect size for the mental health component ($g = 0.42$, 95% CI 0.33–0.51) and, after removing an outlier, small but statistically significant effect size for the physical health component ($g = 0.16$, 95% CI 0.05–0.27). Psychotherapy for depression has a positive impact on the QoL of patients with depression. Improvements in QoL are not fully explained by improvements in depressive symptom severity.

In *Chapter 6* a study investigates the cost-effectiveness of an Internet-based problemsolving guided self-help intervention compared to enhanced usual care for outpatients on a waiting list for face-to-face treatment for major depression. An economic evaluation

was performed alongside a randomized controlled trial with 12 months follow-up. Mean societal costs for the intervention group were €1,579 higher than in usual care, but this was not statistically significant (95% CI -1,395 to 4,382). Cost-effectiveness acceptability curves showed that the maximum probability of the intervention being cost-effective in comparison with usual care was 0.30 for an extra QALY, at a ceiling ratio of €30,000. Offering an Internet-based intervention to depressed outpatients on waiting list for faceto-face treatment was not considered cost-effective in comparison with enhanced usual care from a societal perspective.

Chapter 7 demonstrates an individual-participant data meta-analysis evaluating the cost-effectiveness of guided Internet-based interventions for depression compared to controls. Data from five randomized controlled trials studies, including 1,426 participants, were combined. The guided Internet-based interventions were more costly than the controls, but not statistically significant (12-months mean difference = €406, 95% CI: -611 to 1,444). The mean differences in clinical effects were not statistically significant (e.g. 12-months mean difference = 1.75, 95% CI: -0.09 to 3.60 in CES-D score). Costeffectiveness acceptability curves indicated that high investments are needed to reach an acceptable probability that the intervention is cost-effective compared to control for (e.g., at 12-month follow-up the probability was 0.29 and 0.31 at a ceiling ratio of 24,000 and 35,000 €/QALY, respectively). Based on the present findings, guided Internet-based interventions for depression are not considered cost-effective compared to controls. However, only a minority of RCTs investigating the clinical effectiveness of guided Internet-based interventions also assessed cost-effectiveness and were included in this IPD meta-analysis.

Chapter 8 summarizes the main findings of this PhD thesis. Furthermore, various limitations as well as implications for future research and clinical practice based on the included studies are discussed. Overall, psychological treatments for depression have a positive impact on QoL of patients. Moreover, it is demonstrated that currently there is no adequate evidence to support the cost-effectiveness of guided Internetbased treatments for depression compared to control treatments. It is recommended

that more cost-effectiveness studies are performed alongside clinical trials examining Internet-based treatments for depression.