

From THE DEPARTMENT OF CLINICAL NEUROSCIENCE  
Karolinska Institutet, Stockholm, Sweden

# INDIVIDUALLY TAILORED INTERNET- BASED TREATMENT FOR DEPRESSION AND COMORBID CONDITIONS

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**Karolinska  
Institutet**

Stockholm 2019

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Published by Karolinska Institutet.

Printed by E-Print AB 2019

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ISBN 978-91-7831-268-9

# INDIVIDUALLY TAILORED INTERNET-BASED TREATMENT FOR DEPRESSION AND COMORBID CONDITIONS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*Till pappa*



## ABSTRACT

**Background:** Depression is a large societal problem. People suffering from depression are heterogeneous and have a high degree of comorbid conditions. Pharmacological treatment is widespread, but not effective for all sufferers, and patients often have a preference for psychological treatment. There are effective psychological treatment alternatives, but access to treatment is low. Individually tailored internet-based treatment has the ability to target several conditions within the same treatment. It has shown promising effects on depression and anxiety but needs to be further evaluated against other interventions. The effects of specific treatment components also need to be explored.

**Aims:** The aims of this thesis were to evaluate the effects and cost-effectiveness of individually tailored internet-based treatment compared to other treatment alternatives, to compare its effects to disorder-specific benchmark treatments, and to explore if compliance to treatment components for specific conditions predict reductions in the targeted symptoms.

**Methods:** Study I-IV were based on the randomized trial REGASSA ( $n = 946$ ) where an individually tailored internet-based treatment (TAIL) were compared to structured physical exercise (PE) and to treatment as usual in primary care (TAU). In Study I, the effects of TAIL and PE on depression symptoms were evaluated against TAU. Study II evaluated the cost-effectiveness of TAIL and PE against TAU. In Study III, TAIL was compared to similar, but disorder-specific, benchmark treatments for depression ( $n = 2358$ ), panic disorder ( $n = 1176$ ) and social anxiety disorder ( $n = 1335$ ). In Study IV, the participants' compliance to the different specific components in the TAIL-intervention were rated, and related to symptom reductions.

**Results:** The effects of TAIL on depression symptoms were large ( $g = 1.47$ , 95% CI 1.29-1.66), and there were significantly larger reductions in depression symptoms than in the TAU-group. There were no significant differences in effects on depression symptoms between TAIL and PE. TAIL and PE had 90 and 76 % probabilities respectively, of being cost-effective compared to TAU, given standard health care provider willingness to pay-thresholds. The effects of TAIL on depression symptoms were non-inferior to disorder-specific internet-based treatment. The effects of TAIL on panic or social anxiety symptoms however, could not be concluded to be non-inferior to disorder-specific treatment. Overall compliance with TAIL was strongly related to symptom reductions in depression, panic, social anxiety, stress and insomnia, weakly related to reductions in worry, but not related to reductions in pain symptoms. Compliance to specific components for social anxiety was related to reductions in specific social anxiety symptoms. Compliance to specific components for stress and insomnia were particularly important since they were related to both specific symptom reductions and reductions of depressive symptoms.

**Conclusions:** The results in this thesis support that individually tailored internet-based treatment is an effective and cost-effective treatment alternative to be considered for implementation. It is as effective as the disorder-specific internet-based treatments for depression already used in routine care, but more comparisons are needed to conclude if it is

as effective as disorder-specific anxiety treatments. Since specific treatment components for stress and insomnia were important for both specific and depressive symptom reductions, it is probable that individual tailoring for these conditions is worthwhile in the treatment of depression.



## LIST OF SCIENTIFIC PAPERS

- I. Hallgren M, **Kraepelien M**, Öjehagen A, Lindefors N, Zeebari Z, Kaldo V, Forsell Y. Physical exercise and internet-based cognitive behavioural therapy in the treatment of depression: randomised controlled trial. *British Journal of Psychiatry*. 2015; 207(3): 227-234, reproduced with permission.
- II. **Kraepelien M**, Mattsson S, Hedman-Lagerlöf E, Petersson I, Forsell Y, Lindefors N, Kaldo V. Cost-effectiveness of internet-based cognitive-behavioural therapy and physical exercise for depression. *British Journal of Psychiatry Open*. 2018; 4(4), 265-273, reproduced with permission.
- III. **Kraepelien M**, Forsell E, Karin E, Johansson R, Lindefors N, Kaldo V. Comparing individually tailored to disorder-specific internet-based cognitive-behavioural therapy: Benchmarking study. *British Journal of Psychiatry Open*. 2018; 4(4), 282-284, reproduced with permission.
- IV. **Kraepelien M**, Blom K, Lindefors N, Johansson R, Kaldo V. *The effects of component-specific treatment compliance in individually tailored internet-based treatment*. Submitted manuscript.

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## LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
CBT	Cognitive behavioral therapy
CI	Confidence interval
CSQ-8	Client Satisfaction Questionnaire – 8 item
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	EuroQol-5D-3L - health related quality of life scale
GAD	Generalized anxiety disorder
ICER	Incremental cost-effectiveness ratio
ISI	Insomnia Severity Index
LSAS-SR	Liebowitz Social Anxiety Scale – Self-Rated
MADRS (-S)	Montgomery–Åsberg Depression Rating Scale (– Self-rated)
MPI	Multidimensional Pain Inventory
PDSS-SR	Panic Disorder Severity Scale – Self report
PE	Physical exercise
PHQ-9	Patient Health Questionnaire – 9 item
PSS-10	Perceived Stress Scale – 10 item
PSWQ	Penn State Worry Questionnaire
QALY	Quality-Adjusted Life-Years
REGASSA	Rehabiliteringsgaranti, samlad satsning och ansökan
SD	Standard deviation
SE	Standard error
SSRI	Selective serotonin reuptake inhibitor
TAIL	Individually tailored internet-based treatment
TAU	Treatment as usual
TiC-P	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness
WAI	Work Ability Index

# 1 INTRODUCTION

*“Ever since psychology, thanks to its impartial investigation of the facts, has risen to the status of a natural scientific discipline, it has succeeded in creating strictly empirical research methods that might, upon further development, be applied to the difficult study of morbid mental states.”*

Emil Kraepelin, 1887.

## 1.1 PSYCHOLOGY IN PSYCHIATRY

Emil Kraepelin (1856-1926) was an influential German psychiatrist, famous for separating affective disorders from what is now known as schizophrenia when classifying mental illnesses. Kraepelin is also known for considering the affective disorders as a spectrum which included dimensions, such as mania. In the late 20<sup>th</sup> century, Kraepelin became an icon for medical-model psychiatrists (sometimes known as neo-Kraepelinians) who needed a historical role model when debating the then dominant psychoanalytic theories of Sigmund Freud.<sup>1</sup>

The real Kraepelin however, was not a pure medical-model psychiatrist. The name of his doctoral thesis from 1882 translates as *The Place of Psychology in Psychiatry*, and he argued for there to be such a place many times, such as in his inaugural lecture at the University of Dorpat in 1887, which the quote above is an excerpt from. The quote highlights that the kind of psychology Kraepelin wanted in psychiatry was empirical psychology, a subsection of natural science, and not the introspective psychology such as that of the psychoanalysts. Kraepelin’s interest in psychology was influenced by working in the experimental psychologists Wilhelm Wundt’s newly opened laboratory in Leipzig,<sup>2</sup> where he often preferred to spend time doing experiments instead of doing clinical work during his early career.<sup>3</sup>

Following my namesake, I will make my thesis an attempt to make place for increased amounts of psychology in psychiatry. More precisely, my aim is to make use of knowledge based on empirically driven psychological science (psychology), in the treatment of mental disorders (psychiatry).

## 1.2 MAJOR DEPRESSIVE DISORDER

The merits of Kraepelinian dimensional definitions of mental illness are sometimes argued for by researchers, but categorical definitions are currently the most used in clinical practice.<sup>4</sup> Hence, we will now take a look at the most widely used categorical definition of the most well-known of mental illnesses: depression. The criteria for a major depressive episode (major depression) in The Diagnostic and Statistical Manual of Mental Disorders 5th ed. (DSM-5)<sup>5</sup> follows in Table 1. The patient needs to fulfill A, B *and* C to reach the diagnostic criteria for major depression.

**Table 1.** DSM-5 criteria of major depression

**A.** Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

**B.** The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

**C.** The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

### **1.3 THE IMPACT OF DEPRESSION FOR INDIVIDUALS AND SOCIETY**

Depression, as defined in the DSM diagnostic system, has a large impact on mortality, disability and quality of life, burdening both individuals and societies worldwide. <sup>6</sup> The World Health Organization projects major depression to be the leading cause of burden of disease in 2030. <sup>7</sup> In Sweden, clinically significant depressive symptoms are experienced by 10.8 % of the adult population, and 5.2 % qualifies as having major depression. <sup>8</sup> Depression is also

associated with high societal costs, both in Sweden and internationally.<sup>9,10</sup> These costs consist of direct costs such as health care resource use, but also large indirect costs such as when sufferers are on sick-leave or have lower productivity at work.

#### **1.4 HETEROGENEOUS DEPRESSION**

The categorical DSM-type definition of major depression has the advantage of being unambiguous; either you have it or not, but it also has some problems to consider. One artifact of the above DSM-definition of depression is that many different symptoms are described as being part of the same disorder.<sup>11</sup> An example of this would be that a patient with insomnia and weight loss could belong to the same category (major depression) as a patient with hypersomnia and weight gain.

Another artifact of the categorical definition is that a patient with a diagnosis of major depression often qualifies for one or a number of other distinct DSM-diagnoses. This is often referred to as psychiatric comorbidity. Some recent research into the interactions of psychiatric symptoms describes how comorbidity can occur when diagnoses such as major depression and generalized anxiety disorder share a large part of DSM-symptom criteria.<sup>12</sup>

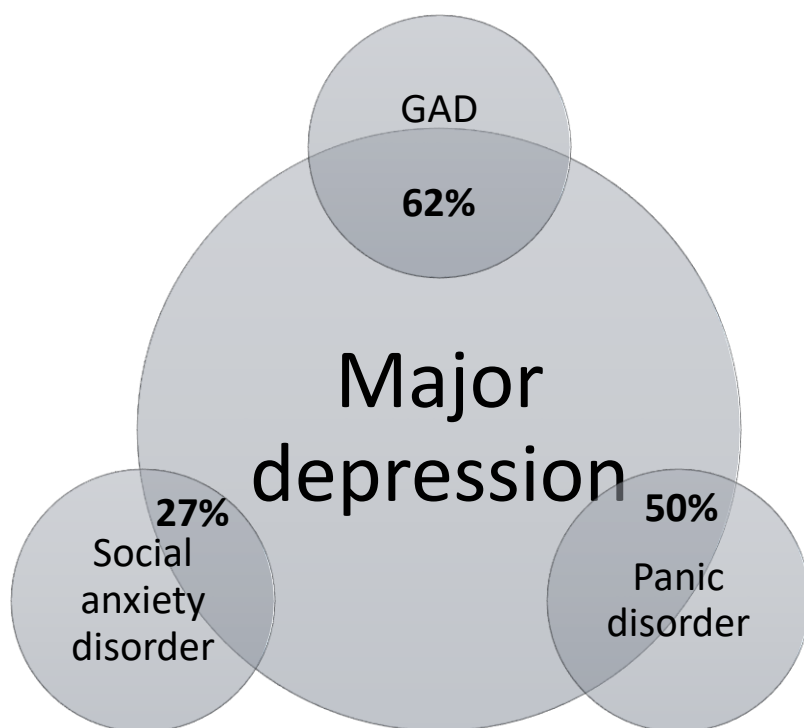
#### **1.5 DEPRESSION AND COMORBIDITY**

Depression and anxiety often co-occur. In the United States 58 % of patients with major depression also has an anxiety disorder, and as many as 95 % show anxiety symptoms.<sup>13</sup> In a survey of the Swedish general population, over 50 % who had clinically significant symptoms of depression or anxiety, had both problems simultaneously.<sup>8</sup> In a survey of primary care visitors, 60 % who listed psychological distress as the main reason for visit, reported a high degree of symptoms in at least two problem areas such as depression, anxiety or stress/fatigue.<sup>14</sup> In a register study of a Swedish primary care population (N = 5 397 675) diagnosed comorbid disorders were high in patients with major depression, especially for anxiety disorders (40.7 %) and adjustment disorder (32.1 %).<sup>15</sup> Figure 1 further illustrates the high comorbidity between depression and three common anxiety disorders.

Pain is highly comorbid to depression. 65 % of depressed patients have been estimated to have at least some pain symptoms, and conversely do around 27 % of pain patients in a primary care context fulfill the diagnostic criteria for major depression.<sup>16</sup>

Insomnia is also very common in depression. Up to 90 % of depressed patients reports insomnia symptoms.<sup>17</sup> In contrast, only 14 % of insomnia patients qualifies as having major depression, implying that insomnia is the more common condition in the population.<sup>18</sup>

Since there is, as we have seen, a risk of artifactual relationships between depression and other conditions, causal relationships have to be further examined. There is, for example, some recent evidence of a causal relationship between treating insomnia symptoms and preventing depression in the longer term.<sup>19</sup>



**Figure 1.** The concurrence between major depression and anxiety disorders is high. The figure aims to illustrate the overlap of estimated lifetime prevalence of major depression, in patients with generalized anxiety disorder (GAD), panic disorder or social anxiety disorder. The size of the bubbles does not represent absolute prevalence estimates. All estimates are from Gorman J. “Comorbid depression and anxiety spectrum disorders”.<sup>13</sup>

### 1.5.1 Conditions and disorders

Since having comorbid disorders can be a non-intended side-effect of the diagnostic system, and having multiple mental disorders is possibly stigmatizing, we shall in this thesis aim to consider the comorbidity of depression as one of co-occurring psychological *conditions*, and not of multiple mental *disorders*. A condition is here defined as a broader term than disorder, that encompasses states of health that is not considered pathological, but still has implications for treatment (an example of such a condition would be pregnancy). The condition *depression* is additionally not the same as the disorder *major depressive disorder*. A condition is here considered not as categorical, but as a dimensional or *pseudo-dimensional* construct, where you can have no, mild, moderate or severe symptoms of the condition.<sup>20</sup>

The reason for using dimensional constructs of various conditions in depression is the mentioned high somatic and anxious comorbidity in people who present with depression in primary care or other general medical settings.<sup>21</sup> A patient seeking care for depression who is moderately anxious or stressed, but only mildly depressed, might for example not receive treatment because the depression is considered sub-clinical, although the aggregated burden is quite severe. By considering several dimensional conditions, we aim to better describe the



problems facing the majority of patients with psychological complaints than we would be able to by using categorical definitions only. Figure 2 illustrates a population with depression and comorbid conditions.



**Figure 2.** Depression and comorbid conditions. Schematic illustration on the relation between depressive symptoms and the symptoms of the other conditions assessed in the individually tailored internet-based treatment of this thesis. The size of the bubbles, or of the overlap with the depression bubble, does not represent the size of the comorbidities. In reality, the comorbid conditions also overlap each other.

## 1.6 PHARMACOLOGICAL TREATMENT

### 1.6.1 Antidepressants

To put psychological treatments in context, we first need to mention the currently dominating treatment paradigm of pharmacological treatment. The prescription of antidepressant medication is widespread in primary care. Antidepressants are with 79.4 % the most common treatment prescribed to people with depression in Swedish primary care.<sup>15</sup> In the United States, only one out of five prescriptions of antidepressants is done by a psychiatrist, and in most cases there is no diagnosis of depression.<sup>22</sup> Primary care patients who are prescribed antidepressants without a diagnosis of depression are often elderly, with somatic complaints, and milder mood or anxiety symptoms.<sup>22</sup>

A Cochrane review of randomized trials of antidepressants in primary care settings found that antidepressants of both the older tricyclic type, and the newer selective serotonin reuptake inhibitor type (SSRI), were more effective than placebo in lowering depression levels.<sup>23</sup> These results were however based on a sample of primary care patients with a diagnosis of major depression, and not the whole diverse population currently receiving antidepressant treatment in primary care. The advantage over placebo was on average small with a number needed to treat of 8-10 depression patients on antidepressants for one additional responder.<sup>24</sup> Active treatment also seem to have somewhat increased the risk of dropping out because of negative side effects.<sup>24</sup>

In addition to the small effect compared to placebo, a critique of the most widely used SSRI type of antidepressants is that they are used on everything from heterogeneous “primary care depression” to very severe depression (melancholia), in spite of there probably being different biological underpinnings for all the different states that share the name depression.<sup>25</sup>

Proponents of SSRI use for depression has pointed out that the response to SSRI seems to be heterogeneous rather than universally poor.<sup>26</sup> Since the effects of different SSRI types affect different depression patients differently, and a quarter of patients also show a poorer response on SSRI than they would have on placebo, pharmacological treatment needs to be personalized. One effect of personalization is that patients who seem to be better off avoiding SSRIs should be identified and diverted to other treatments for depression.<sup>26</sup>

### **1.6.2 Other pharmacological treatments**

Benzodiazepines have a rapid anxiolytic and sedating effect, and can be efficacious in the short-term treatment of anxiety disorders such as generalized anxiety disorder, panic disorder and social anxiety disorder.<sup>27</sup> Benzodiazepines are extensively used in primary care for anxiety and insomnia, but tolerance and dependence are common negative side-effects, together with risks of hazardous sedation and cognitive impairment.<sup>28</sup> Benzodiazepines may also interfere with the psychological treatment of anxiety and insomnia.<sup>29,30</sup> Some commonly prescribed pain medications, i.e. opioids, also have great risks of tolerance and dependence, and the widespread legal prescription has resulted in an increased use of illegal opioids.<sup>31,32</sup>

## **1.7 PSYCHOLOGICAL TREATMENT**

In addition to the risks of side-effects from medications prescribed for common psychological conditions, there is a preference in a majority of patients for psychological treatment over pharmacological.<sup>33</sup> This suggests that access to effective and safe psychological treatment should be a priority. Psychological treatment is now also often prioritized before pharmacological treatment in national guidelines for common mental health disorders, such as the UK NICE guidelines,<sup>34</sup> and Swedish national guidelines.<sup>35</sup>

Although negative side-effects are traditionally less well described in psychological compared to pharmacological treatments, they are far from negligible.<sup>36,37</sup> In some psychological interventions, such as the debriefing of trauma victims, the negative effects even seems to

outweigh the positive effects.<sup>38</sup> But negative side-effects are also possible results of treatment components that have a solid evidence base of their effectiveness. Some examples would be patients who deteriorate, or who discontinue their otherwise effective treatment early, as a result of not coping with the emotional stress accompanying some treatment components, such as exposure.<sup>37</sup> Negative side-effects, such as deterioration, therefore needs to be estimated in studies of psychological treatment, to be able to make a fair comparison to other treatment alternatives.

### **1.7.1 Psychological treatment for depression**

The current versions of psychological treatment are known by many different names. A meta-analysis of psychological treatments for depression by Cuijpers and colleagues discriminates between a few major subtypes of treatment that have some evidence: Cognitive behavioral therapy (CBT), behavioral activation, interpersonal psychotherapy, psychodynamic therapy, problem solving therapy, and supportive counselling.<sup>39</sup> These types of treatment are, according to the meta-analysis, all effective in reducing symptoms of depression compared to controls, but with some varying efficacy. When looking at the proportion of participants not meeting criteria for major depression after treatment there was a slight difference between the most successful treatment behavioral activation (74 %) and the least successful treatment supportive counselling (49 %).<sup>39</sup> The results of different psychological treatments also needs to be contrasted against the surprisingly good results of active control conditions (43 %), and the not so good waiting list control conditions (17 %).

There are both differences and common factors in these subtypes of psychological treatment. The most extensively researched type of psychological treatment for depression, CBT, has since the early days of Aaron Beck included cognitive reappraisal as well as elements of behavioral activation, interpersonal aspects, problem solving, and supportive aspects.<sup>40</sup> This means that many of the above mentioned subtypes of psychological treatment are actually included as components within the CBT-family of interventions.

The treatment compliance, i.e. the extent to which you actually perform the homework of the components, has been related to outcome in CBT for depression, and the relation seemed to be that better compliance caused larger symptom reductions.<sup>41</sup> Currently there is no consensus on which components, or combinations of components, that are the most effective at reducing depression.<sup>42</sup> Future dismantling studies may provide new valuable insights into the role of different components in psychological treatment.<sup>43</sup>

The treatment component of behavioral activation is however already a promising candidate of being a sufficient treatment component in its own for many people with depression. Behavioral activation usually refers to the structured scheduling of pleasant and important activities, and the reduction of the avoidance behaviors that are common in depression. In 1996 a dismantling study of the components in Becks CBT for depression suggested that the behavioral activation component was as effective as the full treatment package.<sup>44</sup> A more recent study has suggested that behavioral activation might even be superior to some other types of psychological

treatment for the more severely depressed patients.<sup>45</sup> In addition to being a possibly sufficiently effective component of psychological treatment, behavioral activation also has the advantage of being uncomplicated, time-efficient and not requiring complex skills from either participants or therapists.<sup>44</sup>

### **1.7.2 Psychological treatment components for other common conditions**

Interventions belonging to the CBT-family of psychological treatment are also efficacious for anxiety disorders, and when the target is the reduction of anxiety, the treatment component of exposure seems critical.<sup>46</sup> Exposure refers to systematically and gradually approaching situations and stimuli that evoke an excessive fear response. For some anxiety disorders, such as social anxiety, exposure alone has been shown to be at least as effective as full CBT.<sup>46</sup>

Stress management interventions based on components in the CBT-tradition are also effective in reducing long-term negative effects of stress.<sup>47</sup> A core treatment component for effective stress management appears to be to schedule more time for recovery<sup>48,49</sup>

Psychological treatments classified as CBT also have evidence for the treatment of insomnia and pain.<sup>50</sup> For pain, important treatment components include education about pain, relaxation training and activity scheduling.<sup>50</sup> For insomnia symptoms, the component of sleep restriction (to restrict the time in bed to the time asleep) appears to be critical,<sup>51</sup> together with stimulus control.<sup>52</sup>

In summary, psychological treatment has evidence for many conditions that are often comorbid to depression, but the core components of those treatments vary with the specific symptoms being targeted.

### **1.7.3 Guided self-help and internet-based treatment**

Psychological treatments offered as guided self-help are often seen as a way to improve access to treatment as well as reducing cost of treatment. These treatments can be administered through psychoeducation and homework assignments in self-help-books, with guidance by phone or visits face to face. But a convenient way to add guidance, structure or information feedback is to give guided self-help as entirely internet-based treatments.<sup>53</sup>

Internet-based treatment of depression has been shown to have a small effect also when administered without therapist guidance, but minimal guidance by a therapist is often regarded as an effective way to boost adherence and efficacy of treatment.<sup>54,55</sup> The additive effects of this guidance seems to be maintained when given by a technician as well as a trained clinician,<sup>56</sup> and even when the guidance consisted automated messages, reinforcing progress and reminding about availability of new material.<sup>57</sup>

Adherence to treatment, defined as how much of the intervention individuals access, is an important predictor in internet-based treatments for depression and anxiety.<sup>58</sup> A study of a guided self-help treatment for insomnia, suggested that the boosting effect of guidance was mediated by how much the therapist succeeded in involving the participant in using the most

relevant treatment components, in this case sleep restriction and stimulus control.<sup>59</sup> When given together with guidance (or other structure that promotes adherence up to comparable levels), self-help treatments seem to be as effective as the more traditional face to face-treatments for depression and some anxiety disorders.<sup>60</sup>

#### **1.7.4 Internet-based treatment in routine care settings**

Internet-based treatment has also been tested in a routine care-context. Although given from a specialized psychiatric clinic, the Internet psychiatry clinic in Stockholm, Sweden have treated mostly self-referred patients from the general population for depression and panic disorder since 2007,<sup>61,62</sup> and for social anxiety since 2009.<sup>63</sup> The treatment program for depression used at this clinic is based on behavioral activation, cognitive reappraisal and some worry- and sleep management components. The results from routine care showed that internet-based treatment of depression was effective for patients who received a diagnosis of depression and were included in treatment, which was around 50 % of people who applied for treatment.<sup>61</sup> Note that there was no control condition in this study. The inclusion process at the clinic also excluded patients who for example presented with depressive and comorbid symptoms, but who didn't meet the DSM-criteria for major depression.

In another Swedish study, patients were randomized to either internet-treatment for depression given with guidance from the patients' local primary care facility, and treatment as usual in primary care.<sup>64,65</sup> There was no difference in effect on depression symptoms between the internet-treatment and treatment as usual. The treatment setting used in this study differed substantially from the one at the Internet psychiatry clinic by using guidance from therapists at separate primary care units and presenting all treatment modules at once.

In a British study, depressed patients were randomized to either one of two internet-based treatments for depression as an adjunct to treatment as usual in primary care, or to treatment as usual in primary care alone.<sup>66</sup> There was no evidence of better depression outcomes in the groups receiving an internet intervention, compared to treatment as usual alone in this study. This result could be explained by the fact that the grade of use of the adjunct treatments in this study was, despite scheduled support phone calls, very low.<sup>66</sup>

In a study in an Australian primary care setting, an internet-based treatment of depression and generalized anxiety was found to be effective when compared to a wait list-control, but this treatment showed increased problems with treatment adherence when given fully in primary care.<sup>67</sup> Another Australian study of a combined depression and anxiety internet intervention in routine care showed large effects of treatment. In this case the treatment included both a large degree of automated support, and support from a centralized internet-treatment clinic.<sup>68</sup> These results taken together may suggest some advantages of administering the treatment from a specialized clinic even if recruiting patients at the primary care level or by self-referral.

### **1.7.5 Individually tailored internet-based treatment**

Most internet-based treatments have traditionally been given with the treatment modules in a fixed order, and therefore also with the same treatment components for all participants. In contrast, in an individually tailored treatment, the different treatment components are chosen to build an individual treatment plan for each participant. Some possible advantages of the individually tailored over the disorder-specific procedure could be:

- The possibility to treat more than one condition within one treatment, reducing the need for costly serial treatments.
- The ability to include a larger share of help seeking patients in a treatment with suitable evidence based components by better treatment-patient matching and better handling of patients with comorbid conditions.
- The boosting of treatment credibility and compliance because of a high degree of experienced treatment specificity and personalization.

There is some early encouraging evidence for individually tailored internet-based treatments. One individually tailored treatment was found to be effective for patients in a group with mixed anxiety disorders and also to be effective and cost-effective in a primary care population.<sup>69,70</sup> Individually tailored treatment for anxiety disorders has also showed similar results as disorder-specific treatment for social anxiety, panic disorder and generalized anxiety.<sup>71</sup>

In another study, there was no difference between individually tailored treatment and disorder-specific internet-based treatment for depression, when compared head to head regarding effects on depression symptoms.<sup>72</sup> No evidence of a difference is however not the same as evidence of no difference. Studies with more participants are needed to show if individually tailored treatment can be regarded as non-inferior to disorder-specific treatment for depression, and other conditions. A subgroup analysis in the above mentioned study did however suggest that the individually tailored treatment was possibly more effective than disorder-specific treatment in reducing depression for participants with many comorbid conditions.<sup>72</sup>

### **1.7.6 Remaining research questions**

Although there is a rising number of studies on psychological treatments that have included participants with comorbid conditions, only a minority of them actually have examined the effects on the conditions comorbid to the targeted main condition.<sup>73</sup> The effectiveness and cost-effectiveness of individually-tailored treatment also needs to be compared to other feasible treatment alternatives in primary care before we can be able to recommend broader implementation of this treatment type. Another question that remains to be answered about individually tailored treatment is which treatment components that are important for symptom reductions in depression and the other targeted conditions.

## **1.8 INTRODUCTION SUMMARY**

- Depression is a large societal problem.
- Depression sufferers are heterogeneous and have many comorbid conditions, partly because of how depression is defined.
- Pharmacological treatment is widespread for depression and comorbid conditions, but it is not effective for all, there are considerable side-effects, and patients often prefer psychological treatment.
- Some kinds of psychological treatment are effective and recommended in guidelines, but access is low.
- Individually tailored internet-based treatment is a treatment alternative with promising effects on depression and anxiety, but questions remain.

## **1.9 AIMS OF THE THESIS**

The overall aims of this thesis were to compare individually tailored internet-based treatment to other viable treatment alternatives, and to explore which treatment components in individually tailored treatment that were important for specific effects on targeted conditions.

Specific research questions were:

- What are the effects of individually tailored internet-based treatment on depression levels compared to treatment as usual in primary care? (Study I)
- What are the preliminary effects of individually tailored internet-based treatment on the comorbid conditions of depression? (New data)
- Is individually tailored internet-based treatment cost-effective compared to treatment as usual in primary care? (Study II)
- Is individually tailored internet-based treatment non-inferior to disorder-specific internet-based treatment for depression, panic disorder and social anxiety in routine psychiatric care? (Study III)
- Can compliance to specific treatment components in individually tailored internet-based treatment predict specific effects on the conditions they are meant to improve? (Study IV)





## **2 METHODS**

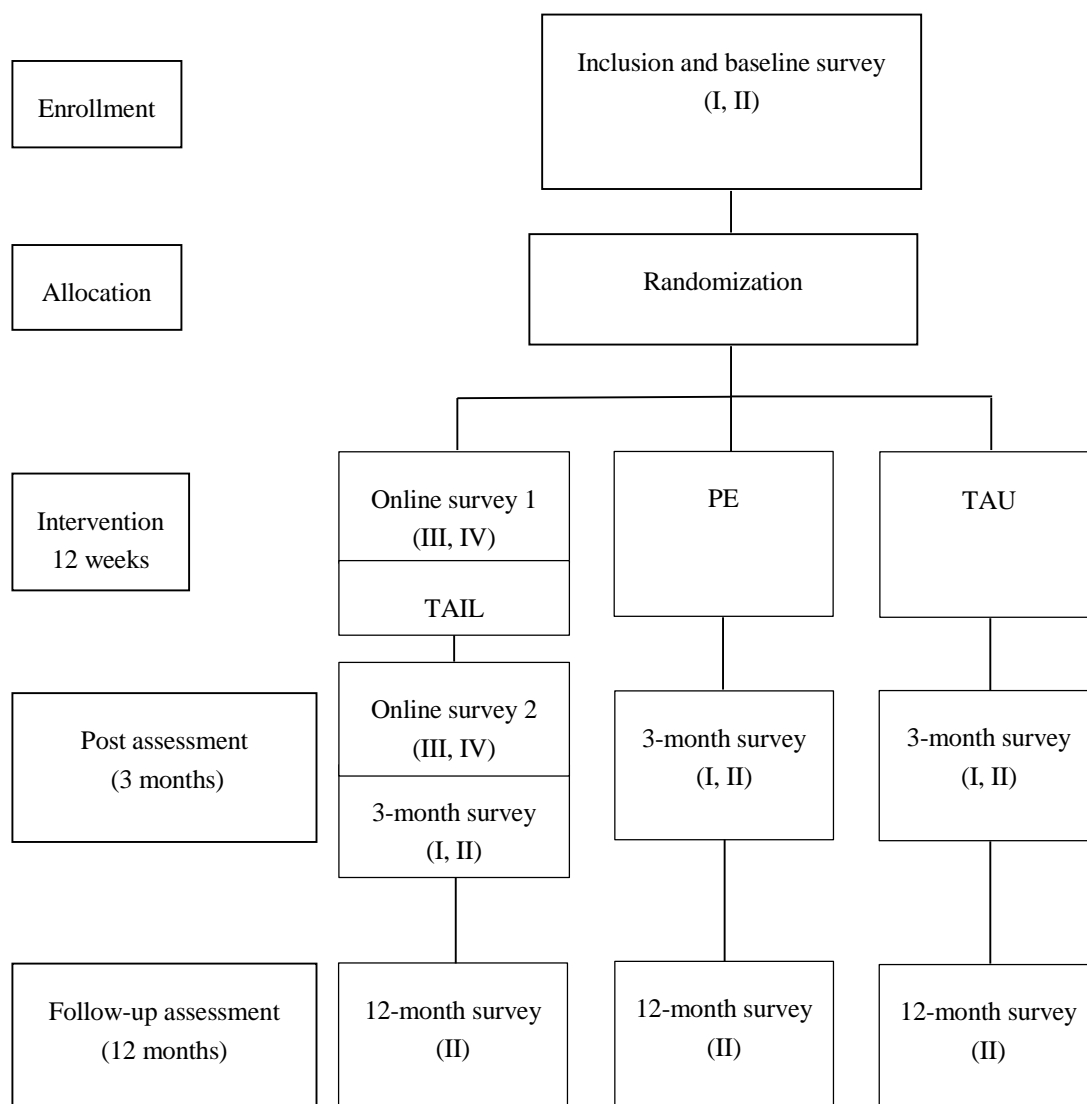
### **2.1 THE REGASSA-PROJECT (STUDY I-IV)**

All four studies in this thesis are based on REGASSA, a project aimed at examining feasible treatment alternatives for depression, anxiety and stress-related mental ill-health. The treatment alternatives examined in REGASSA were individually tailored internet-based treatment based on CBT (TAIL) and structured physical exercise (PE). These treatment alternatives were contrasted against the treatment as usual that the participants would receive at their primary care unit (TAU). REGASSA was carried out in collaboration with six Swedish county councils (Blekinge, Kronoberg, Skåne, Stockholm, Västmanland and Västra Götaland) and two universities (Karolinska Institutet and Lund university). REGASSA was approved by the Regional ethics review board in Stockholm (2010/1779-31/4), first preregistered at Karolinska Clinical Trial Registration registry (KT20110063) and later registered at German clinical trials (DRKS00008745).

The REGASSA-project was funded by REHSAM, a Swedish government initiative that funded research projects examining effects of treatments on sick-leave and employment for patients with pain, or mental ill-health like depression, anxiety and stress-related conditions. The primary aim of the REGASSA-project as a whole was consequentially to examine the effects on sick-leave and employment on patients with mild to moderate depression, anxiety and stress-related mental ill-health. Patients with pain were not the focus of REGASSA although they were not excluded if they had pain comorbid to mental ill-health. This thesis will only mention the effects on sick-leave and employment briefly while the included studies I-IV focus on the effects on symptoms and costs.

#### **2.1.1 Participants and design**

Participants were initially recruited only at the primary care units in the six participating county councils. To speed up the recruitment process in Stockholm county, some of the participants there were recruited with the help of newspaper ads and a primary care research center (KTA Prim). Recruited participants were screened for at least mild symptoms of depression, and those who were at least 18 years old and had a Patient Health Questionnaire (PHQ-9) score of > 9 were invited to participate. Exclusion criteria included severe somatic illness, alcohol or drug use disorder or severe psychiatric problems such as psychosis. A total of 946 participants were included between February 2011 and March 2013. Please see Figure 3 for overall trial design and measurement time points.



**Figure 3.** Trial design and measurement time points for the studies included in this thesis. TAIL, individually tailored internet-based treatment; PE, structured physical exercise; TAU, treatment as usual in primary care; I, Study I; II, Study II; III, Study III; IV, Study IV.

### 2.1.2 Outcomes

Clinician-rated depression (Study I and II) was assessed by a clinician at three time points (baseline, 3-months and 12-months after baseline) with Montgomery-Åsberg Depression Rating Scale (MADRS).<sup>74</sup> All included participants completed a battery of questionnaires at all three time points with the help of a clinician. These questionnaires were used in Study I and II and included single-item Work Ability Index (WAI)<sup>75</sup> which was used to measure self-rated work capacity, the Client Satisfaction Questionnaire-8 (CSQ-8)<sup>76</sup> which was used to measure satisfaction with treatment using both quantitative ratings and written comments, the EuroQol-5D-3L (EQ-5D)<sup>77</sup> which was used to construct Quality-Adjusted Life-Years (QALYs), and the Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness (TiC-P)<sup>78</sup> which was used to calculate healthcare resource use and costs in both the primary health care and societal perspectives. Costs and QALYs were then used to construct incremental cost-effectiveness ratios (ICERs) as a way to compare the cost-effectiveness of TAIL or PE to TAU.

The ICERs were then compared to an often-used threshold of healthcare provider willingness-to-pay of €21 536 (£20 000) per QALY.<sup>79</sup>

After the baseline survey, the participants were randomized to 12 weeks of TAIL, PE or TAU. Participants in the TAIL condition also completed additional online surveys before and after treatment (used in Study III and IV) including the following seven self-report measures (cut-off scores used in this thesis for representing at least mild symptoms are included):

- **Depression** symptoms was assessed with the Montgomery–Åsberg Depression Rating Scale – Self-rated (MADRS-S ; Cut-off  $\geq 13$ ).<sup>80</sup>
- **Worry** symptoms was assessed with the Penn State Worry Questionnaire (PSWQ ; Cut-off  $\geq 45$ ).<sup>81</sup>
- **Panic** symptoms was assessed with the Panic Disorder Severity Scale – Self report (PDSS-SR ; Cut-off  $\geq 6$ ).<sup>82</sup>
- **Social anxiety** symptoms was assessed with the Liebowitz Social Anxiety Scale – Self-Rated (LSAS-SR ; Cut-off  $\geq 30$ ).<sup>83</sup>
- **Stress** symptoms was assessed with the Perceived Stress Scale – 10 item (PSS-10 ; Cut-off  $\geq 13$ ).<sup>84</sup>
- **Insomnia** symptoms was assessed with the Insomnia Severity Index (ISI ; Cut-off  $\geq 8$ ).<sup>85</sup>
- **Pain** symptoms was assessed with the Multidimensional Pain Inventory (MPI ; Cut-off  $\geq 1.7$ ).<sup>86</sup>

Additional assessments were also collected in all three groups at other time points by an automated telephone technique (Interactive Voice Response, IVR) but results from these were not a part of this thesis and will only be mentioned briefly.

### 2.1.3 Individually tailored internet-based treatment (TAIL)

An early version of TAIL was tested in a small clinical, unpublished pilot study with 10 participants in 2011. After the pilot study, the treatment program was revised and finalized as described below.

TAIL consisted of mandatory and optional treatment modules. A module included psychoeducation that was based on text and illustrations and ended with a practical homework assignment in the form of interactive worksheets. See Figure 3 for an example of a worksheet and Table 1 in Study IV for a complete list of modules in TAIL. The homework was to be completed by the participant within a week, and after feedback from the therapist, the next module was made available. Therapists aimed at limiting support and feedback to 15 minutes per participant and week. Therapist-support consisted in most cases of written messages, but sometimes also of short phone calls if needed.

## Problemlösning

Steg	
1. Välj en situation:	EXEMPEL: Jag väljer att ta mig an att städa mitt hem.
2. Formulera vad som är själva problemet:	EXEMPEL: Jag har låtit mitt hem bli mer smutsigt än vad jag vill ha det. Nu är det så smutsigt att jag inte vill bjuda hem folk.
3. Formulera ett mål:	EXEMPEL: Det är viktigt för mig att ha det fint hemma.
4. Lista alla dina alternativ:	EXEMPEL: Ringa en städfirma. Bara städa ett rum. Släcka lamporna (så jag inte ser hur smutsigt det är). Dammsuga. Kasta ut allt jag äger för att komma åt bättre.
5. Välj ett alternativ:	EXEMPEL: Jag väljer att städa ett rum i taget.
6. Planera när, var och hur:	EXEMPEL: I morgon klockan 9 på morgonen ska jag gå till mitt städskåp, ta ut en dammtrasa och sedan börja med att damma bokhyllan i hallen, sedan ska jag hämta dammsugaren och börja dammsuga hallen.
7. Pröva:	EXEMPEL: Hämta grejer, damma, dammsug.
8. Utvärdera:	EXEMPEL: Det gick ganska bra. Jag dammade och dammsög i hallen. Jag önskar att jag hade orkat göra fler rum, men det här var ett steg i rätt riktning. Jag känner mig mer handlingskraftig än innan.

Spara

**Figure 3.** Screenshot of a worksheet from the homework assignment in the module for problem solving. The worksheet helps the participant to break down a problem in manageable steps that helps the participant to formulate the problem, to try possible solutions, and then to evaluate the tried solutions.

### 2.1.3.1 Mandatory treatment modules

Participants had to complete the first three treatment modules to get to the individually tailored part of TAIL. The main components of these three modules were identification of personal values, behavioral activation and handling avoidance behaviors, and they were planned to be completed within the three first weeks of treatment. This mandatory treatment content was based on the depression treatment used in routine care at the Internet psychiatry clinic,<sup>61</sup> but redeveloped and adapted to also fit participants with comorbid anxiety symptoms.

### 2.1.3.2 Selection of optional treatment content

In addition to the online self-report-measures, the participants in TAIL also rated their recognition, as well as their subjective severity levels, of the seven types of symptoms, after reading a brief description of each symptom area. Before the start of the individually tailored part of treatment, the therapist and participant used both pre-treatment questionnaires and other ratings to agree on the remaining part of the treatment plan. The therapist also presented the proposed treatment plan during weekly group supervision sessions with all clinicians engaged in delivering TAIL.

### 2.1.3.3 *Optional treatment modules*

The individually tailored part of treatment was mostly based on the individually tailored treatment for depression used in the study by Johansson and colleagues,<sup>72</sup> but redeveloped and adapted to fit within the rest of TAIL. These treatment modules were basically shortened versions of full internet-treatment programs for other conditions that had been tested in earlier disorder-specific treatment studies. The following is a list of the main symptom areas, of which participants had one to three in their treatment plan. There are also examples of the treatment content of the individually tailored modules for each symptom area.

- **Depression (continued).** Treatment modules focusing on continued behavioral activation, and adding cognitive restructuring of depressive thoughts. This content was similar to the content of the depression treatment implemented in routine care with large effects on depressive symptoms.<sup>61</sup>
- **Worry.** Treatment modules focusing mainly on relaxation, worry exposure, problem-solving and worry time. A somewhat similar treatment program has been tested in a randomized study with promising results for problems related to worry and generalized anxiety.<sup>87</sup>
- **Panic.** Treatment modules focusing mainly on exposure for both panic symptoms and agoraphobia. This content was similar to the content of the panic treatment implemented in routine care with large effects on panic- and agoraphobic symptoms.<sup>62</sup>
- **Social anxiety.** Treatment modules focusing mainly on exposure. This content was similar to the content of the social anxiety treatment implemented in routine care with medium-to-large effects on social anxiety symptoms.<sup>63</sup>
- **Stress.** Treatment modules focusing mainly on relaxation, mindfulness, problem-solving and focus-shifting. A somewhat similar treatment program has been tested in a randomized study with promising results on perceived stress.<sup>88</sup>
- **Insomnia.** Treatment modules focusing mainly on sleep restriction and stimulus control. A similar treatment program has been tested in a randomized study with large effects on insomnia symptoms.<sup>89</sup>
- **Pain.** Treatment modules focusing mainly on relaxation and behavioral activation. A somewhat similar treatment program has been tested in a randomized study with promising results for disability associated with pain.<sup>90</sup>

In addition to the treatment content mentioned above there were optional modules with content for initiating physical exercise, assertiveness training, maintaining healthy habits and handling perfectionism. There were also work-related modules, developed and adapted for participants with different work-related problems. These modules included content for staying in contact with authorities, returning to work after sick-leave, handling problems at work, and finding new a job. The module for finding a new job was a novel internet-adaptation of Azrin and colleagues' work on job finding clubs from the 1970's.<sup>91</sup> Finally, there was also module for all patients at the last week of treatment containing summary and relapse prevention.

## **2.1.4 The comparison treatments**

### *2.1.4.1 Physical exercise (PE)*

Participants randomized to the PE condition in REGASSA were sub-randomized to three exercise intensity levels: low, medium or high intensity. The analysis of the relationship between exercise intensity and outcome is not included in this thesis; the results of all PE participants were instead analyzed together. Participants in all PE intensity groups were expected to attend three 60-minute group sessions per week during the 12-week treatment period giving a maximum of 36 hours of scheduled exercise. The intervention also included a weekly meeting with a personal trainer or physiotherapist, and phone reminders when not attending any PE sessions for a week.

### *2.1.4.2 Treatment as usual (TAU)*

REGASSA was conducted in the context of the National Rehabilitation Guarantee, an agreement between government and county councils in Sweden during 2008-2015 in which adults with pain, or mental ill-health like depression, anxiety and stress-related conditions were to be guaranteed evidence-based interventions. This context was interpreted as that participants receiving TAU at their primary care unit were entitled to receive individual or group-CBT at their primary care unit, although not necessarily by a clinician with more experience delivering the method than a five-week course in CBT. How well this worked out differed greatly between different primary care centers. The content of the TAU-condition is for that reason handled in the results-section in this thesis. Study II reports the healthcare use during the treatment period in TAU compared to TAIL and PE.

## **2.2 THE INTERNET PSYCHIATRY CLINIC BENCHMARKS (STUDY III)**

The evaluation of the treatments given in routine care at the Internet psychiatry clinic was approved by the Regional ethics review board in Stockholm (2011/2091-31/3). The samples used as benchmarks in Study III consisted of 4 869 patients receiving disorder-specific internet-based treatment at the clinic from October 2007 to July 2017 for depression, panic disorder or social anxiety. These patients were mostly self-referred, and those included in treatment underwent a 12-week treatment for their main condition that equaled TAIL in length and intensity of both support and amount of text.

The content of the disorder-specific treatments is described in detail elsewhere.<sup>61-63</sup> In short, the depression treatment focused mainly on behavioral activation and cognitive restructuring and outcome was the MADRS-S.<sup>80</sup> The panic disorder treatment focused on exposure for panic symptoms and agoraphobic situations and outcome was the PDSS-SR.<sup>82</sup> Finally, the social anxiety treatment focused on exposure and behavioral experiments for social situations and outcome was the LSAS-SR.<sup>83</sup>

## 2.3 ETHICAL CONSIDERATIONS

All studies were conducted with approval from an appropriate ethics review board. All participants gave their informed consent to participate and were informed that they could withdraw their participation at any time. Participants in the internet-based treatments were monitored weekly for suicidal ideation and were contacted if showing any sign of suicidality. All written communication between therapists and participants in the internet-based treatments were encrypted and the procedure to log in to the treatment platform used the same level of protection as online bank services.

## 2.4 SUMMARY AND COMPARISON OF METHODS STUDY I-IV

Both Study I and II used all three randomized groups in REGASSA. In Study I, differences between the three treatment groups at post-treatment were explored using analysis of covariance (ANCOVA) with pre-treatment depression score and self-rated work capacity entered as covariance factors. Pairwise comparisons were then used to explore which groups that differed significantly at post-treatment.

Within- and between-group effect sizes were used to facilitate the comparison of effects between studies. The types of effect sizes used, Cohen's *d* and Hedge's *g*, are interchangeable (except for in very small samples where *g* is a more conservative estimate) and can be interpreted roughly as: <sup>92</sup>

- > 0.2 = small effect
- > 0.5 = moderate effect
- > 0.8 = large effect.

In the cost-effectiveness of Study II, non-parametric bootstrapping was used to simulate ICERs to account for the uncertainty of the ICER point estimates. These simulated ICERs were then used to estimate the probabilities of the treatment alternatives being cost-effective compared with TAU at the chosen willingness to pay-threshold.

While Study I and II examined all three treatment alternatives in REGASSA in randomized designs, Study III and IV only looked at TAIL. In Study III, TAIL was instead contrasted to the disorder-specific treatments of the Internet psychiatry clinic. For the comparison with the disorder-specific depression treatment all participants in TAIL with at least mild depressive symptoms were used. For the comparison with the disorder-specific panic disorder and social anxiety disorder treatments, only participants with a probable diagnosis of panic disorder and social anxiety disorder who also had at least mild symptoms on the corresponding specific symptom scale were used. To be classified as non-inferior to the disorder-specific benchmark treatment the comparison treatment needed to have a lower end of the 95 % confidence interval of the effect size that were at least as high as the point estimate of the the benchmark treatment effect size, minus the minimally clinically relevant effect ( $\Delta$ ). <sup>93</sup> The value  $\Delta$ , was set to 0.24 following an empirically derived proposal for minimally clinically relevant effect for depression. <sup>94</sup>

Study IV used hierarchical regression to explore if expert-rated treatment compliance could predict reductions on a number of specific symptom scales. Expert-rated compliance with the whole treatment, or with condition-specific components, was used as a predictor in the regression model with specific symptoms as dependent variable. The guide to scoring of treatment compliance in Study IV was created for this analysis and can be found in the supplementary material to the Study IV-manuscript included in this thesis.

All studies used different designs and statistical analysis methods. See Table 2 for an overview of the methods used in Study I-IV which are also described fully in the scientific papers included in this thesis.

**Table 2.** Summarizing comparison of methods in Study I-IV.

	<b>Study I</b>	<b>Study II</b>	<b>Study III</b>	<b>Study IV</b>
<b>Primary aim</b>	To evaluate the effects of TAIL, PE and TAU on depression	To evaluate the costs and cost-effectiveness of TAIL and PE in relation to TAU	To benchmark the effects of TAIL against disorder-specific internet-based treatment	To explore if compliance to components in TAIL predicted specific symptom reductions
<b>Design</b>	Randomized controlled trial	Randomized controlled cost-effectiveness trial	Benchmarking design with non-randomized control conditions	Longitudinal correlational design
<b>Primary statistical analysis</b>	ANCOVA	Non-parametric bootstrapping of ICERs	Benchmarking of an effect size difference against a clinically relevant effect	Hierarchical regression
<b>Primary outcomes</b>	MADRS	TiC-P, QALYs	MADRS-S, PDSS-SR, LSAS-SR	Expert-rated compliance, MADRS-S, PSWQ, PDSS-SR, LSAS-SR, PSS-10, ISI, MPI

TAIL, individually tailored internet-based treatment; PE, structured physical exercise; TAU, treatment as usual in primary care; ANCOVA, analysis of covariance; ICERs, incremental cost-effectiveness ratios; MADRS, Montgomery-Åsberg Depression Rating Scale; TiC-P, Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness; QALYs, Quality-Adjusted Life-Years; MADRS-S, Montgomery-Åsberg Depression Rating Scale – Self-rated; PSWQ, Penn State Worry Questionnaire; PDSS-SR, Panic Disorder Severity Scale – Self report; LSAS-SR, Liebowitz Social Anxiety Scale – Self-Rated; PSS-10, Perceived Stress Scale – 10 item; ISI, Insomnia Severity Index; MPI, Multidimensional Pain Inventory.



## 3 RESULTS

### 3.1.1 Treatment use and satisfaction

Please see Table 3 for a summary of treatment use and treatment satisfaction in REGASSA. The measurements of treatment use were not directly comparable between treatment alternatives. The mean results for TAIL was 3.2 hours of therapist-support per treatment, which translates to 16 minutes of therapist-time per participant and week, and 7.8 received modules out of an expected 12 (65 %). For PE, number of exercise sessions were 14.6 out of a maximum of 36 (41 %). TAU consisted of more use of primary care resources during the treatment period than TAIL and PE which also translates into higher mean costs for the primary health care provider. Please see Table 3 in Study II for a complete breakdown of costs, and resource use, during treatment. Noteworthy is that 20 % of TAU participants reported going to counselling sessions during the treatment period compared to 13 % of PE, and 5 % of TAIL participants, and that 9 % received individual CBT compared to 3 % in the PE and TAIL groups.

The satisfaction scale CSQ-8 has a range from 8 to 32 and established cut-off scores states that 8–13 indicates poor, 14–19 fair, 20–25 good and 26–32 excellent satisfaction.<sup>95</sup> With these cut-offs as guidelines the satisfaction with both TAIL and PE can be said to have been good, but participants in the TAU condition were only fairly satisfied with their treatment. The post-treatment survey also revealed that a majority of participants who chose to actively drop out of treatment did so because of dissatisfaction with the randomization outcome.

**Table 3.** Summary of treatment use and satisfaction in the main REGASSA treatment alternatives.

	Treatment use (95% CI)	Primary care costs representing resource use during treatment (SE)	Treatment satisfaction, CSQ-8 (95% CI)
<b>TAIL</b>	3.2 (2.9-3.5) support in h 7.8 (7.2-8.4) modules	€310 (10.9)	23.7 (22.9-24.5)
<b>PE</b>	14.6 (12.6-16.6) sessions	€355 (15.4)	23.6 (22.9-24.4)
<b>TAU</b>	-	€513 (20.7)	19.5 (18.5-20.5)

Adherence in TAIL is described with mean time in hours of therapist support and mean number of received modules. Adherence in PE is described as mean number of attended 1-hour exercise sessions. TAIL, individually tailored internet-based treatment; PE, structured physical exercise; TAU, treatment as usual in primary care; CI, confidence interval; SE, standard error.

Some quotes from the satisfaction questionnaire function as illustrative examples of when participants receiving the different treatment alternatives were dissatisfied:

- “I would rather have had physical activity” (Participant in TAIL)
- “It would have been better if it was in my language, Spanish” (Participant in TAIL)
- “I never started training. The training times did not suit me. [...] It did not fit my work situation.” (Participant in PE)
- “Too bad I could not participate the maximum in physical exercise because I got work elsewhere.” (Participant in PE)
- “Far too unstructured - no overall plan.” (Participant in TAU)
- “I have not received any treatment.” (Participant in TAU)
- “Incompetent psychologist.” (Participant in TAU)

### 3.1.2 Treatment effects (Study I)

#### 3.1.2.1 Effects on clinician-rated depression at post-treatment (Study I)

All three treatment groups reduced their depression symptoms significantly from pre to post-treatment with large effect sizes. See Table 4 for the within-group effects on clinician-rated depression during the treatment period. The interaction effect between treatment group and time was also significant with symptom reduction in TAIL and PE significantly larger than in TAU. All three groups also showed significant improvements in self-rated work capacity, but there was no significant difference between the groups.

**Table 4.** Within-group effects on clinician-rated depression.

	MADRS pre (SD)	MADRS post (SD)	Effect size, <i>g</i> (95% CI)
<b>TAIL</b>	21.5 (6.7)	11.2 (7.3)	1.47 (1.29-1.66)
<b>PE</b>	22.2 (6.8)	11.3 (7.9)	1.49 (1.30-1.68)
<b>TAU</b>	20.9 (7.5)	13.8 (8.9)	0.88 (0.70-1.05)

TAIL, individually tailored internet-based treatment; PE, structured physical exercise; TAU, treatment as usual in primary care; SD, standard deviation; *g*, Hedge’s *g*; CI, confidence interval.

#### 3.1.2.2 Effects on clinician-rated depression including follow-up data (previous study)

An analysis of REGASSA not included in this thesis looked at effects on clinician-rated depression including the follow-up time point of 12 months after baseline.<sup>96</sup> Within-group effect sizes with 95 % confidence intervals from pre to follow-up based on data from this article were: TAIL,  $g = 1.64$  (1.45-1.82); PE,  $g = 1.57$  (1.39-1.76); and TAU,  $g = 1.22$  (1.04-1.40). There were still significantly lower depression levels in the TAIL and PE groups compared to TAU at follow-up. Between-group effect sizes for TAIL compared to TAU were  $g = 0.66$  (0.50-0.82) post-treatment and  $g = 0.46$  (0.31-0.62) at follow-up, in this analysis. Between-group effect sizes for PE compared to TAU were  $g = 0.57$  (0.41-0.73) post-treatment and  $g = 0.24$

(0.08-0.40) at follow-up. There were no significant differences between TAIL and PE at any time point. <sup>96</sup>

### 3.1.2.3 Other treatment effects in REGASSA (previous studies)

Some other analyses of treatment effects in REGASSA not included in this thesis are also worth mentioning. There were no significant differences in effects on clinician-rated depression between the three exercise intensity levels in PE, strengthening the decision to analyze PE as one intervention. <sup>97</sup> In an analysis of the earlier mentioned IVR-data, both TAIL and PE improved psychological functioning and sleep better than TAU up to three months after treatment. <sup>98</sup> In the analysis of effects on sick-leave and employment, all three groups were associated with reductions in long-term sick leave but there were no differences between the participants' employment or sick-leave status in the TAIL or PE group compared to TAU. <sup>99</sup>

### 3.1.2.4 Preliminary effects of TAIL on symptoms of comorbid conditions (new data)

Since the self-report measures that participants in the TAIL condition completed included scales of symptoms comorbid to depression, we can describe the TAIL participants' comorbid symptoms more clearly than participants in PE and TAU. The proportion of participants in TAIL, before and after treatment, with a score above the pre-defined cut-off indicating at least mild symptoms can be found in Table 5.

**Table 5.** Proportion of participants in TAIL indicating at least mild symptoms of six conditions comorbid to depression, before and after treatment.

Comorbid condition	Worry	Panic	Social anxiety	Stress	Insomnia	Pain
<b>Proportion ≥ Mild symptoms, Pre-treatment</b>	88%	42%	66%	96%	83%	60%
<b>Proportion ≥ Mild symptoms, Post-treatment</b>	70%	24%	45%	78%	56%	48%

The change of self-rated symptom levels from pre to post-treatment in the whole sample with complete online self-report measures translated into the following within-group effect sizes (Hedge's *g*) with confidence intervals, found in Table 6. When we in Study IV examined the subgroups of participants with a probable diagnosis, or higher degree of problem severity, of the specific comorbid condition, the symptom reductions and within-group effect sizes were generally higher than in the whole sample seen in Table 6. This was especially especially the case for participants with conditions that were not as common in the sample such as Panic (effect on PDSS-SR in subgroup panic,  $g = 1.01$ ) and Social anxiety (effect on LSAS-SR in subgroup social anxiety,  $g = 0.73$ ). See Table 2 in Study IV for the complete list of effects in

the subgroups. The proportion of participants who had higher self-reported symptom levels after treatment (deteriorated) on each scale is also presented below in Table 6. For comparison, the proportion who deteriorated on self-rated depression (MADRS-S) was 12 %.

**Table 6.** Change of mean comorbid symptom levels including within-group effect sizes and proportion of participants who deteriorated from pre- to post-treatment.

Comorbid condition	Scale	<i>n</i>	Pre-treatment, <i>m</i> (SD)	Post-treatment, <i>m</i> (SD)	Effect size, <i>g</i> (95% CI)	Proportion deteriorated
Worry	PSWQ	207	58.2 (11.9)	52.0 (12.2)	0.51 (0.31-0.70)	23%
Panic	PDSS-SR	204	5.1 (5.2)	3.1 (4.1)	0.44 (0.24-0.64)	20%
Social anxiety	LSAS-SR	204	42.4 (28.9)	34.0 (25.4)	0.31 (0.11-0.50)	32%
Stress	PSS-10	203	24.0 (6.2)	18.6 (7.0)	0.82 (0.62-1.02)	20%
Insomnia	ISI	204	13.6 (6.3)	9.4 (6.5)	0.66 (0.46-0.85)	17%
Pain	MPI	207	3.2 (3.2)	2.8 (3.2)	0.13 (-0.06-0.32)	35%

PSWQ, Penn State Worry Questionnaire; PDSS-SR, Panic Disorder Severity Scale – Self report; LSAS-SR, Liebowitz Social Anxiety Scale – Self-Rated; PSS-10, Perceived Stress Scale – 10 item; ISI, Insomnia Severity Index; MPI, Multidimensional Pain Inventory; *g*, Hedge’s *g*; CI, confidence interval.

### 3.1.3 Cost-effectiveness (Study II)

The TAU group had a higher mean resource use during treatment than TAIL and PE as we saw in Table 3. When adding the calculated costs of the TAIL and PE interventions however, these treatment alternatives became more costly for the primary health care provider (Cost (SE)): TAIL, €811 (11.5); PE, €999 (18.7); TAU, €513 (20.7). When switching to the cost perspective of the society as a whole and also adding cost data for the whole year since baseline, TAIL and PE were still more costly than TAU (Cost (SE)): TAIL, €11685 (586.8); PE, €11890 (731.1); TAU, €10623 (809.9).

Both TAIL and PE produced more QALYs than TAU during the 12 month follow up-period (TAIL, 0.034 more QALYs than TAU; PE, 0.033 more QALYs than TAU). Together with the cost data, this led to the incremental cost per QALYs (ICERs) as seen in Table 7. At the health care provider willingness-to-pay threshold of €21 536 per QALY, the probability of TAIL being cost-effective versus TAU was 90 % and for PE versus TAU it was 76 %.

**Table 7.** Incremental cost per QALY for TAIL and PE compared to TAU.

	<b>Incremental cost per QALY: primary healthcare perspective</b>	<b>Incremental cost per QALY: 1-year societal perspective</b>
<b>TAIL vs. TAU</b>	€8817	€31471
<b>PE vs. TAU</b>	€14571	€37974

TAIL, individually tailored internet-based treatment; PE, structured physical exercise; TAU, treatment as usual in primary care; QALY, Quality-Adjusted Life-Year.

### 3.1.4 Non-inferiority to disorder-specific routine care benchmarks (Study III)

For the participants in TAIL, the within-group effect size for depression was above the non-inferiority margin based on the disorder-specific depression group (Table 8). The effect size of the subgroup in TAIL with probable panic was slightly lower than the effect of the disorder-specific panic group and not above the non-inferiority margin. The effect size of the subgroup in TAIL with probable social anxiety was similar to the effect of the disorder-specific social anxiety group, but the lower end of the confidence interval was not above the non-inferiority margin.

**Table 8.** Comparison off within-group effect sizes between disorder-specific benchmark treatments and the TAIL intervention.

<b>Condition and group</b>	<b>Effect size, <i>d</i></b>	<b>Benchmarking comparison</b>
<b>DS-depression</b>	1.35	$d - \Delta = \mathbf{1.11}$
<b>TAIL-depression</b>	1.33	95% CI = <b>1.14</b> -1.52
<b>DS-panic</b>	1.47	$d - \Delta = \mathbf{1.23}$
<b>TAIL-panic</b>	1.11	95% CI = <b>0.66</b> -1.56
<b>DS-social anxiety</b>	0.81	$d - \Delta = \mathbf{0.57}$
<b>TAIL-social anxiety</b>	0.74	95% CI = <b>0.27</b> -1.21

TAIL-panic and TAIL-social anxiety were the subgroups of TAIL with a probable diagnosis of panic disorder or social anxiety disorder, respectively. If the lower end of the confidence interval of the TAIL effect was higher than the point estimate of the disorder-specific effect minus  $\Delta = 0.24$ , TAIL was considered non-inferior to disorder-specific treatment for that condition. All symptom scores used to calculate effect sizes were self-rated. DS, disorder-specific benchmark treatment; TAIL, individually tailored internet-based treatment; *d*, Cohen's *d*; CI, confidence interval.

### **3.1.5 The relationship between treatment compliance and symptom reductions (Study IV)**

Expert-rated scores of treatment compliance to the whole TAIL intervention (Overall Compliance) predicted reductions on self-rated depression ( $p < .001$ ) and explained 15 % of the outcome variance. Expert-rated scores of treatment compliance of the specific components for a condition (Specific Compliance) only predicted reductions on specific symptoms for participants with social anxiety, stress and insomnia, but not for worry, panic and pain. Specific Compliance with the stress and insomnia components were also significant predictors of reductions in self-rated depression symptoms.

## 4 GENERAL DISCUSSION

### 4.1 PRIMARY FINDINGS

The overall aims of this thesis were to compare TAIL to other viable treatment alternatives, and to explore which treatment components in TAIL that were important for specific effects on the targeted conditions. TAIL compared well with the other treatment alternatives and the importance of specific treatment components differed between the conditions included in the intervention. The following is a discussion of the implications of these results.

#### 4.1.1 Treatment use and satisfaction

The results on treatment use of TAIL indicates that overall treatment adherence was similar to the disorder-specific internet-based depression in routine care (7.8 received modules out of an expected 12 for 12 weeks of TAIL corresponding to 65 %, versus 7.2 received modules out of an expected 10 for 12 weeks of disorder-specific treatment corresponding to 72 %) <sup>61</sup>

It is not possible to do a direct comparison between the treatment use of TAIL with that of PE, but use of resources in the PE condition of REGASSA was shown to be rather high in the Study II calculations, which gave a somewhat higher mean estimated treatment cost than TAIL. The high resource use in PE was probably a result of the weekly physiotherapist sessions and phone reminders for inactivity making the PE condition of REGASSA a rather ambitious intervention compared to Exercise On Prescription, and similar concepts for primary care. <sup>100</sup>

Study II also showed that resource use in primary care was higher for TAU than for TAIL and PE during the treatment period, but only a minority of participants in TAU actually received an evidence-based psychological intervention, or even supportive counselling. This is a testament to the shortcomings of the experimental National Rehabilitation Guarantee, where participants were to be guaranteed to receive evidence-based psychological interventions, such as individual or group-CBT, in primary care.

Treatment satisfaction with TAIL and PE was almost as high as with disorder-specific depression treatment despite the occurrence of dissatisfaction with the outcome of randomization to treatment in REGASSA (mean CSQ-8 (95% CI) score of TAIL 23.7 (22.9-24.5) and PE 23.6 (22.9-24.4), compared to mean CSQ-8 score of 24.5 for disorder-specific depression treatment). <sup>61</sup> Satisfaction with TAU however, was much lower at mean CSQ-8 (95% CI) score 19.5 (18.5-20.5). This comparatively high dissatisfaction with TAU could be a placebo effect of being randomized to what often appeared as the inferior treatment alternative, <sup>101</sup> and sometimes an effect of being randomized to an alternative that, as revealed by the quotes, contained bad, or no actual treatment.

## 4.1.2 Treatment effects

### 4.1.2.1 Depression

The within-group effect of TAIL on clinician-rated depression symptoms was  $g = 1.47$  in Study I. This effect is based on a pre-treatment measurement made before randomization which can somewhat inflate the effect estimate. The within-group effect of TAIL on self-rated depression was however based on the pre-treatment measurement made after randomization, adjacent to treatment start. This estimate was  $d = 1.33$  in Study III.

Both these within-group effects were in any case large, and even slightly larger than in an earlier study of a similar, but disorder-specific treatment, and the effect seen in other guided internet interventions for depression.<sup>61,102,103</sup> More importantly, the effects of TAIL were significantly larger than the effects of TAU, and this difference in effect was at least of a clinically relevant size ( $\geq 0.24$  effect size).<sup>94</sup> As noted in the introduction, other studies of internet-based treatment for depression has not been able to conclude superiority over treatment as usual in primary care.<sup>64,66</sup> This difference could be a result of the participants higher use of the internet-based intervention in REGASSA compared to the other primary care studies, but it could also be a result of the shortcomings of the TAU-condition in REGASSA. Still, TAU in REGASSA was ecologically valid as it really was treatment as it usually were in Swedish primary care, 2011 to 2013.

Although there were no significant differences between TAIL and the other treatment alternative being evaluated, PE, this does not mean that TAIL and PE necessarily had equivalent effects on depression. If we exploratively use the within-group effect sizes of TAIL and PE and apply the benchmarking procedure of Study III, TAIL is non-inferior to PE both at post-treatment and at follow-up. PE is non-inferior to TAIL at post-treatment, but we can no longer conclude non-inferiority at follow-up when using TAIL as the benchmark. On the other hand, to really be able to conclude equivalence or non-inferiority between TAIL and PE, a prospectively designed trial with that purpose would have been preferable.

### 4.1.2.2 Worry

The within-group effect sizes for symptoms of worry were moderate, both for the whole sample (Table 6) and for the subgroup with probable GAD (Table 2 in Study IV). Earlier studies of disorder-specific internet-based treatment for GAD has demonstrated larger effects on worry symptoms than TAIL.<sup>87,103,104</sup>

### 4.1.2.3 Panic

The within-group effect size for panic symptoms was small for the whole sample, but large in the subgroup with probable panic disorder. The within-group effect size for the subgroup was very similar to the effect size in the earlier study of a similar, but disorder-specific, internet-based treatment for panic disorder, and to the effects on panic seen in a meta-analysis on internet interventions.<sup>62,103</sup> As we shall see in the direct comparison of Study III however,



disorder-specific panic treatment seemed to have a slight advantage, although not statistically significant.

#### *4.1.2.4 Social anxiety*

The within-group effect size for social anxiety symptoms was small for the whole sample, but moderate in the subgroup with probable social anxiety disorder. The within-group effect size for the subgroup was similar to the effect size in the earlier study of a disorder-specific internet-based treatment for social anxiety disorder, and to effects on social anxiety seen in a meta-analysis.<sup>63,103</sup>

#### *4.1.2.5 Stress*

The within-group effect sizes for symptoms of stress were large, both for the whole sample and for the subgroup with a higher degree of perceived stress. These effect sizes were slightly smaller than those seen in earlier internet-based treatments solely for stress.<sup>88,105</sup>

#### *4.1.2.6 Insomnia*

The within-group effect size for insomnia symptoms was moderate for the whole sample, but large in the subgroup with probable insomnia. The effect sizes were similar to effect sizes of a meta-analysis of internet-based insomnia treatment.<sup>106</sup> These within-group effect sizes were on the other hand much smaller than the very large effects seen in an earlier similar, but disorder-specific, guided internet-based treatment for insomnia.<sup>89</sup> The effect size for the subgroup with probable insomnia was however very similar to the effect size of a similar, but disorder-specific, insomnia treatment given to patients with comorbid insomnia and depression which implies that TAIL can be as effective as disorder-specific treatment for a population with concurrent insomnia and depression.<sup>107</sup>

#### *4.1.2.7 Pain*

The within-group effect size for symptoms of pain was minimal, with the confidence interval overlapping zero, for the whole sample. For the subgroup with a higher degree of pain the within-group effect size was small. This small effect-size was comparable in size to the small effects compared to waiting list-conditions seen in a review of internet-based pain interventions.<sup>108</sup>

### **4.1.3 Cost-effectiveness**

The result of Study II that TAIL is probably cost-effective in the health care provider perspective at the willingness to pay-threshold of €21 536 (£20 000) per QALY was similar to other cost-effectiveness trials of internet-based treatments for depression,<sup>109–111</sup> strengthening the case for implementation of TAIL in routine care. Cost per QALY was higher in the societal perspective of Study II, but can still be considered as moderate costs in the Swedish context.

The cost-effectiveness results for TAIL compared to TAU in Study II depends a great deal on the conservatively estimated intervention cost. To explore a scenario with less conservatively

estimated costs we can do a kind of reversed sensitivity analysis using halved intervention costs. If the costs of TAIL were to be reduced by 50 %, by for example increased automation of therapist-support, TAIL would dominate TAU in cost-effectiveness in the health care perspective, i.e. TAIL would be both cheaper and more effective than TAU. The probability for TAIL to be cost-effective compared to TAU at the willingness to pay-threshold of €21 536 per QALY would then also be 100 %. This explorative reasoning can function as incentive to keep striving to lower the costs of TAIL. Previous research has shown that even a small procedure change in internet-based treatment, can lead to considerably lowered costs with retained effects.<sup>112</sup>

#### **4.1.4 Non-inferiority to disorder-specific routine care benchmarks**

The non-inferiority to the well-established disorder-specific depression treatment is another argument in favor of implementing TAIL in routine care. The inability to attain non-inferiority to the disorder-specific benchmarks for panic disorder or social anxiety disorder was on the other hand slightly discouraging. The subgroups of TAIL used in these comparisons were rather small, so the result could partly be due to low statistical power. Two previous studies of internet-based treatment for panic disorder and social anxiety disorder did not find any differences in effect between a transdiagnostic and a disorder-specific approach.<sup>113,114</sup> One possibly decisive difference between these studies and REGASSA was that the inclusion criteria in REGASSA was solely based on depression symptoms, while the studies of transdiagnostic versus disorder-specific treatment, used condition-specific inclusion criteria for panic and social anxiety symptoms. In any case, the conclusions from REGASSA should be restricted to be about patients with at least some depressive symptoms.

#### **4.1.5 The relationship between treatment compliance and symptom reductions**

The structured scoring of treatment compliance in Study IV was a novel method created for this analysis but hopefully useful in other analyses, and to other researchers, in the future. The guide to compliance scoring can be found in the supplement to Study IV. The following is a discussion of the results from Study IV together with some preliminary clinical recommendations based on all results.

##### *4.1.5.1 Depression*

The fact that overall compliance to TAIL were related to reductions on depression symptoms supports that working with the treatment content had an effect on depressive symptoms, although caution about causal conclusions always needs to be pointed out in correlational designs like Study IV. Specific compliance to components for stress and insomnia were also related to better depression outcomes which can be interpreted as these components being important to add to any internet-based depression treatment, where comorbid symptoms of stress and insomnia are high.

#### *4.1.5.2 Worry*

The earlier established moderate within-group effect sizes of TAIL on worry symptoms, together with the rather small association between overall compliance and specific symptom reductions, and no association between specific compliance and specific symptom reductions, leads us to a fairly disappointing conclusion on the worry components in TAIL. Although depressed participants in TAIL reduced their worry symptoms significantly, there are no clear advantages of TAIL over a transdiagnostic treatment approach without individual tailoring. Based on these data compared to previous data on GAD-patients, TAIL cannot be recommended as a replacement for a disorder-specific GAD-treatment.

#### *4.1.5.3 Panic*

Overall compliance, and compliance to transdiagnostic and nonspecific components in TAIL were related to considerable reductions in panic symptoms, but specific compliance to the panic components was not. We therefore need to conclude that although depressed participants in TAIL seemed to reduce their panic symptoms considerably, there was no clear advantage of tailoring specific panic modules. Also, because of the possibly lower within-group effects, TAIL cannot be recommended as a full replacement for a disorder-specific panic disorder-treatment based on this study. Another suggestion for treating patients with concurrent panic and depressive symptoms, based on these results, would be a transdiagnostic anxiety-treatment including components on exposure and avoidance behaviors.

#### *4.1.5.4 Social anxiety*

The result from Study IV that the specific compliance was related to specific outcomes for subgroup with comorbid social anxiety in TAIL leads us to conclude that there is some preliminary evidence of advantages with adding tailored content on social anxiety to the treatment, and together with the magnitude of the effect sizes maybe even that TAIL can lead to sufficient reductions in social anxiety symptoms compared with disorder-specific treatment, for patients with both depression and social anxiety. Since the correlational nature of study IV and the small and underpowered subgroup with social anxiety, this preliminary outcome needs to be replicated with more patients and a randomized design.

#### *4.1.5.5 Stress*

The results that specific compliance with the components associated with handling stress in TAIL were related to reductions in both perceived stress and depression symptoms leads us to the preliminary conclusion that the tailored stress content in TAIL is important for depressed participants with high levels of stress, both for their stress symptoms and depression symptoms. Since stress is such a common comorbid condition in this population, the tailoring of stress components can be preliminarily recommended in internet-based depression interventions. TAIL should however not be recommended as an intervention for patients presenting only with stress and not depression based on this data, since all participants in TAIL had comorbid depressive symptoms.

#### 4.1.5.6 *Insomnia*

As with stress, the results from Study IV indicated that specific compliance with the insomnia components in TAIL were related to reductions in both insomnia symptoms and depression symptoms. This, together with the high concurrence of insomnia and depression symptoms in the population, leads us to the conclusion that the tailoring of insomnia components can be preliminary recommended in internet-based depression interventions. That the patients' involvement in the main components in psychological treatment for insomnia, sleep restriction and stimulus control, is important for reductions in insomnia symptoms replicate earlier findings from guided self-help.<sup>59</sup> The results from Study IV also highlight the importance of improving sleep as a means to reducing symptoms of depression, which strengthens the conclusions from earlier research on internet-based treatment for patients with insomnia and depression.<sup>107</sup> Since many findings in psychological science are hard to replicate,<sup>115</sup> these findings on insomnia treatment actually appear as unusually stable.

#### 4.1.5.7 *Pain*

Since neither overall compliance, nor specific compliance to the pain components in TAIL, were related to reductions in pain or depression symptoms, we can conclude that the individual tailoring of pain components was unnecessary for the patient group in TAIL, and that patients with pain may need specific pain interventions to reduce pain symptoms. This can possibly be explained by that, although concurrent pain symptoms were high in TAIL, the intervention was probably not viewed as a credible pain intervention by the participants. The small effect on pain symptoms was because of symptom reductions in patients with low initial levels of pain, while participants with more severe pain did not improve at all. The results from Study IV do however show that working with the other components in treatment seemed to lead to symptom reductions in depression, even for participants with pain. In addition, it can be argued that reductions in pain symptoms should not be the outcome in pain interventions, which should instead focus on for example, increased psychological flexibility.

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## 4.2 STRENGTHS AND LIMITATIONS

Each study included in this thesis include discussions of their respective strengths and limitations. Here we will briefly discuss some of the strengths and limitations of the thesis as a whole.

### 4.2.1 Strengths

- In comparison to other randomized trials of psychological treatment, a strength with REGASSA was the large amount of participants leading to a reduced risk of type II errors, i.e. false negative findings.
- Another strength with REGASSA was the use of, at least partly, credible treatment alternatives, and not waiting list-controls that are at great risk of inducing placebo effects.

- A third strength with REGASSA was the high ecological validity of the treatments. By using treatment alternatives set in routine care, the results have a high degree of generalizability to routine care for future implementation.

#### 4.2.2 Limitations

- A limitation in Study I-IV was the existence of missing data. This issue was handled in different ways in the different studies. For Study I, some patients with missing post assessments did reserve interviews including the most important outcome measurements, such as MADRS, bringing the response rate of these main outcomes up to an acceptable 78 %. In Study II the procedure of multiple imputation was necessary because of diverse missing data in many different variables. Study III used generalized estimating equations for better handling of missing data points, while Study IV used a complete case analysis, with a separate analysis of participants with and without missing data points, that can be found in the supplement of Study IV.
- Despite using real treatment alternatives, and not waiting list-conditions, a limitation of Study I and II is the already mentioned nocebo effects of randomization, illustrated by quotes from the credibility questionnaire. The impact of this limitation is partly reduced by the fact that the disappointment of being randomized to TAIL or PE were seen in both these groups. There were participants in TAIL that had preferred to receive PE and participants in PE that had preferred to receive TAIL.
- Since the analyses in Study III and IV lacked a control condition, there was no control for the effect of spontaneous recovery, measurements or the passing of time, when for example estimating within-group effect sizes. For the outcome on depression symptoms, the results of the TAU control condition of Study I and II supports the conclusion that the effects go beyond spontaneous recovery, while for the comorbid conditions the conclusions by necessity have to be preliminary. The similarity of some within-group effect sizes to effect sizes in previous research partly reduces this limitation.
- Similarly, in the correlational design of Study IV, the possible existence of confounding variables, influencing both compliance and outcome, cannot be completely controlled for. The found relations between compliance and outcome are not evidence of causal relations, but together with some earlier findings in randomized studies these results seem at least partly credible. These preliminary results can also generate hypotheses for future testing.
- Although the generalizability to routine care situations probably is high, it has to be remembered that REGASSA was carried out in a Swedish primary care context which is perhaps not fully generalizable to other countries. How internet interventions and physical exercise are perceived as credible interventions for depression can be culturally dependent.

### 4.3 FUTURE DIRECTIONS

Hopefully, the results in this thesis can stimulate further research on individually tailored internet-based treatment. Here are some possible directions.

- What is the exact role of guidance, and how minimal can guidance be for effects to be maintained? There are already some results and ideas on how to use for example automated messages to enhance treatment compliance in treatments initiated by a clinician, but otherwise unguided.<sup>117</sup>
- What are the effects of specific components in treatment, down to the smallest building blocks? Dismantling studies with randomized and factorial designs will deepen our knowledge and guide us to build more efficient treatments packages.
- Can we enhance TAIL by adding treatment components for more conditions? Some evidence for example, suggest that alcohol use causes depression symptoms more than depression symptoms causes alcohol use.<sup>118</sup> The addition of modules on alcohol use would probably help the patients with concurrent depression and problematic alcohol use. Other examples of interesting conditions to add components for would be loneliness, procrastination behaviour, and intrusive memories.
- How can we gather weekly symptom ratings of many specific conditions without increasing the work load of patients filling out the assessment forms? There are already a number of very brief scales, such as the PHQ-2 for depression,<sup>119</sup> and mini-SPIN for social anxiety.<sup>120</sup> By constructing and testing new brief scales, with acceptable sensitivity to change, we can keep track of specific symptom changes week by week more easily.
- How can we overcome the challenges of implementing an individually tailored treatment in a health care system with up and running procedures made for disorder-specific treatments? Some clinicians working with implemented internet-based treatments, experience problems with the current technology being inflexible for patients without a distinct primary condition, or that stigma is a barrier for patients to self-refer to treatment.<sup>121</sup> More research on implementation can help clinics to create simpler inclusion procedures for individually tailored treatments that possibly both reduces health care administration and patient stigma.

## 5 CONCLUSIONS

This thesis provides support for the implementation of individually tailored internet-based treatment (TAIL) for patients with depression and comorbid conditions. More specifically, the thesis has demonstrated that:

- TAIL leads to larger reductions in depression symptoms than treatment as usual in primary care, and participants are also more satisfied with their treatment. There were however no differences in effect compared to structured physical exercise.
- TAIL does not seem to help much for participants with comorbid symptoms of pain, but reductions in worry-, panic-, social anxiety-, stress- and insomnia symptoms were considerable, at least for participants that had problematic symptoms of these conditions at treatment start.
- When choosing treatment between TAIL and treatment as usual in primary care, it is probable that TAIL is the more cost-effective alternative for the health care provider.
- TAIL is as effective as the disorder-specific internet-based treatments for depression already used in routine care. There is insufficient evidence to conclude if TAIL is as effective as disorder-specific treatment for panic disorder and social anxiety disorder, but there is suggestive evidence that disorder-specific panic treatment is superior for clear cases of panic disorder.
- Specific treatment components in TAIL for stress and insomnia were associated with both specific symptom reductions, and reductions in depression symptoms. These treatment components should not be ignored when treating patients with depression and these comorbid conditions. Specific treatment components for pain were not necessary for symptom reductions, indicating that these components were redundant.

## 6 ACKNOWLEDGEMENTS

*“To get someone dressed, for example, requires putting on a shirt. But first, the person must reach for the shirt. And before that, the person must get up and go toward it. And even more basically, you need to say to the person, ‘Look at me,’ and get them to make eye contact.”*

Nathan Azrin, 1930-2013.



Behavioral psychology legend Nathan Azrin, PhD, and the author in Stockholm, 2011. We adapted Dr Azrins job club methodology to the internet for the TAIL intervention and I had the opportunity to thank him in person. Photo credit: Samir El Alaoui.

First, I wish to acknowledge Viktor Kaldo, probably the most valuable main supervisor in the world. Working with you is always a pleasure and we have accomplished a lot together since I was as a master student hang around, 9 years ago. You have always given me big responsibilities, a lot of freedom, AND a lot of help and emotional support to back that freedom up. Are you a behavioral psychologist?

Robert Johansson, co-supervisor and sort of mentor by proxy. Right from the project start in 2010 we used your master thesis and the modules from the TAILOR-project to create TAIL. And now the last couple of years of years we have gone full circle and you have been coaching me to the finish line of this thesis.

Nils Lindefors, co-supervisor and boss. The environment you have created at Psychiatry Southwest in Flemingsberg stimulates both research and rapid implementation of new effective treatments in the clinic. Without you this project would never have happened.

Per Svenningsson, co-supervisor of Parkinson projects. At half-time I decided to remove the Parkinson project from this thesis. But we still managed to finish both the pilot and the large randomized trial. I learned a lot about conducting research by coordinating the Parkinson project, and I even learned some neurology and pharmacology by joining you at patient visits.

Gerhard Andersson, mentor and godfather of Swedish internet-based treatment in general, and individually tailored treatment in particular. From the first time I heard you cracking an outlandish joke, I knew I found my research field. Much thanks to you this is a research field



where students can join in on papers and valuable research is being done to a low cost in a short time. In addition, you are always a fun and friendly person to hang out with at conferences.

Kerstin Blom, clinical supervisor in the early days of the project, and a brilliant research group colleague and friend ever since. I have learned so much from you of how to supervise students effectively, how to write better manuscripts, and I try to learn how to just be a fun and witty person in general by observing your good example.

Johanna Törnevik, language consultant who did the first revisions of the treatment program together with me. Behavior change can last - I still do the 30-day shred from time to time.

Simon Mattsson, R-script master. Study II was an epic battle for us. Together we defeated the foes of missing data and diverging TiC-P-versions at different time points.

The rest of CPF Kaldo: Susanna Jernelöv, Berkeh Nasri, Erik Forsell, Ann Rosén, Nils Isacson & Cecilia Svanborg. Let's keep doing research and implementation together. And the alumni: Ekaterina Ivanova & Max Rubinsztein, come back any time.

The Internet psychiatry clinic in Stockholm: Monica Hellberg, Nina Lind, Jennifer Söderdahl, Susanna Österman and absolutely all my former colleagues from this gem of a work place. Keep producing cost-effective psychological treatment. Samir El Alaoui, I will never forget the Ipsy-anthem.

There were many people involved in the larger REGASSA trial, and I am thankful to you all: Elisabeth Erwall, Yvonne Forsell, Mats Hallgren, Agneta Öjehagen, Catharina Strid, everybody at KTA Prim, and all the rest involved in some stage of the project.

All clinicians and students who helped out with the project in Flemingsberg since 2010: Hannes Hedvall, Garin Alarcon Alanes, Nina Tall, Lovisa Lidevei, Eva Ernstson, Teresia Åbro, Linda Ankartjärn, Erik Eklöv, Thomas Olsson, Maria Fridlund, Sara Edström, Klas Johannesson, Charlotte Rosander, Emil Rosander, Joakim Ivarsson, Niels Éék, Kristina Aspvall, Erika Sundqvist, Sahar Gaveli, Annika Norlin, Maria Cassel, Anne-Sofie Rosenthal, Charlotta Barder, Poljana Matini, Tone Nordling and Madeleine Lindberg. Not to forget Victoria Sennerstam and Lovisa Lallerstedt who helped out with the latest version of the individually tailored treatment.

Christopher Sundström, my buddy mentor. To work with alcohol interventions with you and Niels was one of the most rewarding parts of the PhD-years.

Christian Rück + lab. Without you as colleagues, Flemingsberg would be a dull place. Special recognition to old timers Jesper Enander, Volen Ivanov, Erik Andersson and Evelyn Andersson.

Robert Schibbye, my own PTP, PT and table tennis tormentor. Together we made the Parkinson RCT from applying ethics approval to finish in less than 12 months. And of course

thanks to the rest of the Parkinson crew: Nathalie Riddarlans, Kent Sahin and Jon Westman. You put the art in MS Office clip art.

The Department of Clinical Neuroscience: Robert Harris and everybody at CNS admin. I also feel proud to belong to the same department as fantastic people like Brjánn Ljótsson, Erik Hedman-Lagerlöf, Sarah Vigerland, and many more.

Research School in Clinical Psychiatry: Nitya Jayaram-Lindström, Kristoffer NT Månsson and all my former class mates.

MindSpot Clinic and Macquarie University in Sydney for being great hosts and collaborators: Eyal Karin, Nick Titov, Blake Dear and all the rest of you. Goodonya!

ISRII-, ESRII-, and SWESRII-communities: I am very happy to be a part of this world wide community of researchers where there always is a friendly and cooperative atmosphere at meetings. You are too many to even begin name dropping, but in Sweden we have Per Carlbring, Lise Bergman Nordgren and Björn Paxling among others.

Friends: I have some wonderful friends since a very long time, many back from growing up near lake Flaten, Rönninge. You all know who you are. Dr. Carl Björkholm, your experiences with how to navigate the life as a PhD-student has been of great help for me these years.

To my family, Mamma, Ninni, Gabbi, Hannah & Iris: Your support means everything to me. Through you all I also have my extended families where I always feel at home.

I am also grateful to the REHSAM grant that financed this project, Karolinska Institutet and Stockholm county council for giving me a workplace during these years, and the National Library of Sweden where I wrote much of the thesis.

Finally, the most important acknowledgement: all 946 participants that took part in this large clinical trial. My hope is that you benefited from this research being done, as much as this research benefited from your participation.

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