Assessment and treatment of mental health problems in primary care

The course and results of Internet-based CBT and physical exercise on psychological functioning, stress and sleep

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Ja visst gör det ont när knoppar brister. Varför skulle annars våren tveka?
Karin Boye

Contents

Acknowledgements

List of papers

This thesis is based on the following papers referred to in the text by their Roman numerals.

I. Strid, C., Lundh, L-G., Andersson, C., & Öjehagen, A. (2014). Psychometric properties of the Swedish version of the Outcome Questionnaire-45 as administered by automated technique in a large sample of mental ill-health patients in primary care. *European Journal of Psychiatry 14* (4), 242-251

II. Strid, C., Andersson, C., Forsell, Y., Öjehagen, A., & Lundh, L-G. (2016) Internet-based cognitive behavior therapy and physical exercise – Effects studied by automated telephone assessments in mental ill-health patients; a randomized controlled trial. *British Journal of Clinical Psychology* Epub ahead of print 5 April 2016. DOI:10.1111/Bjc.12111

III. Strid, C., Andersson, C., & Öjehagen, A. (2016) The influence of hazardous drinking on psychological functioning, stress and sleep during and after treatment in patients with mental health problems. *Submitted*

Abbreviations

AUD   Alcohol use disorder

AUDIT   Alcohol Use Disorder Identification Test

AUDIT-C   Alcohol Use Disorder Identification Test - Consumption

CBT   Cognitive behavioural therapy

EQ-5D   EuroQol-5Dimensions

GHQ   General Health Questionnaire

GP   General practitioner

HRQoL   Health related quality of life

ICBT   Internet-based cognitive behavioural therapy

IP   Interpersonal problems

ITT   Intention to treat

IVR   Interactive Voice Response

KSQ   Karolinska Sleep Questionnaire

MADRS   Mongomery Åsberg Depression Rating Scale

M.I.N.I.   Mini-International Psychiatric Interview

OQ-45   Outcome Questionnaire-45

PE   Physical exercise

PHQ9   Patient Health Questionnaire-9

PSS   Perceived Stress Scale

RCT   Randomized controlled trial

SD   Symptoms of distress

SR   Social role functioning

TAU   Treatment as usual

Abstract

The present thesis comprises three studies carried out within REGASSA, a multicenter randomized controlled trial in primary care. In the REGASSA study a 12 week treatment of mild to moderate depression and stress-related mental health problems using Internet-based cognitive behavioural therapy (ICBT) and physical exercise (PE) was compared with treatment as usual (TAU). The inclusion criteria were symptoms of depression based on score >9 on the Patient Health Questionnaire-9. The overall aim in this thesis was to examine the course and results of the REGASSA treatment on psychological functioning, perceived stress and sleep assessed repeatedly by an computerized telephone technology, Interactive Voice Response (IVR), during treatment and in follow-up.

The first study aimed to examine the psychometric properties of Outcome Questionnaire-45 (OQ-45) and the way OQ-45 would contribute to the explained variance in depression (MADRS) and health-related quality of life (EQ-5D). OQ-45 is a broad measure for psychological functioning with a total score for overall distress and three subscales, Symptom of distress, Interpersonal relations and Social role functioning. The aim in the second study was to compare the course and results of the treatment alternatives ICBT, PE and TAU, based on IVR data of OQ-45, stress and sleep over a 12- month follow-up period. The hypothesis was that ICBT would be more effective than PE and ICBT and that PE would be more effective than TAU. In the third study we extended the analyses and examined whether hazardous alcohol consumption at baseline influenced the results on OQ-45, stress and sleep during treatment and in follow-up.

REGASSA included 946 patients and at baseline 879 of them registered for IVR and these patients are the focus of this thesis. The IVR system was programmed to automatically call the patient twice during treatment, once at the end of treatment and three times during follow-up. The sample comprised 70 % women and the average age was 43. The comorbidity between depression and several anxiety disorders was high and the proportion of hazardous drinkers was higher compared to the general population.

The main results were (1) OQ-45 showed good psychometric properties with regard to the total score but was weaker with regard to the subscales and the OQ-45 total score was found to predict depression and health related quality of life beyond demographics and perceived stress. (2) ICBT and physical exercise were

more effective than treatment as usual on psychological functioning and sleep but not on perceived stress with small to moderate effect sizes Cohen´s d = 0.20-0.56. (3) Hazardous alcohol drinking negatively influenced the course of perceived stress, but showed no effects on psychological functioning and sleep.

In conclusion the OQ-45 total score is a comprehensive tool with good psychometric properties which seems useful for clinicians and researchers in the field. However, the subscales cannot be recommended for use on the basis of these results and further research is needed.

Treatment of depression also affected psychological functioning, and sleep, but the effect on stress was less clear. The comparison between treatments showed similar results i.e. that ICBT and PE were both superior to TAU and could be implemented as treatments in primary care for mental health problems. It could however be of interest with further research on tailored treatment for patients with various mental health problems. With regard to hazardous alcohol consumption the results emphasized the need for screening for alcohol habits in routine care.

Populärvetenskaplig sammanfattning

Psykisk ohälsa är en vanlig bakgrund till att patienter söker hjälp i primärvården men det är inte alltid dessa problem upptäcks. Patienterna erbjuds inte heller alltid adekvat behandling. Det finns flera väl beprövade bedömningsinstrument och evidensbaserade behandlingar för psykisk ohälsa men tillgängligheten till dessa är begränsad i primärvården.

I avhandlingen ingår tre delstudier som är utförda inom ett större forskningsprojekt, REGASSA, en randomiserad kontrollerad studie som genomfördes under 2011-2014 i sex olika landstingen och regioner i Sverige och i samarbete med Karolinska institutet och Lunds universitet. Projektet finansierades delvis av medel från regeringen i en satsning för att utveckla effektiva behandlingsmetoder för patienter med smärta eller psykisk ohälsa. Målsättningen med projekten var minskad sjukfrånvaro och ökad arbetsförmåga. Syftet med REGASSA var att jämföra effekten av 12 veckor internetbaserad kognitiv beteendeterapi (IKBT) och fysisk träning med sedvanlig behandling hos patienter med depression, ångest och stressrelaterad psykisk ohälsa. Resultatet följdes upp med flera olika utfallsmått så som arbetsförmåga, sjukskrivning och depression.

Fokus för mina studier har varit upprepade mätningar av psykologisk funktion, stress och sömn hos patienterna i REGASSA. Data har samlats in via en automatiserad telefonsvarsteknik, Interactive Voice Response (IVR) före, under och efter behandlingen. Målsättningen var att öka kunskapen om patienternas psykiska problem både under behandlingsförloppet och under uppföljningen genom att mäta inte bara symptom utan andra viktiga områden som kan vara påverkade vid depression så som relationer till andra, sociala funktion, förmåga att hantera stress och sömnsvårigheter. Målsättningen var vidare att jämföra resultaten av behandlingarna på dessa mått och utvärdera hur riskkonsumtion av alkohol påverkade dessa resultat. Ytterligare ett syfte var att få erfarenhet av att samla data med hjälp av en automatiserad teleteknik och därigenom kunna följa ett stort antal patienter med psykisk ohälsa i primärvården.

Patienterna rekryterades via primärvården där de fick besvara en kort enkät om depressiva symptom, PHQ-9. De som fick > 9 poäng, hade goda kunskaper i svenska språket och tillgång till internet bjöds in till studien. Patienterna gav sitt skriftliga samtycke till att delta och besvarade ett antal frågeformulär däribland MADRS för skattning av depression, EQ5D för skattning av hälsorelaterad

livskvalité och AUDIT-C för alkoholkonsumtion. Samtidigt registrerade patienterna sitt ID nummer och telefonnummer i IVR för att besvara skattningar av psykologisk funktion med Outcome Questionnaire-45 (OQ-45), stress med Perceived Stress Scale (PSS) och sömn med Karolinska sömnformulär (KSQ). Därefter blev de slumpmässigt tilldelade ett av de tre behandlingsalternativen; internetbaserad KBT, fysisk träning eller sedvanlig behandling i primärvården. Patienter med svår psykisk sjukdom som krävde specialistvård, somatisk sjukdom som i sig krävde sjukskrivning, panikångest och alkoholberoende som primär diagnos exkluderades.

REGASSA inkluderade 946 patienter och av dem registrerade sig 879 i IVR. Övervägande andelen var kvinnor, 73 % och medelåldern var 43. Mer än hälften hade en högre utbildning och ca 80 % arbetade eller studerade, endast 5 % var sjukskrivna. Nästan alla uppfyllde kriterierna för depression och två tredjedelar av dem hade även en samsjuklighet med en eller flera ångeststörningar. En större andel, 14 %, hade en riskkonsumtion av alkohol jämfört med normalbefolkningen. Hälften hade en låg psykologisk funktion och sömnproblem och ca 70 % upplevde svårigheter att hantera stress.

Studie I utgick från data insamlade innan behandlingen d v s vid baslinjen och fokus var att utvärdera frågeformuläret OQ-45 som mäter psykologisk funktion. Det består av ett övergripande generellt mått och tre delskalor, symptom, interpersonella relationer och social rollfunktion. Syftet var att undersöka de psykometriska egenskaperna hos den svenska versionen av OQ-45 men även utvärdera ifall OQ-45 på ett unikt sätt kan bidra till att förstå patienternas svårigheter.

Resultatet visade att de psykometriska egenskaperna var goda för hela skalan av OQ-45 men svagare för delskalorna. OQ-45 helskala bidrog också på ett unikt sätt till att beskriva patienternas problem. Sammantaget visade studien att helskalan i OQ-45 som omfattar flera viktiga områden kan vara användbar både i forskning och i klinisk verksamhet.

I studie II jämförde vi effekten av behandlingsalternativen IKBT och fysisk träning med sedvanlig behandling på de upprepade mätningarna av psykologisk funktion (OQ-45), stress (PSS) och sömn (KSQ). Hypotesen var att IKBT skulle ge bättre effekt än fysisk träning och IKBT och fysisk träning skulle ge bättre effekt än sedvanlig behandling. Mätningarna genomfördes via det automatiska telefonsvarssystemet IVR. Vid sammanlagt 6 tillfällen t o m 12 månader efter baslinjen blev patienterna uppringda av datorn för att besvara frågorna med hjälp av knappvalsteknik. Bortfallet av patienter blev efterhand ganska stort och vid 12 månader var det 25 % som besvarade frågorna.

Resultaten visade att IKBT och fysisk träning gav bättre effekt på psykologisk funktion och sömn än sedvanlig behandling. Däremot var det ingen skillnad i effekt mellan IKBT och fysisk träning. Vad gäller stress fanns inga skillnader mellan behandlingsalternativen; alla tre förbättrades. Beräkningar på OQ-45 visade att ca 60 % av patienterna i IKBT och fysisk träning hade blivit kliniskt förbättrade i sin psykologiska funktion vid behandlingens avslut jämfört med 35 % i sedvanlig behandling. Andelen tillfrisknade vid 3 månader var i IKBT 30 %, i fysisk träning 23 % och i sedvanlig behandling 15 %. Resultaten kvarstod vid 12 månader.

I den tredje studien utvärderade vi ifall riskkonsumtion av alkohol påverkade resultaten av psykologisk funktion, stress och sömn. Vid baslinjen var fler riskkonsumenter män 18 % jämfört med 12 % kvinnor. Riskkonsumenterna hade lägre psykologisk funktion och var mer deprimerade än övriga. Under behandlingen och därefter fann vi att stress inte minskade lika mycket hos riskkonsumenter. Patienter med riskkonsumtion av alkohol hade troligtvis mindre effekt av behandlingen jämfört med övriga. Vi fann ingen skillnad under förloppet mellan riskkonsumenter och icke-riskkonsumenter vad gällde psykologisk funktion och sömn.

Studierna i denna avhandling visar att det går att mäta, följa och få resultat inom flera områden som kan vara påverkade vid psykisk ohälsa. Outcome Questionnaire-45 som mäter både symptom, interpersonella relationer och social funktion kan vara ett användbart instrument både i forskning och i klinisk verksamhet.

Insamlingen av data via ett automatiserat telefonsvarssystem, IVR, gjorde det möjligt att följa en stor patientgrupp över tid. Framtida forskning kring andvändningen av IVR behövs dock med fokus på frågor om följsamhet och orsaker till bortfall.

Studierna visar att internet-baserad KBT och fysisk träning är verksamma behandlingsmetoder som med fördel kan erbjudas patienter i primärvården. Det behövs dock fortsatt forskning kring internet-baserad KBT och fysisk träning vad gäller individanpassade, generella eller diagnosspecifika program.

Studierna visar även att det är viktigt att fråga patienter i vården om deras alkoholvanor då riskkonsumtion kan ha negativa effekter på psykisk ohälsa och stressrelaterade besvär.

Introduction

Patients with mental health problems are common in the primary care (Nordström & Bodlund, 2008) and care providers are responsible for offering efficient treatment alternatives to these patients. The prevalence of mental ill-health in primary care is high, around 25-40 % but these patients are poorly recognized and often receive no treatment for these problems (Serrano-Blanco, et al., 2010, Craven & Bland, 2013, Laufer, et al., 2013). When working as a clinical psychologist in primary care I sometimes met patients with mental health problems who had not been sufficiently assessed or treated. Several well-tested assessments tools and efficient treatments are available for depression and anxiety but new methods are not always being fully implemented in clinical practice or primary care.

The studies in this thesis were conducted within the framework of REGASSA a randomized controlled trial carried out in primary care. The REGASSA study was funded by the Swedish Government which allocated funds to research projects that focused on efficient treatment alternatives for the two groups of patients with highest levels of sick-leave, those with mental ill-health or musculoskeletal pain disorders (Lytzy, Larsson, & Anderzén, 2015). The aim of the funding was to stimulate the development of methods in health care that reduce the patients' sick-leave and increase their work-ability.

The aims of REGASSA were to study the effects of Internet-based cognitive behavioural therapy (ICBT) and physical exercise (PE) compared to treatment as usual (TAU) in patients with light to moderate depression, and stress-related mental ill-health. The purpose was to broaden the treatments available for these patients with easily administered and cost-effective alternatives.

The focus in the present thesis was to study repeated assessments of psychological functioning, perceived stress and sleep in patients with light to moderate depression, anxiety and stress-related mental ill-health. The assessments were conducted within the REGASSA study and data was repeatedly collected by an automated telephone technique, Interactive Voice Response (IVR). The aims were to increase knowledge of the patients' mental health problems both during treatment and during follow-up by broadening the outcome measures to include not only symptoms of distress but other important life areas that can be affected such as interpersonal relations, social functioning, coping with perceived stress

and ability to sleep. Other aims were to collect the assessments in an easily administered way and to learn how well an automated technology system works for repeated assessments in patients with mental health problems works. There was also an interest in considering the patients' alcohol consumption and how it influenced the results in the repeated assessments.

Mental health problems

In the literature several terms are used to describe common mental health problems. It is common to refer to mental disorders as defined in terms of specific diagnoses i.e. major depression and anxiety disorders (Roca, Gili, Garcia-Garcia et al., 2009, Serrano-Blanco, et al., 2010), but also broader concepts including both diagnoses and subthreshold diagnoses such as common mental disorders, mental health problems and mental ill-health (King, et al., 2008, Nordström, & Bodlund, 2008, Dahlberg, Forsell, Damström-Takker, & Runeson, 2007, Vilhelmsson, Svensson, & Meeuwisse, 2011, Fleury, Farand, Aubé, & Imboua, 2012, Lytsy, et al., 2015, Borges, et al., 2016). In the present thesis the term mental ill-health is used for describing common mental health problems including psychological symptoms of distress, stress-related problems, subthreshold depression and anxiety, and specified diagnoses of depression and anxiety.

Mental ill-health is a growing problem in public health and accounts for one of the largest levels of sick-leave (WHO 2008, Lytsy, et al., 2015). The prevalence of mental health problems is high and according to a study in Europe 38 % of the EU population was estimated to have mental disorders each year (Wittchen, et al., 2011). In the US, the 12-month prevalence has been estimated at 26 % and in Norway 33 % (Kessler, Chiu, Demler, & Walters, 2005, Kringlen, Torgersen, & Kramer, 2001) The lifetime prevalence based on the World Mental Health Survey was estimated at 12-47 % (Kessler et al., 2007). There are effective treatments but in high income countries approximately 35-50 % receives no treatment and in low -to-middle income countries the proportions is even higher, around 80 % (WHO 2008).

The prevalence of mental disorders in primary care varies but most studies report that 20-30 % of the patients visiting primary care have mental health problems (Mallon, Broman, Åkerstedt, & Hetta et al., 2014, Nordström & Bodlund, 2008, Rocca, et al., 2009). A large study of the 12 month prevalence of clinically diagnosed disorders in Swedish primary care during 2002 showed lower proportions, 2.4 %, but the results were based on data from diagnosis-registered visits (Lejtzén, Sundquist, Sundquist, & Li, 2014) and many patients are known to seek help for other problems and mental ill-health is not always detected (Castro-Rodriguez, et al., 2015, Picardi, et al., 2016). In a Swedish population-based study (Forsell, 2006) the need of care for mental health problems was examined and

results showed that less than 25 % of the persons in need of care had their needs met. Only 37 % requested care and the reported reasons for not were feelings of shame. Male gender, alcohol problems and low education level were more common among those not requesting care. Sociodemographic risk factors for mental health problems are gender, age, employment status and education level (Kessler, et al., 2003, Dahlberg, et al., 2007, Laufer, et al., 2013). Depression and anxiety are common mental health problems in primary care.

Depression and anxiety

Depression was the focus of selection of patients in the REGASSA study. An estimated 350 million people suffer from depression and the disorder is a major contributor to the global burden of disease (WHO, 2008, Vos, et al., 2015). WHO has forecast depression to be the primary cause of disability in 2030 (WHO, 2008). According to a study conducted in the US, the life-time prevalence for mood-disorders was 21 % (Kessler, Chiu, Demler, &Walters, 2005). An epidemiologic study in Sweden estimated the point-prevalence of major depression in the population to be 5.2 % (Johansson, Carlbring, Hedman, Paxling, & Andersson, 2013).

Depression not only causes symptoms of distress but also has an impact on how a person functions in work, social life and family which are important areas in the quality of life (Cameron, Habert, Anand, & Furtado, 2014). This negative impact in how patients function is a reason for public health systems to give priority to the disease (Ferrari, et al., 2013). Depression has various diagnostic and clinical expressions characterized by being an episodic disorder with a distinct onset and end or a more chronic disorder as in dysthymia. After the first episode there is a risk of relapse, which increases with every episode. Depression manifests itself in different levels of severity (APA, 2013, Ferrari, et al., 2013, Cameron, eta al., 2014). When depressed you feel low, your desire to do things decrease, you lack energy and have sleep and weight problems. You feel worthless and have exaggerated feeling of guilt, less capability to concentrate or make decisions and you have negative thoughts about yourself and thoughts about death and suicide. Your cognitive functioning is also affected with memory difficulties and lack of initiative (Cameron, et al., 2014, APA, 2013). It is important to access suicidal thoughts and ideations in order to prevent suicidal attempts or suicide. A study in Sweden showed that the overall long-term risk for suicide in patients with depression was 5,6 - 6,8 % and severity and male gender were associated with an increased suicide risk (Bråvik, Mattisson, Bogren, & Nettelbladt, 2008). In a recent review, Beck & Bredemeier (2016) present a unified model of depression

integrating clinical, cognitive, biological and evolutionary perspectives. They point out the importance of a multidimensional view in understanding the nature of depression and how it can best be treated and call for more integrative research.

Patients with mild to moderate depression commonly seek help in primary care and, according to WHO Collaborative Study of Psychological Problems in General Health Care, the point-prevalence of depression is 10 %. Depression among primary care patients is also associated with poor quality of life (WHO, 2008, Grandes, Montoya, Arietaleanizbeaskoa, Arce, & Sanchez, 2011, Craven & Bland, 2013,). Although depression is common its detection in primary care is unsatisfactory (Castro-Rodriguez, et al., 2015, Craven & Bland, 2013), and approximately half of the patients receive no recommended treatment (Fernandez, et al. 2007). Even if screening could increase the detection of depression, studies have not shown support for this (Gilbody, Sheldon, & House, 2008, Thombs, Ziegelstein, Roseman, Kloda, & Ioannidis, 2014). However if the screening came with a treatment programme, there was some indication that the detection of depression would increase (Picardi, et al., 2016).

The most common class of mental health problems is anxiety disorders with a 12 months prevalence of 25 %. Onset is early and problems are often long lasting (Bandelow & Michaelis, 2015). The 12-months prevalence for anxiety disorders in primary care varies between 8 and 20 % (Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007, Serrano-Blanco, et al., 2010). Despite the high prevalence, studies have shown low rates of detection by general practitioners (GP) and inaccurate assessments of anxiety diagnoses (Vermani, Marcus, & Katzman, 2011; Olariu, et al., 2015).

Not all get adequate treatment for their anxiety disorder (Stein, et al., 2005). There are several anxiety disorders which manifest themselves in different ways but what they have in common is a perception of threat, a strong feeling of fear, and a low trust in the ability to cope with it. Even if there are specific cognitive and behavioural features for each of the anxiety disorders there are also shared underlying processes such as avoidance, safety-seeking behaviour, dysregulation, distorted reasoning process, and selective attention and memory (Craske, 2012). Within the frame of CBT specific theoretical models and treatment protocols have been developed the past 20 years and have proved to be very helpful in treatment of anxiety disorders (Clark, 1986, Öst, 1989, Salkovskis, 1999, Wells, 2002).

According to a large study in the US (Sherbourne, et al., 2010) comorbidity between different anxiety disorders is common among primary care patients and impairment and disability increase with several disorders. The study also showed that comorbidity between anxiety disorders and depression was high and that comorbidity increased with the number of anxiety disorders i.e. when the patient had several anxiety disorders the comorbidity with depression was more common.

The study reported that these primary care patients had low levels of functioning and health-related quality of life (HRQoL) and/or high levels of disability compared to the general population (Sherbourne, et al., 2010). In a Swedish population study Johansson and co-workers estimated that 50 % of individuals with either anxiety disorder or depression had comorbid disorders and comorbidity was also associated with lower HRQoL (Johansson, et al., 2013). These findings are in- line with other major studies conducted in Europe and the US, which also reported high disability and comorbidity in patients with depression and anxiety (Wittchen, & Jacobi, 2005, Kroenke, et al., 2007). Since comorbidity is common in clinical practice some researchers have argued for the diagnosis of mixed anxiety and depressive disorder to be included in DSM-5 (Möller, et al., 2016).

Psychological functioning

Psychological functioning is a broader description of a patient´s problem than symptom-based diagnosis. In this thesis psychological functioning refers to various aspects of the patient´s mental health problems, including symptoms of distress, interpersonal problems and social functioning. Broad measures are rare in outcome studies on treatment of depression. In a literature review conducted recently Kaloyan and colleagues (2015) found that 80 % of the areas covered by the instruments measured symptomatology and less than 20 % of the instruments addressed other areas of functioning. The review involved 247 studies conducted during 2004-2014 and the interventions were psychotherapy (mainly CBT), pharmacotherapy and alternative therapies and a combination of psychotherapy and medication (Kaloyan, Cabello, Coenen, & Ayuso-Mateos, 2015).

In the past decades much has been done to develop generic outcome measures that capture several dimensions of patients' mental health problems. One well used instrument is the General Health Questionnaire (GHQ) developed by Goldberg for detection of mental illness in the general population and in clinical settings (Goldberg, 1997). The original version consisted of 60 items and several versions have been developed GHQ-30, GHQ-28 and GHQ-12 (Goldberg, et al., 1997, Willmott, Boardman, Henshaw, & Jones, 2008, Lundin, Hallgren, Theobald, Hellgren, & Torgén, 2016). GHQ captures common mental health problems with dimensions of depression, anxiety, somatic symptoms and social dysfunction.

A central measure in this thesis is the Outcome Questionnaire-45 (OQ-45) developed by Lambert and colleagues (Lambert, et al., 1996) to improve outcomes of psychotherapy in routine care by tracking the course of therapy with individualized feedback (Lambert, Hansen, & Finch., 2001, Slade 2005, Lambert 2007 & 2013). Based on a large amount of psychotherapy outcome reviews, effect

sizes between treated and untreated individuals is, estimated at 0.75 meaning that approximately 67 % of the treated patients will have a positive outcome but studies also show that around 5-10 % deteriorate (Lambert, 2013). In studies where clinically significance is reported more than half of the patients improve or recover but a significant proportion do not respond to treatment and the figures are worse in routine clinical practice compared to clinical trials (Lambert, 2013).

In recent decades, health care providers have become more aware of cost limitations, thereby intensifying the focus on quality and treatment outcome in routine care (Brown, Burlingame, Lambert, Jones, & Vaccaro, et al., 2001, Lambert, 2013). The fact that not all patients improve in psychotherapy and a small proportion even deteriorate lead to an emphasis on the efficacy and effectiveness of psychotherapy especially in routine care. This stimulated the development of patient-focused research to improve efficacy of psychotherapy by monitoring an individual patient's process over the course of therapy (Lambert, et al., 2001).

The model developed by Lambert and colleagues included weekly assessments of the patients' problems during therapy and an alert system for patients at risk of treatment failure. Feedback was given to the therapist only or to both therapist and patient on therapy progress, helping the therapist to get the patient back on track (Lambert, et al., 2001, Lambert, 2007 & 2013). This model aimed to bridge the gap between research and clinical practice by improving treatment outcome before the end of treatment, thereby providing more information about differences in therapeutic change among individual patients, and change patterns in subgroups of patients (Lambert, et al., 2001, Lambert, 2007). An important issue was to limit the length of psychotherapy through a relation between dose and response i.e. the number of sessions needed to reach clinically reliable changes and recovery. The assessments were based on a comprehensive, reliable and valid questionnaire, Outcome Questionnaire-45 which was developed specifically for tracking treatment response. OQ-45 measures both mental and somatic symptoms, interpersonal problems and social role functioning which includes important areas of patients' lives and captures substantial issues for measuring treatment outcome.

Studies have shown that this individualized feedback process based on OQ-45 assessments improve the outcome of psychotherapy in routine care and reduce the risk of treatment failure. The effect is larger in not-on-track patients who comprise approximately 20 % of the patients in treatment. The dose-response rates have ranged between 11-40 sessions for 50-75 % of the patients to reach a clinically significant change in routine care. (Andersson & Lambert, 2001, Lambert, et al., 2001, Harmon, Hawkins, Lambert, Slade, & Whipple, 2005, Shimokava, Lambert, & Smart, 2010, Hansson, Rundberg, Österling, Öjehagen, & Berglund, 2012, de Jong, et al., 2014, Amble, Gude, Stubdahl, Andersen, & Wampold, 2015).

Entering treatment with high level of distress prolonged the therapy and early response to treatment was associated with better outcome (Brown, et al., 2001).

Another more recently developed instrument is the Clinical Outcomes in Routine Evaluation-Outcome Measure (CORE-OM) also constructed within psychotherapy research. The purpose was to create a core battery for routine data collection for evaluating treatment in routine care (Barkham, et al., 1998, Barkham, et al., 2001, Evans, et al., 2002). The UK National Health Service (NHS, 1996) had acknowledged the need for data collection in mental care and also the need for evidence of the efficacy of treatment conducted in routine care. The development of CORE-OM involved a wide group of service users and clinicians giving feedback on the quality of the scale. Important was that it measured the core domains of problems, was easy to administer and also sensitive to change. CORE-OM consists of 34 items covering four domains: subjective well-being, problems/symptoms, life functioning and risk. The risk domain contains questions about self-harm and violent behaviour towards others (Evans, et al., 2002).

OQ-45 and CORE-OM have shown good psychometric properties both in the original and translated version but support for the dimensions has shown varying results (Evans et al., 2002, Lambert et al. 1996, Lo Coco, et al., 2008, Palmieri, et al., 2009, Wennberg, Philips, & de Jong, 2010, Elfström, et al., 2012, Kristjansdottir, et al., 2015). The first factor analyzes of CORE-OM did not support the domains but instead showed a three-factor structure - negatively worded items, positively worded items and risk items (Evans, et al., 2002). Later studies have found that the best factor structure would be two dimensions - psychological distress (total score of subjective well-being, problems/symptoms and life functioning) and risk (Lyne, Barett, Evans, & Barkham, 2006).

Factor analyses of the OQ-45 have shown similar difficulties in confirming the three defined subscales - psychological functioning, interpersonal problems and social role functioning - both in the original version and translated ones (Mueller, Lambert, Burlingame, 1998, de Jong et al., 2007, Lo Coco, et al., 2008, Amble, et al., 2014). Chao & Green (2013) conducted a study on African American students which indicated a two-factor solution - well-being and psychological distress. Another study, also conducted in the US although on a clinical sample, suggested a seven-factor model of psychological problems (Thalmayer, 2014). Wennberg and co-workers (2010) examined the psychometric properties of the Swedish version of OQ-45 in a sample of patients with substance abuse and found an acceptable fit for the three-factor model, but weak support for the subscale social role functioning with an alpha level of 0.63. This was the first conducted psychometric study of the Swedish version of OQ-45 before this thesis.

Stress and sleep

In a public health report from 2009, 13 % of the Swedish population reported stress, and 6 % reported severe stress (Socialstyrelsen, 2009). A consequence of high level of stress over a longer period of time can be exhaustion, manifesting itself in fatigue, cognitive dysfunction, sleep problems and somatic problems. In a study conducted among 587 primary care patients in Sweden, almost 60 % reported moderate to high levels of stress, often combined with symptoms of anxiety and depression (Wiegner, Hange, Björkelund, & Ahlborg, 2015). Lazarus and colleagues developed a stress and coping model, which has had a major influence on the understanding of and interventions for stress-related problems (Lazarus & Folkman, 1984) The model has also been useful in understanding daily mood fluctuations in depression (Dunkley, 2016).

The prevalence rates of insomnia, including both insomnia symptoms and daytime consequences, have been estimated to 6-15 % in different countries (Ohayon & Seagles, 2010, Mallon, et al., 2014, Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014). A population-based study in Canada revealed that poor sleep was associated with reduced work-ability and increased health problems and health care utilization. People with insomnia more often used alcohol as a sleep aid compared to good sleepers (Daley, et al., 2009).

The criteria for insomnia disorder are lack of sleep quantity and quality due to difficulties in falling asleep, maintaining sleep, and early awakening. The sleep disturbances cause daytime consequences in the form of fatigue, sleepiness, poor concentration and inability to perform in important areas of functioning. The sleep difficulties occur three nights a week for at least three months (APA, 2013). Sleep problems are often concomitant with depression and anxiety disorders (Mallon, et al., 2014, Tkachenko et al. 2014), and strongly linked with stress and the social situation at work (Åkerstedt, Knutsson, Westerholm, Alfredsson, & Kecklund, et al. 2002). In a large population study, 3500 individuals were monitored over 25 years and results showed that sleep disturbances increased with stressful life events and this, in turn, increased the risk for symptoms of depression (Legget, Burgard, & Zivin, 2016)

Alcohol consumption

Alcohol consumption is associated with several negative aspects of both mental and physical health and makes a substantial contribution to the global burden of disease. In developed countries, alcohol-related problems account for 6.8 % of the

total burden of disease (WHO, 2014). Between 1995 and 2005 alcohol consumption in Sweden increased by approximately 25 % (Källmén, Wennberg, Leifman, Bergman, & Berman, 2011). The diagnosis alcohol use disorder (AUD) includes both alcohol abuse and dependence and is, in DSM 5, divided into three levels; mild, moderate, and severe (APA, 2013).

Hazardous drinking is a risky alcohol behaviour that can lead to AUD and also negatively affect various health aspects (Dawson, Li, & Grant, 2008, Haynes et al., 2007). Hazardous drinking is defined both by the number of drinks consumed weekly and the number of drinks consumed on a single one occasion, so called binge drinking. Several studies have shown a comorbidity between AUD and depression and anxiety (Sullivan, Fiellin, O´Connor, 2005; Nordström & Bodlund, 2008, Riper, et al., 2013) but it is not clear whether AUD and hazardous drinking affect treatment of depression and anxiety disorders (Haynes, et al. 2007, Gajecki et al. 2014, Wolitzky-Taylor, et al., 2015). In an extensive review based mainly on studies of alcohol use disorders (Sullivan, 2005) it could not be established whether alcohol use disorders had an effect on recovery from depression. One study included in the review found that hazardous drinking had no effect on depression recovery. However, there have been few studies on how hazardous drinking influences treatment conducted so far, so knowledge about whether – and how hazardous drinking is associated with psychological functioning, stress and sleep is unclear, and also how it affects treatment of depression.

Hazardous drinking seems to be common among primary care patients but has not been sufficiently examined or treated (Holmqvist, et al., 2008, Nordström & Bodlund, 2008, Sartre, Leibowitz, Mertens, & Weisner, 2014).

One way to prevent increases in alcohol consumption and to offer interventions could be to assess alcohol habits in health care through systematic screening (Barry, et al., 2006, Nihlen, Fredriksson, & Jansson, 2011, Reinholdz, Fornazar, Bendtsen, & Spak, 2013). The Alcohol Use Disorder Identification Test (AUDIT) (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993, Babor, Higgins-Biddle, & Saunders, 2001) is a well-used screening toll for screening AUD and assessing risky alcohol consumption. AUDIT is divided in two parts - alcohol consumption (AUDIT-C) and alcohol problems.

Using AUDIT Källmén and colleagues (2015) compared alcohol consumption in Sweden in 2014 with data from 2009 and the results showed stable scores during this period with around 15 % hazardous drinkers. The level of risky consumers during these years was higher than in the years before 2009 (Källmen, Wennberg, Ramstedt, & Hallgren, 2015). When the AUDIT scores in REGASSA were compared with the AUDIT scores in the general population, alcohol problems, hazardous drinking and binge drinking were significantly more common among the REGASSA patients (Åhlin, Hallgren, Öjehagen, Källmén, & Forsell, 2015).

Gender differences

Depression is more common among women and several studies indicate that approximately every fifth woman will sometime during her life be depressed, and for men every tenth (Kessler, et al., 2003, Roca et al., 2009). The same proportion is applied for anxiety disorders, which are also twice as high in women (Bandelow, & Michaelis, 2015). The gender differences could be explained through integrated models of affective, biological and cognitive factors that form a vulnerability of stressful life events that lead to depression (Hyde, 2008).

In a Swedish study (Lejtzén, et al., 2014) the estimated prevalence of depression, anxiety or stress in primary care was twice as high in women, and the gender differences were suggested to be due to inequalities in society. Another study conducted in the Swedish population showed that the severity of symptoms of depression is greater in women than men (Johansson, et al. 2013), but an epidemiology study conducted in Spain showed that women had similar effect of depression on disability as men (Gili, Castro, Navarro, et al., 2014).

Cuijpers and colleagues (2014) conducted a study on gender as a predictor and moderator of outcome in CBT and pharmacotherapy treatment for depression. They found no differences between men and women in response to CBT or medication, and the result regarding gender differences was in line with earlier treatment outcome studies.

A recent study on perceived stress and associations with exhaustion, depression and anxiety conducted in primary care in Sweden, found that women more often than men reported high levels of stress. Self-reported exhaustion in patients with high levels of stress was also more common in women compared to men (Wiegner, et al., 2015). In a study in the UK, using the short form of the Perceived Stress Scale (PSS), women also recorded higher stress scores than men (Warttig, Forshaw, South, & White, 2013).

A meta-analysis on gender differences in insomnia found that women are more likely to suffer from insomnia than men, and these results were in-line with a population study in Sweden showing that insomnia symptoms and insomnia disorder were more frequent in women (Mallon, et al., 2014).

Hazardous alcohol consumption is more common among men than women and also larger proportions of men meet the criteria for AUD (Bradley, 2007). In 2004 the estimated world-wide prevalence of AUD was 6.25 % for men and 3.75 % for women and the estimates for Europe were 9 % for men and 5.5 % for women (WHO, 2008).

Data collection

There are various ways of collecting data from patients both in research and in clinical settings. It is important to consider time and cost consuming aspects and also to estimate how much attrition there will be, i.e. how likely it is that the participants will answer the questions repeatedly, which could be important both in studies and in routine care. In RCT studies of treatment outcome the drop-out rates are rather high especially in long-term follow-ups (Ruwaard, Lange, Schrieken, Dolan, & Emmelkamp, 2012, Fernandez, Salem Swift, & Ramtahal, 2015).

Interactive Voice Response

In present thesis Interactive Voice Response (IVR) was used to collect the repeated data on psychological functioning, stress and sleep. IVR is a computerized automated telephone technique that is confidential and easy to use. The computerized system is interactive where the subjects give their responses through a touch-tone phone and the system gathers and reports the information that can be monitored twenty-four hours a day. IVR can handle different questionnaires and follow a large number of individuals over a longer period of time. It can be used for information, data collection or as a reminder for medication compliance or behavior modification (Lee, Friedman, Cukor, & Ahern, 2003, Abu-Hasaballah, James, & Aseltine, 2007).

When a patient has registered in IVR the system is programmed to automatically call the patients registered phone number at specified times and the patients to answer pre-coded questions by pressing a number on the phone. IVR has been used in several studies of depression (Kim et al., 2011; Andersson, Danielsson, Silfverberg-Dymling, Löndahl, & Johansson, 2014; Pfeiffer et al., 2015), substance abuse (Andersson, 2015; Mundt, Moore, & Bean, 2005), and paroled offenders (Andersson, Vasiljevic, Höglund, Öjehagen, & Berglund, 2014). In a randomized controlled trial in which IVR was used to follow up in-patient care for adolescents, there was a significantly higher rate of completers (65%), compared

to postal survey (38 %), and the IVR group also needed fewer reminders (Andersson, Danielsson, et al., 2014).

In this thesis the choice of collecting data by IVR was estimated more neutral to the format of treatment alternatives than online assessments. Since ICBT was the only treatment delivered online, there was a risk that online assessments could generate biases in response rates due to convenience of online assessments for patients in that treatment alternative. Using IVR, the ease of response to the assessments by touch-tone phone was presumed to be equal in the three treatment groups. IVR has the capacity to conduct repeated follow-ups for large patient samples and was therefore useful for collecting data in the REGASSA study.

Treatment

Mental disorders are treated in various ways and guidelines recommend different alternatives depending on diagnosis, severity, and response to treatment. For mild to moderate depression and anxiety, CBT is often the first choice of treatment, while for more severe or unresponsive cases a combination of medication and psychotherapy is recommended (APA, 2010, NICE, 2010, Socialstyrelsen, 2010).

Psychotherapy has been developed within different theoretical frames. For a long time, psychodynamic therapy was the dominating perspective originating from classical psychoanalysis (Freud, 1964), but has since developed and is now often delivered in a more focused short-term form. The therapist technique involves interpretation of the patient's feelings and behaviors in relation to the therapist and in relation to significant others (Malan, 1976). Evidence in favour of psychodynamic therapy has been growing in recent decades and such therapy has shown similar effect on depression as other psychological methods and better effect than waiting-list and treatment as usual (Leichsenring, Raubung, & Leibing, 2004, Cuijpers, van Straten, Andersson, & van Oppen, 2008, Abbass, et al., 2014). Psychodynamic therapy has also been tested in the Internet-delivered format and outcomes for IPDT were better than the control condition showing large to moderate between group effect sizes (Johansson, et al., 2013).

Interpersonal therapy (IPT) developed by Klerman and colleagues (1984), has shown to be equally effective for depression as other therapy methods and medication, and for anxiety disorders the effect was large compared to a control group (Cuijpers, et al. 2016). IPT is a recommended treatment alternative in guidelines for depression (NICE, 2010, Social styrelsen, 2010).

CBT has gained ground in health care the past 20 years and is a well-documented and established psychological treatment for patients with different mental health problems; this has been shown in several meta-analyses (Cuijpers et al 2008, Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010, Cuijpers et al. 2016). CBT was shown to have treatment effects with moderate to high effects sizes for depression and anxiety disorders and was superior for preventing relapse in depression.

Another treatment alternative that has attract increased attention for mental health problems is physical exercise (PE) which has proved effective in treating

depression (Kvam, et al., 2016). In this thesis PE was delivered by fitness centers outside the health care system. The CBT treatment was Internet-delivered and, in an earlier review where ICBT was compared with face-to-face psychotherapy no differences in effects were found and the drop-out rates were also insignificant (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014). Still the use of Internet-delivered CBT is rare in routine care, even if the usage has increased in the past decade it has not yet been fully implemented. CBT, ICBT and PE are described in more detail in the next sections.

CBT

Cognitive behavioural therapy (CBT) is usually directed towards different disorders with specific protocols and manualized treatments. Due to the high comorbidity between depression and anxiety disorders among mental ill-health patients there has been a development towards unified protocols that focus the treatment on common features of the emotional disorders (Barlow, 2004).

CBT both in specific and unified form is a highly structured treatment focusing on problems that occur in patients´ everyday lives. The interventions aim to change negative behaviour patterns and challenge negative automated thoughts and underlying assumptions associated with the main problem or diagnosis.

The most commonly used CBT techniques for treating depression and anxiety are behavioural activation (Veale, 2008), exposure (Abramowitz, 2013) and cognitive restructuring (Beck, 1979). The patients get weekly homework assignments that can be different types of registrations and ratings or behavioural experiments that the patient should do before the next therapy session. CBT is most commonly delivered in individual face-to-face sessions, but also in group therapy or self-help textbooks or Internet-based programs.

ICBT

Internet-based cognitive behaviour therapy (ICBT) is a treatment delivered by Internet as a mainly text-based self-help programme. It can be delivered both in the form of open access programmes and closed programmes with access only through personal identification. In closed programmes the treatment is usually guided and preceded by careful assessments such as screening procedures and diagnostic interviews and this is not the case with open access programmes. The diagnostic procedures before treatment are crucial for matching the patient to the

right treatment and when needed for referring the patient to another part of the health system (Andersson, Carlbring, Berger, Almlöv, & Cuijpers, 2009 & Andersson, Carlbring, Ljótsson, & Hedman, 2013).

The treatment can be supported by phone, e-mail or in person. Meta analyses have shown that therapist guided treatment has larger effects than unguided with better adherence and fewer drop-outs (Spek, et al., 2007, Andersson, et al., 2009, Richards & Richardson, 2012, & Andersson, et al., 2013). However, in a study comparing guided and unguided Internet-based treatment for depression, no differences were found between the treatments, both improved the patient. These results were probably due to strict inclusion criteria, and diagnostic interviews conducted by phone before treatment started (Berger, 2011).

Drop-out levels have been relatively high in ICBT depending on the severity of the disorder, diagnostic procedures, motivation, and support before and during treatment (Fernandez, et al., 2015). Adherence to the Internet-based treatment has shown very different proportions, from 40 % in primary care to 70 % in RCTs (Newby, 2013, Simco, 2014). When implemented in the health-care the ICBT treatment takes little time to administer and is easy to participate in (Hedman et al. 2014)

Physical exercise

Physical exercise (PE) is a well-known treatment for patient with depression and anxiety and is proven to be effective. A Cochrane review of 39 randomized controlled trials (RCT) concluded that exercise is moderately more effective than no treatment or a control intervention for reducing the symptoms of depression. A few smaller trials included in the review examined the effect of PE in comparison with psychological treatment and medication, and found no differences in effect (Cooney et al., 2013).

Another recently conducted review showed evidence that physical exercise reduces symptoms of anxiety. The review involved eight studies and found that for panic disorder, PE was more effective than placebo pill, although antidepressant medication was more effective than PE. If the exercise was low, moderate or high in intensity was insignificant and both aerobic and non-aerobic exercise reduced symptoms of anxiety. No studies were found on anxiety disorders comparing PE with CBT (Jayakody, Gunadasa, & Hosker, 2014). There has been an argument whether mode, frequency, duration and intensity are important for achieve results on depression. In a systematic review Nyström and colleagues (2015) found that mode of exercise was not important both aerobic and non-aerobic had an effect.

They also found that neither intensity nor duration made a difference, but the most common intensity used was 60-85 % of maximum heartrate and the minimum duration seemed to be 30 minutes/exercise session. Frequency had an impact of the results and a frequency of at least three times/week was recommended. They also emphasized that further research is needed to examine the importance of intensity and mode (Nyström, Neely, Hassmén, & Carlbring, 2015). Referring patients to physical exercise is an option in primary care in several countries including Sweden, but it is rarely used and follow-ups are uncommon (Kallings, Helenius, Leijon, & Stahle, 2008, Rome, Persson, Ekdahl, & Gard, 2009).

Psychopharmacological treatment

The new generations of antidepressants have increased the ability to treat depression, but, less than 50 % of the patients will be in remission after 8 weeks of medical treatment (Sicras-Mainar, Maurino, Cordero, Blanca-Tamayo, & Navarro-Artieda. 2012). Meta-analyses have shown medical treatment for mild to moderate depression to be as good as psychological treatment and in combination the effect sizes slightly increase (Cuijpers, van Straten, Warmerdam, & Andersson, 2009). For mild to moderate depression, antidepressants do not seem to be more effective than placebo-pills, but patients with severe depression have a true drug effect of medication (Fournier, et al., 2010). Some studies have shown that for patients with more severe depression, antidepressants have proved more effective than CBT (Dimidjian, et al., 2006), but other studies have shown CBT to be as effective as medication (DeRubeis, et al., 2005). The results for severe depression seem unclear, although the US guideline (APA, 2010) is recommending medication as first-choice treatment. The enduring effect of medication is another issue, and studies have shown that patients treated in remission with medication have a larger risk of relapse compared to psychological treatment and this seems to be the case for both anxiety disorders and depression (Hollon, Stewart & Strunk, 2006).

Aims of the thesis

The main focus of this thesis was on primary care patients with mild to moderate mental health problems. The overall aim was to follow these patients' course and results on psychological functioning, perceived stress and sleep, repeatedly assessed by IVR, as a function of different treatment alternatives and hazardous alcohol consumption. Further to examine the psychometric properties of OQ-45, which was used as a central measure of psychological functioning.

The aim in Paper I was to examine the psychometric properties of the Swedish version of OQ-45. Another aim was to analyze whether OQ-45 could predict level of depression (MADRS) beyond health-related quality of life (EQ-5D), perceived stress (PSS), and demographics, and if OQ-45 could predict health-related quality of life beyond depression, stress and demographics. Did the Swedish version of OQ-45 show acceptable psychometric properties in a large primary care sample? Did OQ-45 contribute uniquely in explaining the patients` problems?

The aims in Paper II were to compare the course and results of the three treatment alternatives based on the repeated data collected by IVR. The hypotheses were that the effects of ICBT would be better than PE and that ICBT and PE would be better than TAU. Did the patients improve or recover after treatment? Were there any differences in effect between ICBT compared to PE and ICBT and PE compared to TAU?

The aims in Paper III were to examine whether hazardous alcohol consumption at base-line influenced the course and results on psychological functioning, perceived stress, and sleep.

Methods

Study design

REGASSA was a multicentre study with a randomized controlled trial (RCT) design. REGASSA was carried out between 2011 and 2014 in six health care regions (Stockholm, Västra Götaland, Skåne, Västmanland, Kronoberg and Blekinge) in Sweden and involved two universities, Karolinska institutet and Lund University and 20 different primary care units. The aim of REGASSA was to study the effects of ICBT and PE compared to treatment as usual (TAU) in patients with mild to moderate depression, anxiety and stress-related mental ill-health. The interventions were delivered for 12 weeks and follow-ups were conducted 3 and 12 months after baseline and repeatedly by IVR before, during, and after treatment.

The treatment inclusion criteria were symptoms of depression based on a score of >9 on the Patient Health Questionnaire-9. The PHQ-9 has shown good validity and reliability for diagnosing depression (Kroenke, Spitzer and Williams, 2001). Another inclusion criterion was good knowledge in the Swedish language since the ICBT programme was only delivered in Swedish. Exclusion criteria were age (< 18 years), severe psychiatric disorders that require psychiatric specialist care, alcohol and drug addiction and severe somatic illness that requires sick-leave per se. The choice of ICBT and PE was based on delivery as stand-alone treatments or in combination with other therapies such as face-to-face CBT or medication. Primary outcome measures were work-ability and sick-leave. Secondary outcomes were effects on depression and repeated measures of psychological functioning, stress and sleep collected by IVR.

The study was approved by the regional ethical board at Karolinska institute in Stockholm (Dnr 2010/1779-31/4) and the study was registered in German clinical trials (DRKS00008745).

Participants

REGASSA included 945 patients with mild to moderate depression, anxiety and stress-related mental ill-health. The mean age was 43, and 73 % were females. Around 60 % had a higher education qualification and 80 % were employed or studied, and only 5 % were on sick-leave. Almost all participants met the criteria for depression based on the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan, Lecrubier, Harnett-Sheehan et al., 1998). Comorbidity with anxiety was high, with 68 % of the patients having both depression and at least one anxiety disorder. The most common anxiety disorder was generalized anxiety disorder (75 %) followed by panic disorder (45 %), social phobia (30 %) and posttraumatic stress syndrome (20 %).

At baseline 879 of the 945 patients in REGASSA registered their personal ID number and telephone number in IVR and answered the questionnaires included. These 879 patients are the patients in focus in this thesis. When comparing the 879 patients with non-participants there were no significant differences in terms of gender, age, education level, civil state, employment and symptom of depression measured with MADRS. The process of downloading data from the IVR data base was complicated so the number of participants in Paper I is different compare to that in II and III due to availability of data. The patients' baseline data, including both sociodemographic and scores on different measures, is described in more detail below and is shown in Table 1.

Table 1. Descriptive Statistics concerning the total sample, male, and female

	Total sample (N=879)	Male (N=234)	Female (N=645)
Age, years M (+SD)	43 (12.2)	44 (12.5)	43 (12.1)
Education level %			
Low	3.8	4.7	3.4
Medium	35.3	41.9	33.3
High	60.3	53.4	63.3
Civil status %			
Living alone	38.0	38.5	38.1
Living together	62.0	61.5	61.9
Employment %			
Employed	78.6	78.1	82.0
Unemployed	12.1	12.9	8.9
Retired	4.0	3.9	4.0
Sick-leave	5.1	5.2	5.1
OQ-45, M (+SD)			
Total score	84.5 (19.5)	82.0 (21.1)	85.3(18.8)
OQ-45, clinical level %			
Low scores	13.0	17.1	11.5
Medium scores	35.0	35.9	34.7
High scores	52.0	47.0	53.8
Perceived Stress Scale (PSS), M(+SD)	8.9 (2.5)	8.9 (2.7)	9.0 (2.5)
Karolinska Sleep Questionnaire (KSQ), M(+SD)	14.7 (4.4)	14.2 (4.6)	14.9 (4.4)
MADRS,depression M (+SD)			
Total score	21.5 (7.1)	22.1 (6.7)	21.3 (7.2)
MADRS, clinical level %			
No depression	8.8	6.8	9.6
Mild depression	31.4	27.4	33.4
Moderate depression	54.8	59.4	54.1
Severe depression	3.0	3.4	2.8
EuroQol-5D(EQ-5D), M(+Sd)	0.55 (0.3)	0.54 (0.3)	0.55 (0.3)
M.I.N.I. diagnosis %			
Depression and anxiety	66.7	64.4	67.7
Depression	8.5	10.7	7.8
Anxiety	20.5	21.0	20.3
Neither depression nor anxiety	4.1	3.8	4.2
AUDIT-C total score M(+Sd)	2.9 (1.9)	3.6 (2.2)	2.6 (1.8)
AUDIT-C alcohol consumption %			
Non-hazardous	86.0	81.5	87.6
Hazardous	14.0	18.5	12.4

Procedure

The patients in REGASSA were recruited at different primary care units and through advertisements to a special research unit during 2011-2014. Patients showing interest in the study were screened with PHQ-9 and if their score was > 9 they were invited to participate. Before inclusion all patients met a general practitioner (GP) for medical assessment. After obtained written informed consent the patients answered a battery of baseline measures including MADRS, EQ-5D and AUDIT and a diagnostic interview, M.I.N.I. was conducted. The patients were then allocated through Karolinska trial alliance an independent clinical research organization, to one of the three treatment alternatives ICBT, PE or TAU. At the same time they also registered their personal ID number and phone number in IVR and answered the three questionnaires included, a total of 55 questions.

The IVR system was programmed to automatically call the patients during treatment on days 50, 80, and at treatment end on day 110, and in follow-ups on days 200, 290, and 380 after baseline. At every call a ʿwindowʾ was open for 7 days during which patients could answer the questions. The IVR system called twice a day every second day until the questionnaires were answered or until these 7 days were ended. Within this time- limit the patients could also call the IVR system at any convenient time. After the 7 days this specific measurement was closed. Before every measurement, the patient was reminded by a text message. It took approximately 13 minutes to answer the questions in IVR.

Treatment alternatives

ICBT

Patients randomized to ICBT received treatment conducted by the Internet Psychiatry Unit in Stockholm. The treatment was based on a tailored ICBT programme originally developed by Andersson and colleagues (Johansson et al., 2012) and modified for the REGASSA study. The treatment was delivered free of charge through a secure website and comprised an individualized self-help programme with on-line therapist support. The programme was mainly text-based but images and sound-clips were also included. Before treatment started the assigned therapist called the patient to explain the process and the patients completed several on-line forms to assess patient-specific mental ill-health and work-related problems.

The ICBT programme consisted of 33 modules where four were common for all patients and the others were flexible modules divided into three groups; mental ill-

health (depression, panic-disorder, social phobia, generalized anxiety disorder, sleep problems, stress and chronical pain), working life and modules to increase health promotive behaviour and specific skills. Among these flexible modules there was a selection of eight modules based on patient request and specific health and working problems. All patients in ICBT received the first three modules and the last one. These modules included standard CBT interventions such as, behavioural activation and psychoeducation, and relapse prevention. During the treatment, the symptoms of depression were monitored weekly through self-assessed forms, and high-risk patients received additional help if needed, which occurred a few times.

Patients completed on average 7.8 (SD = 5.1) modules, the range was 1-31 modules and almost 15 % only received 1 module, an adherence rate of 60 %. Women completed significantly more modules than men, 8.2 (SD = 4.9) versus 6.7 (SD = 5.3), t(300) = 2.31, p < .05. The average time the patient was in on-line contact with the therapist was 16.2 (SD = 13.4) minutes per week. The patients logged into the website on average four times per week, sent 18 messages to their assigned therapist, and received 17 messages.

Physical exercise

The patients in PE were allocated to three different conditions: 'light exercise' consisting of yoga classes or similar, 'moderate exercise' consisting of aerobics with low intensity, and 'vigorous exercise' aerobics with higher intensity. The exercise sessions lasted for 60 minutes and were conducted in small groups with between 5 and 20 participants. Before starting the exercise programme, the participants conducted a fitness test on bicycle and received a short oral rationale on the benefit of exercising when depressed.

The treatment started with one exercise session the first week, two the second week, and thereafter three exercise sessions per week, for a total of 12 weeks. During the exercise the patients wore pulse watches to collect data on the intensity of the exercise and when not exercising they wore an accelerometer to collect data on how much they were moving in everyday life. The exercise took place outside the healthcare at 'Friskis & Svettis' a fitness centre with several locations throughout Sweden. The exercise classes were free of charge for the participants. All exercise classes were calibrated so that patients would get the same intensity in the various fitness centers they attended. Compliance was monitored by weekly meetings with a personal contact responsible for the local exercise treatment, and patients who did not attend two or more exercise classes were given a reminder. Adherence in PE was fairly low, only 60 % started the exercise treatment and they completed on average one exercise class/week altogether 12 attendances out of 36 recommended classes an adherence rate of 33 %.

Treatment as usual

The patients allocated to TAU reported their treatment at follow-up and common was 1-2 visits at GP and/or contact with a psychologist, social worker or physiotherapist. The main interventions were medication (10 %), CBT or psychodynamic therapy (20 %) and a combination of psychotherapy and medication (11 %). The frequency varied between 1-15 visits and on average they received 6.6 (SD 7.4) face-to-face consultations during the 12 weeks of treatment. At baseline 21 % were on antidepressants and at the end of treatment the proportion was 52%. As many as 25 % of the participants reported receiving no treatment at all although they had been recommended to contact their GP and were aware of their mental problems.

Antidepressant medication

One third of the patients in the REGASSA study were on antidepressant medication ahead of the interventions and there were no differences in proportions of the three treatment alternatives.

Measures

Seven different questionnaires were used, three in IVR as automated repeated assessments and four as baseline measures administered by a research assistant who also conducted the M.I.N.I., a structured interview for diagnoses. The questionnaires are presented briefly in Table 2 and in more detail in the text below.

Table 2

Questionnaires included in the thesis

Measures	Items and scores	Paper
Repeated measures included in IVR		
Outcome Questionnaire-45 (OQ-45)	45 items, 5 response alternatives, score 0-180 where 180 is max negative score. 3 subscales; Symptoms of Distress (SD), Interpersonal Relations (IR) and Social Role Functioning (SR)	I, II, and III
Perceived Stress Scale (PSS)	4 items, 5 response alternatives score 4-20 in Paper I and 0-16 in II and III, higher scores indicate more stress	I, II, and III
Karolinska Sleep Questionnaire (KSQ)	4 items, 6 response alternatives score 4-24 where high scores indicate more severe sleep problems	II, and III
Baseline measures		
Montgomery Åsberg Depression Rating Scale (MADRS).	10 items, 6 response alternatives, score 0-60 higher scores indicate more severe depression	I, II, and III
EuroQoL-5D (EQ-5D) Health-related Quality of Life	5 items, 3 response alternatives, index scores 0-1 where 1 is max positive score	I
Alcohol Use Disorder Identification Test - Consumption(AUDIT-C)	3 items, 5 response alternatives, score 0-12 where 12 indicates higher alcohol consumption	III

IVR measures

Outcome Questionnaire-45

OQ-45 total score has shown good test-retest reliability, sensitivity, internal consistency, and validity in several studies (Lambert et al. 1996, Vermeersch et al. 2004). The questionnaire has been translated into several languages and tested in different countries which has resulted in acceptable to good psychometric properties for the total score but weaker for the different subscales (de Jong et al. 2007, Lo Coco, et al., 2008; Wennberg, et al., 2010).

OQ-45 is an easily administered questionnaire consisting of 45 items divided into three subscales; Symptoms of Distress (SD), Interpersonal Relations (IR) and Social Role Functioning (SR). Each item has five response alternatives: never (0) rarely (1) sometimes (2) frequently (3) and almost always (4) and the total score ranges from 0-180 with 180 as the maximum negative score. The SD subscale consists of 25 items about symptoms of distress and somatic symptoms, the IR subscale consists of 11 items assessing problems in intimate relationships with

significant others, and the 9-item SR scale capture functioning in social roles such as work, school, family and leisure activities.

Lambert and colleagues developed norms based on nationally collected data in the US and used the formulas developed by Jacobson and Truax (1991) to analyze clinical and normative data for OQ-45 (Lambert et al., 1996; Umphress, Lambert, Smart, Barlow, Clouse & Hansen, 1997). The scores are related to three different levels of functioning: high 0-63, medium 64-84, and low 85-180 points. The cut-off scores for reliable change were set at 14 points, and a dysfunctional/functional cut-off set at 64/63 points so patients scoring 64 or more are within the clinical population. Patients who reduced their scores by 14 points or more were considered improved, and if they scored below 64 point at the end of treatment they were regarded as recovered. Patients who increased their scores by 14 points or more, were considered to have deteriorated if they ended treatment within the dysfunctional range, > 64 points (Anderson, & Lambert, 2001, Lambert, 2007).

At baseline more than 50 % of the participants in present study scored high (85-180) on the Outcome Questionnaire-45 which means low psychological functioning. The distribution is shown in Figure 1.
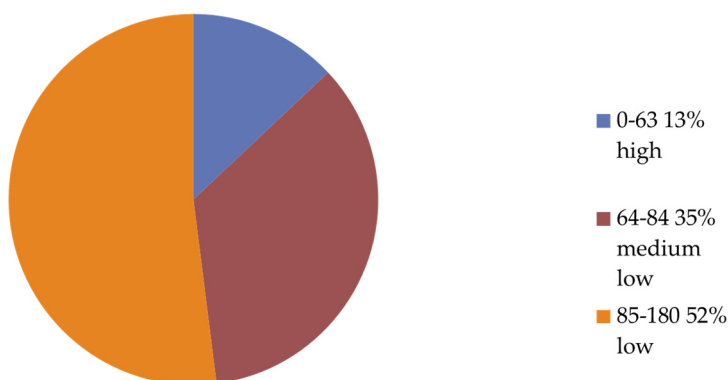
Figure 1
Distribution of level of psychological functioning (OQ-45) in patients (N=879) at baseline

Perceived Stress Scale

The Perceived Stress Scale (PSS) is a worldwide used scale that was developed by Cohen and colleagues for measuring the perception of stress (Cohen, Kamarack & Mermelstein, 1983). The PSS scale consists of 14 items concerning symptoms of distress and ability to cope with feelings and stressful situations in everyday life. It is available in two more versions, a 10-item version and a 4-item version. The longer versions, with 10 and 14 items, have both shown good psychometric properties in different studies in Sweden and other countries (Lee, 2012 & Lee,

Chung Suh, & Jung, 2015; Eklund, Bäckström & Tuvesson, 2014; Nordin, Åkerstedt, & Nordin, 2013).

In this thesis the short 4-item version was used and the questions were about the ability to cope with stressful feelings and situations during the past month. For each item the respondent answered using one of five response alternatives: 'never', 'almost never', 'sometimes', 'fairly often', and 'very often'. Because the PSS was coded differently in the three papers, the total score ranged from 4 to 20 in Paper I, and 0 to 16 in Paper II and Paper III, where higher scores indicate more stress. This short version of 4 items has shown acceptable psychometric properties and has been recommended for telephone follow-ups (Cohen et al., 1983; Karam et al., 2012; Warttig, Forshaw, South, & White, 2013).

Perceived stress was scored for 71.5 % of the patients, and 15 % of them reported having these problems 'fairly often' or 'very often'. The distribution is shown in Figure 2.
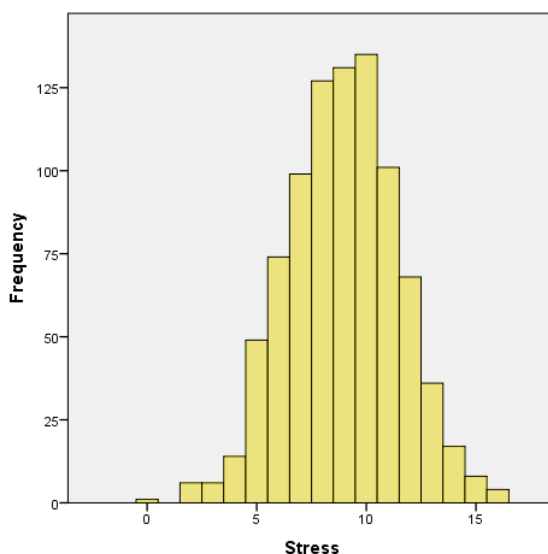
Figure 2
Distribution of participant (N=876) responses on the Perceived Stress Scale

Karolinska Sleep Questionnaire

The Karolinska Sleep Questionnaire (KSQ) is a Swedish scale to measure insomnia and sleep disturbances. The original scale consists of 13 items but in Papers II and III four items that together represent a scale for sleep quality were used. The items were 'difficulties falling asleep', 'repeated awakenings', 'disturbed sleep', 'premature awakening', and there were six response alternatives:

'never', 'seldom', 'sometimes', 'often', 'mostly', and 'always' giving a total score from 4 to 24 where 24 is the maximum negative score.

According to the Stress Research Institute (2005) there is a cut-off between response-alternatives 3 and 4, and response alternatives 4, 5 and 6 on each of the questions indicate problems with sleep that should be further assessed. KSQ has shown good psychometric properties and normative data is available, but this has not been used in this thesis, since they are based on an index of seven items in KSQ (Åkerstedt et al. 2002; Nordin, et al., 2013). In Paper II the number of questions and the score range on KSQ is incorrectly presented but this did not affect the analyses and results.

The cut-off to score minimum 4 on each question meant that 45 % of the participants were estimated as having sleeping problems. Figure 3 shows the distribution for KSQ.
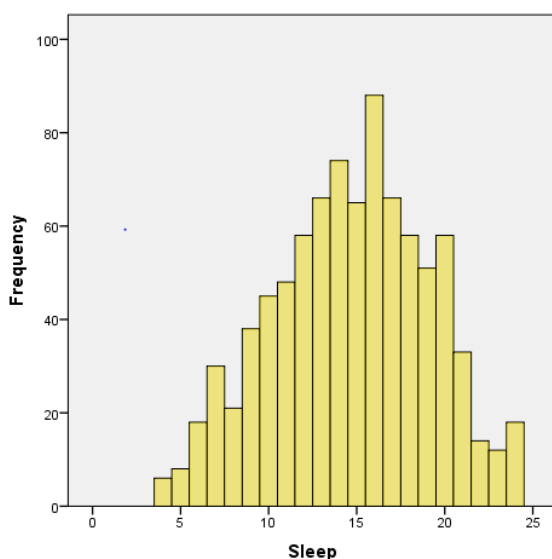
Figure 3
Distribution of participant (N=875) responses in the Karolinska Sleep Questionnaire

Baseline measures

M.I.N.I.

The Mini International Neuropsychiatric Interview (M.I.N.I.) is a structured clinical interview for diagnosing psychiatric disorders based on DSM and ICD

classification systems (Sheehan et al., 1998). In REGASSA it was primarily used for excluding patients who met the criteria for exclusion, for example alcohol and drug addiction, but also for diagnosing comorbid anxiety disorders.

MADRS

Depression was captured by the Montgomery Åsberg Depression Rating Scale (MADRS) a 10 item scale developed by Montgomery & Åsberg (1979) for detecting changes in depressive symptoms following treatment. It has been widely used and showed good psychometric properties and sensitivity to change (Quilty et al. 2013). Each item is scored from 0 to 6, so the total scores range between 0 and 60, where higher scores indicate more severe depression. The rated symptoms are: apparent sadness, reported sadness, inner tension, reduced sleep, reduce appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts.

EQ5D

EuroQol 5D (EQ-5D) is a self-administered questionnaire measuring health-related quality of life (HRQoL). It was developed by the EuroQol Group, an international research network group established in 1987 (Euroqol, 2012). It consists of five items describing dimensions of health status: mobility, self-care, usual activity, pain/discomfort and anxiety/depression with three levels in each dimension indicating no problems, moderate problems or extreme problems. The answers are graded 1-3 and when combined, 243 different health states are defined. In this thesis, an index was used from a large population sample in the United Kingdom where an algorithm was derived for societal preferences; total scores range from -0.59-1.0 where 1 corresponds to full health (Dolan, 1997). EQ-5D has been used in population studies in several countries, and the mean weight score for a normal population is approximately 0.80 (Burström, Johannesson, & Diderichsen, 2001). EQ-5D was only used in the baseline study in Paper I.

AUDIT

At baseline patients in REGASSA completed the Alcohol Use Disorders Identification Test (AUDIT), which has been developed for early detection of individuals with hazardous or harmful alcohol drinking (Saunders et al. 1993). AUDIT is a 10 item scale for measuring alcohol consumption and problems. Each item has a range from 0 to 4 and maximum negative score is 40. The test is validated in primary care and has shown acceptable psychometric properties (Bradley, et al. 2007). The Swedish version of AUDIT has shown good psychometric properties when tested in a population study (Bergman & Källmén, 2002). AUDIT is divided in two parts: items 1-3 measuring alcohol consumption

(AUDIT-C), and items 4-10 alcohol problems (dependency and harms combined). In this thesis only the abbreviated consumption subscale AUDIT-C was used.

The items in AUDIT-C are (1) How often do you drink alcohol? (2) How many glasses do you drink on a typical day when you drink alcohol? (3) How often do you have six or more drinks on one occasion? The scores range from 0-4 and maximum negative score is 12. AUDIT-C has shown high specificity and sensitivity in screening for hazardous alcohol habits (Bradley, et al., 2007, Lundin, et al., 2015).

The cut-off score for hazardous drinking in Paper III was set to > 5 for women and > 6 for men according to Swedish guidelines (Regeringskansliet, 2015). These scores have been shown to be the most optimal for identifying risk drinkers in a Finnish study of occupational health patients (Kaarne, Aalto, Kuokkanen, & Seppä, 2010). These cut-offs are higher than in earlier studies where the cut-off were set to > 3-4 for women, and > 4-5 for men, but it is recommended to determinate cut-off scores empirically in different cultures, since drinking frequency varies largely between countries (Nehlin, et al., 2012, Bradely et al. 2007, Lundin et al., 2015).

Statistics

All statistics were performed in the SPSS 20.0 for Windows.

The statistics used in Paper I were the independent sample t-test for comparing males and females on scales and for proportions the chi-square test. Internal consistency of OQ-45 was measured by Cronbach`s alpha and the factor structure of OQ-45 was examined with Principal Component Analysis (PCA) with oblique rotation. Hierarchical linear regression was used to predict level of depression (MADRS) and health- related quality of life (EQ-5D) by OQ-45.

In Paper II linear mixed-models with heterogeneous ARH (1) rho covariance structure were used to examine the treatment effects. Mixed-models were suitable for this study since the model includes all measures that are available on each measurement occasion. Missing observations were assumed to be unrelated to the observed value i.e. missing at random. The variables included in the model were the three treatment alternatives ICBT, PE and TAU, baseline measure, six measurement points called assessment 1, 2, 3, 4, 5 and 6, and gender. All variables were modelled as fixed effects. The baseline measure was used as a continuous covariate and was not included as an assessment outcome score in order to adjust for any differences at baseline. Time was not linear with the model so assessment data was nominal and each measurement point was separate.

We started with a full model with main effects and interaction effects. Since there were no overall statistically significant interaction effects we reduced the model. Before analyzing the results, the residuals were examined and this showed a normal distribution. Test for robustness showed similar results to those of mixed-models analysis.

On OQ-45 reliable change and recovery were analyzed by cut-off scores of 14 points and dysfunctional/functional cut-off scores of 64/63 points, and to analyze differences in proportions between the treatment alternatives the Chi-square test was used. Reliable change was analyzed on the intention-to-treat sample (ITT), n = 879, using real and predicted values from mixed-model analyses. Effect sizes were analyzed by Cohen`s d.

In Paper III differences between hazardous drinkers and non-hazardous drinkers on continuous baseline measures were calculated, using the independent samples t-test, and differences in proportions of hazardous drinkers in discrete variables were examined with chi-square tests. To examine how alcohol consumption (AUDIT-C) at baseline influenced the course and result on psychological functioning, stress and sleep, the linear mixed-models with first order auto-regressive heterogeneous rho covariance structure was used, the same model as in Paper II.

Each full model included six follow-ups called assessments 1, 2, 3, 4, 5 and 6, the assigned treatments ICBT, PE and TAU, gender and two baseline measures, i.e. hazardous drinking and the baseline scores for one of the three outcome measures (OQ-45, PSS, KSQ). The baseline outcome measures were used as continuous covariate and the control variable hazardous drinking (AUDIT-C) as a categorical covariate. All variables were modelled as fixed effects. AUDIT-C as covariate variable was dichotomous, where 0 was defined as non-hazardous drinking and 1 hazardous drinking.

Summary of papers

The overall results for the different papers in this thesis are summarized in Table 3. All three studies were conducted within REGASSA so the study design is the same but with different aims and methods. The results contributed to the analyses of REGASSA.

Table 3
Aims, methods and results in the different papers of the thesis

Aims	Sample	Statistics	Results
Paper I			
Examine the psychometric properties of OQ-45 and the way OQ-45 would contribute to the explained variance in MADRS and EQ-5D	N= 816	Principal component analysis (PCA), hierarchic regression analysis	Good properties for the total score of OQ-45 but limited for the subscales. OQ-45 was found to predict level of EQ-5D and MADRS beyond sociodemographic and PSS.
Paper II			
Compare the course and results of the treatment alternatives ICBT, PE and TAU, based on IVR data of OQ-45, stress and sleep over a 12 months follow-up period. The hypothesis was that ICBT would be better than PE and ICBT and PE would be better than TAU	N=879	Linear mixed-models with heterogeneous first order auto-regressive rho covariance structure, chi-square test, Cohen´s d.	Both ICBT and PE were effective treatments on OQ-45 and sleep and showed better results than TAU but on stress there were no differences, all three groups improved. There were no differences between ICBT and PE. Weak to moderate effect sizes were obtained. Significantly more patients made reliable changes and recovered in ICBT and PE compared to TAU. The results obtained at 3 months seemed to be sustained at 12 month follow-up.
Paper III			
Examine if hazardous alcohol consumption at base-line influenced the results on OQ-45, stress and sleep during and after treatment	N=879	Independent samples t-test, chi-square test, linear mixed-models with heterogeneous first order auto-regressive rho covariance structure	Hazardous alcohol consumption at baseline influenced the results on stress i.e. patients with hazardous drinking at baseline had on average a higher level of stress in the follow-ups. Hazardous drinking at base-line had no influence on the results on OQ-45 and sleep

Paper I

The REGASSA study included a large sample of mental ill-health patients and presented the opportunity to use baseline data for examining the psychometric properties of OQ-45. Wennberg and colleagues (2010) had previously examined the Swedish version of OQ-45 in a sample of patients with substances use disorders and the results showed acceptable properties for the total scale and of two for the subscales; Symptom of Distress (SD) and Interpersonal Relations (IR) but low internal consistency on the Social Role Functioning subscale (SR).

The aims in this study were to further evaluate the psychometric properties of the Swedish version of OQ-45 administered by automated telephone technique in a large sample of mental ill-health patients in primary care and to examine its ability to predict level of depression and health-related quality of life beyond demographics and MADRS, EQ-5D, and PSS. Thereby investigate whether OQ-45 could make any unique contribution to the description of patients' difficulties and needs.

Methods

Baseline scores (n=814) from two of the measures included in IVR; OQ-45 and PSS were used, together with baseline scores for depression (MADRS) and health-related quality of life (EQ-5D) and sociodemographics.

To examine the psychometric properties of OQ-45, Cronbach´s alpha was used for internal consistency and Principal Component Analysis (PCA) for the factor structure. The prediction of depression (MADRS) and health-related quality of life (EQ-5D) by OQ-45 was conducted with hierarchical linear regression.

Results

At baseline more than half of the patients (n=814) had a moderate level of depression according to MADRS and a low level of functioning according to OQ-45. Their health-related quality of life, measured with EQ-5D, was estimated to be 0.55 and the reported average score on PSS was 12.90. Gender differences appeared for three measures - education, OQ-45 total score, and OQ-45 symptoms subscale - and women had higher levels of education, lower levels of psychological functioning, and more negative symptoms compared to men.

The internal consistency was good for the total score of OQ-45, $\alpha = 0.88$ and for the SD subscale $\alpha = 0.83$, and satisfactory for the IR subscale $\alpha = 0.75$ and the SR subscale $\alpha = 0.70$. The principal component analysis with oblique rotation showed good loadings for the SD subscale but poorer loadings for the IR and SR

subscales. The extraction of factors resulted in 11 factors using the Kaiser criterion eigenvalues > 1 and 3-5 factors using the scree plot. The first factor explained 18.4 % of the variance, three factors 30 %, five factors 38.3 % and all eleven factors explained 55 % of the variance in the model. Of the 25 SD items 18 loaded > 0.40, 15 on factor 1 and three about somatic symptoms on factor 2. Of the IR items six loaded > 0.40, five on factor 1 and one on factor 3. Finally seven SR items loaded > 0.40, four on factor 1, one on factor 2, and two on factor 3.

Tables 4 and 5 show the results from the hierarchical linear regression analysis. The model explained 27 % of the variance in MADRS and OQ-45 contributed uniquely with 8 %, and 24 % of the variance in EQ-5D and the contribution of OQ-45 was 5 %.

Table 4.

Hierarchical Regression, Predicting Depression measured by MADRS from Health-related Quality of Life(EQ-5D), Stress(PSS), Demographic data and Level of function(OQ-45)

	Variables	$R^2 \Delta$	B	SE B	β	F step
Model 1		0.20				50.05***
	EuroQol-5D(EQ-5D)		-7.70	0.90	-2.90***	
	Perceived Stress Scale(PSS)		0.71	0.10	0.25***	
	Civil status		-1.01	0.46	-0.07*	
	Employment		0.23	0.57	0.01	
Model 2		0.08				90.25***
	EuroQol-5D (EQ-5D)		-4.84	0.91	-0.18***	
	Perceived Stress Scale (PSS)		0.11	0.11	0.04	
	Civil status		-0.80	0.44	-0.06	
	Employment		0.24	0.53	0.01	
	OQ-45		0.14	0.02	0.39***	

*p < .05, **p < .01, *** p < .001

Table 5.

Hierarchical Regression, Predicting Health-related Quality of life measured by EQ-5D from Depression (MADRS), Stress (PSS), Demographic data and Level of function (OQ-45)

	Variables	$R^2 \Delta$	B	SE B	β	F step
Model 1		0.19				45.42***
	MADRS depression		-0.01	0.00	-0.29***	
	Perceived Stress Scale(PSS)		-0.02	0.00	-0.22***	
	Age		0.00	0.00	-0.02	
	Employment		-0.04	0.02	-0.06	
Model 2		0.05				52.45***
	MADRS depression		-0.00	0.00	-0.19***	
	Perceived Stress Scale(PSS)		-0.00	0.00	-0.06	
	Age		0.00	0.00	-0.01	
	Employment		-0.04	0.02	-0.05	
	OQ-45		-0.00	0.00	-0.31***	

*p < .05, **p < .01, *** p < .001

Comments

The psychometric properties of the Swedish version of OQ-45 were found to be good regarding the total score, but the results for the subscales were weaker. The total score for OQ-45 was also found to uniquely predict the level of depression and health-related quality of life, beyond demographics and MADRS, EQ-5D and PSS.

Paper II

The first reported study in REGASSA on depression showed that at 3-month follow-up (the end of treatment) ICBT and PE were more effective than TAU (Hallgren, et al., 2015) and the results remained at the 12-month follow-up (Hallgren, et al. 2016). There were no differences between ICBT and PE at 3 months or 12 months.

This study extended the analysis of REGASSA to other outcome measures, using the repeated assessments in IVR completed before, during and at the end of 12 weeks of treatment and in three follow-ups on psychological functioning, stress and sleep. The aims were to compare the treatment alternatives; ICBT, PE, and TAU based on data collected in IVR from patients with light to moderate depression, anxiety and stress-related mental health problems. The hypotheses were that the effect of ICBT would be better than PE, and that the effect of ICBT and PE would be better than TAU on psychological functioning, stress and sleep, and that the proportions of recovered patients would be larger in ICBT and PE compared to TAU.

Methods

The REGASSA study included 945 patients with mild to moderate depression and stress-related mental health problems. The analyses in this study included 879 patients and were based on the data collected by IVR (OQ-45, PSS, and KSQ) at baseline and repeated assessments after baseline on days 50, and 80 during treatment, day 110 at the end of treatment, and days 200, 290 and 380. The consort diagram shows the participants flow through the study (Figure 4).
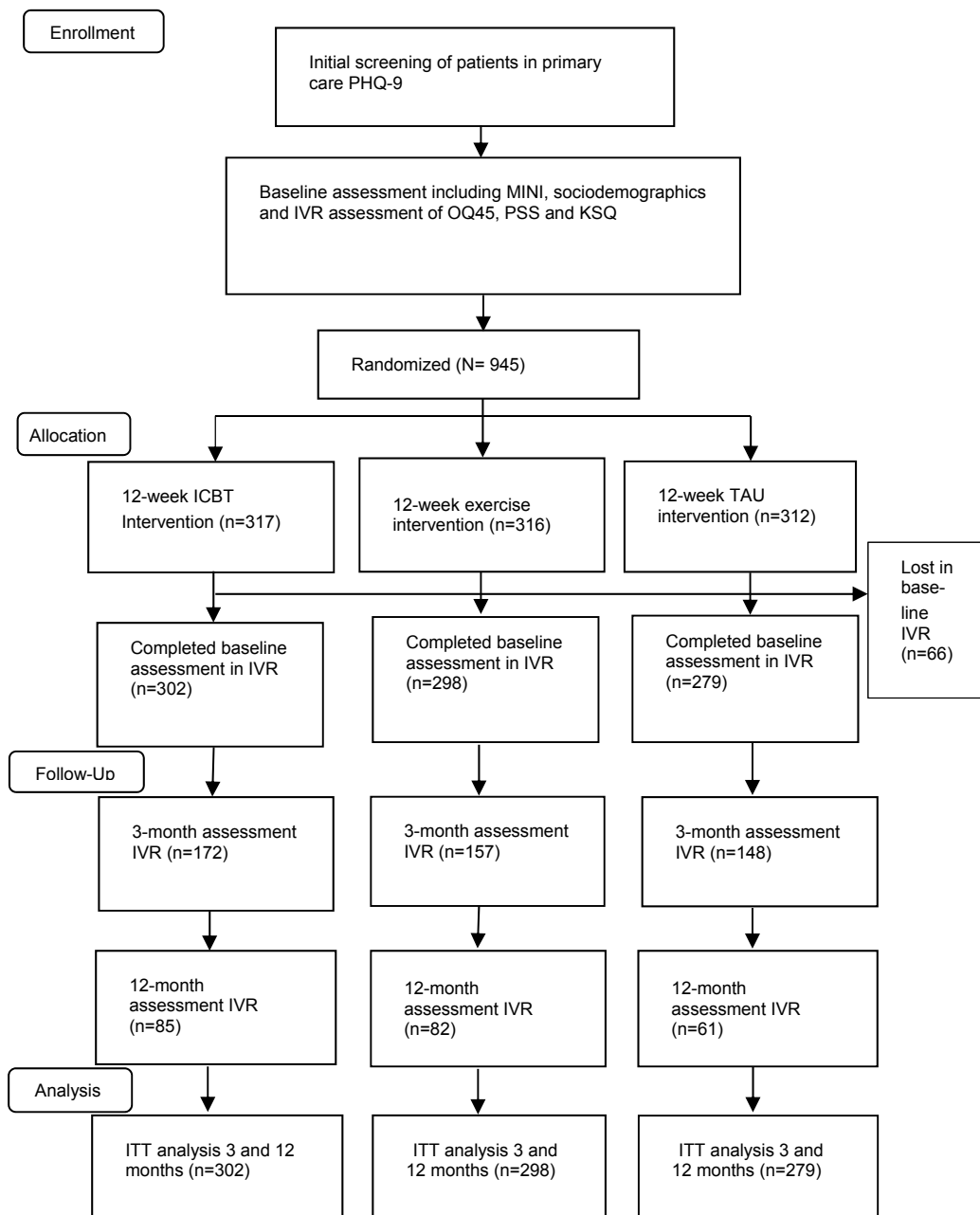
Figure 4
The participant´s flowchart in IVR through the study

Despite support of research assistants 51 patients never registered in IVR, and another 15 answered only a few questions. These 66 patients were excluded since they had no complete baseline data. The flowchart (Figure 4) shows the attrition in IVR which increased through the course of the study.

The treatment effects were examined with linear mixed models. Missing values were assumed to be missing at random. The variables included were the treatment alternatives ICBT, PE and TAU, baseline measures of gender, OQ-45, PSS and KSQ, and six repeated assessments of OQ-45, PSS and KSQ. The formula of Cohen´s d was used to examine effect sizes.

To examine reliable change and recovery on OQ-45, cut off scores of 14 points were used and for functional/dysfunctional cut-off 63/64 points.

Results

The repeated assessments showed an average positive change on psychological functioning (OQ-45), perceived stress (PSS) and sleep (KSQ) in all three treatment conditions. However, on OQ-45 the patients in ICBT and PE made larger improvements than the patients in TAU with a weak effect size for ICBT ($d =$ 0.35) and for PE ($d = 0.20$). On KSQ the average change for ICBT and PE was larger compared to TAU with weak to moderate effects sizes, ICBT ($d = 0.56$) and PE (d 0.22). These differences between the treatment alternatives were not found for stress. Women showed larger effects than men on OQ-45 and stress but for sleep there were no differences.

Figure 5 presents the changes on OQ-45 over time in the three treatment conditions and shows that the differences peaked at assessment 3, immediately after treatment and then decreased, but due to the large attrition in IVR these results should be treated with caution.
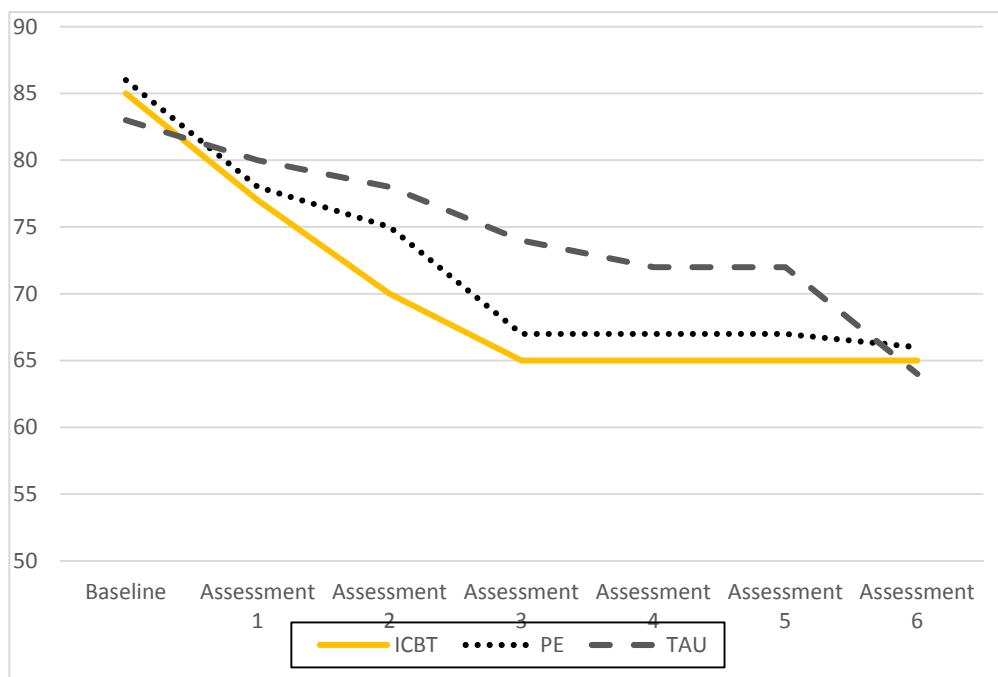
Figure 5.
Change in mean scores on the Outcome Questionnaire-45 over a 12-month period across conditions. ICBT = Internet-based Cognitive Behaviour Therapy. PE = Physical Exercise. TAU = Treatment as Usual.

At 3 months, 60 % of the patients in ICBT made reliable improvements, in PE 57 % and in TAU 36 % and the difference in proportions between ICBT and TAU was significant, χ^2= 35.82 (3), $p < .001$, Similar results were found for PE in comparison with TAU, χ^2=31.02 (3), $p < .001$; between ICBT and PE there were no significant differences, $\chi^2 = 1.50$, $p = .683$. The results remained at twelve months with advantages for ICBT and PE in comparison with TAU, $\chi^2 = 28.08$, $p < .001$ and $\chi^2 = 31.02$, $p < .001$, respectively.

The proportions of patients who recovered in ICBT were larger than in TAU, χ^2=18.68, $p < .001$, and also in PE compared to TAU, χ^2= 6.09, $p = .014$. The difference between ICBT and PE was not significant, χ^2= 3.74, $p = .053$. Similar results were seen at twelve months.

Comments

The hypotheses were partly confirmed, with both ICBT and PE producing larger effects than TAU on psychological functioning and sleep, but not on stress. The hypothesis that ICBT would produce larger effects than PE was not confirmed.

Paper III

The focus in Paper III was to examine hazardous alcohol use in relation to the repeated assessments in IVR, sleep, psychological functioning and stress, factors that could be influenced by hazardous alcohol consumption. To me and my co-workers knowledge, the relationship between hazardous drinking and the secondary variables of REGASSA has previously only been studied with less frequent follow-ups, or not been studied at all.

The aim was to examine whether hazardous drinking at baseline influenced the outcomes of the repeated assessments of psychological functioning, stress and sleep collected by IVR during and after treatment.

Methods

The study was based on the patients registered in IVR (n=879) who had completed the AUDIT at baseline (n=871). Patients with primary substance use disorder were excluded. In this study we used the abbreviated consumption subscale AUDIT-C since the three questions in OQ-45 on negative consequences of drinking behaviour otherwise would interfere with questions 4-10 in AUDIT. The cut-off score for hazardous drinking was set to $\geq$ 5 for women and $\geq$ 6 for men. Other measures included were the repeated assessments of psychological functioning (OQ-45), perceived stress (PSS) and sleep (KSQ) in IVR.

Differences between hazardous and non-hazardous drinkers on continuous baseline measures were examined with the independent samples t-test and differences in proportions of hazardous drinkers in discrete variables were calculated with chi-square tests. To examine how alcohol consumption (AUDIT-C) at baseline influenced the outcome on psychological functioning, stress and sleep during and after treatment we used linear mixed-models.

Results

The proportion of hazardous drinkers at baseline was 14 % and the proportion was significantly higher in men, 18 % compared to women, 12 %, $\chi^2 = 5.23$ $p = 0.022$. Hazardous drinkers were more depressed (MADRS) t (853) = -2.31, p = 0.021 and had lower psychological functioning (OQ-45) t (871) = -2.85, p = 0.004 than non-hazardous drinkers. There were no baseline differences between the groups on perceived stress (PSS), sleep (KSQ) or age, education level, civil state and employment.

The results of the linear mixed-models showed that patients with hazardous drinking had a higher average score on PSS throughout the assessments, and

thereby probably less treatment effect on perceived stress compared to non-hazardous drinkers. The results were maintained after controlling for depression. There were no differences between the treatment alternatives in how hazardous drinking influenced the outcome on stress. The outcome on psychological functioning (OQ-45) and sleep (KSQ) was not predicted by the level of hazardous alcohol use at baseline.

The changes over time on PSS for patients with and without hazardous drinking are presented in Figure 6, showing that the differences for stress between hazardous drinkers and non-hazardous drinkers were higher at the follow-ups after treatment but, these figures should be treated with some caution because of the large attrition.
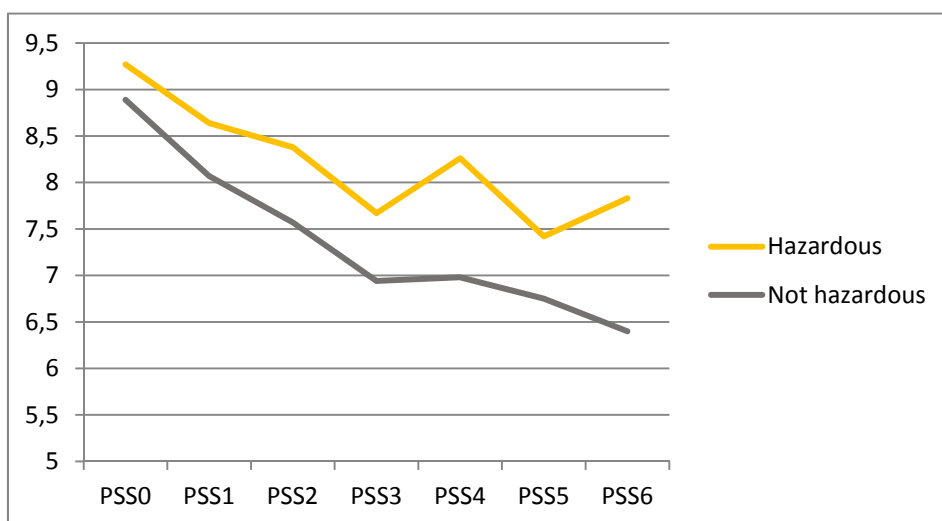
Figure 6
Course on perceived stress for patients with and without hazardous drinking at baseline. PSS0-PSS6 are measure points where PSS0 is baseline measure, PSS1-PSS3 are during and directly after treatment and PSS4-PSS6 are follow ups

Comments

The results in Paper II showed that all three treatments had positive effect on perceived stress. This study adds knowledge that the effect was negatively influenced by hazardous drinking.

Discussion

The overall aim in this thesis was to increase knowledge of primary care patients' mental health problems through examining the course and results for psychological functioning, perceived stress, and sleep, important life areas that can be affected when depressed. Another aim was to analyze the effect of different treatments for depression on these measurements and whether this effect is influenced by hazardous drinking.

The studies reported in the papers were conducted within the REGASSA study which compared three treatment conditions: Internet-delivered CBT, physical exercise (PE) and treatment as usual (TAU).

There are three main results: (1) the instrument used to measure psychological functioning, the OQ-45, showed good psychometric properties with regard to its total score, but was weaker with regard to its subscales; (2) ICBT and physical exercise showed better outcome than TAU on OQ-45 and sleep, but not on stress; (3) hazardous alcohol drinking negatively influenced the course and results on stress, but showed no effects on OQ-45 or sleep.

Outcome Questionnaire-45

Psychological functioning was measured by OQ-45, a well-established questionnaire in psychotherapy research (Lambert, 2007 & 2013). The Swedish version of OQ-45 had been examined in a sample of substance abusers (Wennberg, et al., 2010) and there was an interest in further analysis of the psychometric properties of OQ-45 collected by IVR in a large clinical sample of primary care patients (Paper I), which had not been done before. The choice of an explorative model for factor analysis was based on disparate factor results in earlier studies.

The main findings in Paper I were that OQ-45 total score showed good psychometric properties but support for the three subscales was weaker. OQ-45 is a broad measure developed within the domain of psychotherapy research and includes three subscales to measure symptoms of distress, interpersonal problems, and social role functioning. The total score measures an overall level of

functioning sometimes referred to as a general mental health factor (Lambert, 2007). Earlier studies have shown strong support for the total score of OQ-45 while problems have been found with the psychometric properties of the subscales (Wennberg, et al., 2010, Lo Coco, et al., 2008, de Jong, et al., 2007, & Amble, et al., 2014) which was confirmed in this thesis.

In the psychometric studies of OQ-45, the clinical samples have mostly consisted of students at counselling centers (Boswell, White, Sims, Harrist, & Romans, 2013) psychiatric patients (Lo Coco, et al., 2008, Amble, et al., 2014) and patients at community mental health care centers (Lambert, et al., 1996, & de Jong, et al., 2007). Studies on OQ-45 in primary care patients seem to be rare, making the results in the present thesis of additional interest. Support for the OQ-45 total score is strong and it seems successful for measuring outcome while the weak support for the subscales may cause limitations in using the subscales as separate measures of improvement.

It seems important to assess not only disorder-specific symptoms, but also other essential aspects of patients' lives to get a more comprehensive picture of common mental disorders effects and to obtain a more multifactor view of outcome. Over recent decades there has been extensive development of different instruments, and self-reported disorder-specific measures seem to be the most frequently used in treatment outcome studies (Kayolan, et al., 2015). Disorder-specific measures are narrow, and since mental health problems are often multifaceted a broader questionnaire like OQ-45 could add important information, but it is important to examine the subscales in more detail to find a more robust solution.

The results in Paper I showed that OQ-45 uniquely explained some of the variance in both MADRS and EQ-5D which also may reflect the utility of OQ-45. Other important factors in outcome studies such as the availability of normative data, thresholds for clinical/non-clinical range, established scores of reliable change and recovery based on Jacobson and Truax (1991), and reliable change index (Lambert, 2013) add further strengths to OQ-45.

Effects of treatment on psychological functioning, stress and sleep

The hypothesis in Paper II, that ICBT would be superior in IVR measurements compared to PE and ICBT and that PE would be superior compared to TAU, was partly confirmed. Analyzed with mixed-models ICBT and physical exercise showed better outcome than TAU on OQ-45 and sleep but not on stress. ICBT was not superior in comparison with physical exercise. These results are in line with

studies conducted in REGASSA on depression (Hallgren, et al., 2015 & 2016), but contradict to a previous study in primary care on depression and anxiety where no differences were found between ICBT and ordinary GP care (Kivi, et al., 2014).

In the UK Gilbody and colleagues (2015) compared two different ICBT programmes with routine GP care on depression (PHQ-9), and general mental health (CORE-OM). They found no differences on depression, while on general mental health at 12 months the ICBT programme free of use was better than ordinary care. However, there were no differences at four months and the estimated effect size at 12 months was small, 0.18. The results in this thesis seem to show greater support for ICBT for primary care patients with estimated effect sizes of 0.35 at three months on OQ-45 and 0.56 on KSQ, although there was an indication that the superiority of ICBT and PE compared to TAU was not sustained at twelve months. On the other hand the ITT analyses of reliable change and recovery, with missing data imputed, showed sustained superiority for ICBT and PE compared to TAU at twelve months which contribute to the results. Several previous studies have compared ICBT for depression and anxiety with a control group, often a waiting-list but also other therapy interventions, and the results have shown moderate to large between group effect sizes in favour of ICBT (Andersson, & Cuijpers, 2009, Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010, Richards & Richardsson, 2012, Andersson, et al. 2013). ICBT as a treatment for mental health problems seems well supported.

Most studies using OQ-45 have examined the effect of the feedback process in association with the outcome of psychotherapy in psychiatric clinics, mental health care centers, private-sector practices and university training clinics (Anderson, & Lambert, 2001, Brown, et al., 2001, Vermeersch, et al., 2004, de Jong, et al., 2014, & Amble, et al., 2015). The feedback process was not used in this thesis, but the overall effect of treatment shown by OQ-45 also supports its sensitivity in a primary care sample with other treatment interventions, such as Internet-based CBT and physical exercise.

All three groups made improvements on perceived stress, but there was no difference between the treatment alternatives. However, in Paper III stress was the only IVR measure shown to be influenced by hazardous alcohol drinking. These results were somewhat unexpected and raise some interesting questions about the measure of stress, PSS, and why the treatment alternatives did not show better outcome on stress than TAU, and a why hazardous alcohol consumption influenced stress but not sleep and psychological functioning. Perceived stress was measured by the 4-item version of PSS, and to the best of my knowledge, this version has not been used as an outcome measure in repeated assessments. Thus there is no knowledge available on how well this instrument works in this kind of study design and any limitations of the 4-item PSS may have influenced the result.

Although this version is short, it has shown acceptable or marginally acceptable psychometric properties in international studies (Lee, 2012, Warttig, et al., 2013, Lee, et al., 2014), which suggests that the results in the present thesis may not be due to the shortness of the PSS version.

The ICBT treatment programme included modules for stress, applied relaxation and mindfulness but these modules were among those that could be chosen to be individually tailored in treatment and not all patients had access to them. The ICBT treatment was primarily targeted towards depression and the effect on coping with stress may be no better with ICBT for depression than TAU.

The effect of physical exercise, as a treatment of mental health problems, has most commonly been studied with regard to depression. Physical exercise as a treatment of depression has shown evidence of efficacy (Cooney, et al., 2013, Nyström, et al., 2015, Kvam, et al., 2016), and has been shown to be effective when delivered as guided Internet-based self-help (Ström, et al., 2013), and in patients with stress-related exhaustion (Lindegård, Jonsdottir, Börjesson, Lindwall, & Gerber, 2015). In addition, studies have shown that participation in moderate-to-vigorous physical activity is associated with lower levels of psychological distress and depression (Perales, Pozu-Cruz, & Pozu-Cruz, 2014, & Helgadóttir, Forsell, & Ekblom, 2015).

Physical exercise has been shown to reduce perceived stress and increase mental resources in healthy adults (Kettunen, Vuorimaa, & Vasankari, 2015). However, another study has shown that young adult women participating in a physical exercise programme experienced a higher level of perceived stress and fewer symptoms of depression compared to non-exercisers at 12-month follow-up (O'Dougherty, Hearst, Syed, Kurzer, & Schmitz, 2012).The results in this thesis and in the REGASSA studies on depression (Hallgren, et al., 2015, & Hallgren, et al., 2016) were similar; physical exercise was more efficient than TAU on depression, sleep, and psychological functioning but not on perceived stress. A tentative explanation could be that engaging in a physical exercise programme changes the routines in every-day life and may even increase stress which was also the hypothesis suggested in the study conducted by O´Dougherty and colleagues (2012).

To the best of my knowledge, KSQ has not previously been used to measure sleep in such a large outcome study in primary care before. The results in this thesis may indicate that KSQ is sensitive to changes in these patient populations although only 45 % were estimated to have sleeping problems at baseline. Sleep disturbances have been shown to be associated with stressful life events and increased symptoms of depression (Vargas, et al., 2015, & Legget, et al., 2016). Previously it has also been shown that ICBT for depression could be efficient on sleep (Blom, et al., 2015).

Hazardous alcohol consumption

The relationship between hazardous drinking and perceived stress, sleep and psychological functioning has to the best of my knowledge not been studied before in an outcome study with repeated measures in primary care patients or may not even been studied at all. The result that hazardous drinking influenced the course and results of perceived stress is not in line with the hypothesis that alcohol reduces stress but findings of Sher and co-workers (2007), showed that this hypothesis is unclear and probably related to both individual and situational aspects of life. Furthermore the focus of this thesis was hazardous alcohol consumption, which may not have a reducing effect on stress.

The finding that hazardous drinking negatively influenced the course and results on stress but not on sleep and psychological functioning is unclear. The mean scores at baseline on OQ-45 were higher for hazardous drinkers compared to those with non-hazardous drinking, although this difference was not sustained in the follow-ups. The effect of risky drinking on psychological functioning based on these results is still unclear. The fact that hazardous drinking did not affect the course and results on sleep was in line with the results of Vinson and colleagues (2010) in a cross-sectional study in primary care. They examined the associations between alcohol consumption and sleep and found no associations between hazardous drinking and sleep quality, while hazardous drinkers were more inclined to use alcohol to promote sleep. Further research is needed to explore the effect of different treatments on various outcome measures and how these are influenced by hazardous alcohol consumption.

Mental health problems in primary care

The focus of present thesis was on patients in primary care with common mental health problems. A majority of the participants was women and we found some gender differences in the results. The higher proportion of women corresponds with gender being a risk factor for depression and anxiety; the risk for women is twice as high compared to men (Kessler, 2003, Bandelow & Michaelis, 2015). A higher frequency among women is also found in other primary care studies (Roca, et al., 2009, Serrano-Blanco, et al., 2010, Lejtzén, et al., 2014).

Based on MADRS at baseline most of the patients were mildly to moderately depressed and no gender differences in severity of depression were shown. This is similar to what has been seen in other study samples (Parker, 2014). On psychological functioning (OQ-45) 54 % of the women at baseline scored in the

dysfunctional range, and the total score was higher compared to men. No gender differences were found on health-related quality of life (EQ-5D), and the same results were seen in perceived stress and sleep. This is inconsistent with previous studies, where both symptoms of stress and sleep disturbances have been reported more frequently in women (Nordin, et al., 2013, Mallon, et al., 2014, Warttig, et al., 2013, Wiegner, et al., 2015).

The majority of patients had comorbid disorders and no gender differences were seen, which is in contrary to other primary care samples where women have shown higher levels of comorbidity (Roca, et al., 2009, Serrano-Blanco, et al., 2010, Parker, 2014). In terms of alcohol consumption higher proportions of men were hazardous drinkers and this gender distribution has previously been reported in the Swedish population, among Finnish occupational health-care patients, and in several primary care studies (Bergman, & Källmén, 2002, Bradley, 2007, Bellos, 2013, and Kaarne, et al., 2010).

The baseline average total score on OQ-45 in our sample was in line with other clinical samples (Lambert, et al., 1996, de Jong, et al., 2007, Wennberg, et al., 2010, & Amble et al., 2014). According to M.I.N.I., the majority of patients in the present study had comorbid disorders - depression with one or more anxiety disorder, which is also shown in other studies in primary care (Roca, et al., 2009, Serrano-Blanco, et al., 2010, Parker, 2014).

The health related quality of life (EQ-5D) was substantially lower compared with the general population in Sweden (Burström et al., 2001) and the average score on stress was also markedly higher than in the general population in the UK (Warttig, et al., 2013). More participants in REGASSA were also estimated to be hazardous drinkers compared to the general population (Åhlin, et al., 2015)

In conclusion, our sample shows similar features to other clinical samples with mild to moderate mental ill-health in primary care; mostly women with high levels of comorbidity, higher levels of stress compared to the general population, sleeping problems and decreased psychological functioning, lower health related quality of life and higher levels of alcohol consumption compared to the general population. However, the gender differences were less evident than have been shown previously. The results call for more research to investigate relationships between gender and general symptoms of distress, psychological functioning and hazardous drinking in order to increase the understanding of common mental health problems in primary care, and thereby also increase knowledge on how to treat them.

The inclusion of patients at the primary care unit turned out to be somewhat problematic. From research and experience we knew that many patients in primary care have mental health problems, but they did not seem to approach our study.

We then supported the inclusion through advertisements, which did increase the number of interested. One explanation could be that the participants needed treatment although they had never sought care or, when in contact with health care had not received adequate treatment. This could reflect the WHO estimates that 35-50 % of people suffering from mental ill-health get no treatment and similar proportions have been found in Europe where only 26 % of all cases with mental health problems had a consultation with a professional (WHO, 2004, Wittchen, & Jacobi, 2005). A study in Sweden showed similar results in that most individuals with mental health problems do not seem to seek help, and only half of them do appear to benefit from treatment (Forsell, 2006).

Interactive Voice Response

Collecting data through IVR has been an interesting and challenging experience. The data collection lasted for three years and during this period it has been essential to keep an up-dated list of the patients´ telephone numbers in IVR and to offer technical support when needed. The importance of this has been shown in other studies as well (Abu-Hasaballah, 2007). At baseline 66 patients never registered in IVR or registered but answered only a few questions. Studies have shown that to increase the participation in IVR, it is important to provide some training in the system before start (Lee, et al., 2003). This failed in some cases in REGASSA due to shortage of time at the baseline assessments.

During the 12 month study period drop-out showed varying but increasing levels, e.g. at 3-month follow-up 54 % completed the questionnaires and at the last follow-up at 12-month only 25 % did. Compliance with IVR was rather low which have been reported in earlier studies (Mundt, et al., 2005, Falconi, Johnston, & Hogg, 2016). Several studies have used reminders to improve participation in IVR (Lee, et al., 2003, Falconi, et al., 2016) and we sent a reminder before every assessment in the form of a text-message but compliance was still low. One explanation could be, that 55 questions were too many for repeated assessments, and recommendations for increasing response rates are shorter forms (Lee, et al., 2003, & Falconi, et al., 2016). Also 12 months is a long period and the last three assessments occurred at longer intervals so the participants may have forgotten about IVR. This could be compared with a study of paroled offenders, who were followed with daily IVR assessments for 30 consecutive days; the estimated response rate was 71 % (Andersson, et al., 2014).

Strengths and limitations

The randomized controlled design and the large sample size are considerable strengths in this thesis. The comparison of two structured active treatments with standard treatment in primary care also provides strength to the results. The repeated measures in IVR provided useful possibilities to compare the results both during and after treatment.

One limitation is the selection of patients since we have no information about how many patients were screened, how many did not meet the screening criteria and how many met the criteria but declined participation. This may have affected the generalizability of the results. There was no information available about whether the patients were having their first episode of depression or a relapse, which could influence the severity of their problems. A majority of the patients had a high level of education and were in work despite their mental health problems and this may not reflect the general primary care patient with mental health problems.

There were also difficulties with treatment adherence. In ICBT the rated adherence was 60 % and 15 % of the patients only received the first module. In PE the rated adherence was low, 33 %. Only 60 % of the patients allocated to PE started the treatment and this was partly due to disappointment with allocation, but more likely insufficient support in getting started. In TAU, 25 % of the patients did not receive any treatment at all. The treatments in TAU were mixed, probably mirroring the usual care and there is some uncertainty about what was actually delivered. Also the REGASSA was a multicentre study, involving six different health care regions and several primary care units, which may have influenced the treatment in TAU.

The IVR system has the advantage of automatically handling different questionnaires and follow large groups of patients over long periods of time. However attrition in IVR could be a problem and was in this thesis rather high. This may have biased the results especially at twelve months where the sample consisted of only 25 % of the baseline sample so the results should be treated with caution. Also, we do not know whether the IVR calls during and after treatment influenced the patients and their outcome.

Paper I, an explorative factor analysis model was used, but a confirmatory model could have been considered since OQ-45 was an original model with a global score and three subscales. The studies in this thesis were based on ITT analyses and patients completing the treatment were not examined separately. Mixed-models were used to analyze the repeated measures in IVR, which is a method with the advantage of including all available measures at each assessment, and including individuals who only answered some of the total number of assessments.

In the ITT analyses the missing data was compensated for by predicted values in mixed-models which is a recommended method for imputing data (Fielding, 2012) and made the ITT analyses relatively robust.

Future research

In future research it would be important to study further how gender, comorbidity, perceived stress, and alcohol consumption influence common mental disorders and treatment outcome in primary care. Another area of interest would be to examine different instruments that, in easy and valid ways, capture essential aspects of the patients' difficulties in primary care. In this thesis, data, based on well-established measures, was repeatedly collected with computerized telephone technique and this has never been studied before in primary care. The results call for further research into how well OQ-45, the short version of PSS, and KSQ work as outcome measures of different treatments in primary care.

Collecting data in an easy, secure and cost-effective way would be of increasing interest in monitoring the results in large samples of patient. The IVR system is promising, but further research is needed to address problems of compliance and attrition.

The results for physical exercise and ICBT call for future research to further examine these treatments in primary care, with the aim of increasing knowledge about who benefits most from ICBT and physical exercise, and whether it should be a stand-alone treatment or combined with antidepressant medication.

In this thesis the ICBT treatment was partly tailored and some choices were available within the physical exercise arm. Further research is needed in the field of individually tailored treatments since the primary care samples, in this and other studies, have involved many cases of comorbid disorders and various individual problems and levels of impairment. This calls for more individually adjusted or transdiagnostic treatment. Transdiagnostic treatment focuses on common factors across disorders, and addresses different emotional difficulties and diagnostic comorbidities within the same treatment programme. The interventions towards shared cognitive, emotional, and behavioural problems consist of core components of CBT treatment. Previous studies have shown some evidence for transdiagnostic ICBT, and tailored ICBT for anxiety and depression and comorbid disorders (Johansson, 2012, Newby, 2016). Johansson and co-workers (2012) showed that the patients with more severe symptoms and higher levels of comorbidity were better off with a tailored treatment compared to a standard programme for depression. Newby and colleagues (2016) recently conducted a meta-analysis and

found transdiagnostic ICBT treatment as good as disorder-specific for anxiety disorders, and even slight superiority for depression (Newby, et al., 2016). However, only four studies were included in the meta-analysis so more research is needed to increase our knowledge about different ICBT treatments for patients in primary care.

Nyström and colleagues (2015) conducted a systematic overview with the aim of determining the most effective mode and dose for treatment for depression. They found that neither intensity, duration nor mode made a difference in treatment of depression. The recommendation based on the included studies was to focus on the preference of the patient and to tailor the physical exercise treatment. The low adherence found for PE, where the participants were allocated to certain intensity and only limited modes were available, also indicates the need for further research into tailored physical exercise in treatment of mental health problems.

One important aim in using OQ-45 is to estimate the best relation between dose and response. In the present thesis the relation between the dose in ICBT and PE and reliable change and recovery was not analyzed. This would be of interest for future studies to increase knowledge about how much treatment or physical exercise is needed.

Concluding remarks

This thesis has shown that the Outcome Questionnaire-45 total score is a comprehensive tool with good psychometric properties useful for both clinicians and researchers in the field. However the support of the different subscales was weaker and the subscales could not be recommended as separate measures on the basis of the results.

The results have also shown support for different treatment alternatives for mild to moderate depression, anxiety and stress-related mental health problems in primary care. The comparison between ICBT and PE provides to the best of my knowledge the first evidence regarding the comparative effectiveness of ICBT and PE on psychological functioning, stress and sleep and the results showed the treatments to be equally effective. This indicates that both ICBT and physical exercise could be implemented as treatments for mental health problems in primary care.

The influence of hazardous drinking on stress accentuates the need for screening for alcohol habits in routine care, to identify hazardous consumption that may have an impact on treatment effects for patients with depression, anxiety, and stress-related mental health problems.

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Paper I

Psychometric properties of the Swedish version of the Outcome Questionnaire-45 as administered by automated technique in a large sample of mental ill-health patients in Primary Health Care

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ABSTRACT – *Background and Objectives:* Mental health problems are common in Pri-
mary Health care and clinicians require valid and reliable instruments to make good treat-
ment plans for these patients. The Outcome Questionnaire-45 (OQ-45) was developed by
Lambert and colleagues in order to help improve outcomes of treatment.

The aims of this study were to examine the psychometric properties of the Swedish
version of OQ-45 when administered by an automated technique and to evaluate if the
OQ-45 uniquely could contribute to the description of the patients' difficulties and needs
beyond demographic characteristics and other instruments.

Methods: The study comprised 816 patients with mental ill-health taking part in a large
randomized controlled trial, Regassa.

The OQ-45 data were collected by Interactive Voice Response IVR, a computerized,
automated telephone technique. The OQ-45 consists of 45 items summarized in a total
score and in three subscales; Symptoms of distress, SD, Interpersonal relations, IR, and
Social role functioning, SR. Depression was measured by MADRS and health-related
quality of life by EQ-5D.

Results: The OQ-45 total score showed good psychometric properties, but there was
little support for its three factor structure. The OQ-45 significantly predicted level of de-
pression and health-related quality of life in patients.

Conclusions: The OQ-45 contributed uniquely to the description of the patients prob-
lems. The results indicate that the total score of the Swedish version of OQ-45 can be
valuable to use for clinicians in the field.

Introduction

Mental ill-health is common in Primary Health care, 25-30% of the patients having mental health problems and some of them are not getting the treatment they need[1,2,3]. It is important for clinicians to use reliable and validated instruments to make good decisions about the patient's treatment. Automated techniques can be an effective and less cost consuming way of administering different measures and to follow large samples of patients[4,5,6]. Regular uses of patient-reported outcome measures can provide an efficient way of improving the assessments, processes and outcomes of health care[7,8].

The Outcome Questionnaire-45 (OQ-45) was developed by Lambert and colleagues[9,10] to improve the results of psychotherapy by tracking the treatment response during treatment. These process measures have been found useful to decrease the risk for treatment failure and to improve positive outcomes[10,11,12,13]. OQ-45 has shown good test-reliability, sensitivity, internal consistency and validity in different studies[14,15] and has been translated into several languages including Swedish[16]. Wennberg and co-workers concluded that the psychometric properties of the Swedish version of the OQ-45 in a substances use disorders sample were acceptable except for a low internal consistency of the Social function subscale. This was in accordance with other cross-cultural studies[17,18].

Our interest was to further evaluate the OQ-45 in a large sample of primary health care patients with mental ill-health problems. The purpose of this study was to examine the psychometric properties of the Swedish version of OQ-45 administered by automated telephone technique and to examine its ability to predict level of depression and health-related quality of life in primary health care

patients, beyond demographic characteristics and other standard instruments. Thereby we aimed to investigate whether OQ-45 could make any unique contribution to the description of the patients` difficulties and needs.

Methods

Study design

The present study was carried out within Regassa, a Swedish national multicenter Randomized Controlled Trial (RCT), which aims to study the effects of Internet based Cognitive Behavioral Therapy, ICBT, and physical activity compared to treatment as usual on sick-leave and work-ability in patients with mild to moderate depression, anxiety and stress related mental ill-health. The Regassa project took place in six different health care regions in Sweden, during 2011 to 2014, and twenty primary health care units were engaged. The project offered three months intervention and patients were followed up 3 and 12 months after baseline. Additionally the patients were followed during and after treatment through an automated telephone technique, Interactive Voice Response (IVR). The regional ethical review board in Stockholm approved the study.

Selection and description of participants

The patients in Regassa were included by a central research unit in Stockholm and different Primary Health care units. The study was based on voluntariness, informed consent and confidential treatment of data. After the patient had signed the agreement to take part

in the study, they answered a battery of different scales and questionnaires administrated by a research assistant. At this point they registered in IVR. Thereafter they were randomized to the three treatment alternatives.

IVR

IVR is a computerized, automated telephone system which is programmed to handle questionnaires to be responded to by a touchtone telephone. At baseline the patients called the system and registered their personal telephone number and answered the questionnaires included. The computerized system was programmed to perform six follow-up assessments to capture the patients view after one, two and three months in treatment and thereafter another three times until 12 months after baseline. At each follow-up the system called the patients' registered phone number and the patient answered the questionnaires. The results will be reported in a forthcoming paper.

Inclusion of patients

In Regassa 946 persons, aged 18-67, 689 women and 257 men, with mild to moderate depression, anxiety disorders and stress related mental health problems were included. The inclusion criteria were symptoms of depression, defined by ≥ 10 points on the Patient Health Questionnaire (PHQ9) and good knowledge in the Swedish language. Knowledge of Swedish was necessary for participation in the Internet based CBT program which was only available in Swedish. Exclusion criteria were alcohol and substance use disorders, need for psychiatric specialist care and severe somatic illness that motivated sick-leave per se.

Of the 946 patients, 816 completed all the 55 questions in the IVR system at baseline,

and were included in the present study. The 130 patients who did not answer all 55 questions were regarded as drop-outs. Seventy-nine of them had answered only a few questions and the other 51 patients had not registered in IVR at all. When comparing the study group of 816 patients with the 130 drop-outs there were no significant differences regarding gender, age, education level, civil state, employment, depression (MADRS) and health-related quality of life (EQ-5D). The patients' characteristics are shown in table 1.

Instruments

Questionnaires in IVR

Three instruments were used in the IVR system: OQ-45, the four- item version of the Perceived Stress Scale, (PSS-4)[19], and the Karolinska Sleep Questionnaire (KSQ), which contains of six questions about sleep patterns. The KSQ was not used in this study.

The OQ-45 measures the patients level of functioning and consists of three subscales essential to define outcome: Symptoms of distress (SD), Interpersonal relations (IR) and Social role functioning (SR). The 45 items have five response alternatives: never (0), rarely (1), sometimes (2), frequently (3) and almost always (4). The SD subscale consists of 25 items, the IR subscale of 11 items and the SR of 9 items. Possible scores on the scale range from 0-180 points where 180 is the maximum negative score. The scores are related to three different levels of functioning: High 0-63, medium 64-84 and low 85-180 points[20]. The cut-off point between clinical and normal population as established by normative data from the US is 64 points[21].

The Perceived Stress Scale (PSS) has been developed in three different versions. The

Table 1
Descriptive Statistics for the Total Group N816 and a Comparison between Male N = 216 and Female N = 600.

	Total group	Male	Female	Male/Female
Age, years M (± Sd)	43 (12.1)	44 (12.5)	42 (11.9)	ns
Education %				P = 0.006**
Low	3.40%	4.60%	3.00%	
Medium	34.40%	43.50%	32.40%	
High	60.40%	51.90%	63.50%	
Civil status %				ns
Living alone	41.00%	42.10%	40.20%	
Living together	59.00%	57.90%	59.80%	
Employment %				ns
Employed	78.50%	74.90%	80.20%	
Unemployed	12.40%	16.70%	10.90%	
Retired	3.70%	4.20%	3.50%	
Sick-leave	5.00%	4.20%	5.40%	
OQ-45, M (± Sd)				
Total score	84.50 (19.50)	82.20 (20.90)	85.30 (18.90)	P = 0.045*
Symptom scale	49.80 (12.00)	48.10 (12.80)	50.40 (11.60)	P = 0.016*
Interpersonal scale	18.20 (6.50)	18.00 (6.70)	18.30 (6.40)	ns
Social scale	16.40 (5.50)	16.00 (5.40)	16.60 (5.50)	ns
OQ-45, clinical level %				ns
Low scores	13.00%	17.10%	11.50%	
Medium scores	34.90%	35.60%	34.60%	
High scores	52.10%	47.20%	53.80%	
MADRS,depression M (± Sd)				
Total score	21.50 (7.20)	22.10 (6.80)	21.30 (7.30)	ns
MADRS, clinical level %				ns
No depression	8.90%	7.20%	9.60%	
Mild dep	32.10%	27.30%	33.80%	
Moderate dep	56.00%	62.20%	53.80%	
Severe dep	3.00%	3.30%	2.90%	
EuroQol-5D(EQ-5D), M (± Sd)	0.55 (0.27)	0.54 (0.27)	0.55 (0.26)	n
Perceived Stress Scale (PSS), M (± Sd)	12.90 (2.50)	12.80 (2.70)	13.00 (2.40)	n
MINI diagnosis, Depression and Anxiety				
Both Dep and Anx	74.30%	74.00%	74.70%	
Dep	8.40%	10.20%	7.90%	
Anx	14.00%	12.60%	14.60%	
No Dep or Anx	2.80%	3.30%	2.80%	ns

PSS 14-items scale constructed by Cohen is translated into several languages and has shown good psychometric properties in different studies[19,22,23]. The Swedish version of the 10-items scale has shown good validity and internal consistency[24]. The PSS 4-items version has shown acceptable psychometric properties in different studies and has been recommended for telephone follow-ups[19,25,26].

Other questionnaires at baseline

The Montgomery Åsberg Depression Rating Scale (MADRS) consists of 10 items with six response alternatives and has shown good psychometric properties[27,28]. The EuroQol 5D (EQ-5D) is a self-report questionnaire for the measurement of health-related quality of life and consists of 5 items describing five dimensions of health with three levels in each dimension[29,30]. The Mini-International Neuropsychiatric Interview (MINI) was used for diagnostics[31]. Further the patients answered a battery of socio demographic questions previously used in a longitudinal population based study in Stockholm, the PART study[32].

Statistics

All the analyses were done in SPSS 20.0. The comparison between groups on scales and age was made with independent sample t-test and for proportions the Chi-square test was used. Internal consistency was measured by Cronbach s alpha and the factor structure of OQ-45 was studied by Principal Component Analysis (PCA). To predict the level of depression (MADRS) and health related quality of life (EQ-5D) by OQ-45, a hierarchical linear regression was used.

Results

Table 1 shows the results on the different measures for the total group and for males and females separately. The proportion of woman was high, 74%. The education level for the total group was high; two-thirds had a post gymnasium or university education. Most of the patients were working or studying and only 5% was on sick-leave. According to their scores on OQ-45, half of the patients had a low level of functioning. The scores on MADRS showed that more than half of the patients had a moderate level of depression and only a few were severely depressed. The total score on EQ-5D was 0.55 which is in level with the mentally ill patients in a National rehabilitation program[33]. Three quarters of the patients had both depression and anxiety diagnoses, i.e. the comorbidity was high. Women and men differed on three measures: educational level, OQ-45 and OQ-45 symptoms subscale.

The correlations between OQ-45 and the other included psychometric measures are strong. The results are shown in table 2.

The internal consistency was good for the total OQ-45, $\alpha = 0.88$, and for the SD subscale, $\alpha = 0.83$. The internal consistency was satisfactory for the IR subscale $\alpha = 0.75$ and for the SR scale, $\alpha = 0.70$. The principal component analysis with oblique rotation showed good loadings for the SD subscale but less for the IR and SR subscales. The extraction of factors resulted in 11 factors using the Kaiser criterion eigenvalues > 1 and 3-5 factors using the scree plot. When the number of factors was set to three, 15 of the 25 SD subscale items loaded > 0.40 on factor 1. Three SD items about somatic problems loaded > 0.40 on factor 2. Five IR items out of 11 loaded > 0.40 on factor 1, one IR item loaded negatively -0.42 on factor 2 and

Table 2
Correlations between level of function measured by Outcome Questionnaire-45 (OQ-45) and depression (MADRS), health-related quality of life (EQ-5D) and perceived stress (PSS).

	OQ-45	MADRS	EQ-5D	PSS
OQ-45	–			
MADRS	0.50***	–	-0.37***	0.35***
EQ-5D	-0.45***	-0.37***	–	-0.33***
PSS	0.63***	0.35***	-0.33	–

*p < 0.05, **p < 0.01, *** p < 0.001.

one IR item loaded > 0.40 on factor 3. Four of the total 9 SR items loaded > 0.40 on factor 1, one SR item loaded > 0.40 on factor 2 and finally two SR items loaded > 0.40 on factor 3.

Table 3 shows the results of the hierarchical multiple regression analysis to predict the level of depression using different relevant measures to explain the variance in step 1 and the contribution of the OQ-45 in step 2. The choice of measures to put into the model was based on correlations with the dependent variable, MADRS. The model explained 27% of the variance in the MADRS and the OQ-45 contributed uniquely with 8% which was statistically significant. The EQ-5D also contributed significantly to the prediction of scores on the MADRS.

Table 3
Hierarchical Regression, Predicting Depression measured by MADRS from Health-related Quality of Life (EQ-5D), Stress (PSS), Demographic data and Level of function (OQ-45).

Variables	$R^2 \Delta$	B	SE B	β	F step
Model 1	0.20				50.05***
EuroQol-5D(EQ-5D)		-7.70	0.90	-2.90***	
Perceived Stress Scale(PSS)		0.71	0.10	0.25***	
Civil status		-1.01	0.46	-0.07*	
Employment		0.23	0.57	0.01	
Model 2	0.08				90.25***
EuroQol-5D (EQ-5D)		-4.84	0.91	-0.18***	
Perceived Stress Scale(PSS)		0.11	0.11	0.04	
Civil status		-0.80	0.44	-0.06	
Employment		0.24	0.53	0.01	
OQ-45		0.14	0.02	0.39***	

*p < 0.05, **p < 0.01, *** p < 0.001.

In table 4 the results of a similar hierarchical multiple regression analysis with the EQ-5D as dependent variable is shown. The model explained 24% of the variance in the EQ-5D and the contribution of the OQ-45 was 5% which was statistically significant.

The MADRS also contributed significantly to the prediction of scores on the EQ-5D.

The interaction with gender did not alter the picture with regard to the results of OQ-45 as a predictor.

Table 4
Hierarchical Regression, Predicting Health-related Quality of life measured by EQ-5D from Depression (MADRS), Stress (PSS), Demographic data and Level of function (OQ-45).

Variables		$R^2 \Delta$	B	$SE\ B$	β	$F\ step$
Model 1		0.19				45.42***
	MADRS depression		-0.01	0.00	-0.29***	
	Perceived Stress Scale (PSS)		-0.02	0.00	-0.22***	
	Age		0.00	0.00	-0.02	
	Employment		-0.04	0.02	-0.06	
Model 2		0.05				52.45***
	MADRS depression		-0.00	0.00	-0.19***	
	Perceived Stress Scale (PSS)		-0.00	0.00	-0.06	
	Age		0.00	0.00	-0.01	
	Employment		-0.04	0.02	-0.05	
	OQ-45		-0.00	0.00	-0.31***	

*p < 0.05, **p < 0.01, *** p < 0.001.

Discussion

We found that the psychometric properties of the Swedish version of the OQ-45 administered by automated telephone technique in a large clinical sample were good with regard to the total OQ-45 score. However the results for the different subscales were weaker which is in accordance with results of other studies[17,18,34,35]. Further the total score of the OQ-45 was found to predict level of depression and health-related quality of life in patients, beyond demographic characteristics and other instruments. Similar to other studies in Europe and USA the results indicate that the total score of the OQ-45 can be of valuable use for clinicians and researcher in the field[17,37,38]. The regression analyses showed that the OQ-45 contributed uniquely to describe the patients' problems. This is probably due to the fact that the OQ-45 is a comprehensive patient reported outcome measure that includes both the patients` symptoms, interpersonal problems and social functioning. Comprehensive scales are essential for assessment, treatment planning and measuring outcome and the implications are that OQ-45 seems to be a useful tool. However separate use of the different subscales of the OQ-45 cannot be recommended on the basis of the present results.

The depression scale, MADRS, was also found to contribute uniquely to the prediction of health-related quality of life and the EQ-5D likewise contributed uniquely to the prediction of degree of depression. The latter is interesting in view of the brief nature of this instrument as it shows the usefulness of the EQ-5D as a patient reported outcome measure in clinical settings.

The large clinical sample of Primary Health Care Patients is an advantage of the study and the technique of data collecting of OQ-45 has to our knowledge not been used before. A limitation is however that the sample is not a random sample of Primary Health care patients. On the other hand, the sample seems representative both in terms of gender and education. The large proportion of women reflects the gender distribution in the Primary health Care in Sweden[39] and other European countries[40,41]. Also in terms of education level the sample is similar to a large Swedish cohort study in the Primary Health Care[39].

The automated data collecting technique of OQ-45 showed results similar to other samples where the data collection was made by paper and pencil[11,16,36]. These results are promising for both the use of OQ-45 total score and for the automated data collecting technique. Further evaluation of administering OQ-45 by automated technique will nevertheless be important in order to generalize these findings. Forthcoming studies using Regassa follow-up data may contribute to this.

Conflict of interest

There is no conflict of interest to declare.

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Paper II

Paper II

Strid, C., Andersson, C., Forsell, Y., Öjehagen, A., & Lundh, L-G. (2016). Internet-based cognitive behavior therapy and physical exercise – Effects studied by automated telephone assessments in mental ill-health patients: a randomized controlled trial. *British Journal of Clinical Psychology 55*, 414-428
http://dx.doi.org.ludwig.lub.lu.se/10.1111/bjc.12111

Paper III

Paper III

Strid, C., Andersson, C., & Öjehagen, A. (2017). The influence of hazardous drinking on psychological functioning, stress and sleep during and after treatment in patients with mental health problems. *Submitted manuscript*

Foto Peter Strid "Haväng"

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