TESIS DOCTORAL

Universidad Autónoma de Madrid
Departamento de Psiquiatría

Interventions for psychosocial difficulties in depression: Research recommendations for improving measurement of treatment effectiveness in depression

Intervenciones para las dificultades psicosociales en depresión: Recomendaciones científicas para la mejora de la medición de la efectividad de los tratamientos en depresión

Kaloyan Kamenov

Directores

José Luis Ayuso-Mateos

María Cabello

Madrid, 2016

To the three women in my life who form my heart – my mom, my sister and Laura

To my father who would have been proud

A las tres mujeres en mi vida que forman mi corazón – mi madre, mi hermana y Laura

A mi padre, quien estaría orgulloso

На мама, Дико и Лаура, които обичам с цялото си сърце

На тати, който би се гордял с мен

AGRADECIMIENTOS

Quiero expresar mis agradecimientos a todas las personas que me han ayudado en la realización de esta tesis doctoral.

Al Prof. José Luis Ayuso, por haber confiado en mí y haberme dado la oportunidad de trabajar en su equipo.

A la Dra. María Cabello, por su enorme ayuda día a día, por sus consejos, paciencia y disponibilidad siempre que la he necesitado.

Al Dr. Francisco Félix Caballero, por sus enseñanzas en estadística y su apoyo en todo momento

A todos mis compañeros – Marta Miret, Itziar Leal, Pilar López, Blanca Mellor, Laura Rico, Natalia Martin-María, Carolina Ávila, Ana Izquierdo, Mónica Nieto y Beatriz Vicario por los tres años que hemos trabajado juntos, por su ayuda y disponibilidad, y por ser tan amables siempre conmigo.

A la Prof. Alarcos Cieza por su destacada coordinación del proyecto y su confianza en mí.

A la Dra. Carla Sabariego por toda su ayuda y su siempre apoyo.

A todos mis compañeros del proyecto MARATONE por haber compartido con ellos un tiempo tan entretenido juntos y por convertir nuestros encuentros en una reunión de amigos.

INDEX

Abstract

2. Objectives of the thesis

3. Hypotheses

7. Conclusions

ABSTRACT

Introduction: Despite the continuously escalating psychological, societal and economic burden of depression, there is a lack of evidence regarding the effectiveness of available interventions on important functional areas beyond specific depressive symptoms. Therefore, the main objective of this thesis is to give an insight into the current measurement of treatment effectiveness in depression and to provide recommendations for its improvement.

Methods: The first part of the thesis critically reviews the current measurement of treatment effectiveness in depression and provides a systematic assessment of the effectiveness of available psychological and pharmacological interventions on psychosocial functioning in depression. The section consists of three articles - a systematic literature review and two meta-analyses. The second part of the thesis is dedicated to the collection of empirical evidence designed as a response to all the limitations of the current research identified in the first part of the thesis. The evidence is collected from a multi-country cross-sectional study, a qualitative study with patients with depression, and an expert survey with representatives from clinical practice. At the end research recommendations for improving treatment effectiveness measurement in depression are provided.

Results: The effectiveness of available interventions for depression is assessed mainly in terms of reduction of clinical symptoms, whereas other areas of functioning are neglected. In addition, all interventions for depression perform better at reducing symptom severity than at improving areas of functioning others than symptomatology. Several limitations in research were identified – 1) a very small number of studies to apply functional outcome measures; 2) a majority of studies with poor quality; 3) heterogeneous instruments addressing distinct areas of functioning; 4) lack of long-term reports on the effectiveness of interventions; 5) high percentage of papers reporting sum-scores rather than domain-specific information; and 6) lack of personalized information on the effectiveness of specific treatments on specific areas of functioning or particular group of individuals.

As an answer to these limitations, results from the multi-country epidemiological study revealed that there was a variation in the level of impairment in different functioning domains across countries. Gender differences in the functional impairment of depression were also found. Clinical experts and depressed patients highlighted the importance of both depressive symptoms and functional areas beyond symptoms. A set of the most important functional areas in depression, namely mental functions, sleep, energy level, somatic problems, interpersonal relationships and interaction, recreation and daily activities, communication, social participation, daily tasks and demands, work and educational difficulties, and personal factors such as self-efficacy or self-awareness was defined. In addition, clinicians and patients identified a number of differences regarding the areas improved by psychotherapeutic or pharmacological interventions that were not addressed by the pertinent literature.

Conclusions: Five main recommendations for future improvement of the measurement of treatment effectiveness in depression were derived from the research we carried out. Firstly, a new instrument comprehensively assessing all relevant psychosocial difficulties in depression has to be created. Secondly, the new

functional tool has to be cross-nationally applicable. Thirdly, report of domain-specific information has to be included in clinical trials. Fourthly, broader remission criteria for depression including psychosocial functioning beyond symptoms are needed. Finally, there is a need of a more personalized approach in treatment decision making, acknowledging specific patient needs and accounting for a more comprehensive array of functional domains.

RESUMEN

Introducción: A pesar de la creciente carga psicológica, social y económica de la depresión, hay escasa evidencia sobre la eficacia de las intervenciones disponibles en áreas funcionales importantes distintas de los síntomas depresivos específicos. Por lo tanto, el objetivo principal de esta tesis es informar sobre el estado de la cuestión en la medición de la efectividad de los tratamientos en la depresión y proporcionar recomendaciones para su mejora.

Metodología: La primera parte de la tesis se dedica a una revisión crítica de la medición actual de la efectividad de los tratamientos en la depresión y proporciona una evaluación sistemática de la efectividad de las intervenciones psicológicas y farmacológicas en el funcionamiento psicosocial de la depresión. La sección consta de tres artículos - una revisión sistemática de la literatura y dos meta-análisis. La segunda parte de la tesis se dedica a la recolección de evidencia empírica diseñada como una respuesta a todas las limitaciones de la investigación actual previamente identificadas en la primera parte de la tesis. La evidencia fue recogida a través de un estudio transversal en diversos países, un estudio cualitativo con pacientes con depresión, y una encuesta con clínicos expertos en depresión. Finalmente, se proporciona una lista de recomendaciones científicas para mejorar la medición de la efectividad de los tratamientos en la depresión.

Resultados: La eficacia de las intervenciones en depresión se evalúa principalmente en términos de una reducción de los síntomas depresivos, mientras que otras áreas de funcionamiento no se abordan. Además, todas las intervenciones en depresión obtuvieron mejores resultados en la reducción de la severidad de los síntomas que en

la mejora de áreas de funcionamiento no relacionados con la sintomatología. Asimismo, se identificaron varias limitaciones en la investigación - 1) un número muy pequeño de estudios aplicaron medidas de funcionamiento; 2) la mayoría de los estudios fueron de baja calidad; 3) los instrumentos fueron heterogéneos y abordaron áreas distintas de funcionamiento; 4) hubo escasos estudios sobre la eficacia de las intervenciones en términos de funcionamiento a largo plazo; 5) un alto porcentaje de artículos presentaron puntuaciones totales en lugar de información sobre dominios de funcionamiento específicos. Como resultado a todas estas limitaciones hubo una falta de información personalizada sobre la eficacia de los tratamientos específicos en áreas concretas de funcionamiento o grupos de individuos particulares.

Para dar respuesta a estas limitaciones, los resultados del estudio epidemiológico con datos recogidos en varios países revelaron la existencia de una variación en el nivel de importancia de los diferentes dominios de funcionamiento en todos los países. También se encontraron diferencias de género en las áreas de deterioro funcional en las personas con depresión. Los médicos y los pacientes deprimidos subrayaron la importancia de los síntomas y las diferentes áreas funcionales de los síntomas. Se definió un conjunto de áreas funcionales más importantes de la depresión - las funciones mentales, el sueño, el nivel de energía, los problemas somáticos, las relaciones interpersonales, la recreación y las actividades diarias, la comunicación, la participación social, las tareas y las exigencias diarias, el trabajo y las dificultades educativas, y factores personales como la auto-eficacia y la auto-conciencia. Además, los médicos y los pacientes identificaron una serie de diferencias con respecto a las áreas mejoradas por las intervenciones psicoterapéuticas o farmacológicas que no fueron abordadas por la bibliografía pertinente.

Conclusiones: Como corolario de la investigación llevada a cabo en esta tesis doctoral, se derivaron cinco recomendaciones principales para la mejora de la futura medición de la efectividad en los tratamientos de la depresión.

En primer lugar, se debería crear un nuevo instrumento de evaluación que integre las dificultades psicosociales más relevantes en la depresión. En segundo lugar, la nueva herramienta funcional tendría que ser aplicable a nivel internacional. En tercer lugar, información específica de diferentes dominios tendría que ser incluida en los ensayos clínicos como medidas de resultado. En cuarto lugar, se necesitarían crear criterios de remisión más amplios para la depresión, incluyendo en la definición áreas de funcionamiento psicosocial más allá de los síntomas. Por último, existe la necesidad de un enfoque más personalizado de evidencia científica que guie la toma de decisiones sobre los tratamientos, reconociendo las necesidades específicas del paciente y considerando una gama más amplia de áreas funcionales.

1. INTRODUCTION

1.1.Prevalence of depression

Depression[1] is characterized by symptoms such as sadness, loss of interest in activities, decreased energy, loss of confidence and self-esteem, feeling of guilt, thoughts of death and suicide, disturbance of sleep and appetite, etc. The most commonly used classification systems for mental disorders - DSM-5 and ICD-10 identify main depressive symptoms needed to be met in the two weeks previous to the assessment for a diagnosis of depression (American Psychiatric Association, 2013; World Health Organization, 1992). In DSM-5 these are depressed mood and anhedonia, as at least one of them must be present for a diagnosis, whereas in ICD-10 there are three typical depressive symptoms - depressed mood, anhedonia, and reduced energy, two of which should be present for a diagnosis.

The prevalence of depression varies across countries, but is always among the most highly prevalent disorders. Statistics states that 11% of EU citizens experience depression at some point in their life (European Pact for Mental Health and Well-being, 2008). A population-based study with more than 38000 participants from 10 countries revealed differences in the lifetime prevalence of depression ranging from 1.5/100 adults in Taiwan to 19.0/100 adults in Beirut (Weissman et al., 1996). The World Health Organization (WHO) Psychological Problems in General Health Care (PPGHC) study further showed a 15-fold variation in major depression prevalence, from lowest prevalence in Japan and

---

[1] Depression in this thesis refers to major depressive disorder, depressive episode and dysthymia. Other disorders that are also characterized by the presence of depressive symptoms such as bipolar disorder, adjustment disorders or cyclothymic disorder are not subject of the present study.

China to highest prevalence in Brazil and Chile (Simon et al., 2002). A subsequent study found lifetime prevalence estimates of MDD of 16.9% in the US, 8.3% in Canada and 9.0% in Chile (Andrade et al., 2003).

1.2.Interventions for depression

There are various methods of managing depression (Chisholm et al., 2004). The WHO mhGAP Intervention Guide (World Health Organization, 2010) recommends as first choice treatment options psychosocial support together with antidepressant medication (Selective serotonin reuptake inhibitors [SSRIs], Serotonin–norepinephrine reuptake inhibitors [SNRIs], Tricyclic antidepressants [TCAs]) or psychotherapy (e.g. Cognitive Behavior Therapy [CBT], Interpersonal Psychotherapy [IPT], Problem Solving Therapy [PST]). Results from randomized controlled trials and clinical guidelines suggest that internet based treatments and some complementary or alternative therapies, such as exercise or sleep deprivation, are also effective in the short term (Caliyurt and Guducu, 2005; Kvam et al., 2016).

1.2.1 Pharmacotherapy

Pharmacotherapy is the most studied and best evidenced treatment for depression. Since year 2000, at least 250 randomized controlled trials and 145 meta-analyses have been published on antidepressant medications for major depressive disorder. The most recognized guidelines (Kennedy et al., 2016; McAllister-Williams, 2006) indicate that the SSRIs and SNRIs are considered as first-line medications due to their better safety and tolerability profiles, whereas older medications like TCAs and monoamine oxidase (MAO) inhibitors are second-line medication. However, the choice of first-line medication still depends on individual assessment and clinical factors like tolerability, patient and health professional preference, costs, and other health system related variables. The most commonly known antidepressant groups are presented below:

1.2.1.1. Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitors **(**SSRIs) are the most commonly prescribed antidepressants against depression. Citalopram, escitalopram, fluoxetine, paroxetine, and sertraline are among the most commonly used SSRI agents. The mechanism of work involves the increase of the extracellular level of the neurotransmitter serotonin by stopping its reabsorption into the presynaptic cell, thus increasing the level of serotonin in the synaptic cleft (Preskorn et al., 2004). The SSRIs are commonly prescribed for severe depression in many countries. They are recommended by the National Institute for Health and Care Excellence (NICE) as a first-line treatment of severe depression and for the treatment of mild-to-moderate depression (McAllister-Williams, 2006). However, their efficacy in mild or moderate cases of depression has been disputed (Fournier et al., 2010; Pies, 2010). Two meta-analyses found the effect of SSRIs in mild and moderate depression to be small or none compared to placebo (Fournier et al., 2010; Kirsch et al., 2008).

1.2.1.2. Serotonin–norepinephrine reuptake inhibitors (SNRIs)

SNRIs are second-generation antidepressants commonly prescribed for depression. Unlike SSRIs, which act upon serotonin alone, SNRIs are powerful inhibitors of the reuptake of serotonin and norepinephrine, thus controlling the mood (Cashman and Ghirmai, 2009). Studies have shown that SNRIs are generally as effective as SSRIs, having a modest efficacy advantage compared to SSRIs in treating MDD (Papakostas et al., 2007), but being slightly less well tolerated (Nemeroff and Thase, 2007). Venlafaxine, duloxetine, milnacipran and levomilnacipran are among the most commonly used SNRI agents.

1.2.1.3. Tricyclic antidepressants (TCAs)

TCAs have been for many years the first choice pharmacological treatment for clinical depression. They have been first discovered and marketed in the early 1950s (Carson, 2000). They are named after their chemical structure based on three rings of atoms. In recent times TCAs have been largely replaced in clinical use worldwide by newer antidepressants such as SSRIs and SNRIs due to their improved safety and side effect profile (Trindade et al., 1998). However, some evidence suggests that tricyclic antidepressants are more effective for melancholic depression than other antidepressants (Mitchell and Mitchell, 1994). The most commonly used TCA agents are clomipramine, imipramine, nortriptyline and doxepin.

In general, recent meta-analyses have not found evidence for significant differences among different groups of agents (Linde et al., 2015). Recent meta-analytical studies have focused on comparing individual antidepressants rather than bigger groups of agents. Evidence from systematically comparative meta-analyses for individual agents have indicated that only sertraline had evidence for superior efficacy compared to other antidepressants (Cipriani et al., 2008). Later on, a multiple comparisons network meta-analysis compared 12 antidepressants and identified a small superiority in response rates for escitalopram, mirtazapine, sertraline and venlafaxine compared to the others (Cipriani et al., 2009).

Despite its wide proliferation, the efficacy of antidepressant treatment for depression has been a matter of numerous debates due to three main reasons. Firstly, some of the RCTs for antidepressants are conducted by pharmaceutical companies selecting patients that may not reflect the real world clinical practice (Kennedy, 2001). Even the most recent larger scale effectiveness trials addressing generalizability, such as the U.S. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Rush et al., 2004) are still limited by numerous methodological deficiencies, such as the presence of study participants with comorbidities or concomitant psychotropic medications, or the lack of measures of adherence to medication (Hu et al., 2007). Secondly, early discontinuation rates of antidepressants are moderate-to-high. Clinical practice guidelines recommend minimum 6–12 months duration of antidepressant treatment for MDD, but more than about 30% of patients discontinue medications within 30 days and more than 40% within 90 days (Olfson et al., 2006). The main reasons for discontinuation are lack of quick response, stigma associated with having a psychiatric illness, and side effects (Hodgkin et al., 2007). Thirdly, several serious adverse effects of antidepressants have been reported during the use of antidepressants. People on TCAs at therapeutic doses have higher risk for seizures compared to general population (0.4–1.2%) (Deshauer, 2007). Studies using systematic assessment of sexual function report rates up to 50% of sexual dysfunction with SSRIs and slightly lower rates with SNRIs (Taylor et al., 2005), greater for fluoxetine and paroxetine, and lower for citalopram/escitalopram.

1.2.2. Psychotherapy

Psychotherapy refers to a treatment approach through a method of communicating between a patient who seeks alleviation of current or prevention of recurrence of symptoms and a therapist. Nowadays, with the advent of computers, internet and other technologies, a relationship could be established between the patient and the psychological model itself. Despite the existence of dozens of psychological modalities for depression, all of them share some key components: (1) maintenance of a professional but fully supportive and working alliance between patient and psychotherapist (2) alleviation of the core factors responsible for the health condition , (3) following of a specific method to deliver the therapy (typically a manual), (4) current state monitoring, (5) psychoeducation, and (g) time-limits (Hunsley et al., 2013). The therapy can be delivered in a group or individual format.

The provision of psychotherapy depends on many factors – patient preferences, provider and health system. Clinical guidelines usually recommend psychotherapy for mild and moderately depressed patients, but discourage monotherapy with psychotherapy for severe cases or suicidal patients (Kennedy et al., 2016; McAllister-Williams, 2006). There is no clear economic evidence that psychotherapy should be a preferable treatment choice compared to pharmacotherapy (Bosmans et al., 2008). However, a recent meta-analysis reveals a strong patient preference for psychological treatment over medication (McHugh et al., 2013). Moreover, evidence states that the majority of people expressing personal preference for psychological therapy choose not to get treated at all rather than receive medication (Layard et al., 2007).

In the next section the most commonly used psychotherapies for depression are presented:

1.2.2.1. Cognitive Behavioral Therapy (CBT)

CBT is the most researched therapy within the last 30 years. It is an intensive, symptom focused psychotherapy built on the premise that distorted beliefs about the self and the world trigger depressive affect. The aim of CBT is to change these maladaptive thinking patterns and to convert them in adaptive ways of responding. CBT is especially effective for symptoms of social withdrawal, anhedonia, and the engagement of persons in their environment (Parikh et al., 2016). The evidence coming from more than hundred randomized controlled trials published since 1977 indicates that CBT is an effective therapy in treating MDD (mild to moderate severity), being equivalent to antidepressant medication (effect size 0.38) for the acute phase episode and superior over control conditions (effect size 0.82) (Gloaguen et al., 1998).

Furthermore, no difference between CBT and antidepressant medication has been found in severely depressed patients (DeRubeis et al., 2005; Luty et al., 2007). Findings from the STAR*D project show that there are no significant differences in remission rates and fewer side effects when patients have switched antidepressant to CBT compared to switching to a different antidepressant (Thase et al., 2007). Lastly, a meta-analysis shows that after stopping CBT and medication after successful acute treatment, patients who initially received CBT have lower rates of relapse (Vittengl et al., 2007).

1.2.2.2.Interpersonal Therapy (IPT)

IPT was initially developed in the 1970's for the outpatient treatment of individuals with MDD. IPT is focused on improving interpersonal relationships and immediate social context. More specifically, the 16 sessions center on role transitions, interpersonal role disputes, grief or interpersonal deficits, etc. The most extensive meta-analysis on IPT to date (Cuijpers et al., 2011) shows an overall effect size of 0.63 in favour of IPT over control conditions, a nonsignificant differential effect size of 0.04 comparing IPT to other psychological treatments, and 0.19 in favour of pharmacotherapy over IPT.

1.2.2.3.Other psychotherapies

CBT and IPT had been recommended as first line treatments for MDD by all clinical guidelines. Other psychotherapies, such as Psychodynamic Psychotherapy, Problem Solving Therapy, Behavioral activation, Cognitive-Behavioral Analysis System of Psychotherapy, Motivational Interviewing, Acceptance and Commitment Therapy, Mindfulness Based Cognitive Therapy and Emotion Focused Therapy, have all shown significantly better results compared to control conditions, but the amount of research is still not sufficient to be proposed as first-line treatments (Barth et al., 2013).

1.2.3. Combination of psychotherapy and pharmacotherapy

Combined treatment for MDD can be either sequential (first acute medication, followed by psychotherapy) or concurrent (starting both treatments together). There is not much literature comparing combined therapy versus each treatment alone due to the various modes of delivery, differential dosage or number of sessions (Parikh et al., 2016). However, a meta-analysis with over 1800 subjects revealed that concurrent medication and psychotherapy was superior to psychotherapy alone, with a small to moderate effect size of 0.35 (Cuijpers et al., 2009). Another meta-analysis showed clear superiority of combined concurrent therapy in terms of symptom reduction and reduction of patient drop-out rates (Pampallona et al., 2004). A study by de Jonghe et al. (2004) reveals strong preference of the patients for combined treatment. Even though the evidence is still not sufficient and cost-effectiveness analyses comparing combined approach to treatment alone are scarce, given that the patient preference is a major concern in psychiatric treatment, this result needs serious consideration in treatment recommendations.

1.2.4. Other interventions, complementary and alternative treatments

Aside from the psychotherapeutic and pharmacological treatments, there exist other therapies that can be simply categorized as complementary and alternative treatments. A big group of alternative treatments is the group of neurostimulation treatment. Neurostimulation refers to the delivery of a physical intervention through electric current or a magnetic field to reach specific brain regions (Kennedy et al., 2009). Electroconvulsive therapy (ECT) has the most extensive evidence. Repetitive transcranial magnetic (rTMS) and vagus nerve stimulation (VNS) are well established for treating MDD (Kennedy et al., 2009), and deep brain stimulation (DBS) is effective for treatment resistant depression

(Lozano et al., 2008), but all three having much smaller evidence base. Light therapy, sleep deprivation, yoga, exercise, acupuncture, nutraceutical therapies, and herbal therapies like St. John’s wort, have been also studied in depression and found to be superior to placebo, but the evidence is still limited (Ravindran et al., 2009). Nevertheless, with the continuous failure of both psychotherapy and pharmacotherapy to show better than just small to moderate effects for improving depression, these alternative therapies become more and more attractive for individuals seeking treatment (Ravindran et al., 2009).

1.3. Escalating burden of depression

In spite of the large number of available interventions for depression and the huge evidence on their effectiveness, data show that up to 30% of all cases of depression are not adequately solved by first-agent treatments (National Collaborating Centre for Mental Health, 2010). The meta-analytical evidence of treatment effectiveness of these first agents is also modest (Cuijpers et al., 2010; Khan and Brown, 2015). Moreover, depression has been consecutively ranked as one of the leading causes of burden in the Global Burden of Disease studies since 1990 (Whiteford et al., 2013). It is predicted to be the greatest cause of disability worldwide by 2030 (Ferrari et al., 2013; World Health Organization, 2003). According to the World Health Organization (WHO), approximately one million people die from suicide every year (World Health Organization, 2003), as the majority of cases appear in people suffering from depression (Mann et al., 2005). Depression affects not just the individuals, but also their closest circle of friends and relatives. Studies show that family members are affected enormously by the burden of the disease and sometimes even develop depression themselves (Shah et al., 2010). Besides the psychological burden on individuals, depression has also significant socio-economic costs. The direct and indirect costs of depression in the EU are estimated at €92 billion in 2010 (Olesen et al., 2012). Nearly half of the costs are result of productivity loss, indicating the enormous negative impact depression has on populations' economy.

1.4. Measurement of treatment effectiveness

To be effective, one treatment has to address individual´s needs and return his level of functioning as before suffering from depression. There are various operational definitions of critical change points in the course of a major depressive episode, such as remission, recovery, relapse and recurrence (Furukawa et al., 2008). Remission of depression, considered as the optimal outcome in clinical research (Keller, 2003), is currently defined solely in terms of symptom reduction (Zimmerman et al., 2006b) according to cut-off scores on symptom severity scales such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967), Beck Depression Inventory (BDI) (Beck et al., 1961) or the Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979). Other studies operationalize remission as a state with no more than one or two mild depressive criterion symptoms, and recovery as eight or more weeks of remission (Keller et al., 1982).

Recent literature has suggested that improvement of functioning areas other than symptomatology, such as social and occupational functioning or quality of life might be equally important for people with depression as their symptom amelioration (IsHak et al., 2011; Lam et al., 2015; Zimmerman et al., 2006a). Patients have prioritized general functioning over symptomatic outcomes and determined the return to a normal level of functioning at work, home or school as a significant factor for remission in depression (Zimmerman et al., 2006a). Research suggests that functional recovery appears later than the symptomatic one and certain level of impairment continue even after the symptomatology is ameliorated (Kennedy et al., 2007). This residual functional impairment has been found to evoke relapse and recurrences in depressed patients (Vittengl et al., 2009). Furthermore, it has been suggested that depressive symptoms and QoL do not share high proportion of common variance (Coryell et al., 1993; Trompenaars et al., 2006).

The concept of functioning problems have been included for diagnosing depressive disorders both in WHO's ICD-10 and in APA's DSM-IV-TR and DSM-5 (American Psychiatric Association, 2000; American Psychiatric Association, 2013; World Health Organization, 1992). According to the DSM criteria, "impaired function: social, occupational, educational" is one of the requirements for establishing a diagnosis of depression, whereas the ICD considers "social, work or domestic activities" as considerably impaired in depression. Thus, the measurement of functioning has always been implicitly included in all classificatory systems but rarely taken into practice to establish diagnosis.

In summary, there are number of psychological, pharmacological and complementary interventions with large evidence for their effectiveness in terms of reduction of symptoms. However, depression still represents a huge problem to society. Further investigation of all relevant functional areas in depression is needed.

1.5. Psychosocial difficulties in depression

It is generally accepted that a psychosocial difficulty refers to any type of difficulty related to one's psychological state or social environment (Ro and Clark, 2009). There have been multiple definitions of psychosocial functioning in literature throughout the years. Definitions are generally broad and typically describe the interaction between individuals and their social environment. Some authors refer to psychosocial functioning only in terms of social functioning within the context of daily living, that is, individuals’ performance in their environment in terms of significant aspects of daily living (e.g., work, relationships). More specifically, Weissman et al. (1981) describes social functioning as “the interplay between the individual and the social environment”. Tyrer (1993) elaborates and adds that in this interplay, the functioning ranges from self-preservation and basic living skills to the relationship with others in society. Keller (2001) adds that “social function defines an individual’s interaction with work, family and social contacts”.

On the other hand, many authors consider quality of life/satisfaction as a measure of psychosocial functioning. Some authors refer to psychosocial functioning as the individuals’ performance in their environment in terms of significant aspects of a vital life (e.g., quality of life, pursuit of values) (Ro and Clark, 2009). WHO defines QoL as the "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (Whoqol Group, 1998). Satisfaction has been identified as a necessary component in defining psychosocial functioning fully, as people with disabilities may have difficulties carrying out day-to-day tasks, but differ in terms of satisfaction with their life.

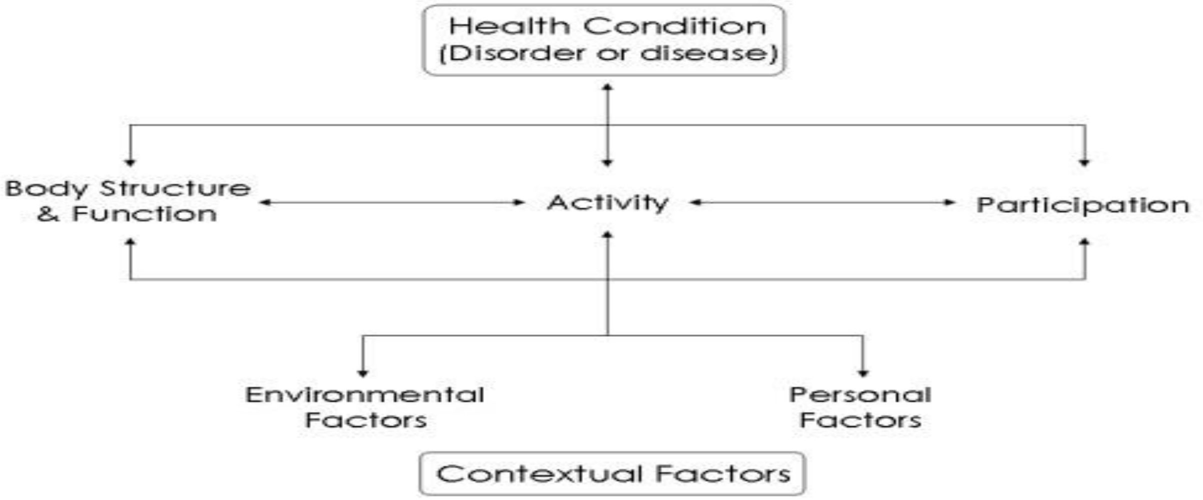
Some of these definitions, however, focus only on specific areas directly affected by the disorder (e.g. psychopathological symptoms, social functioning). Thus, instruments assessing psychosocial outcomes cover only fragments of the generic health state and do not provide an overall picture of the psychosocial functioning of depressed individuals.

A universal, common language embracing not just the health condition (symptomatology), but also the activities problems, participations restrictions and the interaction between the underlying depression and the contextual factors (environmental or personal) is needed to facilitate the process of assessment, diagnosis and treatment of depression. A step towards achieving this goal is the creation of the WHO International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001), a framework and classification defining the spectrum of problems in functioning in patients with mental disorders and in particular - depression.

1.5.1. ICF approach for psychosocial difficulties

The ICF provides a comprehensive conceptual framework and a unified language to describe the psychosocial difficulties and functioning. Originally developed as a complement of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, 1992), ICF provides a biopsychosocial perspective, comprising six components of health: Health Condition, Body Functions and Structures, Activities, Participation, Environmental Factors, and Personal Factors. The central concepts within this model are functioning and disability. Both terms have been used interchangeably in previous literature, but within the frames of this model functioning has been considered as an umbrella term for body functions, body structures, activities and participation. More specifically, functioning depicts the complex interaction between the individual and his/her health condition and his/her contextual environment. Disability indicates the impairments of body functions and body structures, the activity limitations and participation restrictions. More specifically, disability represents the negative outcome of interaction between the individual and his/her health condition and his/her contextual environment. These conceptualizations are useful for clarifying communications among researchers and clinicians (Ro and Clark, 2009). Figure 1 shows the interaction between the components of the ICF model for psychosocial difficulties.

Figure 1. ICF model of disability and health



An important difference between the ICF and other disability classifications is that the ICF conceptualizes functioning as a holistic component of health rather than merely consequence of suffering a disease (World Health Organization, 2001). The ICF framework considers as problems of functioning the areas directly affected by health condition (symptoms) as well as other areas not directly derived by health condition but also impaired. The DSM, in contrast, separates symptoms from functioning. Another very important difference is that the ICF includes multiple categories (i.e., bodily, individual, and societal level functioning), providing a stronger theoretical basis for comprehensive and multidimensional assessment of functioning (Ro and Clark, 2009).

The ICF book consists of more than 1400 categories, organized within a hierarchically nested structure, representing the actual units of the classification. Each category is denoted by a code composed by a letter (b: Body Functions; s:

Body Structures; d: Activities and Participation and e: Environmental Factors), followed by a numeric code. Series of ICF Core Sets for individual disorders have been created lately to simplify this long list of functioning problems and to facilitate the assessment process. Even though the model has not been sufficiently implemented in research studies until now perhaps due to its complexity or large number of categories selected (Alvarezz, 2012), it still provides a universal terminology to describe functioning and disability independently of place, culture, country, or health care system.

The ICF approach for classifying and assessing psychosocial difficulties was used in this thesis, mainly because it is a comprehensive research tool, facilitating the process of selection of study populations and measurement of generic health, but also because it can be used in clinical settings and rehabilitation to structure and lead through the treatment process. Within the frames of the ICF, psychosocial difficulties are defined as any "impairments of mental functions, activity limitations and participation restrictions that include both the individual's mental capacities and his or her social interactions (such as in work, family life and leisure activities)". Impairments of body functions under central nervous system control such as pain and sexual interest problems are also included as PSDs (Cabello et al., 2012).

1.5.2. Evidence for psychosocial difficulties in depression

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 319634, 11 pages
http://dx.doi.org/10.1155/2014/319634

Research Article

Analysing Psychosocial Difficulties in Depression: A Content Comparison between Systematic Literature Review and Patient Perspective

Kaloyan Kamenov,[1] Blanca Mellor-Marsá,[1,2,3] Itziar Leal,[1,2,3] Jose Luis Ayuso-Mateos,[1,2,3] and Maria Cabello[1,2,3]

[1] *Instituto de Salud Carlos III, Centro Investigación Biométrica en Red (CIBER), C/Diego de León 62, 28006 Madrid, Spain*
[2] *Departamento de Psiquiatría, Universidad Autónoma de Madrid, C/Arzobispo Morcillo 4, 28029 Madrid, Spain*
[3] *Instituto de Investigación de la Princesa (IIS-IP), Hospital Universitario de la Princesa, C/Diego de León 62, 28006 Madrid, Spain*

Correspondence should be addressed to Maria Cabello; maria.cabello@uam.es

Received 4 February 2014; Revised 6 May 2014; Accepted 27 May 2014; Published 9 June 2014

Academic Editor: François Beck

Despite all the knowledge on depression, it is still unclear whether current literature covers all the psychosocial difficulties (PSDs) important for depressed patients. The aim of the present study was to identify the gaps in the recent literature concerning PSDs and their related variables. Psychosocial difficulties were defined according to the World Health Organization International Classification of Functioning, Disability and Health (ICF). A comparative approach between a systematic literature review, a focus group, and individual interviews with depressed patients was used. Literature reported the main psychosocial difficulties almost fully, but not in the same degree of importance as patients' reports. Furthermore, the covered areas were very general and related to symptomatology. Regarding the related variables, literature focused on clinical variables and treatments above all but did not report that many psychosocial difficulties influence other PSDs. This study identified many existing research gaps in recent literature mainly in the area of related variables of PSDs. Future steps in this direction are needed. Moreover, we suggest that clinicians select interventions covering not only symptoms, but also PSDs and their modifiable related variables. Furthermore, identification of interventions for particular psychosocial difficulties and personalisation of therapies according to individuals' PSDs are necessary.

1. Introduction

Depression is a major public health issue due to its prevalence, high mortality rates [1], suicide risk [2], and economic impact on the society [3]. It is considered to be the major cause of years lived with disability (YLD) and by 2020 is expected to be among the two main causes of disability adjusted years (DALYs) together with ischemic heart disease [4]. The functional limitations caused by depression are equal to or even sometimes greater than the ones engendered by many other chronic medical conditions [5]. In spite of the great advances achieved in treatment of depression during the last decades, between 20 and 30% of cases are not adequately solved by first agent treatments (also known as treatment-resistant depression in literature) [6].

This evidence suggests that usual management strategies do not address sufficiently relevant areas of depression. One substantial dimension of depression comprises the psychosocial difficulties (PSDs) which people experience. PSDs constitute the impairment on psychological and social daily functioning of individuals, linked with their particular health condition [7]. The broad range of PSDs encompasses not only the personal, but also the economic and social impacts of the disorder. Therefore, it is of extreme importance that these psychosocial difficulties and their related variables are analyzed accordingly. Such information can throw light on patients' real needs, can help clinicians determine the areas in depression that are to be improved and investigated further, may help to prevent the onset of disability, and last, but not least, may guide policy makers to design better health policies.

Previous scientific literature provides different definitions of psychosocial difficulties in depression but has some limitations: the methods either focus only on specific areas or consider the PSDs as a result of depression. Recent studies [7–9], however, provide a new definition of PSDs, based on WHO's International Classification of Functioning, Disability and Health (ICF) [10]. This new approach covers the whole course, determinants and onset of psychosocial problems, and embodies an innovative holistic model of health. More specifically, it states that PSDs are "...impairments of mental functions, activity limitations and participation restrictions that include both the individual's mental capacities and his or her social interactions (such as in work, family life and leisure activities)" [7]. Moreover, impairments of body functions under central nervous system control such as pain and sexual interest problems are also included as PSDs. A detailed description of the utility of the ICF classification for depression can be found elsewhere [11].

Once this comprehensive definition of psychosocial difficulties has been extracted from the literature, it is very important to incorporate the patient perspective in clinical practice and research. The majority of studies on this topic are quantitative; however, the literature that uses qualitative methodologies—which could provide deeper, richer, and more elaborated data, exploratory analyses on patients' needs and standpoints, and thus more objective results—is sparse. Furthermore, this kind of studies can provide a general view if particular psychosocial difficulties, named by patients as important, are missing in the literature.

There are few existing studies using qualitative research to identify a full list of PSDs which depressed people experience. Yet, none of them has applied a comprehensive approach in order to encompass all the psychosocial difficulties from different perspectives. An example is a study by Lasch et al. [12], which aimed to develop a specific questionnaire to assess symptoms for adult major depressive patients and to track their functional status. The authors have conducted ten focus groups and individual cognitive interviews and identified several general domains containing different concepts. However, this study does not combine the patient perspective with information from the literature.

An article by Brütt et al. [13] based itself on a three-dimensional design—systematic review of literature, patient focus groups, and an expert panel aimed to identify a core set of activities and participation for individuals with mental disorders. Moreover, this research paper relied on the International Classification of Functioning, Disability and Health (ICF) as a conceptual framework for describing functional impairments in patients. Despite the comprehensive approach, the study has focused only on ICF categories of the component activities and participation and has not taken into account the other elements of the framework. Furthermore, it has not included information regarding related variables of psychosocial difficulties in depression.

To date, no study has analyzed the full set of PSDs and their related variables in depression by including both literature and patient perspective. The aim of the present study is to tackle this research gap and discover whether the recent scientific literature actually reports the PSDs and their related variables that are important for depressed patients. Our objective is to obtain information about whether the latest literature extensively covers the issues that are pointed out as problematic by depressed individuals, or if there are particular areas, which should receive more attention. Moreover, a potential identification of these missing previously-ignored questions in literature will enhance the quality of future research and enable new strategies for treatment and rehabilitation in depression.

2. Materials and Methods

In order to compare whether the psychosocial difficulties experienced by depressed patients are actually reported by recent literature in depression, we included a step by step methodology.

2.1. Extraction of the Information. We gathered information from three different studies.

2.1.1. Systematic Literature Review. First, a systematic review to directly collect information reported in recent literature, consulting the MEDLINE and PsycINFO databases, was conducted. Search terms were adapted to each database combining the MeSH headings of "Depression," "Depressive Disorder," and "Depressive Disorder, Major" with "depress*" (title) in MEDLINE database and (DE=) "Major Depression," "Recurrent Depression," and "Depressive disorder" in PsycINFO. For psychosocial difficulties the following keywords were used: "psychosocial*," exp Quality of life/, exp Personal satisfaction/exp Human activities/exp social support/disabilit*, homelessness, environmental factor*, exp Interpersonal relations/, exp Quality of life/, exp personal satisfaction/, exp human activities/, exp paternalism/, prejudice/, psychosocial deprivation/, social values/, exp Social Problems/, Social Adjustment/, social isolation/stereotyping/, exp Social environment/, exp emotions/, exp family/, exp socioeconomic factors/exp life style/exp Disability evaluation/, exp Communication Barriers/, "Adaptation", exp Psychological/, exp Aggression/, exp Psychological stress/, exp community (no microbial community)/, Sexual* or intimacy. Inclusion criteria were articles reporting information on psychosocial difficulties in people with a diagnosis of major or minor depression according to DSM-III-TR, DSM-IV, or DSM-IV-TR [14–16], or a depressive episode or depressive disorders according to ICD-10 criteria [17]. Qualitative articles and longitudinal observational and interventional studies were also considered. Additional criteria required the studies to be published in English between 2005 and 2010. Full results of the literature review can be seen elsewhere [7]. Furthermore, studies were also excluded if they were cross-sectional and psychometric or if they had not included a standardized diagnosis of depression. Articles reporting patients with bipolar depression, dysthymia, or postpartum depression were also excluded.

Once all the included studies were selected, we extracted information about the sample characteristics and then collected the variables, the tools, the psychosocial difficulties and their related variables. Related variables in literature refer to determinants of PSDs since only longitudinal studies were included. Determinants in literature were those variables that were longitudinal predictors for incidence or changing of psychosocial difficulties, so consequently a causal relationship with the PSDs can be hypothesized. Extraction of the information was double checked by two independent reviewers in 20% of the articles (MC and BM) (Kappa = 0.80). Kappa's coefficient was calculated according to Fleiss and Cohen rules [20].

2.1.2. Focus Group. On the other hand, the collection of patients' perspectives was performed including information from two studies. The first one consisted of one focus group composed of seven depressed patients. We based our sample size decisions on literature recommendations, "The ideal size of a focus group for most noncommercial topics is five to eight participants" [21] and the concern that a larger group could make participants reserved or there would not be enough time to hear everyone's contribution. Inclusion criteria for participating in the session were patients older than 18 years, with a diagnosis of a depressive episode or a depressive disorder according to ICD-10 during the last year. Eight patients from the *Hospital Universitario de la Princesa* in Madrid were invited to participate. Selection was done by their main mental health care provider (psychiatrist) taking into consideration the maximum variability of sampling in gender, work status, and clinical status (totally remitted, partially remitted, and nonremitted), consulting the patients' clinical records. Eight patients were invited to participate and one of them did not consent to participate reporting having no time for this. Participation in this study was not mandatory and only patients with motivation to participate were included in the final sample; therefore a selection bias could have affected our results. Participation was formally agreed after signing a consent informed form. One moderator and one assistant (MC and IL), who had been previously trained, encouraged all the members to participate during the session.

Four open questions were posed: (1) which psychosocial difficulties are usually experienced due to participant's depression; (2) which ones are more relevant (ranking the five most important ones for each participant); (3) how these difficulties changed overtime; and (4) which events are responsible for the onset or change of these psychosocial difficulties overtime. All the dialogues were digitally recorded and subsequently transcribed.

2.1.3. Individual Interviews. Finally, in order to gather other difficulties that are not usually reported during focus group sessions because of potential unwillingness of self-disclosure [22], we included data from 80 individual interviews. The preselection of participants was done by their health care providers (psychiatrist and GPs) according to the study inclusion and exclusion criteria. All the patients that fulfilled the inclusion criteria were invited to participate and providedbasic information (name and telephone) to researchers to make an appointment. Only four patients did not agree to participate. From these, two justifiedtheir denial with the argument *"I have no time to participate,"* one had no interest in research studies, and one showed no interest in this particular study. During the initial interview researchers verified the fulfillment of the inclusion criteria. At that point five patients that were derived from the primary care center were excluded because they met diagnostic criteria for other different disorders: bipolar disorders (2), generalized anxiety disorder (1), substance use disorder (1), and complicated grief ($n = 1$) and thus satisfied one of the exclusion criteria.

Patients were singly asked, among other questions, which were the five most disabling psychosocial difficulties that they experienced due to depression and which were the variables that were responsible for the onset or the change of these problems. A causal relationship with the PSDs and extraction of determinants, unlike in the literature, cannot be established, because of the nature of the focus group and the individual interviews; therefore we will refer to these variables of onset or change of PSDs according to the patient perspective as related variables.

Trained interviewers (MC, BM) conducted all the individual interviews. Inclusion criteria for individual interviews were patients older than 18 years with a diagnosis of depressive episode or major depression criteria according to ICD-10. All patients were collected in "*Santa Hortensia*" Primary Care center of Madrid or in the outpatient psychiatric service at the Hospital *Universitario de la Princesa* in Madrid. In both study sites patients were chosen according to their availability and were invited to participate by their primary care doctors or psychiatrists. All participants signed an informed consent form. Both studies were independently reviewed and approved by the Hospital Ethics Committee for Clinical Research.

2.2. Agreement on the Terminology to Describe PSDs and Their Related Variables. After gathering information from the three different studies, we needed to establish a common language necessary to directly compare outcomes. For that purpose a list of common categories for classifying psychosocial difficulties was agreed on during one research group meeting. Participants were researchers who had been involved in data collection for different health conditions. Researchers involved in the data collection of depression (IL, BM, and MC) also participated. All of them were requested to share with the group the PSDs that they had identified in the different studies and the terminology they had used to name them. After each naming, the working group was asked whether they agreed with the terminology proposed. After a brief discussion, stating pros and cons for the proposal, an agreed-on term was decided and documented for each PSD. The same procedure was followed to extract the names of related variables in subsequent working group sessions with the same participants.

2.3. Linking Process of Concepts. After obtaining the list of common categories, we associated the different concepts extracted in the studies to the agreed category list. For *personal factors* we used the definition given by the WHO's International Classification of Functioning, Disability and Health: "Personal factorsare the particular background of an individual's life and living, and comprise features of the individual that are not part of a health condition or health states. These factors may include gender, race, age, other health conditions, fitness, lifestyle, habits, upbringing, coping styles, social background, education, profession, past and current experience (past life events and concurrent events), overall behaviour pattern and character style, individual psychological assets and other characteristics, all or any of which may play a role in disability at any level. Personal factors are not classified in ICF." [10]. The liking process was made by two independent researchers according to ICF linking rules [23]. BM and MC participated in the linking process for the focus group and literature review information (Kappa = 0.92 and 0.88, resp.,) and KK and MC performed it for individual interviews (Kappa = 0.85). Disagreements on categories were solved consulting a third expert opinion.

2.4. Analysis of Data. Focusing on the information extracted from the literature, a frequency analysis was performed regarding how many different studies particularly reported the psychosocial difficulties or related variables. In the case of individual interviews, the number of times that the different participants reported the psychosocial difficulties and their related variables was calculated. Finally, for the focus group, digital recordings were analyzed in order to extract the number of times in which psychosocial difficulties and related variables had been a topic during the session (i.e., number of times that these issues had been repeated by a different participant). These analyses were performed with the software for qualitative research NVIVO.

3. Results

3.1. Characteristics of the Participants in the Focus Group and the Individual Interviews. Tables 1 and 2 show the characteristics of the participants in the focus group and the individual interviews.

3.2. Does Recent Literature Report the Main PSDs? Comparison between the literature review and the studies reporting patient's opinion showed that literature does cover almost fully the main psychosocial difficulties directly addressed by depressed individuals. There were relatively few PSDs, not covered by the recent scientific literature. Table 3 summarizes these outcomes.

Emotional functions [24–26], *energy and drive functioning* [27–29], *cognitive functions* [30–32], *employment* [33–35], and *relationship with the others* [36–38] were the most common psychosocial problems emerging both in the literature and the patients' answers. The frequency of the appearance of PSDs was also comparatively identical.

However, some main PSDs in the patient reports were not covered enough by the literature. *Carrying out daily routine* was pointed out by ten patients in the individual interviews (making it the fifth most important PSD), but it has been investigated less than three times in the revised literature.

Communication with others was among the most important psychosocial problems, according to the participants in the focus group, but our systematic review did not find it mentioned anywhere in the literature. Moreover, *weight maintenance functions* and *doing housework* were highlighted by the patients in the individual interviews, but literature omitted them as significant and important psychosocial difficulties in depression. In addition, there were some main categories, which did not meet the same ranking of significance when the different sources of information were compared. *Pain* [39–41] and *sleep* [42, 43], for example, were among the most important categories according to the literature, but in the focus group and individual interviews they were not emphasized notably by patients.

3.3. Specific PSDs. Regardless of these few above mentioned PSDs, literature in general addresses substantially the main psychosocial difficulties in depression. Therefore, we conducted an elaborate second level analysis to investigate whether the specific psychosocial difficulties (components within the main PSD categories), reported in the focus group and individual interviews, were also identified in the literature. Once more, the results demonstrated that the literature, with some exceptions, almost fully covers the range of specific psychosocial difficulties, experienced by depressed patients.

However, as can be seen in Table 4, some specific PSDs were reported with different degrees of importance when the three sources of information were compared. *Loneliness* and *distress* (part of *emotional functions*) were among the most important and commonly mentioned difficulties by the patients, whereas these specific PSDs were reported less than three times in the literature. The same is valid for *attention* and *memory* (part of *cognitive functions*), *efficiency (employment*), and *intimate relationships (relationships with others*).

3.4. Does Recent Literature Report the Related Variables of PSDs? Additionally, we investigated whether literature sufficiently reports the most important related variables of change and onset for psychosocial problems in depression that are addressed by patients. All related variables can be seen in Table 5. Literature reported only few related variables of onset of PSDs. In fact, scientific literature reported clinical variables and treatments above all. In contrast, the patients' perspective, extracted by the focus group and individual interviews we conducted, focused on how particular psychosocial difficulties lead to other PSDs. For instance, *treatment* [44–46] was a related variable of change in several studies as reported in literature, but participants in the focus group identified it also as a related variable of onset for specific PSDs. The same was valid for the role of the emotions in change of PSDs, which was frequently indicated by literature,

Table 1: Characteristics of the participants in the focus group.

Case	Gender	Age	Work status	Comorbidity	Mental health status
1	Female	51	Retired	Fibromyalgia	Partial remission
2	Male	44	Self-employed	No	Total remission
3	Male	50	Employed	Hepatitis C	Partial remission
4	Female	50	Disabled	Cancer	Depression
5	Male	49	Unemployed	No	Partial remission
6	Female	46	Disabled	Arthrosis	Total remission
7	Male	55	Retired	No	Depression

whereas patients reported these *emotional functions* as a cause of psychosocial difficulties as well. Specifically, results showed that the literature did not analyse sufficiently *cognitive functions*, *relationships with others, energy and drive,* and *employment problems* as causes of PSDs.

4. Discussion

The current study aimed to analyse whether the recent scientific literature reports those psychosocial difficulties and their related variables that are important for depressed patients. Our findings indicated that the literature does report almost fully the main psychosocial difficulties, experienced by patients with depression, but the degree of importance of each PSD depended on the source of information. The same refers to the specific PSDs, extracted by a second level analysis. Contrary to the main PSDs reported, however, only a few related variables of onset of PSDs were currently reported in literature. In addition, literature was specifically focused on clinical variables as related to the PSDs, whereas it ignored that some PSDs can also become related variables for other PSDs.

To our knowledge, this is the first study to throw light on whether the latest scientific literature actually reflects the issues that are indicated as problematic by depressed patients. However, all the subsequent comments on the literature have to be considered with respect to the only 103 existing studies within our period of search that covered the whole spectrum of PSDs in depression and the fact that their average quality rate is not high [7]. In this sense, this amount of articles seems insufficient, since the literature review aimed to identify a list of studies examining a wide range of psychosocial problems in depression. It is not in the scope of the current paper to elaborate on this deficit, but, given the present results, it is important to mention that besides the existing information gaps in the specialized publications, the quantity of adequate studies addressing the most common difficulties and related variables represents an additional limitation in the literature.

With regard to the most common psychosocial difficulties, the literature and the patients' outcomes matched almost entirely. *Emotional functions* stood out as an evident problem for depressed patients, as part of the outcomes of 62 research studies and being mentioned more than 100 times during the focus group and individual interviews. A review by Brockow et al. [47], based on the ICF classification, confirms the notion that the emotional functioning is among the most affected areas of depression. A second level analysis, conducted to examine the specific segments of the main categories, however, showed some discrepancies between the literature and the patients' perspective. Incongruence regarding *depressive mood and symptoms* [48–50] (being highlighted in literature whereas downplayed by patients) or feelings of *loneliness* and *distress* (emphasized notably by depressed patients but narrowly explored in the literature) can be explained through the literature tendency to focus mainly on those PSDs which belong to the symptomatology spectrum. In addition, according to our results, the literature usually reported major PSD concepts. However, other more specific and smaller categories, also highly affecting the emotional functioning of individuals—like *loneliness* and *distress*—were neglected.

The same applies to other groups like *cognitive functions*, where research studies have focused on capital subcategories of the main PSDs, such as *cognitive functions in general, thought functions, employment in general,* or *relationships with the others in general*, but have not elaborated on smaller features. According to the present results, patients emphasize the importance of the specific problem they experience, even if it is very distinctive and differential. Therefore, the literature should include adequate instruments to address these particular psychosocial issues and encompass the most delicate and uncovered features of the psychosocial functioning of individuals with depression.

Furthermore, another interesting discrepancy between research and patient perspective regarding the consideration of *pain* and *sleep* as important PSDscan be noticed. Both problems have been frequently emphasized by different research studies as essential for depression, while only few participants in the focus group and individual interviews mentioned them as important. One possible explanation is the hiatus in people's perceptions between depression and physical symptoms. Although somatic symptoms are a common feature of depression [51], a substantial percentage of patients, diagnosed with depression, understand

Table 2: Characteristics of the participants in the individual interviews.

Variables	Setting	
	Specialized care (n = 61, 75.3%)	Primary care (n = 20, 24.7%)
Age	(n = 61)	(n = 20)
18–34	4 (6.6%)	4 (20.0%)
35–49	14 (23.0%)	6 (30.0%)
50–64	29 (47.0%)	5 (25.0%)
65+	14 (23.0%)	5 (25.0%)
Gender		
Female	50 (82.0%)	17 (85.0%)
Level of education		
Less than primary school	11 (18.0%)	3 (15.0%)
Primary school completed	9 (14.8%)	4 (20.0%)
Secondary school completed	5 (8.2%)	4 (20.0%)
High School	10 (16.4%)	4 (20.0%)
University	20 (32.8%)	2 (10.0%)
Postgraduate studies completed	6 (9.8%)	3 (15.0%)
Work situation		
Working	14 (23.0%)	8 (40%)
Working (sick leave)	9 (14.7%)	1 (5.0%)
Unemployed	18 (29.5%)	4 (20.0%)
Homemaker	8 (13.1%)	4 (20.0%)
Student	1 (1.6%)	—
Retired	7 (11.5%)	1 (5.0%)
Disability pension	3 (4.9%)	—
Others	1 (1.6%)	2 (10.0%)
Number of previous depressive episodes	(n = 48)	(n = 80)
0 (first episode)	7 (11.5%)	3 (15.0%)
1-2	26 (41.7%)	11 (55.0%)
+2	15 (24.5%)	2 (10.0%)
Self-administered Comorbidity Questionnaire (SCQ) [18], MD (SD)	12.8 (5.1)	11.8 (5.1)
Hamilton Depression Rating Scale-17 (HDRS)*	(n = 59)	(n = 20)
Mild	4 (6.6%)	11 (55.0%)
Moderate	13 (21.3%)	8 (40.0%)
Severe	42 (68.9%)	1 (5.0%)
Suicide attempts	(n = 57)	(n = 19)
No	48 (78.7%)	15 (75.0%)
Yes	9 (14.8%)	4 (20.0%)

*Cutoff points based on [19].

both as separate entities. Moreover, they frequently indicate only physical symptoms as the reason for seeking medical assistance [52]. Therefore, many depressed outpatients in the present studies might have omitted some physical complaints, disregarding any association between them and their depressive condition. Another reason could be the nature of the commonly used outcome instruments in depression studies. Most of them, such as the Hamilton Rating Scale for Depression (HRSD) [53], the Short Form Health Survey (SF-36) [54], or the WHOQOL-100 [55], include physical symptom items. Therefore, outcomes such as pain and sleep disturbances are often included in scientific studies. Further qualitative studies should confirm whether or not these PSDs are really important for depressed patients, because in that case literature might be overestimating their relevance in depression.

Regarding the related variables of PSDs, the results of our analysis revealed interesting and alarming gaps in the recent literature. Essentially, only few related variables of onset of PSDs were reported in research. *Emotional functions*, for example, being the leading related variable of onset for participants in the focus group, have been considered only as a determinant of change in literature. The same applies for *treatment*. Depressed patients very often stated that the cause of their PSDs was the type of treatment they received. As can be extracted from literature, however, *treatment* is only able to change the course of the disease (generally as a facilitator). Literature should therefore consider the positive and negative consequences of treatments on patient's PSDs and not only report the positive impact on them. This type of information would be useful to help clinicians decide among the wide range of interventions available.

On the other hand, current scientific literature concentrates on clinical variables and treatments as the only PSDs' related variables, whereas patients additionally highlight the relationships between different PSDs. Specifically, if the patient perspective is considered, literature on *cognitive functions*, *relationships with others, energy and drive,* and *employment problems* as related variables of PSDs would have to be described as insufficient. These components are fundamental to the understanding of the psychosocial functioning of depressed patients. Hence, if the aim is to reach a general development in this direction, future research needs to focus on these gaps.

Overall, these findings reveal the fact that there is a discrepancy between the patient's and the health science researchers' perspective when analysing not only the biological and psychological factors of depression, but also the socioeconomic and environmental variables. The subject's view of his health and functioning is not usually taken into account when designing research studies in depression. In this sense, future studies may address this wider view in a more accurate way by taking into account additional sources that are primarily focused on the subject and its sociological environment. From a sociological point of view it could be claimed that the mainstream perspective from which most institutions and professionals develop their work is not reflecting the quotidian environmental stressors that interfere with an adaptive and healthy development of everyday life in people with depression. It could be hypothesized that this is a result of the current and most common definition of depression through a list of symptoms facilitated by

Table 3: Ranking of the main psychosocial difficulties according to literature and patient reports.

Literature review (number of studies) [ICF code]	Focus group (number of times the PSDs were a topic) [ICF code]	Individual interviews (number of people) [ICF code]
(1) Emotional functions (62) [b152]	(1) Emotional functions (49) [b152]	(1) Emotional functions (52) [b152]
(2) Pain (20) [b280–b289]	(2) Cognitive functions (11) [b140–b189, b117]	(2) Energy and drive (31) [b130, b640]
(3) Energy and drive (18) [b130, b640]	(3) Employment (11) [d845–d859]	(3) Relationship with others (24) [d7]
(4) Cognitive functions (17) [b140–b189, b117]	(4) Perception and experience of social support (9) [pf]	(4) Cognitive functions (23) [b140–b189, b117]
(5) Employment (13) [d845–d859]	(5) Self-perception (9) [pf]	(5) Carrying out daily routine (10) [d230]
(6) Relationship with others (13) [d7]	(6) Energy and drive (8) [b130, b640]	(6) Self-perception (8) [pf]
(7) Self-care (12) [d5]	(7) Communication with others (7) [d350]	(7) Pain (7) [b280–b289]
(8) Sleep (11) [b134]	(8) Participating in social activities (6) [d920]	(8) Employment (6) [d845–d859]
(9) Temperament and personality functions (10) [b126]	(9) Relationship with others (6) [d7]	(9) Participating in social activities (5) [d920]
(10) Perception and experience of social support (7) [pf]	(10) Coping strategies (5) [pf]	(10) Sleep (5) [b134]
(11) Participation in social activities (6) [d920]	(11) Psychopathological symptoms (4) [b160, b147, b152, b130]	(11) Weight maintenance functions (5) [b530]
(12) Self-perception (6) [pf]	(12) Self-care (4) [d5]	(12) Mobility (5) [d4]
(13) Psychopathological symptoms (5) [b160, b147, b152, b130]	(13) Carrying out daily activities (3) [d230]	(13) Doing housework (3) [d640, d630]
(14) Mobility (5) [d4]	(14) Perception and experience of stigma (3) [pf]	
(15) Locus of control (4) [pf]	(15) Sleep (3) [b134]	
(16) Psychomotor functions (4) [b147]		
(17) Driving (3) [d475]		
(18) Perception and experience of stigma (3) [pf]		
(19) Self-efficacy (3) [pf]		
(20) Coping strategies (3*) [pf]		

*Only PSDs addressed more than three times in the literature or mentioned more than three times by the participants in the focus group and the individual interviews are shown here.

Table 4: Ranking of the specific psychosocial difficulties according to literature and patient reports.

Main PSD categories	Literature review (number of studies)	Focus group(number of times the PSDs were a topic)	Individual interviews (number of persons mentioned the PSD)
Emotional functions	Depressive mood and symptoms (54) Anxiety (8) In general (5) Emotional regulation (3*)	In general (20) Anxiety (10) Depressive mood and symptoms (7) Loneliness (6) Distress (4)	Depressed mood (14) Anxiety (14) Emotional regulation (9) Loneliness (8) In general (5)
Cognitive functions	In general (5) Thought functions (5) Executive functions (3)	Thought functions (6) Attention (3)	Attention (10) Memory (7)
Employment	In general (10)	In general (11)	Efficiency (5) In general (3)
Energy and Drive	Fatigue (8) Vitality (7) Libido (3) Motivation (3)	In general (8)	Motivation(3) In general (10) Fatigue (9) Family (10)
Relationship with others	In general (6) Family (5)	In general (6)	Intimate relationships (9) In general (4)

*Only PSDs addressed more than three times in the literature or mentioned more than three times by the participants in the focus group and the individual interviews are shown here.

Table 5: Related variables of psychosocial difficulties in literature and patient reports.

Literature review (type of determinant and number of studies)	Focus group (number of times PSD was a topic)	Individual interviews (number of people mentioned with PSD)
Patient treatment (DC*) (26)	Emotional functions (RVO) (18)	Relationship with others (RVC) (29)
Health condition: symptoms (DC) (16)	Stressful life events (RVO) (7)	Patient treatment (RVC) (23)
Health condition: severity (DC) (8)	Employment (RVO) (7)	Emotional functions (RVC) (19)
Temperament and personality (DC) (6)	Cognitive functions (RVO) (7)	Stressful life events (RVC) (7)
Comorbidity (DC) (5)	Perception and experience of social support (RVO) (6)	Health condition: symptoms (RVC) (7)
Perception and experience of social support (DC) (5)	Energy and drive (RVO) (5)	Attitudes (RVC) (7)
Patient treatment $*$ treatment duration (DC) (4)	Temperament and personality (RVO) (4)	Comorbidity (RVC) (6)
Emotional functions (DC) (3)	Self-perception (RVO) (4)	Energy and drive (RVC) (6)
Overall score: ADL (DC) (3)	Comorbidity (RVO) (4)	Self-perception (RVC) (5)
Health condition: duration of episode (DC) (3)	Patient treatment (RVC) (4)	Coping strategies (RVC) (4)
Stressful life events (DC) (3)	Self-perception (RVO) (4)	Participation in social activities (RVC) (4)
Stigma (DO) (3)	Patient treatment (RVO) (3)	Ageing (RVC) (3)
Self-perception (DO) (3**)		Cognitive functions (RVC) (3)
		Employment (RVC) (3)

*DC, determinant of change; DO, determinant of onset; RVC, related variable of change; RVO, related variable of onset.

**Only PSDs addressed more than three times in the literature or mentioned more than three times by the participants in the focus group and the individual interviews are shown here.

established diagnostic manuals: the DSM and ICD. They are based on passive categorical labelling (mainly by health care professionals), which list a number of prototype behaviours that could occur if certain psychological problems occur. This conceptualization within the medical model does not take into account the life circumstances and biographical context, which the individual interacts with, and thus the psychological sense that provides the key to understanding how this problem has been generated and why it remains is disregarded.

The ICF model has been created by WHO as a complementary tool to the diagnostic systems (DSM and ICD) to describe the day-to-day functioning of people. Within the ICF model, psychosocial difficulties are seen as a continuum and as a result of the complex interaction of environmental variables, mental functions, personal variables, activities and participation, and health status. Another option for personalization of medicine and treatment in real clinical settings might be the inclusion of evaluations of daily functional problems experienced by patients. Therefore we suggest customization of healthcare—with therapeutic decisions being tailored to the individual patient. The diagnostic testing has to be adjusted accordingly for selecting appropriate therapies. Eventually, engagement of patients in identifying specific personal problems (e.g., dysfunctional patterns of emotional, cognitive, and behavioural reactivity to natural environments in daily life) could provide more personalized information and change the pattern of diagnosing. For example, ecological momentary assessments of patients via different technologies, eventual self-monitoring, or even more collaborative interactions with therapists and professional carers would enhance research in this direction and give us a new insight. Recent literature based on ecological momentary assessments (EMA) gives us promising results in this line. Different studies [56, 57] have found the experience of positive affect to be prominent in resilience against depression and to predict recovery [58]. Depression has been found to influence work performance with significant decrease in task focus and productivity [59]. Evidence shows that patients with major depressive disorder experience fewer positive events and perceive them as more stressful [60]. Among adolescents, depressive symptoms have been found related to less effective emotion regulation [61]. The EMA have been implemented in research not only on depression, but also on schizophrenia, anxiety, ADHD, bipolar disorder, and so forth.

Ecological momentary assessments have been initially used to identify moment-to-moment patterns and mechanisms of psychopathology [62], but with the development of technologies and especially web based applications, real-life data become available to patients and clinicians, making the transformation of implicit real-life patterns into explicit ones possible, thus improving personalized mental health care [63]. The method has been recently successfully implemented in studies, aiming to explore whether self-monitoring can also be used as an intervention to increase patients' insights in personalized patterns of positive affect [64]. The EMA approach is just one promising way of overcoming the discrepancy between the patient's and the health science researchers' perspective when analysing the variety of factors for depression. Its aim is not to replace the traditional face-to-face contact with practitioners but to allow patients to take an active role in their recovery process and to personalize the treatment process.

Moreover, the patient perspective on PSDs and their related variables has also an impact on the clinical arena. Results of this study highlight the need for change and adjustment of future strategies for treatment and rehabilitation in depression. The process could be more productive, when clinicians select interventions covering PSDs and their modifiable determinants or related variables, and not only symptoms. Solving some activity problems, for example, can help in improving other areas as well. Furthermore, personalization of therapies according to individuals' PSDs will enhance the treatment process. In general, identification of specific interventions for particular psychosocial difficulties is necessary and future research should address this issue.

4.1. Limitations. The findings of this study, however, have to be interpreted assuming its limitations. First, only one focus group of seven patients was performed and saturation point—considering the quantity of information regarding the analysed PSDs—was not reached; therefore the focus group can be considered by some as nonrepresentative. As a partial solution we included a heterogeneous group through maximum sampling variation regarding sex, working status, and clinical status. The age range, however, was between 44 and 55 years, which might have caused a potential bias in the identification of PSDs. This is an important limitation, since some psychosocial difficulties, usually experienced in particular ages, like physical pain in older adults, or problems with intimate relationships or loss of life goals in younger adults, might have been omitted by the nonpresence of representatives of these age groups in our focus group. During the selection process, the psychiatrists who were responsible for the recruitment of participants took into consideration the maximum variability of sampling, but the time frame and the profile of patients in the catchment area of the Hospital *Universitario de la Princesa* in general did not allow us to have a more representative sample in terms of age. However, we decided to proceed with the focus group, because, in fact, a more homogeneous sample of participants is often preferable in terms of age, since it might increase the group comfort level when discussing sensitive topics. Therefore we could assess a wide variety of PSDs including sexual problems, relationships with the therapist, and somatic problems. Finally, in order to achieve more reliable results, we conducted individual interviews with 80 patients ranging substantially in terms of age. Thereat, in spite of this limitation, we found a high variability of PSDs and the valuable finding about the discrepancies between literature and patient reports. Further studies reaching saturation points should be done to test if there are other underexplored PSDs.

Second, a limited period of time was included for the literature search (studies between 2005 and 2010). The search was performed over papers published within the cited period of time because of temporal limitations and because we were interested in the recent literature outcomes rather than general literature. However, we made replication of the original search from 2011 to September 2013 in order to check if any new PSDs will occur in comparison with the initial search and the results did not identify new PSDs. The results of the review have to be read in light of the limitations due to the type of databases consulted. This review study was a component of a larger project that gathered psychosocial factors from several mental health and neurological conditions where only Medline and PsycINFO were included. As a consequence, an amount of studies might have not been identified. As a limitation concerning the reliability of the extraction process we have to indicate that only 20% of articles were independently double checked. Finally, by limiting our search to English literature, we might have omitted relevant papers in other languages.

5. Conclusions

The present study is, to our knowledge, the first to analyse the full set of psychosocial difficulties and their related variables in depression through the literature and the patient perspective. We made an elaborate comparison between both sources of information in order to verify whether recent research literature reported all the PSDs and related variables that are important for depressed patients and to identify the existing gaps in this area. Regarding the research on depression, the results obtained within our study show the existence of many literature gaps and encourage future studies to focus on them more in depth. Concerning the clinical implications, this study emphasizes the need for change and adjustment of future strategies for treatment and rehabilitation in depression. We suggest that clinicians should select interventions that cover PSDs and their modifiable related variables and not only improve symptoms. Furthermore, eventual identification and personalization of therapies according to individuals' PSDs would potentially enhance the rehabilitation process.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

The research leading to these results was funded by the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant agreement no. 241572.

References

[1] P. Cuijpers and R. A. Schoevers, "Increased mortality in depressive disorders: a review," *Current Psychiatry Reports*, vol. 6, no. 6, pp. 430–437, 2004.

[2] World Health Organization, "World suicide prevention day," 2012, http://www.who.int/mental_health/prevention/en/.

[3] P. Sobocki, B. Jönsson, J. Angst, and C. Rehnberg, "Cost of depression in Europe," *Journal of Mental Health Policy and Economics*, vol. 9, no. 2, pp. 87–98, 2006.

[4] T. B. Üstün, J. L. Ayuso-Mateos, S. Chatterji, C. Mathers, and C. J. L. Murray, "Global burden of depressive disorders in the year 2000," *British Journal of Psychiatry*, vol. 184, pp. 386–392, 2004.

[5] K. B. Wella, A. Stewart, R. D. Hays et al., "The functioning and well-being of depressed patients. Results from the medical outcomes study," *Journal of the American Medical Association*, vol. 262, no. 7, pp. 914–919, 1989.

[6] NCCMH, *Depression: The Treatment and Management of Depression in Adults*, NICE Clinical Guidelines, No. 90,

British Psychological Society, National Institute for Health and Clinical Excellence: Guidance, Leicester, UK, 2010, http://www.ncbi.nlm.nih.gov/books/NBK63748/ .

[7] M. Cabello, B. Mellor-Marsá, C. Sabariego, A. Cieza, J. Bickenbach, and J. L. Ayuso-Mateos, "Psychosocial features of depression: a systematic literature review," *Journal of Affective Disorders*, vol. 141, no. 1, pp. 22–33, 2012.

[8] P. Świtaj, M. Anczewska, A. Chrostek et al., "Disability and schizophrenia: a systematic review of experienced psychosocial difficulties," *BMC Psychiatry*, vol. 12, article 193, 2012.

[9] R. Quintas, A. Raggi, A. M. Giovannetti et al., "Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010," *Epilepsy and Behavior*, vol. 25, no. 1, pp. 60–67, 2012.

[10] World Health Organization, *International Classification of Functioning, Disability and Health (ICF)*, World Health Organization, Geneva, Switzerland, 2001.

[11] A. Cieza, S. Chatterji, C. Andersen et al., "ICF Core Sets for depression," *Journal of Rehabilitation Medicine*, vol. 36, no. 44, pp. 128–134, 2004.

[12] K. E. Lasch, M. Hassan, J. Endicott et al., "Development and content validity of a patient reported outcomes measure to assess symptoms of major depressive disorder," *BMC Psychiatry*, vol. 12, article 34, 2012.

[13] A. L. Brütt, H. Schulz, and S. Andreas, "Development of an ICF-based core set of activities and participation for patients with mental disorders: an approach based upon data," *Clinical Rehabilitation*, vol. 27, no. 8, pp. 758–767, 2013.

[14] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 3rd edition, 1987.

[15] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 4th edition, 1994.

[16] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 4th edition, 2000.

[17] World Health Organization, *International Classification of Diseases and Related Health Problems*, Revision (ICD-10), World Health Organization, Geneva, Switzerland, 10th edition, 1992.

[18] O. Sangha, G. Stucki, M. H. Liang, A. H. Fossel, and J. N. Katz, "The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research," *Arthritis Care and Research*, vol. 49, no. 2, pp. 156–163, 2003.

[19] E. Frank, R. F. Prien, R. B. Jarrett et al., "Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence," *Archives of General Psychiatry*, vol. 48, no. 9, pp. 851–855, 1991.

[20] J. L. Fleiss and J. Cohen, "The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability," *Educational and Psychological Measurement*, vol. 33, no. 3, pp. 613–619, 1973.

[21] R. A. Krueger and M. A. Casey, *Focus Groups: A Practical Guide for Applied Research*, Sage, 4th edition, 2009.

[22] D. L. Morgan, "Focus groups," *Annual Review of Sociology*, vol. 22, pp. 129–152, 1996.

[23] A. Cieza, S. Geyh, S. Chatterji, N. Kostanjsek, B. Üstün, and G. Stucki, "ICF linking rules: an update based on lessons learned," *Journal of Rehabilitation Medicine*, vol. 37, no. 4, pp. 212–218, 2005.

[24] I. Skärsäter, A. Langius, H. Ågren, L. Häggström, and K. Dencker, "Sense of coherence and social support in relation to recovery in first-episode patients with major depression: a one-year prospective study," *International Journal of Mental Health Nursing*, vol. 14, no. 4, pp. 258–264, 2005.

[25] C. Choenarom, R. A. Williams, and B. M. Hagerty, "The role of sense of belonging and social support on stress and depression in individuals with depression," *Archives of Psychiatric Nursing*, vol. 19, no. 1, pp. 18–29, 2005.

[26] J. Jaeger, S. Berns, S. Uzelac, and S. Davis-Conway, "Neurocognitive deficits and disability in major depressive disorder," *Psychiatry Research*, vol. 145, no. 1, pp. 39–48, 2006.

[27] S. N. Seidman and S. P. Roose, "The sexual effects of testosterone replacement in depressed men: randomized, placebo-controlled clinical trial," *Journal of Sex and Marital Therapy*, vol. 32, no. 3, pp. 267–273, 2006.

[28] A. Y. Dombrovski, E. J. Lenze, M. A. Dew et al., "Maintenance treatment for old-age depression preserves health-related quality of life: a randomized, controlled trial of paroxetine and interpersonal psychotherapy," *Journal of the American Geriatrics Society*, vol. 55, no. 9, pp. 1325–1332, 2007.

[29] M. C. ten Doesschate, M. W. J. Koeter, C. L. H. Bockting, and A. H. Schene, "Health related quality of life in recurrent depression: a comparison with a general population sample," *Journal of Affective Disorders*, vol. 120, no. 1–3, pp. 126–132, 2010.

[30] X. Cui, J. M. Lyness, X. Tu, D. A. King, and E. D. Caine, "Does depression precede or follow executive dysfunction? Outcomes in older primary care patients," *The American Journal of Psychiatry*, vol. 164, no. 8, pp. 1221–1228, 2007.

[31] A. Brunnauer, G. Laux, I. David, M. Fric, I. Hermisson, and H.-J. Möller, "The impact of reboxetine and mirtazapine on driving simulator performance and psychomotor function in depressed patients," *Journal of Clinical Psychiatry*, vol. 69, no. 12, pp. 1880–1886, 2008.

[32] I. Skärsäter, A. Baigi, and L. Haglund, "Functional status and quality of life in patients with first-episode major depression," *Journal of Psychiatric and Mental Health Nursing*, vol. 13, no. 2, pp. 205–213, 2006.

[33] H. Gilmour and S. B. Patten, "Depression and work impairment," *Health Reports/Statistics Canada, Canadian Centre for Health Information*, vol. 18, no. 1, pp. 9–22, 2007.

[34] U. Leskelä, T. Melartin, H. Rytsälä, P. Sokero, P. Lestelä-Mielonen, and E. Isometsä, "The influence of major depressive disorder on objective and subjective social support: a prospective study," *Journal of Nervous and Mental Disease*, vol. 196, no. 12, pp. 876–883, 2008.

[35] T. Fujiwara and I. Kawachi, "A prospective study of individual-level social capital and major depression in the United States," *Journal of Epidemiology and Community Health*, vol. 62, no. 7, pp. 627–633, 2008.

[36] V. G. Vitriol, S. T. Ballesteros, R. U. Florenzano, K. P. Weil, and D. F. Benadof, "Evaluation of an outpatient intervention for women with severe depression and a history of childhood trauma," *Psychiatric Services*, vol. 60, no. 7, pp. 936–942, 2009.

[37] J. C. Markowitz, A. E. Skodol, E. Petkova et al., "Longitudinal effects of personality disorders on psychosocial functioning of patients with major depressive disorder," *Journal of Clinical Psychiatry*, vol. 68, no. 2, pp. 186–193, 2007.

[38] I. Skärsäter, "Parents with first time major depression: perceptions of social support for themselves and their children," *Scandinavian Journal of Caring Sciences*, vol. 20, no. 3, pp. 308–314, 2006.

[39] A. Sir, R. F. D'Souza, S. Uguz et al., "Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptoms," *Journal of Clinical Psychiatry*, vol. 66, no. 10, pp. 1312–1320, 2005.

[40] O. Caliyurt and F. Guducu, "Partial sleep deprivation therapy combined with sertraline induces more rapid improvements in quality of life items in major depressive disorder," *Journal of Affective Disorders*, vol. 88, no. 1, pp. 75–78, 2005.

[41] J. F. Karp, D. Weiner, K. Seligman et al., "Body pain and treatment response in late-life depression," *The American Journal of Geriatric Psychiatry*, vol. 13, no. 3, pp. 188–194, 2005.

[42] M. H. Rapaport, R. B. Lydiard, C. D. Pitts et al., "Low doses of controlled-release paroxetine in the treatment of late-life depression: a randomized, placebo-controlled trial," *Journal of Clinical Psychiatry*, vol. 70, no. 1, pp. 46–57, 2009.

[43] G. I. Keitner, S. J. Garlow, C. E. Ryan et al., "A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression," *Journal of Psychiatric Research*, vol. 43, no. 3, pp. 205–214, 2009.

[44] R. Saghafi, C. Brown, M. A. Butters et al., "Predicting 6-week treatment response to escitalopram pharmacotherapy in late-life major depressive disorder," *International Journal of Geriatric Psychiatry*, vol. 22, no. 11, pp. 1141–1146, 2007.

[45] P. Lee, L. Shu, X. Xu et al., "Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil," *Psychiatry and Clinical Neurosciences*, vol. 61, no. 3, pp. 295–307, 2007.

[46] P. Sokero, T. Melartin, H. Rytsälä, U. Leskelä, P. Lestelä-Mielonen, and E. Isometsä, "Adequacy of, attitudes toward, and adherence to treatments by suicidal and nonsuicidal depressed patients," *Journal of Nervous and Mental Disease*, vol. 196, no. 3, pp. 223–229, 2008.

[47] T. T. Brockow, K. Wohlfahrt, A. Hillert et al., "Identifying the concepts contained in outcome measures of clinical trials on depressive disorders using the International Classification of Functioning, Disability and Health as a reference," *Journal of Rehabilitation Medicine*, vol. 36, no. 44, pp. 49–55, 2004.

[48] M. Versiani, R. Moreno, C. J. A. Ramakers-Van Moorsel, and A. J. Schutte, "Comparison of the effects of mirtazapine and flouxetine in severely depressed patients," *CNS Drugs*, vol. 19, no. 2, pp. 137–146, 2005.

[49] R. Mann, S. Gilbody, and D. Richards, "Putting the "Q" in depression QALYs: a comparison of utility measurement using EQ-5D and SF-6D health related quality of life measures," *Social Psychiatry and Psychiatric Epidemiology*, vol. 44, no. 7, pp. 569–578, 2009.

[50] C. Nickel, C. Lahmann, K. Tritt et al., "Topiramate in treatment of depressive and anger symptoms in female depressive patients: a randomized, double-blind, placebo-controlled study," *Journal of Affective Disorders*, vol. 87, no. 2-3, pp. 243–252, 2005.

[51] M. H. Trivedi, "The link between depression and physical symptoms," *The Primary Care Companion to the Journal of Clinical Psychiatry*, vol. 6, pp. 12–16, 2004.

[52] G. E. Simon, M. VonKorff, M. Piccinelli, C. Fullerton, and J. Ormel, "An international study of the relation between somatic symptoms and depression," *The New England Journal of Medicine*, vol. 341, no. 18, pp. 1329–1335, 1999.

[53] J. B. W. Williams, "Standardizing the Hamilton Depression Rating Scale: past, present, and future," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 251, no. 2, pp. 6–11, 2001.

[54] J. E. Ware Jr. and B. Gandek, "Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project," *Journal of Clinical Epidemiology*, vol. 51, no. 11, pp. 903–912, 1998.

[55] M. Power, A. Harper, and M. Bullinger, "The World Health Organization WHOQOL-100: tests of the universality of quality of life in 15 different cultural groups worldwide," *Health Psychology*, vol. 18, no. 5, pp. 495–505, 1999.

[56] M. C. Wichers, D. Q. C. M. Barge-Schaapveld, N. A. Nicolson et al., "Reduced stress-sensitivity or increased reward experience: the psychological mechanism of response to antidepressant medication," *Neuropsychopharmacology*, vol. 34, no. 4, pp. 923–931, 2009.

[57] M. Wichers, F. Peeters, N. Geschwind et al., "Unveiling patterns of affective responses in daily life may improve outcome prediction in depression: a momentary assessment study," *Journal of Affective Disorders*, vol. 124, no. 1-2, pp. 191–195, 2010.

[58] N. Geschwind, N. A. Nicolson, F. Peeters, J. van Os, D. Barge-Schaapveld, and M. Wichers, "Early improvement in positive rather than negative emotion predicts remission from depression after pharmacotherapy," *European Neuropsychopharmacology*, vol. 21, no. 3, pp. 241–247, 2011.

[59] P. S. Wang, A. L. Beck, P. Berglund et al., "Effects of major depression on moment-in-time work performance," *The American Journal of Psychiatry*, vol. 161, no. 10, pp. 1885–1891, 2004.

[60] F. Peeters, N. A. Nicolson, J. Berkhof, P. Delespaul, and M. De Vries, "Effects of daily events on mood states in major depressive disorder," *Journal of Abnormal Psychology*, vol. 112, no. 2, pp. 203–211, 2003.

[61] J. S. Silk, L. Steinberg, and A. S. Morris, "Adolescents'emotion regulation in daily life: links to depressive symptoms and problem behavior," *Child Development*, vol. 74, no. 6, pp. 1869–1880, 2003.

[62] M. Wichers, C. J. P. Simons, I. M. A. Kramer et al., "Momentary assessment technology as a tool to help patients with depression help themselves," *Acta Psychiatrica Scandinavica*, vol. 124, no. 4, pp. 262–272, 2011.

[63] K. E. Heron and J. M. Smyth, "Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments," *British Journal of Health Psychology*, vol. 15, no. 1, pp. 1–39, 2010.

[64] I. Kramer, C. J. Simons, J. A. Hartmann et al. et al., "A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial," *World Psychiatry*, vol. 13, pp. 68–77, 2014.

1.5.3. Attempts for classification of psychosocial difficulties and limitations of current research

Classification of all relevant functional areas is needed to provide comprehensive information on the domains affected in depression. The above study by Kamenov et al. (2014) identified a large number of PSDs applied in the literature, but demonstrated that these areas are very general and related primarily to symptomatology. The study identified many gaps in current research mainly in the area of functional domains beyond symptoms.

There are several attempts for classification of psychosocial difficulties. The ICF Research Branch and the WHO developed an evidence-based Core Set for depression (Cieza et al., 2004) based on the ICF in an attempt to address the broad spectrum of functional limitations in individuals with depression. The set includes 45 categories representing mental and body functions (more closed to symptomatology) and 48 covering different activities and social participation. The Core Set for depression, however, has not been sufficiently implemented in clinical research studies, perhaps due to its complexity or the great number of categories within (Alvarezz, 2012).

Apart from the ICF Core Set, there have been also other attempts for creating a universal instrument covering different areas of functioning in depression, but all of them are either limited or still in their infancy. The National Institute of Mental Health Affective Disorders Workgroup in USA created the Individual Burden of Illness Index for Depression (IBI-D) metric conceptualizing the individual burden of illness to include symptom severity, impairment in functioning and reduction in quality of life (Cohen et al., 2013). However, the metric does not report domain-specific information and has been validated in only one study. Zimmerman et al. (2013) developed a new instrument – The remission from Depression Questionnaire - to capture a more comprehensive array of domains considered by depressed patients relevant to remission. The instrument, however, has shown methodological weaknesses concerning its feasibility and validity. Thus, its broader usage in international research is limited.

Furthermore, two recently published studies evaluated the available instruments for measuring functioning in clinical trials. In search of an integrative measure of functioning, Madden et al. (2015) evaluated over 30 different commonly used instruments in literature using ICF as a reference, but did not find a generic measure of functioning relevant to people with a variety of functioning experiences, and capable of indicating support needs, progress and outcomes. The authors conclude that this failure has strong implications internationally for policy-relevant information for disability and rehabilitation. Later on, the Canadian Network for Mood and Anxiety Treatments together with representatives from clinical practice, professional societies, academia, industry, and government highlighted the lack of a gold standard tool for measuring functional capacities in depression as one of the research gaps in current literature (Lam et al., 2015).

Thus, despite the various attempts for a more comprehensive classification and assessment of psychosocial areas, literature is still limited and does not provide exhaustive information on the relevant affected areas in depression. A possible reason for the limited coverage of relevant psychosocial areas in literature might be the narrowness and limitations of the available outcome measures. This, per se, questions the accuracy of the evidence and the measurement of treatment effectiveness in depression. These two research gaps are the main impetus for the present thesis.

2. OBJECTIVES

General objective: To give an insight into the current measurement of treatment effectiveness for psychosocial functioning in depression and to provide recommendations for its improvement.

Specific Objective 1: To provide an overview of the current assessment of treatment effectiveness for psychosocial impairment in depression.

- To analyze which are the functioning outcome measures used in literature
- To identify the gaps and the psychosocial areas addressed in literature

Specific objective 2: To identify the efficacy of available interventions for psychosocial functioning in depression

- To identify the absolute and relative efficacy of psychotherapeutic and pharmacological interventions on functioning and quality of life in depression
- To identify the absolute and relative efficacy of Cognitive Behavioral Therapy on functioning and quality of life in depression
- To critically review the level of evidence that current measures of functioning used in clinical trials for depression are providing

Specific Objective 3: To provide empirical evidence for further improvement of treatment effectiveness measurement in depression

- To test if the psychosocial areas affected in depression have different level of importance in terms of their impact on quality of life
- To test in an empirical study the cross-national commonalities across functional domains and the feasibility of a universal outcome measure for psychosocial functioning.
- To obtain the perspectives of representatives of clinical practice and patients experiencing depression on the effectiveness of the available interventions for depression on psychosocial functioning.

Specific objective 4: To provide research recommendations for improving measurement of treatment effectiveness in depression based on the comparison between current scientific literature, empirical evidence, and the perspectives of representatives from clinical practice and patients with depression.

2. OBJETIVOS

Objetivo general: Informar sobre el estado de la medición actual de la efectividad de los tratamientos en la depresión y proporcionar recomendaciones para su mejora

Objetivo específico 1: Proporcionar una visión general de la evaluación actual de la efectividad de los tratamientos en la mejora del deterioro psicosocial en la depresión.

- Analizar cuáles son los instrumentos de funcionamiento usados en la literatura clínica
- Identificar las áreas psicosociales abordadas en la literatura y cuáles son las áreas que no son tan abordadas por la misma

Objetivo específico 2: Identificar la eficacia de las intervenciones en el funcionamiento psicosocial en la depresión

- Identificar la eficacia absoluta y relativa de las intervenciones psicoterapéuticas y farmacológicas sobre el funcionamiento y la calidad de vida en la depresión
- Identificar la eficacia absoluta y relativa de la terapia cognitivo conductual en el funcionamiento y la calidad de vida en la depresión
- Revisar de forma crítica el tipo de evidencia que las medidas actuales de funcionamiento utilizadas en los ensayos clínicos de la depresión están proporcionando

Objetivo específico 3: Proporcionar conocimiento empírico para la mejora de la medición de la efectividad de los tratamientos en la depresión

- Verificar si las áreas psicosociales afectadas en la depresión tienen diferentes niveles de importancia en términos de su impacto sobre la calidad de vida
- Poner a prueba en un estudio empírico la concordancia de los dominios funcionales entre países y la viabilidad de una medida de funcionamiento psicosocial universal
- Obtener el punto de vista de los clínicos expertos en el tratamiento de pacientes con depresión y la de los pacientes con depresión sobre la eficacia de las intervenciones disponibles para la depresión en el funcionamiento psicosocial.

Objetivo específico 4: Aportar recomendaciones para mejorar la medición de la efectividad de los tratamientos en la depresión basadas en la comparación entre la literatura científica actual, la evidencia empírica, y las perspectivas de los clínicos y los pacientes con depresión.

3. HYPOTHESES

In the context of depression, some issues remain unclear with regard to the true effectiveness of different interventions on the overall psychosocial functioning of individuals. It is essential to add empirical evidence to the existing body of epidemiological literature in terms of investigation of the existing evidence, identification of limitations and provision of recommendations for improving the measurement of treatment effectiveness in depression.

The specific hypotheses corresponding to the objectives of this thesis dissertation are:

Hypothesis 1: Scientific literature puts emphasis on symptomatic outcomes and neglects other psychosocial areas beyond symptomatology

Hypothesis 2: Clinical trials applying functional outcome measures are scarce

Hypothesis 3: Available psychotherapeutic and pharmacological interventions for depression are more efficacious for reducing symptom severity than improving other psychosocial areas beyond symptomatology

Hypothesis 4: Psychosocial domains have differential impact on the quality of life of individuals with depression

Hypothesis 5: There is a cross-national variability in the impact of different psychosocial domains on quality of life in depression

Hypothesis 6: Clinicians and patients provide different and a more comprehensive array of psychosocial difficulties affected in depression compared to the ones applied in literature

3. HIPÓTESIS

En el contexto de la depresión, algunas cuestiones relativas a la verdadera efectividad de las diferentes intervenciones sobre el funcionamiento psicosocial global de los individuos siguen sin estar claras. Es esencial agregar evidencia empírica al conjunto existente de la literatura epidemiológica en relación a la investigación de las pruebas existentes, la identificación de las limitaciones y la provisión de recomendaciones para la mejora de la medición de la efectividad de los tratamientos en la depresión.

Las hipótesis específicas que corresponden a los objetivos de esta tesis son:

Hipótesis 1: La literatura científica pone énfasis en los resultados sintomáticos, no abordando otras áreas psicosociales diferentes de la sintomatología

Hipótesis 2: Los ensayos clínicos que aplican como medidas de resultado, instrumentos de funcionamiento, son escasos

Hipótesis 3: Las intervenciones psicoterapéuticas y farmacológicas para la depresión son más eficaces a la hora de reducir la gravedad de los síntomas depresivos que a la hora de mejorar otras áreas psicosociales más allá de la sintomatología depresiva

Hipótesis 4: La afectación de unos dominios psicosociales y no otros tendrá un diferente impacto y relevancia en la calidad de vida de las personas con depresión

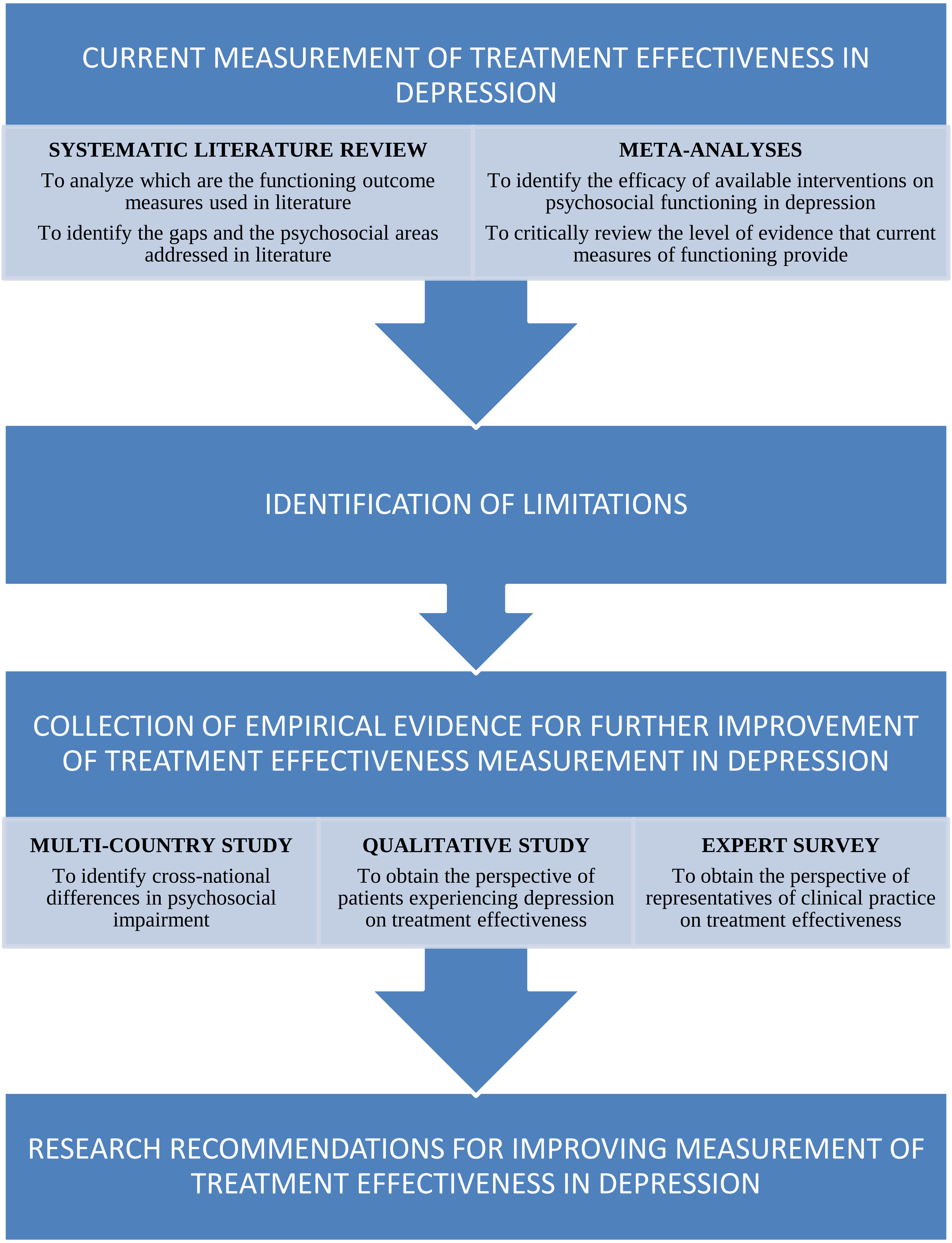
Hipótesis 5: Hay una variabilidad entre países en el efecto que tienen diferentes dominios psicosociales en la calidad de vida en las personas con depresión

Hipótesis 6: Los médicos y los pacientes proporcionan una gama diferente y más amplia de dificultades psicosociales afectadas en la depresión en comparación con las analizadas en la literatura

4. METHODS

This thesis is based on a multi-informant approach, including data from a systematic literature review, two meta-analyses, a multi-country cross-sectional study, an online survey with expert clinicians in the field of depression, and individual qualitative interviews with patients having depression (figure 2). The systematic literature review is essential for exploring the current status quo of scientific research and identifying the gaps and the areas addressed in studies. The two meta-analyses provide comprehensive information on the efficacy of different interventions on psychosocial functioning, but also serve as a basis for critical review of the level of evidence of the efficacy of treatments. The empirical study includes data on functioning from nine low-, middle-, and high-income countries and provides excellent opportunity for investigating cross-national differences in psychosocial areas affected by depression, and for identification of the most burdensome functional areas. Clinical experts opinion is essential for informing the context of clinical research and necessary to overcome the gap between clinical research and the care of individual patients (Tonelli, 1999). On the other hand, qualitative research with patients living with a mental disorder was identified as one of the research priorities for public mental health in Europe (Forsman et al., 2015). Obtaining the patient perspective provides a fundamental knowledge on the complexity of public mental health and enhanced understanding of the community context.

Figure 2. Methodological plan of the thesis



CURRENT MEASUREMENT OF TREATMENT EFFECTIVENESS IN DEPRESSION

SYSTEMATIC LITERATURE REVIEW

To analyze which are the functioning outcome measures used in literature

To identify the gaps and the psychosocial areas addressed in literature

META-ANALYSES

To identify the efficacy of available interventions on psychosocial functioning in depression

To critically review the level of evidence that current measures of functioning provide

IDENTIFICATION OF LIMITATIONS

COLLECTION OF EMPIRICAL EVIDENCE FOR FURTHER IMPROVEMENT OF TREATMENT EFFECTIVENESS MEASUREMENT IN DEPRESSION

MULTI-COUNTRY STUDY

To identify cross-national differences in psychosocial impairment

QUALITATIVE STUDY

To obtain the perspective of patients experiencing depression on treatment effectiveness

EXPERT SURVEY

To obtain the perspective of representatives of clinical practice on treatment effectiveness

RESEARCH RECOMMENDATIONS FOR IMPROVING MEASUREMENT OF TREATMENT EFFECTIVENESS IN DEPRESSION

4.1. Current measurement of treatment effectiveness in depression

4.1.1. Summary of methodology of a systematic literature review

Studies were included if (1) participants were older than 18 years, (2) the diagnosis was established by a standardized diagnostic tool including major depressive episode, major depressive disorder or dysthymic disorder according to Diagnostic and Statistical Manual of Mental Disorders DSM-IV, DSM-IV-TR or DSM-5 criteria (American Psychiatric Association, 1994; American Psychiatric Association, 2000; American Psychiatric Association, 2013), or a depressive episode, recurrent depressive disorder or dysthymia according to the International Classification of Diseases, 10th edition criteria (World Health Organization, 1992), and (3) the sample included at least 10 participants.

Randomized controlled trials, quasi-experimental studies and longitudinal observational studies were included. Interventions were grouped in three main categories: psychotherapy, pharmacotherapy and complementary and alternative medicine therapies (Patten et al., 2009). Customized electronic search for studies assessing interventions in depressive disorders was performed in four databases – PsycINFO, PubMed, Web of science, and the Cochrane Central Register of Controlled Trials for studies published in English from January 2005 to January 2014. Studies were identified by combining terms indicative for intervention: intervention* OR *therapy OR treatment OR pharmacotherapy OR psychotherapy OR behavior therapy OR cognitive analytic therapy OR cognitive behavior therapy OR cognitive behavior therapy OR counseling OR family therapy OR marital therapy OR psychoanalytic therapy OR psychoanalysis OR psychodynamic OR social Skill OR relaxation therapy OR yoga OR homeopathy OR medication OR reminiscence OR life review OR rehabilitation; depression: Depression/ Depressive/Major Depressive disorder [MeSH]; and functioning: psychosocial* OR Quality of Life OR Life Satisfaction OR Unemployment OR Employability OR Reemployment OR Retirement OR Traveling OR Leisure Time OR Exercise OR Physical Activity OR Physical Fitness OR Driving Behavior OR Aggressive Driving Behavior OR Driving Under the Influence OR Activities of Daily Living OR Social Support. The reference lists of included articles and relevant systematic reviews were also checked manually for additional studies.

Content analysis was done after all individual items from the outcome instruments were extracted and linked to the ICF by applying the established linking rules (Cieza et al., 2005). The linking process was done by two researchers. In order to identify gaps in the measurement of treatment effectiveness, the list of functional areas extracted was compared to the ICF Core Set for depression (Cieza et al., 2004). The ICF Core Set includes 45 categories representing mental and body functions (symptomatology) and 48 from the component Activities and Participation. The comparison between our results and the ICF Core Set allowed us to identify all the functional areas that were selected as crucial for persons living with depression but not considered in the treatment effectiveness measurement process.

4.1.2. Meta-analysis on the efficacy of psychotherapy, pharmacotherapy and their combination for functioning and quality of life in depression: Summary of Methodology

Methods and results were presented according to the PRISMA statement for reporting systematic reviews (Moher et al., 2010). A systematic literature search combining the terms depressive disorder OR depression OR major depressive disorder (MeSH terms) AND functioning OR disability OR disability evaluation OR disabled persons OR sick leave OR activities of daily living OR leisure activities OR quality of life AND treatment OR intervention OR clinical trial OR therapy (MeSH terms, key words and text words) was performed in Pubmed, PsycINFO and the Cochrane Central Register of Controlled Trials. In the first two databases, the relevant option was selected to limit the search to Randomized Controlled Trials.

The review included all randomized controlled trials that compared 1) psychotherapy or pharmacotherapy against treatment as usual (TAU), placebo, waiting list (WL) or other control group, 2) psychotherapy against pharmacotherapy or 3) the combination of psychotherapy and pharmacotherapy against either one. All studies had to report at least one validated outcome measure assessing functioning (any difficulty experienced in maintaining daily activities or participation in social life (Lam et al., 2015) or quality of life (one's satisfaction with these activities and perception of his/her health (IsHak et al., 2002; World Health Organization Quality of Life Group, 1997). The diagnosis of depression had to be established by a standardized diagnostic interview according to ICD or DSM criteria (American Psychiatric Association, 1980, 1987, 2000; World Health Organization, 1992). Four criteria of the Cochrane Collaboration risk of bias tool were used for assessing methodological quality of the studies — sequence generation, allocation concealment, blinding of assessors, and incomplete outcome data (Higgins et al., 2011).

Statistical analyses were performed using the program Comprehensive Meta-Analysis, version 2.0. The effect size for each individual meta-analysis was calculated, aggregating the pooled difference between the two groups of treatments at the end of the intervention. Hedges' *g* was preferred as an effect estimate because of its capability to provide a better effect estimate for small sample sizes (Deeks et al., 2008). Publication bias was assessed in each of the meta-analyses by visual inspection of the funnel plots and the trim-and-fill procedure to analyze the changes after the accounting for publication bias (Duval and Tweedie, 2000).

Sensitivity analyses were performed to detect differences between studies with higher and lower quality. Since the selected studies were heterogeneous with respect to comparator groups, study populations, included interventions and outcome measures, series of subgroup analyses were performed. We examined whether there were differences in terms of age groups (adults vs. older adults), psychotherapies (CBT, IPT, PST), others), medication (SSRIs, SNRIs, TCAs, others), control groups (WL, TAU, Placebo, others), outcome measures and types of depression (Major Depressive Disorder, Dysthymia, Subthreshold depression, others). For the continuous moderators, simple meta-regression analyses were performed to explore whether 1) there was a relationship between the effect sizes of functioning or quality of life and severity of symptoms, 2) sample size had an impact on the estimates, 3) the year of publication was associated with the effect estimates and 4) the amount of psychotherapeutic sessions or dosage of medication were relevant.

4.1.3. Meta-analysis on the efficacy of Cognitive Behavioral Therapy for functioning and quality of life in depression: Summary of Methodology

Methods and results are presented according to the PRISMA statement for reporting systematic reviews (Moher et al., 2010). A systematic literature search combining the terms depressive disorder OR depression OR major depressive disorder (MeSH terms) AND functioning OR disability OR disabled persons OR sick leave OR activities of daily living OR leisure activities OR quality of life AND treatment OR intervention OR clinical trial OR therapy (MeSH terms, key words and text words) was performed in Pubmed, PsycINFO and the Cochrane Central Register of Controlled Trials. The search in the first two databases was limited to randomized controlled trials. Terms specifically related to cognitive behavioural therapy were not included to guarantee the inclusion of any possible relevant study applying CBT but not as a central topic._ Articles, published in English between January 2000 and August 2015 were considered.

Manuscripts were included if they met the following criteria: 1) use of a randomized controlled research design; 2) inclusion of a CBT treatment arm (CBT had to include at least cognitive restructuring and behavioural activation procedures for depression); 3) inclusion of participants aged 18 or more; 4) report of at least one validated outcome measure assessing functioning or quality of life (functioning was defined as any difficulty experienced in maintaining daily activities or participation in social life (Lam et al., 2015), whereas QoL as one’s satisfaction with these activities and perception of one’s health (IsHak et al., 2002; World Health Organization Quality of Life Group, 1997)); 5) diagnosis of depression, established by a standardized diagnostic interview according to DSM-IV, DSM-IV-TR and ICD-10 criteria (American Psychiatric Association, 1994; American Psychiatric Association, 2000; World Health Organization, 1992). Four over six criteria of the Cochrane Collaboration risk of bias tool were used for assessing methodological quality of the studies —sequence generation, allocation concealment, blinding of assessors, and incomplete outcome data (Higgins et al., 2011).

All statistical analyses were performed using the program Comprehensive Meta-Analysis, version 2.0. The effect size for each study was calculated aggregating the pooled difference between the two groups of treatments at the end of the intervention. Hedges’ *g* was preferred as an effect estimate because it provides better effect estimate for small sample sizes (Deeks et al., 2008). Statistics were based on intention-to-treat (ITT) data, but when missing, on completer data. Due to the inclusion of a wide range of outcome measures, sensitivity analyses were performed to assess whether one single instrument had a strong impact on the overall effect size. The following subgroup analyses were performed in order to examine whether certain characteristics of the studies were related to the effect sizes: 1) differences between age groups (adults vs. older adults); 2) delivery format (face-to-face vs. internet or telephone delivered CBT); 3) differences in the control group (WL or TAU); 4) quality of studies (high vs. lower quality; ITT vs. completer data).In addition, simple meta-regression analyses were performed to explore whether 1) there was any association between the effect size of depressive symptoms and the estimates of functioning and quality of life, 2) sample size had an impact on the estimates, and 3) the amount of psychotherapeutic sessions were important. Publication bias was assessed by visual inspection of funnel plots and the trim-and-fill procedure to analyze the changes after the accounting for publication bias (Duval and Tweedie, 2000).

4.2. Identification of limitations and collection of empirical evidence for further improvement of the measurement of treatment effectiveness in depression

4.2.1. Empirical multi-country cross-sectional study: Summary of methodology

For this study, data obtained from the World Health Organization's (WHO) Study on Global Ageing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE in Europe), two multi-country projects conducted between 2007 and 2012 (Kowal et al., 2012; Leonardi et al., 2014). The COURAGE survey was conducted in Finland, Poland, and Spain, whereas the SAGE survey was undertaken in China, Ghana, India, Mexico, the Russian Federation, and South Africa. The selected countries represent different geographical locations and levels of socio-economic and demographic status. Both projects collected data on participants aged 18+ years, with an emphasis on people aged 50+ years, from nationally representative samples. The sample comprised 4051 non-institutionalized adults (18+) who were currently experiencing an episode of depression from China (296), Ghana (428), India (1522), Mexico (291), Russia (321), South Africa (168), Poland (288), Finland (136) and Spain (601). Informed consent from all participants was obtained. Ethical approval was obtained from the WHO Ethical Review

Committee for SAGE and by Neurological Institute Besta for COURAGE, and by all local ethics research review boards.

Participants who had been diagnosed with depression by a physician and had been receiving treatment during the last 12 months were included in the study. In addition, since there are many cases of undiagnosed persons who actually experience depressive episodes (Sheehan, 2004; Volicer, 2011), we assessed depression with a set of symptomatic questions derived from the World Mental Health Survey version of the Composite International Diagnostic Interview (CIDI) for depression (Kessler and Ustun, 2004). The individual items were included in a diagnostic algorithm generating a diagnosis of "depressive episode" according to the criteria specified in the *International Statistical Classification of Diseases and Related Health Problems, 10th revision, Diagnostic Criteria for Research* (World Health Organization, 1992).

Functioning was assessed with a multi-domain measure (Salomon et al., 2003), previously used in 70 countries from the World Health Survey (Salomon et al., 2003), assessing the following 8 functioning domains: mobility, self-care, cognition, pain, interpersonal activities, domestic life and work, sleep and energy, and affect. Quality of life was assessed using a short version of the WHO Quality of Life (WHOQOL) instrument (Power, 2003; Skevington et al., 2004). Country, age, sex, marital status, presence of comorbid physical chronic conditions (angina, hypertension, asthma, arthritis or diabetes) and level of education were included in the analysis as control variables.

To examine the independent contributions of all domains of functioning on QoL, a multiple regression analysis was conducted. Age, sex, country, marital status, comorbidity and educational level were introduced as covariates to control for potential confounders. In addition, the analysis was carried out on the entire sample of depressed individuals, on men and women and on each country separately. Standardized (β) coefficients indicated the level of association between the functioning domains and the covariates and QoL, since (β) can be applied as effect size in regression models._STATA version 11.0 (Stata Corp, 2009) was used to analyse the socio-demographic data, to calculate the factor scores and to conduct the regression models. Amos version 22 (Arbuckle, 2013) was used for the confirmatory factor analyses.

4.2.2. Online expert survey: Summary of Methodology

The online survey was available between March 2015 and March 2016. It was designed to collect data from practicing clinicians in the field of depression on the interventions used in their daily practice and the psychosocial difficulties addressed by these treatments. The short survey consisted of two questions: 1) "Choose the type of intervention(s) you usually use in your daily practice"; and 2) "List the psychosocial difficulties that this intervention(s) aims to improve in individuals with depression". Participants could choose up to 10 interventions. The aim was to obtain experts' opinion on the areas that are captured by the specific treatments and that should be included in the assessment of interventions for depression. All the answers concerning psychosocial difficulties were linked to the ICF categories according to the existing rules (Cieza et al., 2005). Demographic data was also collected.

To reflect different opinions and achieve a maximum variation sampling, a wide range of clinicians was approached - psychiatrists, psychotherapists, primary health care doctors, social workers, nurses and physicians amongst others. Selection of experts was based on available people within a purposive sampling. The clinicians were selected according to the following criteria: 1) at least 2 years of clinical expertise treating people with depression; 2) variability by age, gender, nationality and type of therapy used in daily practice. In addition, only European experts were approached, but for comparison purposes data from non-European experts were also collected. Potential participants were identified through a number of sources: internal data bases of international experts working in depression; heads of departments of psychiatric hospitals and departments, professional websites for clinicians working in depression (e.g. www.commonlanguagepsychotherapy.org), and though a snowball approach. Experts were sent an email invitation for participation in the survey. We expected a 50-70% of non-response (Archer, 2008; Horgan and Dimitriou, 2015). Our target was to obtain a sample of 100 experts; therefore the survey was sent to nearly 250 worldwide experts in depression.

4.2.3. Qualitative interviews with patients with depression: Summary of methodology

Unstructured qualitative individual interviews with outpatients diagnosed with depression were performed. The aim of the study was to collect data from individuals living with depression on the treatments they receive/have received for depression and the psychosocial difficulties addressed by the interventions. Participants had to meet the following inclusion criteria: 1) current or experience of depressive episode in the previous 12 months as main diagnosis - depressive episode (F32.), recurrent depressive episode (F33), or currently in partial or total remission (F33.4) according to the International Classification of Diseases (World Health Organization, 1992); 2) enough cognitive capacity to participate in an interview (score > 26 in the mini-mental status examination (MMSE) (Folstein et al., 1975); 3) knowledge of local language (Spanish); 4) age ≥ 18 years; 5) currently receiving treatment for depression, namely psychotherapy, pharmacotherapy or other treatment prescribed by their mental health professional, 6) to be informed of the purpose and rationale of the study, and have understood both; and to sign the patient consent form. Ethics approval was obtained by the “La Princesa” Hospital Ethics Committee for Clinical Research in Madrid.

The recruitment of participants and data collection was performed in a public outpatient mental health unit in Hospital la Princesa (Madrid, Spain). Collection was done by two mental health professionals working in the unit (one psychologist and one psychiatrist) between September 2015 and March 2016. All patients who met the inclusion criteria were informed about the study and invited to participate. All participants who agreed to participate gave their consent. The study consisted of a face-to-face interview with one research team member and comprised of two parts. The first part was series of demographic and clinical questions, which aimed to recollect information on the patients’ background. Data on gender, age, type of depression, number of previous episodes, onset of the disorder, occupation, etc. was collected. The second part assessed the type of treatment (psychotherapeutic, pharmacological or others) patients had received or were receiving, and their experience being under treatment. During an open personal interview, participants were asked about the psychosocial difficulties they experience, and the ones that were improved/not improved by the specific treatment they received.

Data collection continued until reaching a saturation point—when the collection of new data did not shed any further light on the investigation we stopped with the recruitment process (Glaser and Strauss, 1967). More specifically, we defined one major rule for determining saturation – when three consecutive patients under the same group of treatment do not report a new psychosocial difficulty that has not been mentioned before. Medication usage was allowed in the cases receiving psychotherapy only if the dosage had not been changed one month prior to the start of the psychotherapeutic sessions or during the psychotherapeutic treatment. In order to assess the true effects of antidepressants on the overall condition of depression, only patients who had initiated the medication treatment at least three months before the start of the psychotherapy were included.

The recording of the individual interview session was transcribed verbatim. The transcript was checked by the moderator and the information was extracted and double checked. All the contents concerning psychosocial difficulties were translated into English and coded according to ICF categories following the ICF existing linking rules (Cieza et al., 2005). Codification of themes and subthemes for both interventions and psychosocial difficulties was double checked by an independent researcher and analyzed by NVIVO program, version 11, following content-analyses theory (Mayring, 2014). All frequencies were analyzed with SPSS, version 21.

4.3. Research recommendations for improving treatment effectiveness measurement in depression

This thesis dissertation will present a set of final recommendations for improving measurement of treatment effectiveness in depression by linking the limitations identified in the systematic literature review and two meta-analyses to the empirical evidence collected from the cross-national study, expert survey and qualitative interviews with patient.

5. RESULTS

5.1. Overview and evaluation of the current evidence for the measurement of treatment effectiveness on psychosocial impairment in depression

The first part of the Results section is dedicated to the findings of the evaluation of current measurement of treatment effectiveness in depression, collected from the systematic literature review and the two meta-analyses. A brief summary of the results and the weaknesses identified in the papers is presented before the articles. For further information consult full-text articles.

5.1.1. Summary of findings

- The effectiveness of all available interventions for depression is assessed mainly in terms of reduction of clinical symptoms, whereas other areas of functioning are neglected.
- Every study analyzed in the systematic review applied at least one measure of severity of symptoms, but only less than 20% of all questionnaires addressed other areas of functioning.
- Areas of functioning such as interpersonal relationships (family and partner relationships, informal relationships with friends), leisure activities, daily tasks and demands, major life areas, such as employment or education, were neglected in literature
- Psychotherapeutic and pharmacological interventions were efficacious for improving psychosocial functioning, but the effect sizes were modest
- All interventions performed better at reducing symptom severity compared to improving areas of functioning beyond symptomatology

- There was a lack of available studies to perform some of the analyzes
- The instruments were heterogeneous and addressed different areas of functioning
- Few studies reported long-term effectiveness of interventions
- Studies reported sum-scores rather than domain-specific information

Personalized information on the effectiveness of specific treatments on specific areas of functioning or particular group of individuals could not be obtained

Journal of Affective Disorders 188 (2015) 89–96

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

How much do we know about the functional effectiveness of interventions for depression? A systematic review

Kaloyan Kamenov[a], Maria Cabello[a], Michaela Coenen[b], José Luis Ayuso-Mateos[a,c,d,*]

[a] Instituto de Salud Carlos III, Centro Investigación Biomédica en Red, CIBER, C/ Diego de León 62, 28006 Madrid, Spain
[b] Department of Medical Informatics, Biometry and Epidemiology (IBE), Research Unit for Biopsychosocial Health, Ludwig-Maximilians University (LMU), Marchioninistr. 15, 81377 Munich, Germany
[c] Department of Psychiatry, Universidad Autónoma de Madrid, C/ Arzobispo Morcillo 4, 28029 Madrid, Spain
[d] Instituto de investigación de la Princesa, (IIS-IP), Hospital Universitario de la Princesa, C/ Diego de León 62, 28006 Madrid, Spain

ARTICLE INFO

Article history:
Received 23 June 2015
Received in revised form
23 July 2015
Accepted 15 August 2015
Available online 2 September 2015

Keywords:
Depression
Functioning
Intervention
Outcome measure
Treatment effectiveness

ABSTRACT

Background: Functional difficulties are determined as one of the reasons for the public health priority given to depression. However, previous literature shows that the evidence on treatment effectiveness in depression does not reflect all relevant functional areas affected. This paper aimed to review recent literature and identify which areas are addressed and what are the gaps in the measurement of treatment effectiveness in depression.

Methods: Electronic search was performed in PsycINFO, PubMed, Web of science, and the Cochrane Central Register of Controlled Trials. A content item analysis of outcome measures was performed.

Results: Two hundred and fourty-seven studies were included. The functional areas addressed in the measurement process did not vary across studies assessing psychotherapeutic, pharmacological or alternative interventions. The content analysis revealed that 80% of the areas covered by instruments represented symptomatology. Many functional areas were insufficiently covered, whereas others like handling stress, solving problems, maintaining daily routine, problems in education, or participation in community, political or religious life were not addressed at all.

Limitations: Only articles in English were included and the time frame was limited.

Conclusions: More than 10 years after the first global burden of disease studies have been published evidence on the treatment effectiveness in depression is still based primarily on symptoms. Many important functional areas remain unexplored. Consequently the effectiveness of well recognized interventions might be overestimated. Future steps should include use of comprehensive tools, provision of detailed information on functional areas instead of global scores of instruments, and design of functional impairment oriented therapies.

Contents

---

[*] Corresponding author at: Instituto de investigación de la Princesa, (IIS-IP), Hospital Universitario de la Princesa, C/ Diego de León 62, 28006 Madrid, Spain. Fax: +34 914972716.
E-mail address: joseluis.ayuso@uam.es (J.L. Ayuso-Mateos).

http://dx.doi.org/10.1016/j.jad.2015.08.035
0165-0327/© 2015 Elsevier B.V. All rights reserved.

1. Introduction

In spite of all evidence based treatments, unipolar depressive disorders still represent a huge burden to society and health services (Chisholm et al., 2004). Statistical data show that 11% of EU citizens experience depression at some point in their lives (European Pact for Mental Health and Well-being, 2008) and it is the second leading cause for disability worldwide (Ferrari et al., 2013).

Previous studies on global burden of disease underline the importance of functioning in all disorders (Murray and Lopez, 1996; World Health Organization, 2004). More specifically, the reports on depressive disorders particularly point out the negative impact of depression on person's functioning as one of the reasons for the public health priority given to the disease (Ferrari et al., 2013; Ustun et al., 2004). Functioning embraces not only impairment of mental or body functions, indicating symptomatology according to DSM and ICD diagnostic tools (American Psychiatric Association, 2000; World Health Organization, 1992), but also activity limitations or participation restrictions in domains of life, such as social functioning, daily activities, etc. (World Health Organization, 2001).

Existing meta-analyses on the effectiveness of interventions in depression focus primarily on outcome measures that address symptoms, such as the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), Beck Depression Inventory (Beck et al., 1961), or Montgomery Asberg Depression Rating Scale (Montgomery and Asberg, 1979). More specifically, full remission, defined as a significant reduction in the number of symptoms, is considered the optimal outcome in clinical research (Keller, 2003).

However, many studies have reported that other functional areas beyond specific symptoms, like interpersonal problems, communication difficulties, or problems in mobility and self-care are also relevant for depression (McKnight and Kashdan, 2009) and might even predict more accurately the clinical course of the disorder (Stefos et al., 1996). Nevertheless, instruments assessing those areas of functioning, if considered, are mostly secondary outcomes and barely accounted for systematic analyses (Williams et al., 2000). Thus, a possible reason for the continuous burden of the disease might be that the evidence on which the guidelines for depression are built does not consider relevant functional problems for the disorder. Moreover, some authors point out that this lack in evidence might explain to some extent why treatment guidelines are not so widely implemented in mental health care settings (Drake et al., 2001).

A review by Brockow et al. (2004) was conducted to identify the concepts contained in outcome measures of trials on depressive disorders. The content analysis revealed that more than 80% of all functional areas covered in literature represented symptomatology. Activities of daily functioning or participation in life situations were under-represented in the assessment of treatment effectiveness in depression.

The current study was set to analyze whether the way of measuring treatment effectiveness in depression has changed and incorporated all relevant functional areas ten years after the publication of the Brockow's study and the second global burden of disease report, in which depression was marked as the first cause of disability by 2030 (Brockow et al., 2004; World Health Organization, 2004). Our overall objective was to identify which areas are addressed and what are the gaps in the measurement of treatment effectiveness in depression. The study particularly aimed to (1) identify the instruments used as outcome measures of effectiveness in studies assessing psychotherapeutic, pharmacological, and complementary and alternative interventions; (2) analyze the functional areas addressed in the instruments and whether they vary across the three types of interventions; (3) identify gaps in the measurement of effectiveness using an universally accepted framework for functional assessment of depression as a reference, the International Classification of Functioning, Disability and Health (ICF) Core Set for depression. (Cieza et al., 2004). This ICF Core Set provides a list of functioning areas covering the spectrum of symptoms and aspects of activities and participation relevant for individuals with depression. The study and analyses performed had explorative character and specific hypotheses had not been tested.

2. Methods

2.1. Search

Customized electronic search for studies assessing interventions in depressive disorders was performed in four databases – PsycINFO, PubMed, Web of science, and the Cochrane Central Register of Controlled Trials for studies published in English from January 2005 to January 2014. Studies were identified by combining terms indicative for intervention: *intervention* OR *therapy OR treatment OR pharmacotherapy OR psychotherapy OR behavior-therapy OR cognitive analytic therapy OR cognitive behavior therapy OR cognitive behavior therapy OR counseling OR family therapy OR marital therapy OR psychoanalytic therapy OR psychoanalysis OR psychodynamic OR social Skill OR relaxation therapy OR yoga OR homeopathy OR medication OR reminiscence OR life review OR rehabilitation*; depression: *Depression/ Depressive/Major Depressive disorder [Msh]*; and functioning: *psychosocial* OR Quality of Life OR Life Satisfaction OR Unemployment OR Employability OR Reemployment OR Retirement OR Traveling OR Leisure Time OR Exercise OR Physical Activity OR Physical Fitness OR Driving Behavior OR Aggressive Driving Behavior OR Driving Under the Influence OR Activities of Daily Living OR Social Support.* The reference lists of included articles and relevant systematic reviews were also checked manually for additional studies.

2.2. Inclusion and exclusion criteria

Studies were included if (1) participants were older than 18 years, (2) the diagnosis was established by a standardized diagnostic tool including major depressive episode, major depressive disorder or dysthymic disorder according to Diagnostic and Statistical Manual of Mental Disorders *DSM-IV* criteria (American Psychiatric Association, 1994) or *DSM-IV-TR* criteria (American Psychiatric Association, 2000), or a depressive episode, recurrent depressive disorder or dysthymia according to the International Classification of Diseases, 10th edition criteria (World Health Organization, 1992), and (3) the sample included at least 10 participants. Randomized controlled trials, quasi-experimental studies and longitudinal observational studies were included. In case of multiple publications, the journal with the highest impact factor was considered. Comments, letters, editorials, conference reports, primary prevention studies, phase I studies, cross-sectional studies, ecological studies, and case studies were excluded.

3. Procedure

3.1. Abstract check and full text data extraction

Firstly, abstracts were checked according to the inclusion criteria. For quality assurance, 20% of the papers were randomly selected and the abstracts were double checked by another blinded reviewer (MCa). Cohen's kappa was used to estimate the level of agreement and calculated according to Fleiss and Cohen rules (Fleiss and Cohen, 1973). Secondly, full texts of included studies were read to check again inclusion criteria and eligibility for further analysis.

For the included studies the following data were extracted: study-related and demographic data of participants (e.g., sample size, gender, and diagnosis), type of interventions and instruments used as outcome measures. Again, a second reviewer (MCa) checked 10% of the papers independently.

3.2. Identification of outcome measures of treatment effectiveness

Interventions were grouped in three main categories: psychotherapy, pharmacotherapy and complementary and alternative medicine therapies (Patten et al., 2009). A combination of two or more therapies was separated for the analysis in a fourth category: “combined treatment”. Neurostimulation interventions were included within the category of complementary and alternative treatments. The outcome measures assessing effectiveness of interventions were included only if applied at least twice in the assessment process. Only the instruments validated in depression samples and used in more than three studies were taken into consideration for further analysis. The outcome measures included both clinician rated scales and patient-reported outcome instruments.

3.3. Content analysis of the functional areas included in the outcome measures

All individual items of the selected instruments were extracted. This included instruments generally assessing functioning, quality of life but also those ones that covered mainly symptomatology. It has to be noted that many instruments used to measure symptomatology contain single items that also address other areas of functioning as well. For operationalization, the items were linked to the ICF by applying the established linking rules (Cieza et al., 2005). The linking process was done by two researchers. In case of disagreement between the two researchers a structured discussion under the supervision of a third researcher was initiated to agree on the final linking. The items were grouped into 10 overarching categories based on the ICF classification. It is important to note that the current study used the ICF as a framework, but did not intend to follow precisely its hierarchical structure. Thus, if similar psychosocial difficulties were prevalent (at least 3% of all areas identified) (e.g. *maintenance of sleep, onset of sleep*), they were grouped in a single category (*sleep problems*) but not in the ICF higher level category (*global mental functions*).

Furthermore, only functional areas identified more than five times across all studies were included in the analysis. Difficulties identified more than once within an instrument were counted once for statistical analysis. Thus, difficulty in mobility, for example, represented in more than one item of SF-36 (Ware and Sherbourne, 1992), such as “*Lifting or carrying groceries*” and “*Climbing several flights of stairs*”, was counted just once within the instrument. Our goal was to identify areas covered by the instrument, not the number of times they were addressed within. After a list of functional problems was established, a frequency analysis was performed to show the percentage of the areas stratified by type of intervention.

3.4. Identifying gaps in the measurement of treatment effectiveness

The list of functional areas was compared to the ICF Core Set for depression (Cieza et al., 2004). The ICF Core Set includes 45 categories representing mental and body functions (symptomatology) and 48 from the component Activities and Participation. The comparison between our results and the ICF Core Set allowed us to identify all the functional areas that were selected as crucial for persons living with depression but not considered in the treatment effectiveness measurement process.

4. Quality assurance

The methodological quality of the included randomized clinical trials was assessed by the first four components of the Cochrane “Risk of bias” assessment tool: sequence generation, allocation concealment, blinding of assessors, and incomplete outcome data. Selective outcome reporting and other sources of bias are not demonstrated to influence validity (Higgins and Altman, 2008). Since it is impossible for many non-pharmacological studies to apply a double blind design, the blinding of assessors included only outcome assessors in masking procedures.

4.1. Statistical analyses

The data included the number of times one specific functional area was reported in a specific study type (psychotherapy, pharmacotherapy, combined treatment or alternative therapy) and the total number of functional areas reported for that intervention type. Consequently, there were different total numbers for each group (intervention type), mainly because the total number of articles for each intervention type was different. In order to analyze whether there were significantly different percentages of functional areas between the different types of interventions, a logistic regression was performed on STATA version 11 (StataCorp., 2010). Intervention type was taken as independent variable (Ref Cat = pharmacotherapy) and fitted values of the specific functional areas for each of the intervention types were dependent variables. The data were analyzed with the blogit STATA command. In total, 10 different logistic regressions for the 10 functional areas were performed. Wald test Chi-Square was used to verify if logistic regression model detected differences between the different intervention types (using the STATA ttestparm command). If Wald test indicated there were differences between the four types of interventions on a particular functional area, pairwise comparisons were run using the STATA command prtesti to find between which types of therapies the differences appeared.

5. Results

5.1. *Characteristics of studies*

The study selection process can be seen in Fig. 1. Of 2234 hits for potential inclusion through database and manual search, 247 articles were included in the final synthesis. The most frequent reason for exclusion was a non-depressed or mixed sample (52%). The rates of agreement expressed by Kappa of Cohen (Fleiss and Cohen, 1973) were 0.91 in the abstract selection and 0.85 in the selection of papers after reading the full text. A total of 71904 participants were included, the majority of whom female – 65.4%. The studies were mainly randomized controlled trials (71.7%) and included mostly outpatients diagnosed with major depressive disorder or dysthymic disorder (American Psychiatric Association, 2000).

A total of 66 interventions were identified, all of them grouped in three main categories – psychotherapies, pharmacotherapies or complementary and alternative therapies. The most common intervention within the psychotherapeutic category was CBT. Different SSRI antidepressants, especially fluoxetine, were prevalent in pharmacological studies; as for the complementary and alternative treatments, exercise therapy and St. John's wort were the most studied ones. Studies measuring combination of interventions included mostly psychotherapy as an adjunct to pharmacological treatment. Risk of bias varied among studies (0–4), as some clinical trials (12) did not meet any of the four criteria for quality assurance. We performed separate analysis excluding these 12 studies, but no significant changes were observed. There were only 59 (33%) clinical trials meeting the four criteria of quality assessment and consequently high quality. Due to the large number of studies included, full summary of the study characteristics can be found in Supplementary Appendix 1.

5.2. *Identification of outcome measures of treatment effectiveness*

In total, 27 outcome measures were identified for further analysis. The majority of the instruments were patient-reported outcome measures with the exception of HDRS and the Clinical Global Impression scale (CGI) (Guy, 1976), which are clinician-rated tools. Table 1 shows the frequency of each of the questionnaires within the three types of interventions. HDRS was the most common instrument, used in almost 30% of the included studies. In general, instruments exclusively assessing severity of symptoms were included in approximately 80% of all studies. The quality of life measures represented 14%, 15.2% and 18.8% of the overall number of instruments used in studies assessing effectiveness of psychotherapeutic, pharmacological and alternative interventions, respectively. Finally, instruments that assessed other areas of functioning (e.g. social functioning) were 7.5% in psychotherapy, 3.2% in pharmacotherapy and 5.3% in complementary and alternative treatments. More than 90% of all studies reported only total scores of the instruments.

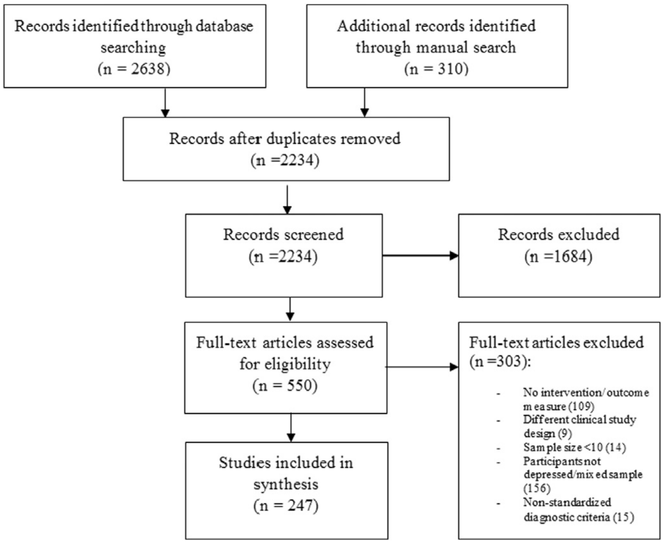


Fig. 1. Flow chart of the paper selection.

5.3. *Content analysis of the functional areas included in the outcome measures*

The total number of functional areas addressed in the instruments was 57. These areas were grouped in 10 main categories. Fig. 2 shows the frequency of each of the 10 categories in psychotherapy, pharmacotherapy, complementary and alternative treatments, and combined treatments (combination of two therapies). The category "others" consisted of functional domains such as mobility, self-care, making decisions, communication, learning and applying knowledge, each of them representing a negligible percentage to be shown as a separate group. Overall, items related to clinical symptoms like global mental functions (optimism, confidence, temperament and personality functions, psychic stability, orientation functions, etc.), specific mental functions (emotional functions, attention functions, body image, experience of self, thought functions, etc.), energy and drive (e.g. energy level, appetite) and sleep functions (maintenance of sleep, onset of sleep) accounted for about 65% of the total number of functional areas addressed within the outcome measures. Other body functions representing somatic symptoms (e.g. pain, digestive or sexual problems) represented additional 15–18% of all functional difficulties in the categories of interventions.

Other areas of functioning beyond symptomatology, such as interpersonal relationships (family and partner relationships, informal relationships with friends), recreation and leisure activities, general tasks and demands (difficulties in maintaining daily activities, domestic life, doing housework, etc.), or major life areas, such as maintaining employment or education, represented a very small percentage – 15–20% varying across the categories of interventions. The analysis showed that there were statistically significant differences in the frequencies reported for "global mental functions" and "others" regarding the type of intervention (Fig. 2). Particularly, psychotherapy was the group with the highest representation of global mental functions (18%), significantly different than the other three interventions types, whereas studies reporting alternative therapies were the second most prevalent group for this functional domain (14.6%). There are also differences in the number of times the category "others" was reported. The group of alternative interventions was significantly higher than the rest, whereas no significant differences were found among pharmacotherapy, psychotherapy and combined treatment.

5.4. *Identifying gaps in the measurement of treatment effectiveness*

Table 2 shows all functional difficulties that are included in the ICF Core Set for depression, but aren't found in any of the outcome measures of effectiveness. Categories such as problems in domestic life or community, social and civic life were not covered by any questionnaire. Many specific areas such as self-care activities

Table 1
Frequency of the instruments used as outcome measures in interventional studies.

Instrument	Author (Year)	Domain	Psychotherapy (%)[a]	Pharmacotherapy (%)	Alternative therapies (%)	Combined treatment (%)	All studies (%)
HDRS	Hamilton (1960)	Severity of depression	22.7	29.1	23.5	25.0	23.55
BDI	Beck et al. (1961)	Severity of depression	10.2	5.2	11.1	5.6	7.68
BDI-II	Beck et al. (1996)	Severity of depression	12.6	1.7	3.27	0.0	5.29
BAI	Beck and Steer (1993)	Severity of anxiety	6.1	0.0	2.0	0.0	2.73
BHS	Beck et al. (1974)	Hopelessness	1.9	0.4	0.0	0.0	0.85
CGI	Guy (1976)	Severity of symptoms	2.8	14.2	5.9	8.3	8.87
GDS	Yesavage et al. (1982)	Severity of depression	2.8	1.4	4.6	0.0	2.73
HADS	Zigmond and Snaith (1983)	Severity of depression/ anxiety	0.0	1.0	1.3	0.0	0.85
HAM-A	Hamilton (1959)	Severity of anxiety	1.4	4.8	2.0	5.6	3.24
MADRS	Montgomery and Asberg (1979)	Severity of depression	4.2	13.2	7.2	5.6	9.04
IDS	Rush et al. (1986)	Severity of depression	1.4	2.4	2.0	2.8	1.88
PHQ-9	Spitzer et al. (1999)	Diagnosis of Depression	1.4	0.4	2.0	2.8	1.37
MMSE	Folstein et al. (1975)	Cognitive impairment	0.0	1.0	1.3	5.6	0.85
SCL-90	Derogatis (1994)	Symptomatology	4.6	0.7	4.6	8.3	3.25
DAS	Weissman and Beck (1978)	Intensity of dysfunctional attitudes	1.9	0.4	2.6	2.8	1.37
EQ-5D	EuroQol Group (1990)	QOL and health outcome	0.9	1.4	2.6	2.8	1.71
GAF	Endicott et al. (1993)	Psychological functioning	2.3	0.4	2.6	0.0	1.71
IIP-64	Horowitz et al. (1988)	Interpersonal difficulties	2.8	0.7	0.7	2.8	1.19
PSQI	Buysse et al. (1989)	Sleep quality	0.5	1.0	1.3	2.8	0.85
QIDS	Rush et al. (2003)	Severity of symptoms	1.9	4.5	0.0	2.8	2.56
QLES-Q	Endicott et al. (1993)	QOL	4.2	6.6	2.6	2.8	5.46
RSES	Rosenberg (1965)	Global Self-Worth	0.9	0.0	0.7	0.0	0.51
SAS	Weissman et al. (1978)	Social functioning	1.9	0.7	0.7	0.0	0.85
SF-36	Ware and Sherbourne (1992)	Health Status	6.1	5.5	10.5	11.1	7.00
SDS	Sheehan (1983)	Disability and Impairment	0.5	1.4	1.3	2.8	1.37
WHOQOL	WHOQOL Group (1995)	QOL	2.8	1.7	3.1	0.0	2.39

HDRS – Hamilton Depression Rating Scale, BDI – Beck Depression Inventory, BAI – Beck Anxiety Inventory, BHS – Beck Hopelessness scale, CGI – Clinical Global Impression, GDS – Geriatric Depression Scale, HADS – Hospital Anxiety and Depression Scale, HAM-A – Hamilton Anxiety Rating Scale, MADRS – Montgomery Asberg Depression Rating Scale, IDS – Inventory of depressive Symptomatology, PHQ-9 – Patient Health Questionnaire-9, MMSE – Mini Mental State Examination, SCL=90, Symptom Checklist-90, DAS – Dysfunctional Attitudes Scale, GAF – Global Assessment of Functioning, IIP-64 – Inventory of Interpersonal problems, PSQI – Pittsburgh Sleep Quality Index, QIDS – Quick Inventory of Depressive Symptoms, Q-LES-Q – Quality of Life Enjoyment and Satisfaction Questionnaire, RSES – Rosenberg Self-Esteem Scale, SAS – Social Adjustment Scale, SF-36 – Short Form (36) Health Survey, SDS – Sheehan Disability Scale

[a] Percentage of the total number of questionnaires used in the studies.

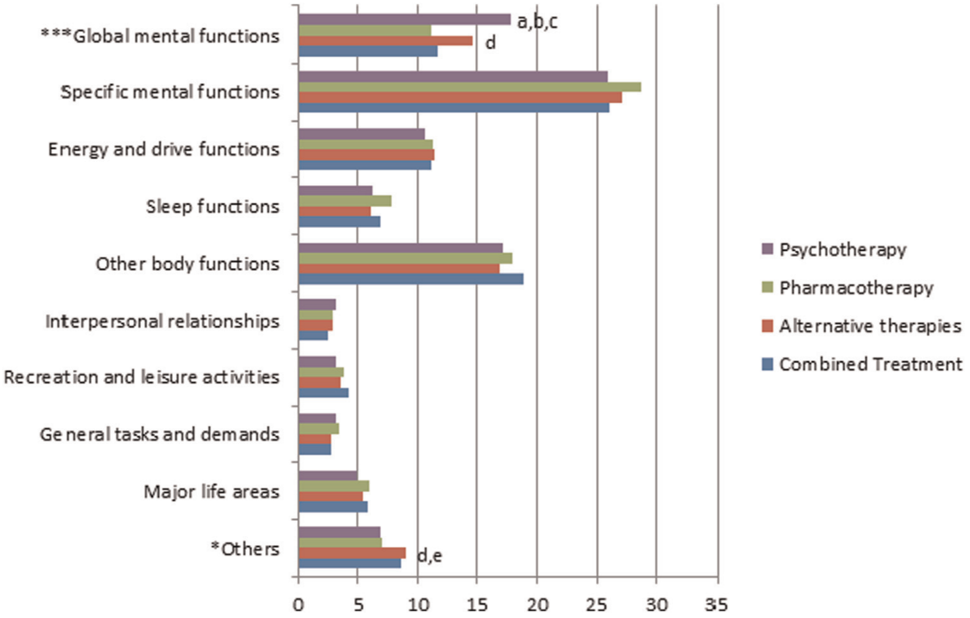


Fig. 2. Percentage of the functional areas contained in the outcome measures used in studies assessing psychotherapeutic, pharmacological, alternative or combination of interventions. Note 1: $^*p<0.05$, $^{***}p<0.001$. Note 2: Pairwise comparisons between different types of interventions: "a" psychotherapy vs pharmacotherapy, "b" psychotherapy vs alternative treatment, "c" psychotherapy vs combined treatment, "d" alternative treatment vs pharmacotherapy, "e" alternative treatment vs psychotherapy.

Table 2
Functional areas included in the ICF Core Set for depression, but not found in the outcome measures of effectiveness.

Domain	Categories	Functional areas
Mental functions (symptoms included)	Global mental functions	Intellectual functions Extraversion Agreeableness Conscientiousness
	Specific mental functions	Psychomotor functions Appropriateness of emotion Regulation of emotion Range of emotion Pace of thought Form of thought Control of thought Organization and planning Management Insight Judgement Experience of self
	Energy and drive functions	Motivation Impulse control
	Sleep functions	Amount of sleep Quality of sleep Functions involving the sleep cycle
Activities and participation (functional areas beyond symptoms)	Interpersonal relationships	Complex interpersonal interactions Relating with strangers Informal social relationships Intimate relationships
	General tasks and demands	Undertaking a single task Managing daily routine Completing the daily routine Managing one’s own activity level Handling stress
	Major life areas	Acquiring, keeping and terminating a job Basic economic transactions Complex economic transactions Economic self-sufficiency
	Others	
	Learning and applying knowledge	Watching Listening Thinking Reading Solving problems
	Communication	Receiving spoken messages Receiving non-verbal messages Speaking Producing non-verbal messages Conversation Receiving spoken messages receiving non-verbal messages speaking roducing non-verbal messages conversation
	Mobility	Using transportation Driving
	Self-care	Washing oneself Carrying for body parts Dressing Eating Drinking Looking after one's health
	Domestic life	Acquisition of goods and services Caring for household objects Assisting others
	Community, social and civic life	Community life Religion and spirituality Political life and citizenship

like dressing, eating or washing oneself, areas related to personal coping such as handling stress and solving problems, or participation restrictions like using transportation, maintaining a job, religious or political life, were not measured in any study. Some important areas related to symptomatology like regulation of emotions, motivation, or psychomotor functions were not measured either.

6. Discussion

This literature review aimed to critically examine the current way of measuring effectiveness of interventions for depression. The results are consistent with the findings of the study of Brockow et al. (2004), which reviewed the literature after the first global burden of disease study was published (Murray and Lopez, 1996). Our results show that almost 20 years after the first and more than ten years after the second burden of disease studies which specifically underlined the need for taking into account disability across all disorders, the effectiveness of all available interventions for depression is still assessed mainly in terms of reduction of clinical symptoms, whereas other areas of functioning are neglected (Murray and Lopez, 1996; World Health Organization, 2004). This is imposingly demonstrated by the fact that every study analyzed in our review applied at least one measure of severity of symptoms, but only less than 20% of the applied questionnaires addressed other areas of functioning. Similarly, the elaborate content item analysis revealed that around 80% of the areas covered by the outcome measures represented clinical symptomatology. This discordance between established research priorities and actual implementation debates the adequacy of published studies and poses the question how much do we know about the level of effectiveness of interventions for depression on vital areas of everyday life.

Another interesting point to emphasize is the contradiction between the theoretical background and the objectives of the interventions and their actual effectiveness assessment in research. In terms of pharmacological treatments, it has been postulated that improvement in specific aspects of social functioning may depend on whether antidepressant treatment targets specific noradrenaline or serotonin neurotransmitters (Dubini et al., 1997). The majority of psychotherapeutic treatments aim to develop coping strategies for solving problems and stress management, communicational skills for appropriate perception and responses to social cues, behavioral changes towards better interpersonal interactions, and skills for increasing occupational functioning (Barth et al., 2013). Cognitive behavioral therapy, for instance, which is the most commonly used psychotherapeutic approach found in this review, includes techniques developed primarily for overcoming obstacles to participating in enjoyable activities or creating coping skills in individuals for handling stress, problem solving and scheduling pleasurable experiences (Hawton et al., 1989). None of these areas, however, has been sufficiently investigated in research. Our results show that there is no difference how effectiveness of psychotherapeutic, pharmacological and alternative treatments has been measured in clinical research. Thus, the primary objectives set in the theoretical foundations of the treatments have not been considered in the measurement process.

Apart from reporting the areas addressed in studies, this is the first study to report the gaps in the measurement process. On this line, results indicate that particular areas of functioning (e.g. interpersonal relationships, general tasks and demands) are insufficiently covered by the identified instruments. Furthermore, there are crucial areas for the experience of depression like handling stress, solving problems, organization and planning, time management, keeping and terminating a job, education, participation in community, political or religious life that are not addressed by any of the analyzed outcome measures. This means that we do not have any information on the effectiveness of the interventions on these affected areas. Given their importance, this again might question the quality of evidence we possess on the effectiveness of commonly used treatments for depression in general.

This status quo might be remodeled by means of certain changes at research and clinical level. On one hand, a more comprehensive measurement in research is needed. It might be achieved by the inclusion of unique tool that should be comprehensive enough in regard to the health condition and quick to administrate if needed to be applied in a clinical setting where practitioners have limited time and resources (Wittchen et al., 2001). This option would provide comparability across studies. Another possibility could be the use of a battery of instruments, each covering a certain domain relevant for depression. However, this predominantly depends on the research study resources, as it might be again time consuming thus causing bias in the answers of the participants. A third option could be the use of particular instruments created to cover not all but at least a wide range of the major functional difficulties. The Social Adaptation Self-evaluation Scale (SASS) (Bosc et al., 1997) is an example of a developed and validated instrument, measuring problems at work, relationships with family, friends, intellectual interests, hobbies, satisfaction with performance, and ability to manage one's environment. It might be used in addition to instruments assessing reduction of symptoms. However, it has to be noted that all the three options provided above are seen through the scope of the ICF philosophy, considering all functional areas as equally important. Future research could classify all functional areas affected in depression based on their importance. Thus, an outcome measure covering the most important and relevant areas could be implemented successfully in research studies.

On the other hand, a change in intervention design in depression might be also necessary to switch the paradigm from symptom oriented therapies to more rehabilitation and functioning oriented therapies, focusing on wider range of deteriorated functions. A recently developed functional remediation intervention for bipolar disorder, for example, combining neurocognitive techniques and training with psychoeducational and problem-solving techniques, shows promising results on patients (Martinez-Aran et al., 2011). Cognitive remediation therapy designed to improve social cognition and thereby better the functioning outcomes in schizophrenic patients also shows significant results (Wykes et al., 2007). Adaptations of these therapies might be applied for depression, accelerating the functional remission of depressed individuals and alleviating wide range of difficulties.

Regardless of the chosen strategy, we recommend authors to report detailed information on specific functional areas covered by the questionnaire(s) instead of reporting the overall scores of instruments (e.g., BDI sum score). Our results show that more than 90% of the studies reported only total scores of questionnaires. Even the studies providing more detailed results were somewhat limited, as they reported changes in a broader subdomain, thus not exploring thoroughly what drove the overall score change. The limitation of reporting total score is that it mixes different concepts that have different levels of relevance and that we do not obtain information on the sequence of improvement (which area is improved first). An elaborate analysis providing detailed information on the outcome measures will enable researchers to follow the changes in particular areas over time. Furthermore, it might provide evidence on which treatments are better in improving specific areas of functioning. This information would be essential to make systematic and evidence-based treatment decisions.

7. Limitations

The current review has to be seen in light of certain limitations. First, the literature search was limited to articles published between 2005 and 2014. However, this time period was chosen because we intended to analyze the trends in measuring treatment effectiveness in depression after the publication of the last review of literature (Brockow et al., 2004). Second, articles were only selected if published in English. This could have left out relevant information published in other languages. Third, because of the wide variety of studies, we analyzed only instruments used in more than three studies included in the review. Thus, we might have omitted a comprehensive outcome measure with a broader scope. Another methodological limitation is the inclusion of trials that did not meet any quality criteria. This was done to avoid any publication bias and capture in a comprehensive way the literature on depression in its current form.

8. Conclusions

This study comprehensively review the current way of analyzing the effectiveness of interventions for depression. The findings encourage researchers to consider the consequences of choosing outcome measures in interventional studies. The effectiveness of many well recognized interventions might be overestimated considering the fact that the evidence so far has been mainly based on reduction of symptoms, whereas other relevant functional areas have been unconsidered. Future steps towards improvement include use of comprehensive assessment tools, obtainment of more detailed information from outcome measures, design of functional impairment oriented therapies, and more qualitative and expert panel studies. This information can personalize our findings by identifying the functional difficulties relevant for each therapy, thus making the treatment decision process easier and meaningful.

Acknowledgements

The authors thank Dr. Carla Sabariego for her assistance in various parts of the project. The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013/ under REA grant Agreement n°316795.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.08.035.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). American Psychiatric Association, Washington, DC.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR). American Psychiatric Association, Washington, DC.

Barth, J., Munder, T., Gerger, H., Nuesch, E., Trelle, S., Znoj, H., Juni, P., Cuijpers, P., 2013. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. PLoS Med. 10, e1001454.

Beck, A.T., Steer, R.A., 1993. Beck Anxiety Inventory Manual. Psychological Corporation, San Antonio, TX.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Beck, A.T., Weissman, A., Lester, D., Trexler, L., 1974. The measurement of pessimism: The Hopelessness Scale. J. Consult. Clin. Psychol. 42 (6), 861–865.

Bosc, M., Dubini, A., Polin, V., 1997. Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 7 Suppl. 1, S57–S70 (discussion S71-53).

Brockow, T., Wohlfahrt, K., Hillert, A., Geyh, S., Weigl, M., Franke, T., Resch, K.L., Cieza, A., 2004. Identifying the concepts contained in outcome measures of clinical trials on depressive disorders using the International Classification of Functioning, Disability and Health as a reference. J. Rehabil. Med. 36, 49–55.

Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28, 193–213.

Cieza, A., Chatterji, S., Andersen, C., Cantista, P., Herceg, M., Melvin, J., Stucki, G., de Bie, R., 2004. ICF Core Sets for depression. J. Rehabil. Med. 36, 128–134.

Cieza, A., Geyh, S., Chatterji, S., Kostanjsek, N., Ustun, B., Stucki, G., 2005. ICF linking rules: an update based on lessons learned. J. Rehabil. Med. 37, 212–218.

Chisholm, D., Sanderson, K., Ayuso-Mateos, J.L., Saxena, S., 2004. Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. Br. J. Psychiatry: J. Mental Sci. 184, 393–403.

Derogatis, L.R., 1994. SSCL-90-R: Symptom Checklist-90-R. NCS Pearson, Minnesota.

Drake, R.E., Goldman, H.H., Leff, H.S., Lehman, A.F., Dixon, L., Mueser, K.T., Torrey, W. C., 2001. Implementing evidence-based practices in routine mental health service settings. Psychiatr. Serv. 52, 179–182.

Dubini, A., Bosc, M., Polin, V., 1997. Do noradrenaline and serotonin differentially affect social motivation and behaviour? Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 7 Suppl. 1, S49–S55 (discussion S71-43).

Endicott, J., Nee, J., Harrison, W., Blumenthal, R., 1993. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol. Bull. 29, 321–326.

European Pact for Mental Health and Well-being, 2008. EU High Level Conference Brussels, Belgium 12–13th June 2008. 〈http://ec.europa.eu/health/ph_determinants/life_style/mental/docs/pact_en.pdf〉 (accessed 15.07.12.).

Group, EuroQol, 1990. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 16, 199–208.

Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., Vos, T., Whiteford, H.A., 2013. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 10, e1001547.

Fleiss, J., Cohen, J., 1973. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. Educ. Psychol. Meas. 33 (3), 613–619.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. Department of Health, Education, and Welfare, Rockville, MD, U.S.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Hawton, K., Salkovskis, P., Kirk, J., et al., 1989. Cognitive Behaviour Therapy Psychiatric Problems: A Practical Guide. Oxford Press, London.

Higgins, J.P.T., Altman, D.G., 2008. Assessing risk of bias in included studies. In: Higgins, J.P.T., Green, S., (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell, Chichester, UK (Chapter 8).

Horowitz, L.M., Rosenberg, S.E., Baer, B.A., Ureno, G., Villasenor, V.S., 1988. Inventory of interpersonal problems: psychometric properties and clinical applications. J. Consult. Clin. Psychol. 56, 885–892.

Keller, M.B., 2003. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. J. Am. Med. Assoc. 289, 3152–3160.

Martinez-Aran, A., Torrent, C., Sole, B., Bonnin, C.M., Rosa, A.R., Sanchez-Moreno, J., Vieta, E., 2011. Functional remediation for bipolar disorder. Clin. Pract. Epidemiol. Mental Health 7, 112–116.

McKnight, P.E., Kashdan, T.B., 2009. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. Clin. Psychol. Rev. 29, 243–259.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry: J. Mental Sci. 134, 382–389.

Murray, C.J.L., Lopez, A.D. (Eds.), 1996. The Global Burden of Disease. A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. GBD Series Vol. I. Harvard School of Public Health on behalf of the World Health Organization and the World Bank, Cambridge, Massachusetts, 1996.

Patten, S.B., Kennedy, S.H., Lam, R.W., O'Donovan, C., Filteau, M.J., Parikh, S.V., Ravindran, A.V., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. J. Affect. Disord. 117 (1), S5–S14.

Rosenberg, M., 1965. Society and the Adolescent Self-image. Princeton University Press, Princeton, NJ.

Rush, A.J., Giles, D.E., Schlesser, M.A., Fulton, C.L., Weissenburger, J.E., Burns, C.T., 1986. The Inventory of Depressive Symptomatology (IDS): Preliminary findings. Psychiatry Res. 18, 65–87.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatry 54, 573–583.

Sheehan, D.V., 1983. The Anxiety Disease. Scribner's, New York.

Spitzer, R.L., Kroenke, K., Williams, J.B., 1999. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. J. Am. Med. Assoc. 282, 1737–1744.

StataCorp, 2010. Stata Statistical Software: Release 11. Stata Corporation LP, College Station, Texas.

Stefos, G., Bauwens, F., Staner, L., Pardoen, D., Mendlewicz, J., 1996. Psychosocial predictors of major affective recurrences in bipolar disorder: a 4-year longitudinal study of patients on prophylactic treatment. Acta Psychiatr. Scand. 93, 420–426.

Ustun, T.B., Ayuso-Mateos, J.L., Chatterji, S., Mathers, C., Murray, C.J., 2004. Global burden of depressive disorders in the year 2000. Br. J. Psychiatry: J. Mental Sci. 184, 386–392.

Ware Jr., J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30, 473–483.

Weissman, A.N., Beck, A.T., 1978. Development and validation of the dysfunctional attitude scale. Paper presented at the Annual meeting of the Association for the Advanced Behavior Therapy, Chicago, November.

Weissman, M.M., Prusoff, B.A., Thompson, W.D., Harding, P.S., Myers, J.K., 1978. Social adjustment by self-report in a community sample and in psychiatric outpatients. J. Nerv. Mental Dis. 166, 317–326.

Group, W.H.O.Q.O.L., 1995. The World Health Organization quality of life assessment (WHOQOL): position paper from the World Health Organization. Soc. Sci. Med. 41 (10), 1403–1409.

Williams Jr., J.W., Mulrow, C.D., Chiquette, E., Noel, P.H., Aguilar, C., Cornell, J., 2000. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann. Intern. Med. 132, 743–756.

Wittchen, H.U., Holsboer, F., Jacobi, F., 2001. Met and unmet needs in the management of depressive disorder in the community and primary care: the size and breadth of the problem. J. Clin. Psychiatry 62 (Suppl. 26), S23–S28.

World Health Organization, 1992. International Classification of Diseases and Related Health Problems, 10th revision (ICD-10). World Health Organization, Geneva.

World Health Organization, 2001. International Classification of Functioning, Disability and Health (ICF). World Health Organization, Geneva.

World Health Organization, 2004. 〈http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/〉.

Wykes, T., Reeder, C., Landau, S., Everitt, B., Knapp, M., Patel, A., Romeo, R., 2007. Cognitive remediation therapy in schizophrenia: randomised controlled trial. Br. J. Psychiatry: J. Mental Sci. 190, 421–427.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1982. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. 17, 37–49.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.

Under Review in Psychological Medicine

The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: A meta-analysis

Kaloyan Kamenov [1, 2]

Conal Twomey[3]

María Cabello[1, 2]

A. Matthew Prina[4]

Jose Luis Ayuso-Mateos[1, 2, 5]*[1]

[1]*Instituto de Salud Carlos III, Centro Investigación Biomédica en Red. CIBERSAM. Madrid, Spain*
[2] *Department of Psychiatry, University Autónoma de Madrid, Madrid, Spain*
[3] *Faculty of Social and Human Sciences, University of Southampton, Southampton, UK*
[4]*Centre for Global Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK*
[5]*Instituto de investigación de la Princesa, (IIS-IP), Hospital Universitario de la Princesa, Madrid, Spain*

Financial Support

The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013/ under REA grant agreement n°316795 and from the Instituto de Salud Carlos III, Centro Investigación Biomédica en Red, CIBERSAM. Spain.

---

*[1] Corresponding author
Hospital Universitario de la Princesa
C/ Diego de León 62,
28006 Madrid, SPAIN
Phone: +34 914972716, Fax: +34 914972716
E-mail: joseluis.ayuso@uam.es

Abstract

Background: There is growing recognition of the importance of both functioning and quality of life (QoL) outcomes in the treatment of depressive disorders, but the meta-analytic evidence is scarce. The objective of this meta-analysis of randomized controlled trials (RCTs) was to determine the absolute and relative effects of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in patients with depression. **Methods:** 153 outcome trials involving 29,879 participants with depressive disorders were identified through database searching in Pubmed, PsycINFO and the Cochrane Central Register of Controlled Trials. **Results:** Compared to control conditions, psychotherapy and pharmacotherapy yielded small to moderate effect sizes for functioning and QoL, ranging from g = 0.31 to g = 0.43. When compared directly, initial analysis yielded no evidence that one of them was superior. After adjusting for publication bias, psychotherapy was more efficacious than pharmacotherapy (g = 0.21) for QoL. The combination of psychotherapy and medication performed significantly better for both outcomes when compared to each treatment alone yielding small effect sizes (g = 0.32 to g = 0.39). Both interventions improved depression symptom severity more than functioning and QoL. **Conclusion:** Despite the small number of comparative trials for some of the analyses, this study reveals that combined treatment is superior, but psychotherapy and pharmacotherapy alone are also efficacious for improving functioning and QoL. The overall relatively modest effects suggest that future tailoring of therapies could be warranted to better meet the needs of individuals with functioning and quality of life problems.

Keywords: *meta-analysis, depression, functioning, quality of life, psychotherapy, pharmacotherapy*

Introduction

A considerable number of meta-analyses published in the last decade have clearly shown that both psychological and pharmacological treatments are efficacious for reducing symptoms in depression (Cuijpers *et al.*, 2011, Cuijpers *et al.*, 2013, Spielmans *et al.*, 2011). Recent literature, however, has suggested that functioning and quality of life improvement might be equally important for people with depression as their symptom amelioration (IsHak *et al.*, 2011a, Lam *et al.*, 2015, Zimmerman *et al.*, 2006). The Canadian Network for Mood and Anxiety Treatments (CANMAT) highlighted the need for evidence-based interventions that demonstrate improvement in functioning (Lam *et al.*, 2015). From a clinical perspective, patients have prioritized functional over symptomatic outcomes and determined the return to a normal level of functioning at work, home or school as a significant factor for remission in depression (Zimmerman *et al.*, 2006). Furthermore, improvement in quality of life has been considered the ultimate outcome measure that indicates whether certain treatments have succeeded (IsHak *et al.*, 2011a).

Despite the importance given to functioning and quality of life, both dimensions remain under-researched in interventional studies (Kamenov *et al.*, 2015). The terms have been used interchangeably in previous studies, but there is agreement that these concepts are not identical (Lam *et al.*, 2015). Generally, functioning refers to one's performance in daily or social activities and QoL as one's satisfaction with these activities and perception of his/her health (IsHak *et al.*, 2002, IsHak *et al.*, 2011a).

The conclusions drawn from the few published meta-analyses on functioning are limited. A review by De Silva et al. (2013) assessed the effect of psychosocial interventions on social functioning in depression. The article, however, reported only data from low- and middle-income countries. A later meta-analysis by Renner et al. (2014) also assessed the effect of psychotherapy on social functioning. The study, however, examined only the absolute efficacy of psychological interventions and certain functional difficulties such as problems in daily activities were not considered in the assessment of functioning. On the other hand, many meta-analyses have included QoL as a secondary measure of efficacy of various interventions (Spielmans *et al.*, 2013, von Wolff *et al.*, 2012). However, research so far has been mainly fragmentary, focusing only on specific types of treatments, and there exists only one narrative systematic review analyzing the impact of pharmacotherapy and psychotherapy on QoL in depression (Ishak *et al.*, 2011b).

To our knowledge, there is no meta-analysis that comprehensively assesses the efficacy of interventions primarily aimed at depression treatment on functioning and QoL in depression. Determining this efficacy would have important implications for clinical decisions and policy making in terms of provision of treatments in primary and secondary mental health services. Therefore, this meta-analysis of randomized controlled trials aimed to assess 1) the effects of psychotherapy and pharmacotherapy compared to control conditions on functioning and quality of life; 2) the effect of both when compared directly, and 3) the effect of their combination against either one. Additional sensitivity, subgroup and meta-regression analyses were performed.

Methods

Methods and results are presented according to the PRISMA statement for reporting systematic reviews (Moher *et al.*, 2010).

Search strategy

A systematic literature search combining the terms depressive disorder OR depression OR major depressive disorder (Mesh terms) AND functioning OR disability OR disability evaluation OR disabled persons OR sick leave OR activities of daily living OR leisure activities OR quality of life AND treatment OR intervention OR clinical trial OR therapy (MeSH terms, key words and text words) was performed in Pubmed, PsycINFO and the Cochrane Central Register of Controlled Trials. In the first two databases, the relevant option was selected to limit the search to Randomized Controlled Trials. Although non-randomized controlled trials provide valuable information in terms of ecological validity, RCTs minimize the influence of errors and bias on findings and offer the most rigorous method of determining whether a cause-effect relation exists between treatment and outcome (Sibbald and Roland, 1998, Spring, 2007). Their sole inclusion safeguarded the validity of the findings and ensured methodological consistency. The search was performed in June 2015. The search was restricted by language (only articles published in English were considered) and age (only participants older than 18). In addition, the references of published meta-analyses and relevant articles were also checked.

Study selection

The review included all randomized controlled trials that compared 1) psychotherapy or pharmacotherapy against treatment as usual (TAU), placebo, waiting list (WL) or other control group: 2) psychotherapy against pharmacotherapy; or 3) the combination of psychotherapy and pharmacotherapy against either one. Psychotherapy was defined by the American Psychiatric Association as “the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable" (Norcross, 1990). More specifically, different psychotherapeutic approaches were defined according to definition previously developed in comparative meta-analyses (Cuijpers *et al.*, 2008a). All studies had to report at least one validated outcome measure assessing functioning (any difficulty experienced in maintaining daily activities or participation in social life (Lam *et al.*, 2015) or quality of life (one's satisfaction with these activities and perception of his/her health (IsHak *et al.*, 2002, World Health Organization Quality of Life Group, 1997). Information on symptom severity was extracted only from validated instruments that explicitly measured symptoms of depression (e.g. Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The diagnosis of depression had to be established by a standardized diagnostic interview according to ICD or DSM criteria (American Psychiatric Association, 1980, 1987, 2000, World Health Organization, 1992). Studies including bipolar or schizoaffective disorder or reporting results from maintenance or continuation therapies were excluded. The abstract screening was done by one researcher (K.K.) and a random selection of 20% of the abstracts was double checked independently by another two researchers (M.C. and C.T.).

Data extraction and quality assessment

Data from the selected studies were extracted by one researcher (K.K) and checked for consistency independently by two other researchers. Divergences were resolved by consensus. In case of missing data, authors were contacted. When results from more than one outcome measure assessing the same concept (either functioning or QoL) were available in a study, data from all were extracted and combined as a mean effect size. To avoid double counting, the effects of different intervention arms representing the same generic intervention (e.g. GP-delivered psychotherapy and clinician-delivered psychotherapy) included in a single study were averaged and entered once in the analysis (Senn, 2009). SF-36 (Ware and Sherbourne, 1992) was considered as an outcome measure of quality of life (Ishak *et al.*, 2011b) but if a study reported post assessment score on the social functioning subdomain, it was included separately as an outcome measure of functioning. Global measures of functioning were considered only if they included domains of social functioning and daily activities (De Silva *et al.*, 2013). Data on effect estimates were extracted at post-assessment. The instruments were patient self-assessments and clinician-rated tools.

Four criteria of the Cochrane Collaboration risk of bias tool were used for assessing methodological quality of the studies —sequence generation, allocation concealment, blinding of assessors, and incomplete outcome data (Higgins *et al.*, 2011). It is impossible for the majority of psychotherapeutic designs to employ a double blind design, therefore blinding of assessors in these studies was adapted to include only outcome assessors in masking procedures.

Statistical analyses

Statistical analyses were performed using the program Comprehensive Meta-Analysis, version 2.0. The effect size for each individual meta-analysis was calculated, aggregating the pooled difference between the two groups of treatments at the end of the intervention. Hedges' *g* was preferred as an effect estimate because of its capability to provide a better effect estimate for small sample sizes (Deeks *et al.*, 2008). The magnitude of the effect size may be interpreted as small (0.2), medium (0.5), and large (0.8) (Cohen, 1988). We used a random effects meta-analysis model which assumes that variance in observed effects is explained not only by sampling variability (as in fixed effect analysis) but also real differences in treatment effects resulting from heterogeneity in study populations, intervention delivery, follow-up length and other factors (Riley *et al.*, 2011). To test the heterogeneity, Higgins' I^2 statistic was calculated. A value of 0% indicates no heterogeneity, 25% indicate low heterogeneity, 50% - moderate heterogeneity, and 75% high heterogeneity (Higgins *et al.*, 2003). Publication bias was assessed in each of the meta-analyses by visual inspection of the funnel plots and the trim-and-fill procedure to analyze the changes after the accounting for publication bias (Duval and Tweedie, 2000). In addition to the analyses on functioning and QoL, we performed a series of individual meta-analyses to assess the effect of psychotherapy, pharmacotherapy and their combination on depression symptom severity. The outcome was a reduction of symptom severity according to the instruments' scores.

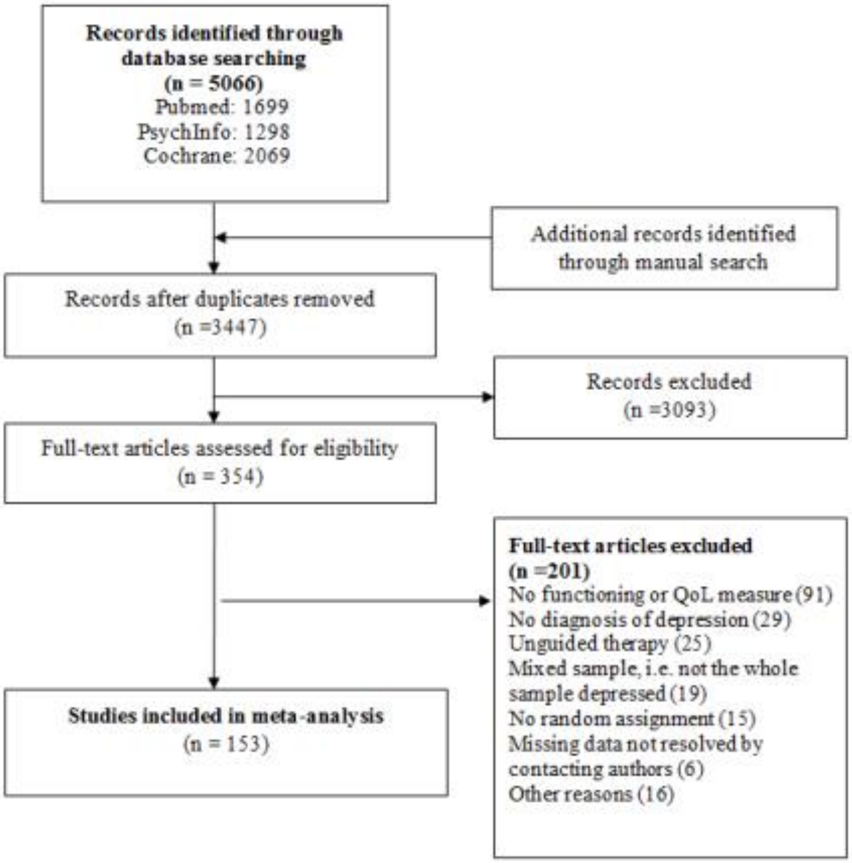
In order to check the robustness of the results, sensitivity analyses were conducted. First, the main analyses were repeated after exclusion of low quality studies. Then, to test whether one single outcome measure had a strong impact on the overall effect size, a series of sensitivity analyses were performed after the exclusion of each of the instruments. Lastly, the effect size was calculated for studies with a treatment duration of 3 months or less and compared with studies with a treatment duration of more than 3 months. The results of the sensitivity analyses were considered "consistent" with the primary analysis if there was no change in the magnitude of the effect size (from high to moderate, from moderate to small, etc.). Since the selected studies were heterogeneous with respect to comparator groups, study populations, included interventions and outcome measures, series of subgroup analyses were performed. We examined whether there were differences in terms of age groups – adults (18-65 years) vs. older adults (65+), psychotherapies (Cognitive Behavioral Therapy [CBT], Interpersonal Therapy [IPT], Problem Solving Therapy [PST], others), medication (SSRIs, SNRIs, TCAs, others), control groups (WL, TAU, Placebo, others), outcome measures, duration of treatment (3 months vs. more than 3 months) and types of depression (Major Depressive Disorder, Dysthymia, Subthreshold Depression, others). Long-term effects were not assessed, because a very small number of studies reported any follow-up data and the reported outcomes differed widely between studies. Follow-up periods differed significantly (e.g. 3 months vs 12 months) and the nature of the follow-ups was different: some studies reported only naturalistic outcomes, whereas others delivered booster sessions and maintenance treatments during the follow-up period. A mixed effect model, combining a random-effects model within subgroups and a fixed-effect model across subgroups, was used. Multivariate meta-regression analyses were conducted using Stata 12.0 for Windows (Stata Corporation, USA). In these analyses the outcome variable was the weighted effect sizes of psychotherapy, pharmacotherapy or their combination on functioning and QoL at posttreatment. The predictors were severity of depression (effect size at posttreatment), number of psychotherapeutic sessions (where possible), duration of treatment in weeks, duration of trial in weeks, and year of publication. All the predictors used were continuous variables. The regression coefficient obtained from the meta-regression analysis revealed how the intervention effect changes with a unit increase in the predictors and whether there was a linear relationship between the intervention effect and the predictors.

Results

Study selection

After removal of duplicates, 3447 articles were identified for abstract check. Of these, 354 were selected for full-text screening. 153 articles met the inclusion criteria and were included in the analyses. The main reasons for exclusion were lack of functional or quality of life measures and non-standardized diagnosis of depression. Some studies included outcome measures for both functioning and QoL, resulting in their inclusion in more than one analysis. The selection process can be seen in Figure 1.

Figure 1. Flow chart of Study Selection



Description of included studies

Selected characteristics of the studies can be seen in Table 1. A total of 29,879 participants were included in all trials. The majority of the participants were adults aged between 18 and 65 years. 60.1% of all individuals had major depressive disorder. The duration of the trials ranged from four weeks to one year. The most common psychotherapeutic intervention found in the literature was CBT, based on two specific tasks - cognitive restructuring and behavioral approach (such as exposure and response prevention). Interpersonal therapy - a structured therapy with a predominant focus on addressing interpersonal issues - was also commonly used in studies. The number and format of psychotherapeutic sessions differed across studies, ranging between 4 and 20, weekly and biweekly, individual and group sessions. We defined pharmacotherapy as any treatment by means of pharmaceutical drugs, e.g. antidepressants. The most frequently used drug in the studies was duloxetine. The dosage given to participants varied depending on the type of drug and the duration of the trials.

In terms of instruments for measuring functioning, Sheehan Disability Scale (SDS) (Sheehan, 1983) and Social Adjustment Scale (SAS) (Weissman et al., 1978) were the most commonly used ones, as for QoL – Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993) and SF-36. The majority of the trials were conducted in USA, UK or The Netherlands. The quality of the studies varied. There were 47 trials (30.7%) meeting all four quality criteria, whereas 75 studies (49%) were missing two or more components. A full table including all study characteristics and references of the included articles can be found in Supplementary Material 1.

Table 1. Selected characteristics of the included studies

Characteristic	N (studies)	%
Diagnosis		
MDD	92	60.1
Dysthymia	22	14.4
Subthreshold Depression	10	6.5
Other	29	18.9
Target Group		
Adults	120	78.4
Older Adults	15	9.8
Women	18	11.8
Type of Psychotherapy		
CBT	31	31.3
IPT	17	17.2
PST	9	9.1
Other	42	42.4
Type of pharmacotherapy		
SSRIs	35	37.6
SNRIs	31	33.3
TCAs	19	20.4
Other	8	8.6
Study Quality		
≤2	75	49
≥3	78	51
Country		
USA	71	46.4
UK	28	18.3
Netherlands	11	7.2
Others	45	29.4

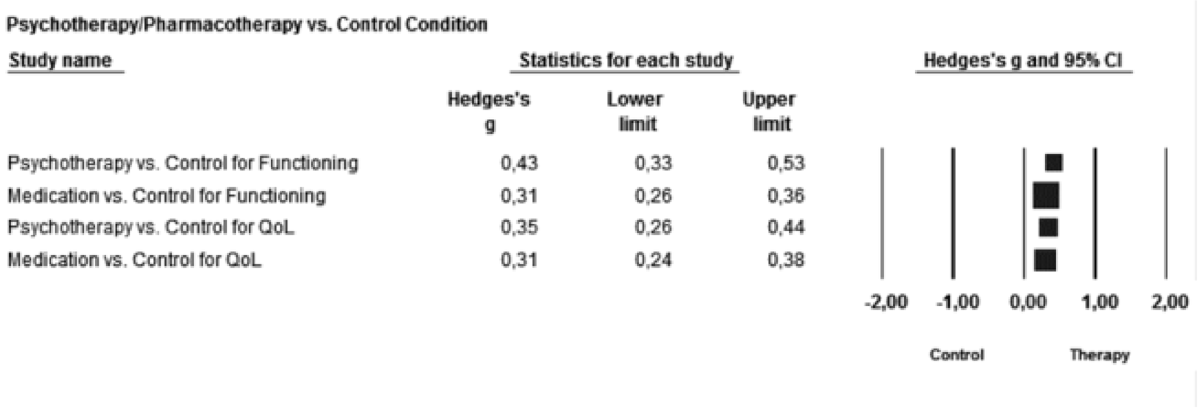
Psychotherapy and pharmacotherapy vs. control condition

Figure 2 provides information on the total effects of each of the 4 individual meta-analyses (full details on individual studies are available in Supplementary Material 2A and 2B). When compared to control conditions, both psychotherapy and pharmacotherapy had small to moderate effects on functioning, with slight superiority of psychotherapy. The mean effect of psychotherapy on functioning resulting from 52 comparisons was g=0.43 (95% CI 0.33-0.54; I^2=74.94, 95% CI 67.24-80.27). After adjusting for publication bias, the effect size decreased to

0.35 (95% CI 0.24-0.46). For pharmacotherapy, the 53 comparisons yielded an effect of *g*= 0.31 (95% CI 0.26-0.36; *I*²=64.91, 95% CI=51.66-73.21). After adjusting for publication bias, the effect size decreased to 0.27 (95% CI 0.21-0.32).

For quality of life, both psychotherapy and pharmacotherapy yielded small effect sizes. The 37 comparisons yielded a mean effect of psychotherapy *g*=0.35 (95% CI 0.26-0.44; *I*²=68.24, 95% CI 53.74-76.65). The effect of pharmacotherapy coming from 33 studies was *g*=0.31 (95% CI 0.24-0.38; *I*²=81.18, 95% CI 74.25-85.55).

Figure 2. Total standardized effect sizes (Hedges' g) of psychotherapy and pharmacotherapy against control condition for functioning and QoL.



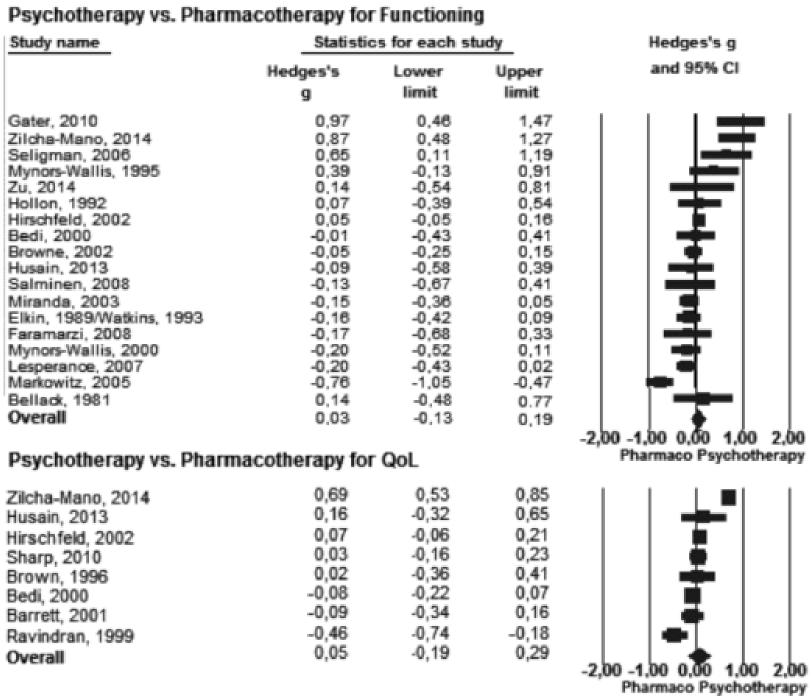
Psychotherapy/Pharmacotherapy vs. Control Condition

Study name	Hedges's g	Lower limit	Upper limit
Psychotherapy vs. Control for Functioning	0,43	0,33	0,53
Medication vs. Control for Functioning	0,31	0,26	0,36
Psychotherapy vs. Control for QoL	0,35	0,26	0,44
Medication vs. Control for QoL	0,31	0,24	0,38

Psychotherapy vs. pharmacotherapy

For both functioning and quality of life, there was no significant difference between therapies. In terms of functioning, the mean effect size was 0.03 (95% CI -0.13-0.19; *I*²=77.85, 95% CI 63.98-84.79) in favor of psychotherapy (Figure 3). After adjusting for publication bias, Hedges' *g* was still insignificant, but increased substantially to 0.12 (95% CI -0.06-0.30) in favor of psychotherapy. For quality of life, the effect size was 0.05 (95% CI -0.19-0.29; *I*²=90.72, 95% CI 84.47-93.71) in favor of psychotherapy. After adjusting for publication bias the effect size was small, but significant in favor of psychotherapy (*g*=0.21, 95% CI 0.01-0.43).

Figure 3. Standardized effect sizes (Hedges' g) of psychotherapy against pharmacotherapy on functioning and QoL



Psychotherapy vs. Pharmacotherapy for Functioning

Study name	Statistics for each study		
	Hedges's g	Lower limit	Upper limit
Gater, 2010	0,97	0,46	1,47
Zilcha-Mano, 2014	0,87	0,48	1,27
Seligman, 2006	0,65	0,11	1,19
Mynors-Wallis, 1995	0,39	-0,13	0,91
Zu, 2014	0,14	-0,54	0,81
Hollon, 1992	0,07	-0,39	0,54
Hirschfeld, 2002	0,05	-0,05	0,16
Bedi, 2000	-0,01	-0,43	0,41
Browne, 2002	-0,05	-0,25	0,15
Husain, 2013	-0,09	-0,58	0,39
Salminen, 2008	-0,13	-0,67	0,41
Miranda, 2003	-0,15	-0,36	0,05
Elkin, 1989/Watkins, 1993	-0,16	-0,42	0,09
Faramarzi, 2008	-0,17	-0,68	0,33
Mynors-Wallis, 2000	-0,20	-0,52	0,11
Lesperance, 2007	-0,20	-0,43	0,02
Markowitz, 2005	-0,76	-1,05	-0,47
Bellack, 1981	0,14	-0,48	0.77
Overall	0,03	-0,13	0,19

Psychotherapy vs. Pharmacotherapy for QoL

Study name	Hedges's g	Lower limit	Upper limit
Zilcha-Mano, 2014	0,69	0,53	0,85
Husain, 2013	0,16	-0,32	0,65
Hirschfeld, 2002	0,07	-0,06	0,21
Sharp, 2010	0,03	-0,16	0,23
Brown, 1996	0,02	-0,36	0,41
Bedi, 2000	-0,08	-0,22	0,07
Barrett, 2001	-0,09	-0,34	0,16
Ravindran, 1999	-0,46	-0,74	-0,18
Overall	0,05	-0,19	0,29

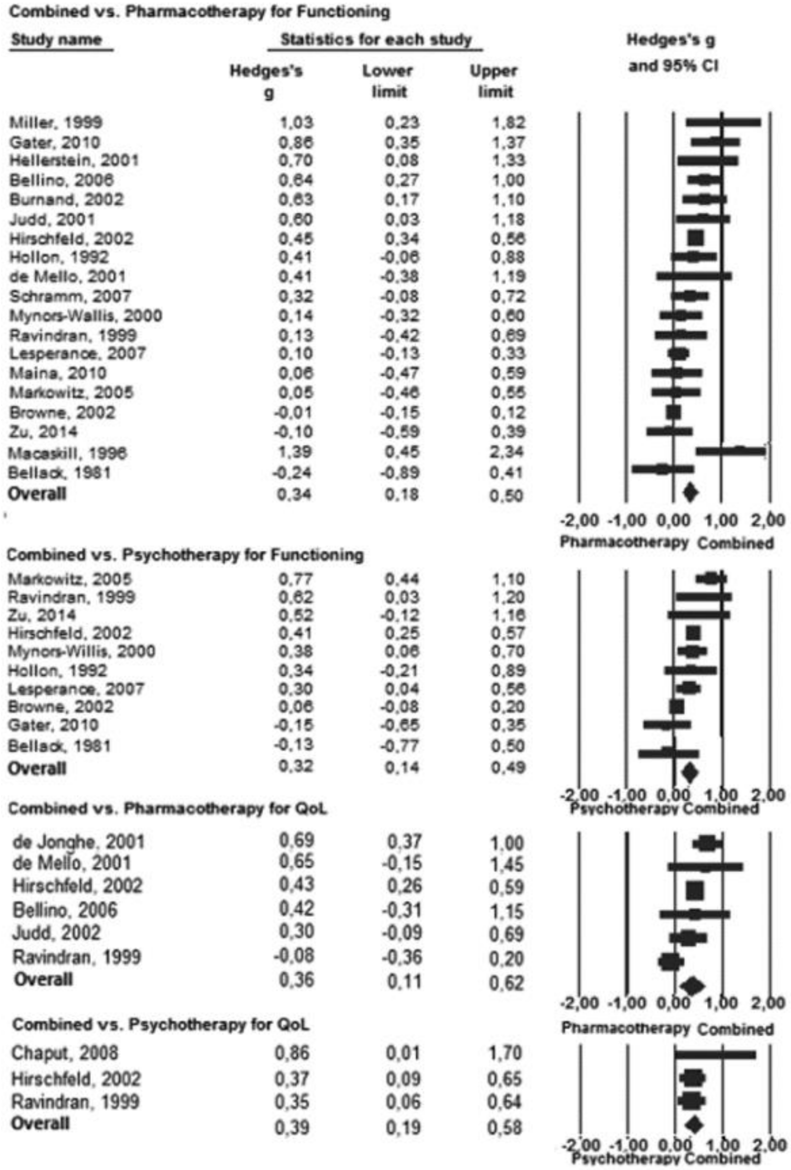
Combination of psychotherapy and pharmacotherapy vs. either one

The effects of the direct comparisons between combination of psychotherapy and pharmacotherapy against either one on functioning or quality of life are presented in Figure 4. In all four analyses, the combined treatment was significantly superior to each treatment alone yielding small effect sizes. For functioning, the 19 comparisons between combined treatment and pharmacotherapy alone resulted in effect size of *g*=0.34 (95% CI 0.18-0.50; I^2=69.51, 95% CI 47.22-79.85) in favor of combined treatment. When combined treatment was compared to psychotherapy alone in 10 studies, the analysis yielded an effect size of 0.32 (95% CI 0.14-0.49; I^2=66.98, 95% CI 21.02-81.43).

Six studies compared combined treatment against pharmacotherapy and three against psychotherapy on QoL. This weakened the power of the analysis. Compared to medication, combined treatment was significantly more efficacious (*g*=0.36, 95% CI 0.11-0.62;

*I*²=66.91, 95% CI 0.00-84.11). The studies comparing combined treatment with psychological interventions yielded an effect size of 0.39 (95% CI 0.19-0.58) in favor of combined treatment.

Figure 4. Standardized effect sizes (Hedges' g) of combined treatment against psychotherapy and medication alone on functioning and QoL



Combined vs. Pharmacotherapy for Functioning

Study name	Hedges's g	Lower limit	Upper limit
Miller, 1999	1,03	0,23	1,82
Gater, 2010	0,86	0,35	1,37
Hellerstein, 2001	0,70	0,08	1,33
Bellino, 2006	0,64	0,27	1,00
Burnand, 2002	0,63	0,17	1,10
Judd, 2001	0,60	0,03	1,18
Hirschfeld, 2002	0,45	0,34	0,56
Hollon, 1992	0,41	-0,06	0,88
de Mello, 2001	0,41	-0,38	1,19
Schramm, 2007	0,32	-0,08	0,72
Mynors-Wallis, 2000	0,14	-0,32	0,60
Ravindran, 1999	0,13	-0,42	0,69
Lesperance, 2007	0,10	-0,13	0,33
Maina, 2010	0,06	-0,47	0,59
Markowitz, 2005	0,05	-0,46	0,55
Browne, 2002	-0,01	-0,15	0,12
Zu, 2014	-0,10	-0,59	0,39
Macaskill, 1996	1,39	0,45	2,34
Bellack, 1981	-0,24	-0,89	0,41
Overall	0,34	0,18	0,50

Combined vs. Psychotherapy for Functioning

Study name	Hedges's g	Lower limit	Upper limit
Markowitz, 2005	0,77	0,44	1,10
Ravindran, 1999	0,62	0,03	1,20
Zu, 2014	0,52	-0,12	1,16
Hirschfeld, 2002	0,41	0,25	0,57
Mynors-Willis, 2000	0,38	0,06	0,70
Hollon, 1992	0,34	-0,21	0,89
Lesperance, 2007	0,30	0,04	0,56
Browne, 2002	0,06	-0,08	0,20
Gater, 2010	-0,15	-0,65	0,35
Bellack, 1981	-0,13	-0,77	0,50
Overall	0,32	0,14	0,49

Combined vs. Pharmacotherapy for QoL

Study name	Hedges's g	Lower limit	Upper limit
de Jonghe, 2001	0,69	0,37	1,00
de Mello, 2001	0,65	-0,15	1,45
Hirschfeld, 2002	0,43	0,26	0,59
Bellino, 2006	0,42	-0,31	1,15
Judd, 2002	0,30	-0,09	0,69
Ravindran, 1999	-0,08	-0,36	0,20
Overall	0,36	0,11	0,62

Combined vs. Psychotherapy for QoL

Study name	Hedges's g	Lower limit	Upper limit
Chaput, 2008	0,86	0,01	1,70
Hirschfeld, 2002	0,37	0,09	0,65
Ravindran, 1999	0,35	0,06	0,64
Overall	0,39	0,19	0,58

Effect of psychotherapy and pharmacotherapy on depressive symptoms

Psychotherapy showed a better result (*g*=0.60, 95% CI 0.51-0.68; *I*²=80.15, 95% CI 75.53-83.52*)* than pharmacotherapy (*g*=0.33, 95% CI 0.29-0.38; I²=54.37, 95% CI 35.77-65.71*)* when both interventions were compared to control condition. After adjusting for publication bias, the effect of psychotherapy dropped to *g*=0.45, whereas the effect of pharmacotherapy remained similar (*g*=0.30). When both treatments were compared directly, there was no statistically significant difference: *g*=-0.03 (95% CI -0.15-0.10) in favor of medication. The combination of treatments was superior to psychotherapy and pharmacotherapy alone, yielding small effect sizes- *g*=0.30, (95% CI 0.16-0.45) and *g*=0.34 (95% CI 0.18-050), respectively.

Sensitivity and subgroup analyses

The sensitivity analyses revealed some major differences in the effects of psychotherapy, pharmacotherapy and their combination on functioning and QoL according to the duration of the interventions applied. When psychotherapy was compared directly to medication on QoL, the trials with three month or less treatment duration yielded an effect of g=-0.08 (95% CI -0.26-0.09) in favor of medication, whereas trials with a treatment duration of more than 3 months showed superiority of psychotherapy (g=0.26, 95% CI -0.24-0.76). The same applied for combined treatment against pharmacotherapy for QoL (g=0.22, 95% CI -0.12-0.56 vs. g=0.64, 95% CI 0.37-0.92 respectively). The subsequent subgroup analyses comparing the duration of treatment, however, found no significant differences among studies. This might be due to low power because of the low number of studies included in the analyses.

Furthermore, sensitivity analyses were performed after the exclusion of low quality studies. For all analyses we found small deviations of the effect sizes, which did not affect the magnitude of the effect estimates. However, subgroup analyses were conducted to compare high quality (meeting three or four components of the Cochrane risk of bias tool) to low quality (missing two or more components). Results revealed significant changes only in studies comparing pharmacotherapy to control conditions on functioning (high-quality studies – g=0.26, 95% CI 0.21-0.31 vs. low quality – g=0.36, 95% CI 0.28-0.44, p=.05) and QoL (high quality g=0.22, 95% CI 0.11-0.33 vs. low quality g=0.36, 95% CI 0.27-0.45 p<.05). Lastly, to investigate the impact of individual outcome measures on the overall effect sizes, we conducted a series of sensitivity analyses. Here, we excluded one instrument at a time and examined consequent deviations in effect sizes. For all analyses, we found small deviations of the effect sizes of no more than 0.10, which indicated that no individual outcome measure had a strong impact on the overall effect size. The subsequent subgroup analyses comparing grouped studies according to the instruments used did not show any significant differences across subgroups.

Differences in the effects of psychotherapy compared to TAU, WL or placebo on functioning and QoL were also assessed in subgroup analyses. The effect of psychotherapy on functioning was significantly higher (p<.05) in studies with waiting list controls (g=0.61, 95% CI 0.40-0.81) than in studies with TAU (g=0.36, 95% CI 0.24-0.48). The effect size of studies comparing psychotherapy to waiting list (g=0.47, 95% CI 0.34-0.59) on QoL was significantly higher (p<.05) than studies with TAU (g=0.34, 95% CI 0.23-0.45) or placebo controls (g=0.20, 95% CI 0.03-0.37). Similar subgroup analyses could not be performed for pharmacotherapy, as 95% of the studies used placebo controls. Furthermore, clinician-rated scales were compared to self-rated tools. Studies applying clinician-rated tools yielded slightly higher effect sizes in all analyses performed, but statistically significant differences were not found. Regarding age groups, only studies comparing pharmacotherapy to control condition for QoL revealed significant difference between age groups (g=0.35, 95% CI 0.27-0.42 for adults vs. g=0.16, 95% CI 0.04-0.27 for older adults). The rest of the subgroup analyses did not reveal any significant differences across subgroups for depression type (Major Depressive Disorder, Dysthymia, Subthreshold Depression, others), type of psychotherapy - CBT, IPT, PST, or others, or type of medication – SSRIs, SNRIs, TCAs, or others. All subgroups were directly compared to each other, or each subgroup was compared to the other subgroups pooled. All subgroup analyses are available upon request.

Meta-regression analyses

Multivariate meta-regression analyses assessing potential predictors were performed. The effect size of depression severity was a significant predictor of the effects of psychotherapy and pharmacotherapy on functioning (B=0.59, 95% CI=0.42-0.76, p<.001 and B=0.94, 95% CI=0.59-1.29, p<.001, respectively) and Qol (B=0.35, 95% CI=0.1-0.61, p<.01 and B=0.94, 95% CI=0.59-1.30, p<.001) when they were compared to control conditions, and when pharmacotherapy was compared directly to psychotherapy (B=29.55, 95% CI= 5.83-53.27, p<.05) and combined treatment (B=0.001, 95% CI=0.0004-0.002, p<.01) for functioning. This indicates when symptom severity is reduced, the effect size of psychotherapy and pharmacotherapy on improving functioning and QoL increases. The remaining predictors—number of sessions, duration of treatment, and duration of trial—were not significant in any of the meta-regression analyses we performed. Number of sessions (B=0.02, 95% CI=0.09-0.60, p<.05) and year of publication (B=0.001, 95% CI=0.0003-0.002, p<.01) were found significant only when the effect of psychotherapy on QoL was compared to control conditions. This indicated that the effect size of psychotherapy on QoL increases with higher number of psychotherapeutic sessions and in recent publications. All analyses can be found in supplementary file 4.

Discussion

This meta-analysis was the first to systematically assess the effects of psychotherapy, pharmacotherapy and their combination on improvements in functioning and QoL in depressive disorders. The study demonstrates that the combination between psychotherapy and pharmacotherapy perform significantly better than each intervention alone for both outcomes. Psychotherapy and pharmacotherapy alone are also efficacious for improving functioning and QoL, although showing only small to moderate effects. When compared directly, in initial analysis there was no significant difference between the interventions. After adjusting for publication bias psychotherapy was more efficacious than pharmacotherapy for QoL.

Our results are consistent with the two previously published meta-analyses on psychotherapy for social functioning. Both Renners et al. (2014) and De Silva et al. (2013) found effect sizes of *g*=0.46 in favor of psychotherapy over control condition, which was similar to the result obtained in this study – 0.43. Even though psychotherapy showed slightly superior absolute effects to medication on both functioning and QoL, it has to be noted that the great majority of included pharmacological studies involved random assignment to a blinded control condition as opposed to the psychological trials, comparing interventions to WL or TAU control groups. It has been argued that awareness of treatment assignment might produce expectancy effects in the intervention group and despair in the control group, leading to inflated effect sizes in favor of psychotherapy. On the other hand, assignment to a blinded condition controls for expectancy effects and induction of hope, thus suggesting eventual underestimation of the effects of medication compared to psychotherapy (Gaudiano and Herbert, 2005). Nonetheless, a recent meta-analysis by Cuijpers et al. (2015) comparing pharmacological studies involving or missing double blind condition to psychotherapy did not find any difference in the effects of both groups.

We compared the effect of both interventions on functioning and QoL but no significant differences were found. This is consistent with previous meta-analytic evidence on depressive symptoms, where no superiority was found for any of the intervention types (Cuijpers *et al.*, 2013). Still, when studies were adjusted for publication bias, psychotherapy was slightly better for improving functioning (*g*=0.12) and statistically superior than pharmacotherapy on quality of life (*g*=0.21). These results, although suggesting the slight superiority of psychological over antidepressant treatment for functioning and QoL, are not robust enough to suggest priority when clinical or policy decisions are made. There is no clear economic evidence that psychotherapy should be a preferable treatment choice compared to pharmacotherapy (Bosmans *et al.*, 2008). However, a recent meta-analysis reveals a strong patient preference for psychological treatment over medication (McHugh *et al.*, 2013). Moreover, evidence states that the majority of people expressing personal preference for psychological therapy choose not to get treated at all rather than receive medication (Layard *et al.*, 2007). Alongside the benefits of pharmacotherapy for depression, it is also worth taking into account that potential side-effects and adverse events related to the use of medication may have a detrimental impact on functioning and QoL. A review by Kelly et al. (2008) showed that people with depression experience diminished quality of life related to troublesome side effects. Further research is needed to investigate the role of side effects in the efficacy of interventions for depression. Even though the number of studies directly comparing psychotherapy and pharmacotherapy was not very high, our results warrant future research to determine the economic costs and benefits of eventual enhanced provision of psychotherapeutic treatment.

The subgroup analyses found higher effect estimates for psychotherapy against waiting list compared to TAU and placebo for functioning and QoL. This finding was somewhat expected and consistent with previous meta-analyses for depression (Cuijpers *et al.*, 2008b). Waiting list control conditions involve no actual treatment and thus positive outcomes for psychotherapy are relatively easy to attain. Comparison to treatment as usual is more demanding, because it involves usual care provided in health care settings and the effect estimate shows the true additional benefit of psychotherapy on the outcome. Although not to a significant level, we found that studies applying clinician-rated scales yielded slightly higher effect sizes than studies that relied on self-rated tools. The absence of significance may be partly explained by an absence of power – only a small number of studies used clinician-rated tools. Tentatively, this trend is in line with the results of previous psychotherapy meta-analyses indicating that clinician-rated instruments are associated with higher effect-sizes of functioning and depressive symptom severity (Cuijpers *et al.*, 2010, Renner *et al.*, 2014). In the absence of a gold standard measure for functioning (Lam *et al.*, 2015, Madden *et al.*, 2015), inclusion of both types of outcome measures may be warranted to facilitate comprehensive assessments in future meta-analyses.

Psychotherapy and pharmacotherapy showed higher effect sizes on reducing depressive symptoms although there was a strong indication for publication bias. When the effects of psychotherapy and pharmacotherapy on depressive symptoms were compared to control conditions, psychotherapy showed better results (g=0.60 vs. g=0.33, respectively). This result, however, has to be considered with caution, because in studies directly comparing both interventions, we did not find a significant difference between the interventions (g=-0.03). Moreover, a previous meta-analysis (Cuijpers *et al.*, 2013) found no superiority of one intervention over another. Future meta-analyses of comparative outcome studies should shed more light on potential differences in efficacy between psychotherapeutic and pharmacological treatments. Such investigations should also take into account patient preferences and costs.

The results from the meta-regression analysis suggest that functioning and QoL improve when symptom severity improves, but which is the leading factor is still unknown. Previous research suggests that functional recovery appears later than the symptomatic one and certain level of impairment continues even after the symptomatology is ameliorated, and that depressive symptoms and QoL do not share high proportion of common variance (Coryell *et al.*, 1993, Trompenaars *et al.*, 2006). The residual functional impairment has been found to evoke relapse and recurrences (Vittengl *et al.*, 2009); therefore functioning and QoL should be directly targeted in the response and remission criteria for a more comprehensive assessment of treatment efficacy. There are already steps in this direction. Individual Burden of Illness Index for depression was created to measure treatment impact and recovery in depression by incorporating symptom severity, functioning, and quality of life outcomes (Cohen *et al.*, 2013). Zimmerman et al. (2014) validated the Remission from Depression Questionnaire, including different domains of functioning and QoL along with symptomatology. However, all attempts for implementation of such criteria are still in their infancy and future research is warranted.

The present meta-analysis demonstrates that the combination of psychotherapy and pharmacotherapy is significantly better than any of the treatments alone for both functioning and QoL. The number of studies comparing treatments for QoL was limited, but still our result has an important clinical implication for primary and secondary mental health professionals when choosing their treatment lines. Recent data showing the trends in treatment of depression report decrease in the use of combined treatment and psychotherapy and a substantial increase in the prescription of antidepressants (Gemmill *et al.*, 2008, Marcus and Olfson, 2010). This might be driven by various factors such as availability of resources in terms of money and personnel. However, a recent analysis by Sado et al. (2009) shows that combined therapy for depression appears to be cost-effective from health-care system and social perspective. More cost effectiveness and comparative long-term data on combined treatment is needed (McAllister-Williams, 2006).

This study has to be seen in light of certain limitations. First, half of the included trials had low quality. This questions the robustness of the results. However, the sensitivity and subgroup analysis we performed did not reveal significant differences in the effects between high and low quality studies. Second, for some of the individual analyses the number of studies was not large enough to allow for generalizability of results. Furthermore, mainly overall improvements in functioning and quality of life were assessed. There was a lack of domain-specific reporting that could have provided information on the effects of interventions on specific areas of functioning and QoL. This meta-analysis was based on study-level data. Individual patient level meta-analysis based on original datasets of the included studies could have revealed differences among first cases of depression and recurrent depression, level of severity, or allowed better analysis of predictors of depression. A further limitation was our inability to analyze long-term outcomes and their interactions, due to the lack of follow-up data. Follow-up data would allow for investigating long-term effects of interventions and temporal relationships between changes in functioning, QoL and severity of symptoms. Future longitudinal epidemiological studies could fill this research gap and provide important information on the course of functioning in depression. Lastly, only articles in English were considered. This might have omitted relevant information.

In conclusion, this meta-analysis provides comprehensive evidence that existing psychological and pharmacological interventions are efficacious for improving functioning and QoL in depression. There is no robust evidence that one of the interventions is superior, although psychotherapy appears slightly superior to medication. The combination between psychotherapy and medication performs significantly better for both outcomes when compared to each treatment alone. The relatively modest effects suggest that future research should focus on tailoring therapies to better cover the needs of individuals, implementation of instruments assessing both outcomes as primary outcome measures in trials, and reporting domain-specific changes across treatments for better understanding of the course of depression.

References

American Psychiatric Association (1980). Diagnostic and Statistical Manual of Mental Disorders, Third Edition. *Washington, DC: American Psychiatric Association*.

American Psychiatric Association (1987). Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-TR). *Washington, DC: American Psychiatric Association*.

American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders, 4th Edition, Text Revision (DSM-IV-TR). *Washington, DC: American Psychiatric Association*.

Bosmans, J. E., van Schaik, D. J., de Bruijne, M. C., van Hout, H. P., van Marwijk, H. W., van Tulder, M. W. & Stalman, W. A. (2008). Are psychological treatments for depression in primary care cost-effective? *J Ment Health Policy Econ* **11**, 3-15.

Cohen, J. (1988). Statistical power analysis for the behavioral sciences. *2nd ed. Erlbaum; Hillsdale, NJ*.

Cohen, R. M., Greenberg, J. M. & IsHak, W. W. (2013). Incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life in the Individual Burden of Illness Index for Depression to measure treatment impact and recovery in MDD. *JAMA Psychiatry* **70**, 343-50.

Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J. & Klerman, G. L. (1993). The enduring psychosocial consequences of mania and depression. *Am J Psychiatry* **150**, 720-7.

Cuijpers, P., Andersson, G., Donker, T. & van Straten, A. (2011). Psychological treatment of depression: results of a series of meta-analyses. *Nord J Psychiatry* **65**, 354-64.

Cuijpers, P., Karyotaki, E., Andersson, G., Li, J., Mergl, R. & Hegerl, U. (2015). The effects of blinding on the outcomes of psychotherapy and pharmacotherapy for adult depression: A meta-analysis. *Eur Psychiatry* **30**, 685-93.

Cuijpers, P., Li, J., Hofmann, S. G. & Andersson, G. (2010). Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. *Clin Psychol Rev* **30**, 768-78.

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T. & Reynolds, C. F., 3rd (2013). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. *World Psychiatry* **12**, 137-48.

Cuijpers, P., van Straten, A., Andersson, G. & van Oppen, P. (2008a). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *J Consult Clin Psychol* **76**, 909-22.

Cuijpers, P., Van Straten, A., Warmerdam, L. & Smits, N. (2008b). Characteristics of effective psychological treatments of depression: a metaregression analysis. *Psychother Res* **18**, 225-36.

De Silva, M. J., Cooper, S., Li, H. L., Lund, C. & Patel, V. (2013). Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. *Br J Psychiatry* **202**, 253-60.

Deeks, J., Higgins, J. & Altman, D. e. (2008). Analysing data and undertaking meta-analyses, in Cochrane Handbook for Systematic Reviews of Interventions. Edited by Higgins JPT, Green S. Chichester. *UK, Wiley-Blackwell* **Chap. 9**.

Duval, S. & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455-63.

Endicott, J., Nee, J., Harrison, W. & Blumenthal, R. (1993). Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull* **29**, 321-6.

Gaudiano, B. A. & Herbert, J. D. (2005). Methodological issues in clinical trials of antidepressant medications: perspectives from psychotherapy outcome research. *Psychother Psychosom* **74**, 17-25.

Gemmill, M. C., Thomson, S. & Mossialos, E. (2008). What impact do prescription drug charges have on efficiency and equity? Evidence from high-income countries. *Int J Equity Health* **7**, 12.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry 23:56-62*.

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L. & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928.

Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-60.

IsHak, W., Burt, T. & Sederer, L. e. (2002). Outcome measurement in psychiatry: a critical review. *Washington, DC: American Psychiatric Publishing*.

IsHak, W. W., Greenberg, J. M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., Fakhry, H. & Rapaport, M. H. (2011a). Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harv Rev Psychiatry* **19**, 229-39.

Ishak, W. W., Ha, K., Kapitanski, N., Bagot, K., Fathy, H., Swanson, B., Vilhauer, J., Balayan, K., Bolotaulo, N. I. & Rapaport, M. H. (2011b). The impact of psychotherapy, pharmacotherapy, and their combination on quality of life in depression. *Harv Rev Psychiatry* **19**, 277-89.

Kamenov, K., Cabello, M., Coenen, M. & Ayuso-Mateos, J. L. (2015). How much do we know about the functional effectiveness of interventions for depression? A systematic review. *J Affect Disord* **188**, 89-96.

Kelly, K., Posternak, M. & Alpert, J. E. (2008). Toward achieving optimal response: understanding and managing antidepressant side effects. *Dialogues Clin Neurosci* **10**, 409-18.

Lam, R. W., Parikh, S. V., Michalak, E. E., Dewa, C. S. & Kennedy, S. H. (2015). Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. *Ann Clin Psychiatry* **27**, 142-9.

Layard, R., Clark DM, Knapp M & G, M. (2007). Cost-Benefit Analysis of Psychological Therapy- Centre for Economic Performance Report. .

Madden, R. H., Glozier, N., Fortune, N., Dyson, M., Gilroy, J., Bundy, A., Llewellyn, G., Salvador-Carulla, L., Lukersmith, S., Mpofu, E. & Madden, R. (2015). In search of an integrative measure of functioning. *Int J Environ Res Public Health* **12**, 5815-32.

Marcus, S. C. & Olfson, M. (2010). National trends in the treatment for depression from 1998 to 2007. *Arch Gen Psychiatry* **67**, 1265-73.

McAllister-Williams, R. H. (2006). NICE guidelines for the management of depression. *Br J Hosp Med (Lond)* **67**, 60-1.

McHugh, R. K., Whitton, S. W., Peckham, A. D., Welge, J. A. & Otto, M. W. (2013). Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry* **74**, 595-602.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & Group, P. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* **8**, 336-41.

Norcross, J. C. (1990). An eclectic definition of psychotherapy. In J.K. Zeig & W.M. Munion (Eds.), What is psychotherapy? Contemporary perspectives (218-220). *San Francisco, CA: Jossey-Bass.*

Renner, F., Cuijpers, P. & Huibers, M. J. (2014). The effect of psychotherapy for depression on improvements in social functioning: a meta-analysis. *Psychol Med* **44**, 2913-26.

Riley, R. D., Higgins, J. P. & Deeks, J. J. (2011). Interpretation of random effects meta-analyses. *BMJ* **342**, d549.

Sado, M., Knapp, M., Yamauchi, K., Fujisawa, D., So, M., Nakagawa, A., Kikuchi, T. & Ono, Y. (2009). Cost-effectiveness of combination therapy versus antidepressant therapy for management of depression in Japan. *Aust N Z J Psychiatry* **43**, 539-47.

Senn, S. J. (2009). Overstating the evidence: double counting in meta-analysis and related problems. *BMC Med Res Methodol* **9**, 10.

Sheehan, D. (1983). The Anxiety Disease. *Scribner's: New York.*

Sibbald, B. & Roland, M. (1998). Understanding controlled trials. Why are randomised controlled trials important? *BMJ* **316**, 201.

Spielmans, G. I., Berman, M. I., Linardatos, E., Rosenlicht, N. Z., Perry, A. & Tsai, A. C. (2013). Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med* **10**, e1001403.

Spielmans, G. I., Berman, M. I. & Usitalo, A. N. (2011). Psychotherapy versus second-generation antidepressants in the treatment of depression: a meta-analysis. *J Nerv Ment Dis* **199**, 142-9.

Spring, B. (2007). Evidence-based practice in clinical psychology: what it is, why it matters; what you need to know. *J Clin Psychol* **63**, 611-31.

Trompenaars, F. J., Masthoff, E. D., Van Heck, G. L., Hodiamont, P. P. & De Vries, J. (2006). Relationship between mood related disorders and quality of life in a population of Dutch adult psychiatric outpatients. *Depress Anxiety* **23**, 353-63.

Vittengl, J. R., Clark, L. A. & Jarrett, R. B. (2009). Deterioration in psychosocial functioning predicts relapse/recurrence after cognitive therapy for depression. *J Affect Disord* **112**, 135-43.

von Wolff, A., Holzel, L. P., Westphal, A., Harter, M. & Kriston, L. (2012). Combination of pharmacotherapy and psychotherapy in the treatment of chronic depression: a systematic review and meta-analysis. *BMC Psychiatry* **12**, 61.

Ware, J. E., Jr. & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* **30**, 473-83.

Weissman, M. M., Prusoff, B. A., Thompson, W. D., Harding, P. S. & Myers, J. K. (1978). Social adjustment by self-report in a community sample and in psychiatric outpatients. *J Nerv Ment Dis* **166**, 317-26.

World Health Organization (1992). International classification of diseases and related health problems, 10th Revision (ICD-10). *Geneva: World Health Organization*.

World Health Organization Quality of Life Group (1997). Measuring quality of life. *http://www.who.int/mental_health/media/68.pdf*.

Zimmerman, M., Martinez, J. H., Attiullah, N., Friedman, M., Toba, C. & Boerescu, D. A. (2014). The remission from depression questionnaire as an outcome measure in the treatment of depression. *Depress Anxiety* **31**, 533-8.

Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N. & Boerescu, D. (2006). How should remission from depression be defined? The depressed patient's perspective. *Am J Psychiatry* **163**, 148-50.

Under review at Clinical Psychology review

The effect of Cognitive Behavioral Therapy on functioning and quality of life in adult depression: A meta-analysis

Kaloyan Kamenov [1, 2], Jose Luis Ayuso-Mateos[1, 2, 3], Conal Twomey[4], María Cabello[1, 2, 3]

[1]*Instituto de Salud Carlos III, Centro Investigación Biomédica en Red. CIBERSAM. C/ Diego de León 62, 28006, Madrid, Spain*

[2] *Department of Psychiatry, University Autónoma de Madrid, C/Arzobispo Morcillo 4, 28029, Madrid, Spain*

[3] *Instituto de investigación de la Princesa, (IIS-IP), Hospital Universitario de la Princesa, C/ Diego de León 62, 28006, Madrid, Spain*

[4]*Faculty of Social and Human Sciences, University of Southampton, University Road, S017 1Bj, Southampton, UK*

Correspondence: Maria Cabello, Hospital Universitario de la Princesa, C/ Diego de León 62, 28006 Madrid, Spain, Phone: +34 914975346, email: maria.cabello@uam.es

Abstract

Background: Despite the strong evidence for the efficacy of Cognitive Behavioral Therapy (CBT) in reducing depression symptoms, less is known about the effects of CBT on other relevant outcomes such as functioning and quality of life (QoL). The aim of this meta-analysis was to examine the absolute and relative efficacy of CBT on functioning and QoL.

Methods: Outcome trials were identified through database searching in PubMed, PsycINFO and the Cochrane Central Register of Controlled Trials.

Results: CBT was superior to control conditions (g=0.38) but not to medication (g=-0.13) at improving functioning. It was superior to control conditions (g=0.41) at improving QoL. CBT showed better results at reducing depressive symptoms (g=0.62) compared to functioning and QoL, although there was a strong indication for publication bias. In a subgroup analysis CBT showed higher effect size (g=0.49) for functioning when studies allowed participants in the treatment group to continue with their prescribed medication compared to studies that did not allow medication (g=0.19).

Conclusions: Despite the relatively modest effect sizes, CBT is an efficacious therapy for improving functioning and QoL. However, the robustness of the results is insufficient due to the small number of trials and the lack of long-term outcome assessment data.

Keywords: Cognitive Behavioral Therapy; functioning; quality of life; depression

Introduction

Several meta-analyses on CBT have demonstrated its efficacy for reducing depressive symptoms (Butler, Chapman, Forman, & Beck, 2006; Cuijpers et al., 2013) and best-practice guidelines recommend CBT (in face-to-face, computerized and guided self-help formats) as a first-line treatment for mild to moderate depression (McAllister-Williams, 2006; Patten et al., 2009). Moreover, based on its efficacy but also economic rationale, many countries have rolled out initiatives aiming to increase the provision of CBT in primary care (Clark, 2011).

Despite the strong evidence for CBT's efficacy for reducing depression symptoms, less is known about the effects of CBT on other relevant outcomes such as functioning and QoL. Recent literature has suggested that functioning and QoL improvement is equally important for people with depression as their symptom improvement (IsHak et al., 2011; Lam, Parikh, Michalak, Dewa, & Kennedy, 2015; Zimmerman et al., 2006). Patients have prioritized functional over symptomatic outcomes and a return to a normal level of functioning at work, home or school has been seen as a significant factor for remission in depression (Zimmerman et al., 2006). Furthermore, despite being a symptom-focused psychotherapy (Patten et al., 2009), CBT also includes techniques initially developed to facilitate functional areas such as participation in enjoyable activities or to create problem solving and social skills in depressed persons (Hawton, 1989). Therefore, evidence pertaining to the efficacy of CBT on functioning and QoL is needed. To our knowledge, only one meta-analysis focused on computerized CBT (CCBT) has addressed functional improvement, but the results show no superiority of CCBT over control conditions (So et al., 2013). In addition, social functioning was the outcome of interest of two other meta-analyses for depression (De Silva, Cooper, Li, Lund, & Patel, 2013;

Renner, Cuijpers, & Huibers, 2014), but the reviews assessed the pooled effect of all psychotherapies without specific focus on CBT.

More comprehensive data on all delivery formats is needed. Meta-analytic data on functioning would provide evidence of the efficacy of CBT for facilitating daily or social activities, whereas data on QoL would demonstrate the performance of CBT on one's satisfaction with these activities and perception of his/her health (IsHak., Burt, & Sederer, 2002). Therefore, the objective of this meta-analysis of randomized controlled trials was to determine the efficacy of CBT for functioning and QoL. Additionally, sensitivity, subgroup and meta-regression analyses were undertaken.

Methods

Methods and results are presented according to the PRISMA statement for reporting systematic reviews (Moher, Liberati, Tetzlaff, Altman, & Group, 2010).

Search Strategy

A systematic literature search combining the terms depressive disorder OR depression OR major depressive disorder (Mesh terms) AND functioning OR disability OR disabled persons OR sick leave OR activities of daily living OR leisure activities OR quality of life AND treatment OR intervention OR clinical trial OR therapy (MeSH terms, key words and text words) was performed in Pubmed, PsycINFO and the Cochrane Central Register of Controlled Trials. The search in the first two databases was limited to randomized controlled trials. We did not include terms specifically related to cognitive behavioral therapy to guarantee the inclusion of any possible relevant study applying CBT but not as a central topic. In addition, references of published meta-analyses were manually checked. Articles, published in English between January 2000 and November 2015 (last search performed in December 2015) were considered.

Manuscripts were included if they met the following criteria:

1) Use of a randomized controlled research design.
2) Inclusion of a CBT treatment arm. CBT had to include at least cognitive restructuring and behavioral activation procedures for depression.
3) Inclusion of participants aged 18 or more
4) Report of at least one validated outcome measure assessing functioning or QoL. Functioning was defined as any difficulty experienced in maintaining daily activities or participation in social life (Lam et al., 2015). QoL is understood as one's satisfaction with these activities and perception of one's health (IsHak. et al., 2002; World Health Organization Quality of Life Group, 1997). Individual measures of marital or employment status were not included.
5) Diagnosis of depression, established by a standardized diagnostic interview according to DSM-IV, DSM-IV-TR and ICD-10 criteria (American Psychiatric Association, 1994, 2000; World Health Organization, 1992). We did not consider papers which included participants merely defined by a self-rated questionnaire scores.

Studies comparing CBT to control conditions, other psychotherapies or pharmacotherapy were included. Studies including bipolar disorder or reporting results from maintenance or continuation therapies were excluded. The abstract screening was done by one researcher (K.K.) and a random selection of 30% of the abstracts was double checked independently by another two researchers (M.C. and C.T.)

Data extraction and quality assessment

Data from the selected studies were extracted by one author (K.K.) and all checked for accuracy by an independent reviewer. Disagreements were resolved through discussion. The selected variables were collected in a standard data extraction form including demographic and clinical data for participants, treatment groups, outcome measures and effect estimates. In cases of missing data, authors of the studies were contacted. When more than one outcome measure assessing the same concept (either functioning or QoL) was used in a study, data from all instruments were extracted and combined as a mean effect size. In the case of SF-36 (Ware & Sherbourne, 1992), the questionnaire was included as an outcome measure of QoL (Ishak. et al., 2011) but if a study reported scores on the social functioning subdomain, it was considered separately as a measure of functioning. To avoid double counting, when a single study reported the effects of different intervention arms representing the same generic intervention (e.g. when both face-to-face CBT and Internet based CBT were compared with a control), they were averaged and entered once in the analysis (Senn, 2009). However, in subgroup analyses, the effects of each treatment arm were entered separately. Information on symptom severity was extracted only from validated instruments that explicitly measured symptoms of depression (e.g. Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Data on effect estimates were extracted at post-assessment. Data on long-term effect of CBT are not presented, because a very small number of studies reported follow-up data and the follow-up periods differed significantly (e.g. 3 months vs 24 months). In addition, the nature of the follow-ups was distinct - some studies reported only naturalistic outcomes, whereas others delivered booster sessions and maintenance treatments during the follow-up period. The instruments extracted were patient self-assessments and clinician-rated tools.

Four over six criteria of the Cochrane Collaboration risk of bias tool were used for assessing methodological quality of the studies —sequence generation, allocation concealment, blinding of assessors, and incomplete outcome data (Higgins. et al., 2011). Since the majority of psychotherapeutic designs cannot employ a double blind design, blinding of assessors in these studies included only outcome assessors in masking procedures. The other two criteria - selective outcome reporting and other sources of bias were not included due to the unavailability of study protocols needed to optimally assess them. Moreover, by examining study methodologies we found no clear indication that these biases were present.

Statistical Analyses

All statistical analyses were performed using the program Comprehensive Meta-Analysis, version 2.0. The effect size for each study was calculated aggregating the pooled difference between the two groups of treatments at the end of the intervention. Hedges' *g* was preferred as an effect estimate because it provides better effect estimate for small sample sizes (Deeks, Higgins, & Altman, 2008). Random effects models accounting for the heterogeneity among studies were used for the mean effect sizes. Higgins' I^2 statistic was calculated to test the heterogeneity. A value of 0% indicates no heterogeneity, 25% indicates low heterogeneity, 50% - moderate heterogeneity, and 75% high heterogeneity (Higgins., Thompson, Deeks, & Altman, 2003). Statistics were based on intention-to-treat (ITT) data, but when missing, on completer data. It has been suggested that this approach is more realistic rather than excluding completer data, on the prerequisite that all subsequent differences between studies will be discussed and considered as a source of heterogeneity (Higgins & Green, 2009).

Due to the inclusion of a wide range of outcome measures, sensitivity analyses were performed. Here, instruments measuring functioning were checked individually for their potential impact on the effect size of CBT on functioning. The same procedure was repeated for QoL. The following subgroup analyses were performed in order to examine whether certain characteristics of the studies were related to the effect sizes:

- Differences between age groups (adults vs. older adults)
- Delivery format (face-to-face vs. internet or telephone delivered CBT)
- Differences in the control group (WL or TAU)
- Quality of studies (high vs. lower quality; ITT vs. completer data)
- Stable medication usage in the CBT group (if not begun or changed in the last month before the trial) (allowed vs. not-allowed)

Subgroup analyses were performed when there were at least five studies per group (to ensure sufficient statistical power). We intended to assess also type of depressive disorder (major depression vs other depressive disorders), but there was not sufficient data on other depressive disorders to allow performance of the analysis. We used a mixed effects model for the subgroup analyses, combining a random-effects model within subgroups and a fixed-effect model across subgroups. In addition, simple meta-regression analyses were performed to explore whether 1) there was any association between the effect size of depressive symptoms and the estimates of functioning and QoL, 2) sample size had an impact on the estimates, and 3) the amount of psychotherapeutic sessions were important. We used a fixed effects model for the meta-regression analyses. Publication bias was assessed by visual inspection of funnel plots and the trim-and-fill procedure to analyze the changes after the accounting for publication bias (Duval & Tweedie, 2000).

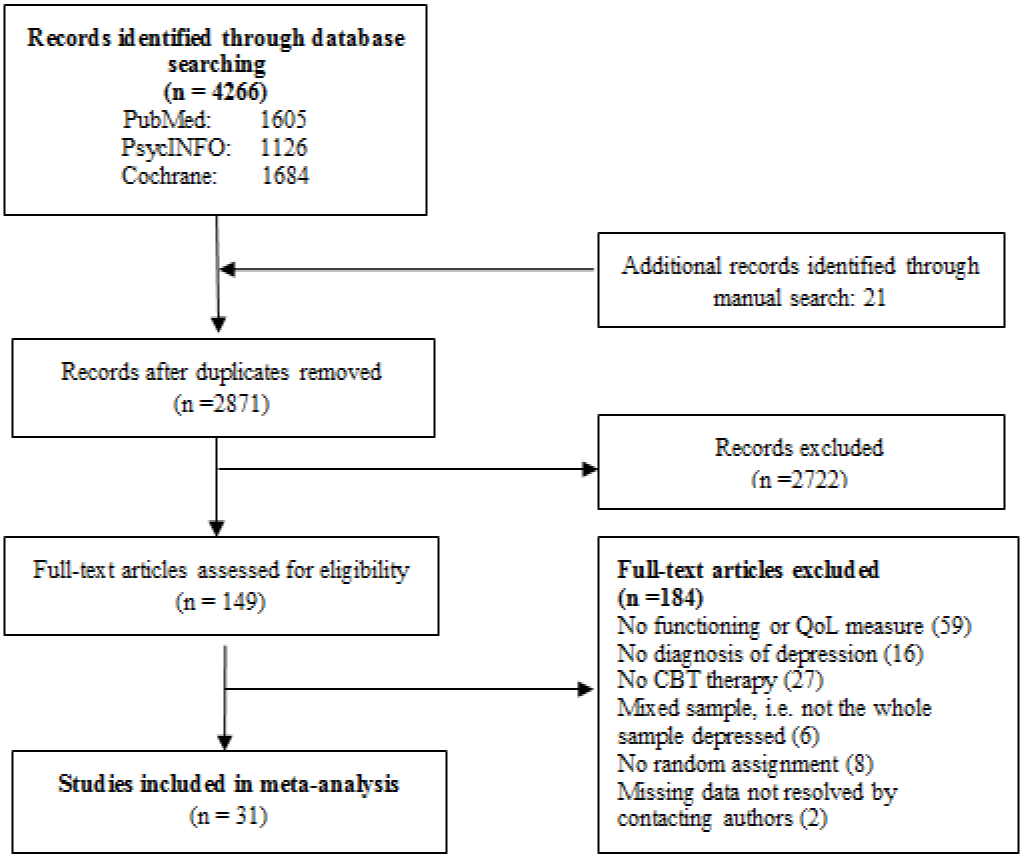
Results

Study Selection

After duplicates were removed, 2851 articles were identified for abstract check. Of these, 149 were selected for full-text screening. Only 31 articles met the inclusion criteria and were included in the analyses. The rest were excluded mainly due to the absence of functioning or

QoL outcome measures, treatment not meeting the criteria for CBT or non-standardized diagnosis of depression. Some of the included studies reported outcomes on both functioning and QoL, which resulted in their inclusion in more than one individual analysis. The whole selection process and exclusion reasons can be seen in Figure 1.

Figure 1. Flow chart of Study Selection



Description of included studies

Selected characteristics of the studies can be seen in Table 1. A total of 4715 participants were included in the trials. Mainly adults, aged between 18-65, diagnosed with major depressive disorder according to DSM IV (American Psychiatric Association, 2000) criteria (53.1%) were recruited. The duration of the trials ranged from five to 20 sessions. The most commonly used instruments for measuring functioning were Sheehan Disability Scale

(SDS) (Sheehan, 1983) and Social Adjustment Scale (SAS) (Weissman, Prusoff, Thompson, Harding, & Myers, 1978), as for QoL – SF-36. The quality of the studies varied. There were 15 trials (48%) meeting all four criteria for publication bias, whereas 8 studies (26%) were missing two or three components of the Cochrane risk of bias tool.

Insert here Table 1. Selected characteristics of the included studies.

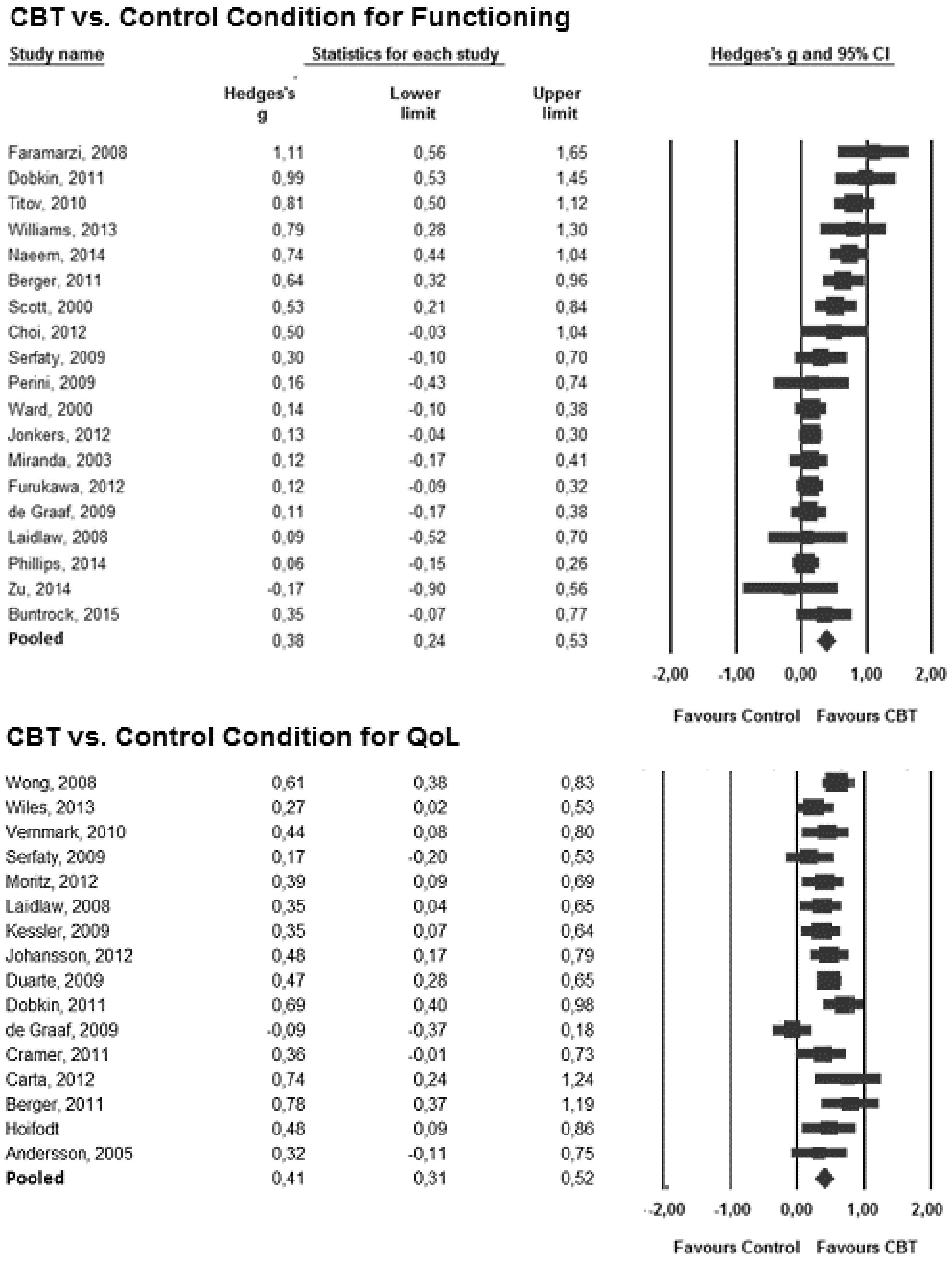
CBT vs. control condition for functioning and QoL

When compared to control conditions (WL or TAU), the effect of CBT on functioning was small to moderate (g=0.38, 95% CI 0.24-0.53). The heterogeneity between the 19 studies included was high (Q=65.74, p<.001, I^2=72.62). No publication bias was observed. The results of the overall analysis are presented in Figure 2.

For QoL, the effect of CBT compared to control condition in 16 studies was also small to moderate (g=0.41, 95% CI 0.31-0.52). The heterogeneity was moderate (Q=28.37, p<.01, I^2=47.12). After adjusting for publication bias, the effect size decreased to 0.38 (95% CI 0.27-0.49).

When the effect of CBT on depressive symptoms was assessed, the pooled estimate of all studies was g=0.62 (95% CI 0.50-0.75, I^2=79.13) (supplementary file 1). After adjusting for publication bias and applying the trim-and-fill procedure, however, the effect size dropped down to g=0.49 (95% CI 0.36-0.62).

Figure 2. Effects of CBT vs. control condition for functioning and QoL



CBT vs. Control Condition for Functioning

Study name	Hedges's g	Lower limit	Upper limit
Faramarzi, 2008	1,11	0,56	1,65
Dobkin, 2011	0,99	0,53	1,45
Titov, 2010	0,81	0,50	1,12
Williams, 2013	0,79	0,28	1,30
Naeem, 2014	0,74	0,44	1,04
Berger, 2011	0,64	0,32	0,96
Scott, 2000	0,53	0,21	0,84
Choi, 2012	0,50	-0,03	1,04
Serfaty, 2009	0,30	-0,10	0,70
Perini, 2009	0,16	-0,43	0,74
Ward, 2000	0,14	-0,10	0,38
Jonkers, 2012	0,13	-0,04	0,30
Miranda, 2003	0,12	-0,17	0,41
Furukawa, 2012	0,12	-0,09	0,32
de Graaf, 2009	0,11	-0,17	0,38
Laidlaw, 2008	0,09	-0,52	0,70
Phillips, 2014	0,06	-0,15	0,26
Zu, 2014	-0,17	-0,90	0,56
Buntrock, 2015	0,35	-0,07	0,77
Pooled	0,38	0,24	0,53

CBT vs. Control Condition for QoL

Study name	Hedges's g	Lower limit	Upper limit
Wong, 2008	0,61	0,38	0,83
Wiles, 2013	0,27	0,02	0,53
Vernmark, 2010	0,44	0,08	0,80
Serfaty, 2009	0,17	-0,20	0,53
Moritz, 2012	0,39	0,09	0,69
Laidlaw, 2008	0,35	0,04	0,65
Kessler, 2009	0,35	0,07	0,64
Johansson, 2012	0,48	0,17	0,79
Duarte, 2009	0,47	0,28	0,65
Dobkin, 2011	0,69	0,40	0,98
de Graaf, 2009	-0,09	-0,37	0,18
Cramer, 2011	0,36	-0,01	0,73
Carta, 2012	0,74	0,24	1,24
Berger, 2011	0,78	0,37	1,19
Hoifodt	0,48	0,09	0,86
Andersson, 2005	0,32	-0,11	0,75
Pooled	0,41	0,31	0,52

CBT vs. other psychotherapies and pharmacotherapy

Meta-analysis comparing directly CBT to other types of psychotherapies on functioning or QoL could not be performed, because there were only two studies reporting functional or QoL outcome measures. The same applied for the direct comparison between CBT and pharmacotherapy on QoL. However, CBT could be compared to pharmacotherapy on functioning in four studies (Faramarzi et al., 2008; Husain et al., 2014; Miranda et al., 2003; Zu et al., 2014). The pooled effect size was *g*=-0.13 (95% CI -0.30-0.04, *p*=.14) slightly in favor of medication. After adjusting for publication bias the effect size increased to g=-0.15 in favor of medication (*p*=NS).

Sensitivity, Subgroup and Meta-Regression Analyses

The sensitivity analyses did not detect any significant difference in the overall effect sizes when each of the instruments was excluded, indicating that no outcome measure had a strong impact on the overall effect estimates. In the subgroup analysis CBT showed significantly higher effect size (g=0.49) for functioning when continuation of previously prescribed medication was allowed in the treatment group compared to the “no medication allowed” group (g=0.19). There were not enough studies without medication usage to perform analysis for QoL. Table 2 shows the effect estimates for all subgroups. Type of depressive disorder could not be assessed due to the insufficient data on depressive disorders different than MDD. The same applied for differences in age groups for both outcomes and the direct comparison between CBT and medication.

Furthermore, a series of simple meta-regression analyses assessing potential predictors were performed. First, associations between depressive symptoms and functioning and QoL were found (slope: 0.60, *p*<.001 for functioning; slope: 0.58, p<.001 for QoL), suggesting that when the effect size of CBT on reducing depressive symptom severity increases with 1 unit, the effect size of CBT on improving functioning and QoL increases with 0.60 and 0.58, respectively. Second, higher number of treatment sessions was significant predictor when CBT was compared to control condition for functioning (slope: 0.02, p=.05). The slope of 0.02 indicated that with an increase of 5 sessions of CBT, the effect size of functioning increased by 0.10. Finally, lower sample size was found to be a significant predictor (*p*<.01) when CBT was compared to control condition for functioning. The heterogeneity in all meta-regression analyses was moderate to high. The analyses performed on the comparison between CBT and pharmacotherapy for functioning did not reveal any significant associations between the variables considered and the effect estimate.

Insert here Table 2. Subgroup analyses exploring associations between effect sizes and study characteristics

Discussion

Main findings

This meta-analysis including 4715 depressed participants was the first to analyze the efficacy of CBT on functioning and QoL in depression. We found that CBT was more efficacious at improving functional outcomes than non-active controls (*g*=0.38) but not pharmacological treatment. Furthermore, CBT was more efficacious at improving QoL (*g*=0.41) than non-active controls. However, CBT showed better results at reducing depressive symptoms (*g*=0.62) than at improving functioning and QoL.

The effect sizes that we found for CBT on functioning (*g*=0.38) in this study are consistent with the pooled effect estimates of all psychotherapies for functioning found in previous meta-analyses (De Silva et al., 2013; Renner et al., 2014). Both Renner et al. (2014) and De Silva et al. (2013) reported an effect size of 0.46 in favor of psychotherapy against non-active control for functioning. Thus, CBT appears to show similar small to moderate efficacy as all psychological therapies pooled. We could not make further investigations on differences among

CBT and other psychotherapies due to the insufficient number of clinical trials directly comparing both. Furthermore, we found significant effect estimate of *g*=0.37 in favor of internet based CBT compared to control conditions, which was inconsistent with the previously found non-significant effect of *d*=-0.05 by So et al. (So et al., 2013). The inconsistence might be due to the fact that the meta-analysis of So and colleagues included studies in which the patients had only depressive symptoms without being formally diagnosed with depression. Another explanation may be that the authors considered instruments assessing well-being and QoL as outcome measures for functional improvement.

We performed series of subgroup analyses to further investigate whether some study characteristics were related to the effect of CBT. We found that CBT had a significantly higher effect size for functioning when the studies allowed participants in the treatment group to continue with their prescribed medication compared to studies that did not allow medication. However, firm conclusions cannot be made due the absence of information on the number of participants within each trial who have taken medication together with CBT, and the number of participants not following a structured pharmacological treatment. Future research is warranted to explore whether combined treatment is more efficacious than CBT alone and whether pre-existing pharmacological treatment might have an impact on the effectiveness of CBT. Furthermore, the effect size of CBT compared to WL was not significantly different to the effect size of CBT on TAU, tentatively indicating that treatment as usual may be no more effective than waiting list conditions for functioning and QoL. For depressive symptoms we found a significant difference between WL and TAU (g=0.78 for WL vs. g=0.54 for TAU). However, these results should be seen with caution considering the low number of studies. The failure to find significant differences may have been due to low statistical power rather than equivalency across subgroups. Secondly, TAU is a broad concept and included studies generally did not define clearly all the elements included within. Some of the studies described TAU as a mixture of psychological and pharmacological treatment monitored by the general practitioner, some as only medication. Finally, there exists the possibility of confounding by additional study-level characteristics.

Furthermore, we did not find sufficient evidence to directly compare the effect of CBT and pharmacotherapy on QoL. However, there were few but enough trials to indicate no significant differences between CBT and pharmacotherapy on functioning. The results can be considered consistent with precedent meta-analyses indicating no superiority of CBT over medication for reducing depressive symptoms (Cuijpers et al., 2013). However, only four studies were included in the analysis. The lack of comparative studies limits any firm conclusions, but future long-term outcome data might reveal superiority of one of the interventions.

Depressive symptoms, functioning and QoL

The results suggest that CBT performs better at reducing depressive symptoms than at improving functioning or QoL. Even though the effect size on depressive symptoms is an overestimation as we found a clear indication for publication bias, this finding calls for attention. There is a large body of research suggesting that functional recovery appears later than the symptomatic one (Kennedy, Foy, Sherazi, McDonough, & McKeon, 2007). Moreover, studies have found that depressive symptoms and QoL do not share considerable proportion of common variance (Coryell et al., 1993; Trompenaars, Masthoff, Van Heck, Hodiamont, & De Vries, 2006). In this line, to further investigate the association between symptomatology, functioning and QoL, we performed meta-regression analyses. The results suggest that functioning and QoL improve when symptom severity improves, but the design does not reveal which is the leading factor. It is clear that symptoms and functioning are interconnected, but causal relationships and potential precursors can be explored only through longitudinal research. Nonetheless, the fact that we found lower effect sizes for functioning and QoL than for depressive symptoms has an important prognostic implication for the course of depression after ending treatment. Studies have already found that residual functional impairment evokes relapse and recurrences (Vittengl, Clark, & Jarrett, 2009). The lack of long-term assessment does not allow us to further investigate the interrelations between both outcomes, but this finding stresses the importance of including functioning and QoL tools as primary outcome measures in clinical trials.

Future research

All this said, we think that future steps towards better performance of CBT on functioning and QoL are warranted. Firstly, more studies are needed. We found only 31 trials reporting the efficacy of CBT on functioning or QoL outcomes. This is in line with recent findings that only 5 - 20% of all clinical trials for depression measure and report functional outcomes (Kamenov, Cabello, Coenen, & Ayuso-Mateos, 2015; McKnight & Kashdan, 2009). Furthermore, there is need of long-term assessment data in RCTs. Very few studies reported follow-up data longer than one year. We still do not know what the long-term benefits of CBT on functioning and QoL are. Secondly, there is no gold standard tool for measuring functioning in depression to date (Lam et al., 2015). Therefore, development and application of more sensitive and user friendly instruments assuring a comprehensive assessment of both domains, or simply inclusion of a battery of already existing tools as primary outcome measures is warranted. Second, improvement can be achieved through tailoring of treatment to better meet the needs of people with functional or QoL problems. There are examples of studies that have adapted the original treatment manual of CBT resulting in considerably high effect sizes. Naeem et al. (Naeem et al., 2014) have applied a culturally adjusted CBT manual for treating depressed people with functional impairment in Pakistan, resulting in improved functioning in the treatment group by an effect size of g=0.74. A new functional Cognitive Behavioral Therapy (fCBT) for improving social functioning in schizophrenia created and tested by Cather (Cather, 2005) shows promising results in reducing persistent positive symptoms. Stronger focus on facilitation of relevant functional areas or improvement of QoL areas might be a key for better results.

Lastly, we argue that functioning and QoL should be directly targeted in the response and remission criteria for a more comprehensive assessment of treatment efficacy. There are already initial steps in this direction. Cohen et al (Cohen, Greenberg, & IsHak, 2013) have created an Individual Burden of Illness Index for depression to measure treatment impact and recovery in depression by incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and QoL. Later on, Zimmerman et al. (Zimmerman et al., 2014) have validated a new instrument – the Remission from Depression Questionnaire, encompassing different domains of functioning and QoL along with symptomatology. The authors conclude that the new tool provides a broader perspective of depressed patients’ condition than purely symptom based measures and is more consistent with the biopsychosocial approach in the treatment of depression. Another possibility involves a separate definition of functional recovery in trials. A study by Mancini et al. (Mancini et al., 2012) has applied such criteria based on the Sheehan Disability Scale. However, all attempts for implementation of such criteria in research are still in their infancy. Much needs to be done in order to gain better understanding on the treatment trajectories.

Limitations

This study has to be seen in the light of certain limitations. First, the number of studies was relatively small and we were not able to perform some of the analyses we intended to. Second, half of the studies did not meet one or more quality criteria. Even though the subgroup analyses did not find statistically significant differences between the high and low quality studies, given their small number, it might be that the effect sizes have been overestimated. Third, only overall rather than domain-specific improvements in functioning and QoL were assessed. Hence, we are not able to know whether certain aspect of functioning (e.g. work functioning or interpersonal relationships) improves more. We found an indication of publication bias, which might have led to an overestimation of the effect sizes. Obtaining data from unpublished studies and grey literature may negate this problem in future investigations, although locating such literature is challenging, for various reasons (e.g. its diverse origins, the unwillingness of authors to provide data) (Sterne, Egger, & Moher, 2011). Only articles published in English between 2000 and 2015 were included. We selected studies within this search period, as more than 80% of the clinical trials on CBT have been published since year 2000 (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012) and functioning has not been investigated extensively as an outcome of interest before that year (Hirschfeld et al., 2000). Furthermore, one of our aims was to explore the impact of different delivery formats on the results- e.g. face-to-face vs. computerized CBT. The first internet-delivered CBT trials were conducted in late 1990s and early 2000s (Andersson G, Carlbring P, Ljótsson B, & E, 2013), therefore we assert that this time frame adequately captures the effectiveness of the whole range of CBT delivery formats on functioning and QoL in depression.

Conclusions

Despite these limitations, this meta-analysis has important clinical and research implications. It shows that despite the relatively modest effect sizes, CBT is an efficacious therapy for improving both functioning and QoL. This is a substantial finding considering the importance of both outcomes from patient perspective. The study also shows that CBT is as efficacious as medication for improving functioning outcomes. The small number of studies and lack of long-term outcome assessment, however, warrants future research to provide more robust results. Lastly, our findings suggest that CBT works better for symptoms than for functioning and QoL. This is in line with the current state-of-art of research on depression, focused more on symptom severity rather than functioning and QoL. Inclusion of existing or application of new and comprehensive instruments assessing both outcomes in longer clinical trials, or therapy adjustment to better meet the needs of patients having functional and QoL deteriorations are the initial steps that have to be taken towards a more complete definition of treatment effects.

References

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders, 4th Edition (DSM-IV). *Washington, DC: American Psychiatric Association*

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders, 4th Edition, Text Revision (DSM-IV-TR). *Washington, DC: American Psychiatric Association*.

Andersson G, Carlbring P, Ljótsson B, & E, H. (2013). Guided Internet-Based CBT for Common Mental Disorders. *Journal of Contemporary Psychotherapy, 43*(4), 223-233.

Andersson, G., Bergstrom, J., Hollandare, F., Carlbring, P., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: randomised controlled trial. *Br J Psychiatry, 187*, 456-461. doi: 10.1192/bjp.187.5.456

Berger, T., Hammerli, K., Gubser, N., Andersson, G., & Caspar, F. (2011). Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help. *Cogn Behav Ther, 40*(4), 251-266. doi: 10.1080/16506073.2011.616531

Buntrock, C., Ebert, D., Lehr, D., Riper, H., Smit, F., Cuijpers, P., & Berking, M. (2015). Effectiveness of a Web-Based Cognitive Behavioural Intervention for Subthreshold Depression: Pragmatic Randomised Controlled Trial. *Psychother Psychosom, 84*(6), 348-358. doi: 10.1159/000438673

Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev, 26*(1), 17-31. doi: 10.1016/j.cpr.2005.07.003

Carta, M., Petretto, D., Adamo, S., Bhat, K., Lecca, M., Mura, G., . . . Moro, M. (2012). Counseling in primary care improves depression and quality of life. *Clin Pract Epidemiol Ment Health, 8*, 152-157. doi: 10.2174/1745017901208010152

Cather, C. (2005). Functional cognitive-behavioural therapy: a brief, individual treatment for functional impairments resulting from psychotic symptoms in schizophrenia. *Can J Psychiatry, 50*(5), 258-263.

Clark, D. M. (2011). Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience. *Int Rev Psychiatry, 23*(4), 318-327. doi: 10.3109/09540261.2011.606803

Cohen, R. M., Greenberg, J. M., & IsHak, W. W. (2013). Incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life in the Individual Burden of Illness Index for Depression to measure treatment impact and recovery in MDD. *JAMA Psychiatry, 70*(3), 343-350. doi: 10.1001/jamapsychiatry.2013.286

Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G. L. (1993). The enduring psychosocial consequences of mania and depression. *Am J Psychiatry, 150*(5), 720-727.

Cramer, H., Salisbury, C., Conrad, J., Eldred, J., & Araya, R. (2011). Group cognitive behavioural therapy for women with depression: pilot and feasibility study for a randomised controlled trial using mixed methods. *BMC Psychiatry, 11*, 82. doi: 10.1186/1471-244X-11-82

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Can J Psychiatry, 58*(7), 376-385.

Choi, I., Zou, J., Titov, N., Dear, B. F., Li, S., Johnston, L., . . . Hunt, C. (2012). Culturally attuned Internet treatment for depression amongst Chinese Australians: a randomised controlled trial. *J Affect Disord, 136*(3), 459-468. doi: 10.1016/j.jad.2011.11.003

de Graaf, L. E., Gerhards, S. A., Arntz, A., Riper, H., Metsemakers, J. F., Evers, S. M., . . . Huibers, M. J. (2009). Clinical effectiveness of online computerised cognitive-behavioural therapy without support for depression in primary care: randomised trial. *Br J Psychiatry, 195*(1), 73-80. doi: 10.1192/bjp.bp.108.054429

De Silva, M. J., Cooper, S., Li, H. L., Lund, C., & Patel, V. (2013). Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. *Br J Psychiatry, 202*(4), 253-260. doi: 10.1192/bjp.bp.112.118018

Deeks, J., Higgins, J., & Altman, D. e. (2008). Analysing data and undertaking meta-analyses, in Cochrane Handbook for Systematic Reviews of Interventions. Edited by Higgins JPT, Green S. Chichester. *UK, Wiley-Blackwell, Chap. 9*.

Dobkin, R. D., Menza, M., Allen, L. A., Gara, M. A., Mark, M. H., Tiu, J., . . . Friedman, J. (2011). Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. *Am J Psychiatry, 168*(10), 1066-1074. doi: 10.1176/appi.ajp.2011.10111669

Duarte, P. S., Miyazaki, M. C., Blay, S. L., & Sesso, R. (2009). Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney Int, 76*(4), 414-421. doi: 10.1038/ki.2009.156

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56*(2), 455-463.

Faramarzi, M., Kheirkhah, F., Esmaelzadeh, S., Alipour, A., Hjiahmadi, M., & Rahnama, J. (2008). Is psychotherapy a reliable alternative to pharmacotherapy to promote the mental health of infertile women? A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol, 141*(1), 49-53. doi: 10.1016/j.ejogrb.2008.07.012

Furukawa, T. A., Horikoshi, M., Kawakami, N., Kadota, M., Sasaki, M., Sekiya, Y., . . . Grothaus, L. C. (2012). Telephone cognitive-behavioral therapy for subthreshold depression and presenteeism in workplace: a randomized controlled trial. *PLoS One, 7*(4), e35330. doi: 10.1371/journal.pone.0035330

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry 23:56-62*.

Hawton, K., Salkovskis, P., Kirk, J. et al. (1989). Cognitive behaviour therapy for psychiatric problems: A practical guide. *London: Oxford Press*.

Higgins, J.P., & Green, S. (2009). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. . *The Cochrane Collaboration, 2009 (http://www.cochrane-handbook.org)*.

Higgins, J.P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., . . . Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343*, d5928. doi: 10.1136/bmj.d5928

Higgins, J.P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560. doi: 10.1136/bmj.327.7414.557

Hirschfeld, R. M., Montgomery, S. A., Keller, M. B., Kasper, S., Schatzberg, A. F., Moller, H. J., . . . Bourgeois, M. (2000). Social functioning in depression: a review. *J Clin Psychiatry, 61*(4), 268-275.

Hofmann, S. G., Asnaani, A., Vonk, I. J., Sawyer, A. T., & Fang, A. (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res, 36*(5), 427-440. doi: 10.1007/s10608-012-9476-1

Hoifodt, R. S., Lillevoll, K. R., Griffiths, K. M., Wilsgaard, T., Eisemann, M., Waterloo, K., & Kolstrup, N. (2013). The clinical effectiveness of web-based cognitive behavioral therapy with face-to-face therapist support for depressed primary care patients: randomized controlled trial. *J Med Internet Res, 15*(8), e153. doi: 10.2196/jmir.2714

Husain, N., Chaudhry, N., Fatima, B., Husain, M., Amin, R., Chaudhry, I. B., . . . Creed, F. (2014). Antidepressant and group psychosocial treatment for depression: a rater blind exploratory RCT from a low income country. *Behav Cogn Psychother, 42*(6), 693-705. doi: 10.1017/S1352465813000441

IsHak, W.W., Greenberg, J. M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., . . . Rapaport, M. H. (2011). Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harv Rev Psychiatry, 19*(5), 229-239. doi: 10.3109/10673229.2011.614099

IsHak, W.W., Burt, T., & Sederer, L. e. (2002). Outcome measurement in psychiatry: a critical review. *Washington, DC: American Psychiatric Publishing*.

Ishak, W.W., Ha, K., Kapitanski, N., Bagot, K., Fathy, H., Swanson, B., . . . Rapaport, M. H. (2011). The impact of psychotherapy, pharmacotherapy, and their combination on quality of life in depression. *Harv Rev Psychiatry, 19*(6), 277-289. doi: 10.3109/10673229.2011.630828

Johansson, R., Sjoberg, E., Sjogren, M., Johnsson, E., Carlbring, P., Andersson, T., . . . Andersson, G. (2012). Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. *PLoS One, 7*(5), e36905. doi: 10.1371/journal.pone.0036905

Jonkers, C. C., Lamers, F., Bosma, H., Metsemakers, J. F., & van Eijk, J. T. (2012). The effectiveness of a minimal psychological intervention on self-management beliefs and behaviors in depressed chronically ill elderly persons: a randomized trial. *Int Psychogeriatr, 24*(2), 288-297. doi: 10.1017/S1041610211001748

Kamenov, K., Cabello, M., Coenen, M., & Ayuso-Mateos, J. L. (2015). How much do we know about the functional effectiveness of interventions for depression? A systematic review. [Review]. *J Affect Disord, 188,* 89-96. doi: 10.1016/j.jad.2015.08.035

Kennedy, N., Foy, K., Sherazi, R., McDonough, M., & McKeon, P. (2007). Long-term social functioning after depression treated by psychiatrists: a review. *Bipolar Disord, 9*(1-2), 25-37. doi: 10.1111/j.1399-5618.2007.00326.x

Kessler, D., Lewis, G., Kaur, S., Wiles, N., King, M., Weich, S., . . . Peters, T. J. (2009). Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet, 374*(9690), 628-634. doi: 10.1016/S0140-6736(09)61257-5

Laidlaw, K., Davidson, K., Toner, H., Jackson, G., Clark, S., Law, J., . . . Cross, S. (2008). A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. *Int J Geriatr Psychiatry, 23*(8), 843-850. doi: 10.1002/gps.1993

Lam, R. W., Parikh, S. V., Michalak, E. E., Dewa, C. S., & Kennedy, S. H. (2015). Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. *Ann Clin Psychiatry, 27*(2), 142-149.

Mancini, M., Sheehan, D. V., Demyttenaere, K., Amore, M., Deberdt, W., Quail, D., & Sagman, D. (2012). Evaluation of the effect of duloxetine treatment on functioning as measured by the Sheehan disability scale: pooled analysis of data from six randomized, double-blind, placebo-controlled clinical studies. *Int Clin Psychopharmacol, 27*(6), 298-309. doi: 10.1097/YIC.0b013e3283589a3f

McAllister-Williams, R. H. (2006). NICE guidelines for the management of depression. *Br J Hosp Med (Lond), 67*(2), 60-61. doi: 10.12968/hmed.2006.67.2.20461

McKnight, P. E., & Kashdan, T. B. (2009). The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. *Clin Psychol Rev, 29*(3), 243-259. doi: 10.1016/j.cpr.2009.01.005

Miranda, J., Chung, J. Y., Green, B. L., Krupnick, J., Siddique, J., Revicki, D. A., & Belin, T. (2003). Treating depression in predominantly low-income young minority women: a randomized controlled trial. *JAMA, 290*(1), 57-65. doi: 10.1001/jama.290.1.57

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg, 8*(5), 336-341. doi: 10.1016/j.ijsu.2010.02.007

Moritz, S., Schilling, L., Hauschildt, M., Schroder, J., & Treszl, A. (2012). A randomized controlled trial of internet-based therapy in depression. *Behav Res Ther, 50*(7-8), 513-521. doi: 10.1016/j.brat.2012.04.006

Naeem, F., Sarhandi, I., Gul, M., Khalid, M., Aslam, M., Anbrin, A., . . . Ayub, M. (2014). A multicentre randomised controlled trial of a carer supervised culturally adapted CBT (CaCBT) based self-help for depression in Pakistan. *J Affect Disord, 156*, 224-227. doi: 10.1016/j.jad.2013.10.051

Patten, S. B., Kennedy, S. H., Lam, R. W., O'Donovan, C., Filteau, M. J., Parikh, S. V., & Ravindran, A. V. (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. *J Affect Disord, 117 Suppl 1*, S5-14. doi: 10.1016/j.jad.2009.06.044

Perini, S., Titov, N., & Andrews, G. (2009). Clinician-assisted Internet-based treatment is effective for depression: randomized controlled trial. [Randomized Controlled Trial]. *Aust N Z J Psychiatry, 43*(6), 571-578. doi: 10.1080/00048670902873722

Phillips, R., Schneider, J., Molosankwe, I., Leese, M., Foroushani, P. S., Grime, P., . . . Thornicroft, G. (2014). Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention. *Psychol Med, 44*(4), 741-752. doi: 10.1017/S0033291713001323

Renner, F., Cuijpers, P., & Huibers, M. J. (2014). The effect of psychotherapy for depression on improvements in social functioning: a meta-analysis. *Psychol Med, 44*(14), 2913-2926. doi: 10.1017/S0033291713003152

Scott, J., Teasdale, J. D., Paykel, E. S., Johnson, A. L., Abbott, R., Hayhurst, H., . . . Garland, A. (2000). Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. *Br J Psychiatry, 177*, 440-446.

Senn, S. J. (2009). Overstating the evidence: double counting in meta-analysis and related problems. *BMC Med Res Methodol, 9*, 10. doi: 10.1186/1471-2288-9-10

Serfaty, M. A., Haworth, D., Blanchard, M., Buszewicz, M., Murad, S., & King, M. (2009). Clinical effectiveness of individual cognitive behavioral therapy for depressed older people in primary care: a randomized controlled trial. *Arch Gen Psychiatry, 66*(12), 1332-1340. doi: 10.1001/archgenpsychiatry.2009.165

Sheehan, D. (1983). The Anxiety Disease. *Scribner's: New York.*

So, M., Yamaguchi, S., Hashimoto, S., Sado, M., Furukawa, T. A., & McCrone, P. (2013). Is computerised CBT really helpful for adult depression?-A meta-analytic re-evaluation of CCBT for adult depression in terms of clinical implementation and methodological validity. *BMC Psychiatry, 13*, 113. doi: 10.1186/1471-244X-13-113

Sterne, J., Egger, M., & Moher, D. (2011). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Intervention. Version 5.1.0 (updated March 2011). The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Titov, N., Andrews, G., Davies, M., McIntyre, K., Robinson, E., & Solley, K. (2010). Internet treatment for depression: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One, 5*(6), e10939. doi: 10.1371/journal.pone.0010939

Trompenaars, F. J., Masthoff, E. D., Van Heck, G. L., Hodiamont, P. P., & De Vries, J. (2006). Relationship between mood related disorders and quality of life in a population of Dutch adult psychiatric outpatients. *Depress Anxiety, 23*(6), 353-363. doi: 10.1002/da.20180

Vernmark, K., Lenndin, J., Bjarehed, J., Carlsson, M., Karlsson, J., Oberg, J., . . . Andersson, G. (2010). Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behav Res Ther, 48*(5), 368-376. doi: 10.1016/j.brat.2010.01.005

Vittengl, J. R., Clark, L. A., & Jarrett, R. B. (2009). Deterioration in psychosocial functioning predicts relapse/recurrence after cognitive therapy for depression. *J Affect Disord, 112*(1-3), 135-143. doi: 10.1016/j.jad.2008.04.004

Ward, E., King, M., Lloyd, M., Bower, P., Sibbald, B., Farrelly, S., . . . Addington-Hall, J. (2000). Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy, and usual general practitioner care for patients with depression. I: clinical effectiveness.*BMJ, 321*(7273), 1383-1388.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.*Med Care, 30*(6), 473-483.

Weissman, M. M., Prusoff, B. A., Thompson, W. D., Harding, P. S., & Myers, J. K. (1978). Social adjustment by self-report in a community sample and in psychiatric outpatients. *J Nerv Ment Dis, 166*(5), 317-326.

Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., . . . Lewis, G. (2013). Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. *Lancet, 381*(9864), 375-384. doi: 10.1016/S0140-6736(12)61552-9

Williams, A. D., Blackwell, S. E., Mackenzie, A., Holmes, E. A., & Andrews, G. (2013). Combining imagination and reason in the treatment of depression: a randomized controlled trial of internet-based cognitive-bias modification and internet-CBT for depression. *J Consult Clin Psychol, 81*(5), 793-799. doi: 10.1037/a0033247

Wong, D. F. (2008). Cognitive and health-related outcomes of group cognitive behavioural treatment for people with depressive symptoms in Hong Kong: randomized wait-list control study. *Aust N Z J Psychiatry, 42*(8), 702-711. doi: 10.1080/00048670802203418

World Health Organization. (1992). International classification of diseases and related health problems, 10th Revision (ICD-10). *Geneva: World Health Organization*.

World Health Organization Quality of Life Group. (1997). Measuring quality of life. *http://www.who.int/mental_health/media/68.pdf*.

Zimmerman, M., Martinez, J. H., Attiullah, N., Friedman, M., Toba, C., & Boerescu, D. A. (2014). The remission from depression questionnaire as an outcome measure in the treatment of depression. *Depress Anxiety, 31*(6), 533-538. doi: 10.1002/da.22178

Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N., & Boerescu, D. (2006). How should remission from depression be defined? The depressed patient's perspective. *Am J Psychiatry, 163*(1), 148-150. doi: 10.1176/appi.ajp.163.1.148

Zu, S., Xiang, Y. T., Liu, J., Zhang, L., Wang, G., Ma, X., . . . Li, Z. J. (2014). A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate-severe major depressive disorders. *J Affect Disord, 152-154*, 262-267. doi: 10.1016/j.jad.2013.09.022

Table. 1 Selected characteristics of the included studies.

Study	**Definition**	**Target Group**	**Therapy (format)**	**N**	**Sessions/ Modules**	**Control**	**N**	**Medication allowed in CBT group**	**Outcome Measure Functioning/QOL**	**Outcome Measure Depression**	**Quality (0-4)**	**Country**
Andersson et al. (2005)	MDD	Adults	ISH, based on CBT	36	5	Web-based discussion	49	Yes	QOLI	BDI/MADRS	4	Sweden
Berger et al. (2011)	MDD	Adults	GSH, based on CBT	25	10	WL	26	Yes	IIP-64/WHOQOL-BREF	BDI-II	4	Switzerland
Buntrock et al. (2015)	SD	Adults	iCBT	202	6	Enhanced TAU	204	Yes	SF-12	CES-D	4	Germany
Carta et al. (2012)	Depression	Adults	CBC	34	12	TAU	30	Yes	WHOQOL-BREF	BDI	1	Italy
Choi et al. (2012)	MDD	Adults	GSH, based on CBT	25	6	WL	30	Yes	SDS	BDI	2	Australia
Cramer et al. (2011)	Depression	Women	Group CBT	45	12	TAU	19	Yes	SF-12	PHQ-9	2	UK
de Graaf et al. (2009)	Depression	Adults	iCBT	100	8	TAU	103	Yes	WSAS/SF-36	BDI-II	2	Netherlands
Dobkin et al. (2011)	MDD/Dys/ D NOS	Adults	CBT (individual)	41	10	TAU	39	Yes	SF-36 Social Functioning/SF-36	HAMD/BDI	4	USA
Duarte et al. (2009)	MDD	Adults	CBT (individual)	41	12	TAU	44	Yes	KDQOL-SF	BDI	3	Brazil
Faramarzi et al. (2008)	MDD	Women	CBT (group)	29	10	TAU/ Fluoxetine	30/ 30	No	GHQ social dysfunction	GHQ depression	1	Iran
Furukawa et al. (2012)	SD	Adults	tCBT	58	8	WL	60	No	HPQ	BDI-II	3	Japan
Hoifodt et al. (2013)	Depression	Adults	Therapist-assisted Web-based CBT	52	5	WL	54	Yes	EQ-5D	BDI-II	4	Norway
Husain et al. (2014)	Depression	Women	PI (group), based on CBT	32	10	Fluoxetine	32	No	BDQ/ EQ-5D	HAMD	4	UK/Pakistan
Johansson et al. (2012)	MDD	Adults	iCBT tailored/no tailored	36/37	8	Other	42	Yes	QOLI	BDI/MADRS	3	Sweden
Jonkers et al. (2012)	MDD/Dys	Older Adults	MPI, based on CBT	125	10	TAU	133	No	ADL/ IPA		4	Netherlands
Kessler et al. (2009)	Depression	Adults	iCBT	99	10	TAU	91	Yes	EQ-5D	BDI	4	UK
Laidlaw et al. (2008)	MDD	Older Adults	CBT (individual)	20	8	TAU	20	No	WHOQOL Social Rel. Scale/WHOQOL	HAMD/BDI/GDS	2	UK
Miranda et al. (2003)	MDD	Women	CBT (individual/group)	90	8	TAU/AD	89/ 88	No	SAS-CR; SF-36 soc. funct.scale	HAMD	4	USA
Moritz et al. (2012)	Depression	Adults	Self Help iDeprexis	80	10	WL	90	Yes	Whoqol-BREF	BDI	3	Germany
Naeem et al. (2014)	DE/RD	Adults	CaCBT	94	9	TAU	89	Yes	BDQ	HADS depression	4	Pakistan
Perini, Titov, and Andrews (2009)	MDD	Adults	GSH, based on CBT	27	6	WL	18	Yes	SDS	BDI-II	3	Australia
Phillips et al. (2014)	Depression	Adults	iCBT: MoodGym	171	5	Other	188	Yes	WSAS	PHQ-9	3	UK
Scott et al. (2000)	RD	Adults	CBT+CM	80	16	CM	78	Yes	SAS-SR	BDI/HAMD/	4	UK
Serfaty et al. (2009)	Depression	Older Adults	CBT (individual)	70	12	TAU	67	Yes	SFQ/EQ-5D	BDI-II	4	UK
Titov et al. (2010)	MDE	Adults	iCBT + technician/ iCBT + clinician	41/46	6	WL	40	Yes	SDS	BDI-II/PHQ-9	4	Australia
Vernmark et al. (2010)	MDD	Adults	iGSH CBT vs. Individualized CBT Email Therapy	29/30	7	WL	29	Yes	QOLI	BDI/MADRS	4	Sweden
Ward et al. (2000)	Depression	Adults	CBT (individual)	67	6	TAU	67	No	SAS-M	BDI	3	UK
Wiles et al. (2013)	Depression	Adults	CBT (individual)	201	12	TAU	209	Yes	SF-12	BDI	4	UK
Williams et al. (2013)	MDE	Adults	iCBT	35	13	WL	28	Yes	WHODAS	BDI/PHQ-9	2	Australia
Wong (2008)	MDD	Adults	CBT (group)	163	10	WL	159	Yes	Q-LES-Q-18	BDI	1	China
Zu et al. (2014)	MDD	Adults	CBT (individual)	12	20	TAU/AT	16/	No	WSAS	HAMD/QIDS-SR	3	China

Note: AT= Antidepressant Treatment, BDI= Beck Depression Inventory, BDI-II= BDI Second Edition, BDQ= Brief Disability Questionnaire, CaCBT= Culturally adjusted Cognitive Behavioural therapy, CBC= Cognitive Behavioural Counselling, CBT= Cognitive Behavioural therapy, GSH= Guided Self-Help, CES-D= Centre for Epidemiologic Studies Depression Scale, D NOS= Depression Non otherwise Specified, Dys= Dysthymia, GDS= Geriatric Depression Scale, HAMD= Hamilton Rating Scale for Depression, HPQ= World Health Organization Health and Work Performance Questionnaire, iCBT=internet-based CBT, IIP= Inventory of Interpersonal Problems, ISH= Internet administered self-help, KDQOL-SF= Kidney Disease and Quality of Life Short Form, MADRS= Montgomery–Åsberg Depression Rating Scale, MDD= Major Depressive Disorder, QIDS= Quick Inventory of Depressive Symptomatology, RD= Recurrent Depression, SAS= Social Adjustment Scale, SAS-SR= Social Adjustment Scale, Self-Report, SCL-90= Symptom Checklist-90, SDS= Sheehan Disability Scale, SF-36= 36-item Short-Form Health Survey, TAU= Treatment as usual, WHOQOL= World Health Organization Quality of Life, WL= waiting list, WSAS= Work and Social Adjustment Scale.

Table 2. Subgroup analyses exploring associations between effect sizes and study characteristics

Comparison	N	*g*	95% CI	Q	*I*²	*P**
CBT vs. control for functioning						
Delivery format						
Face-to-face	10	0.40	0.18-0.61	36.06	75.04	0.9
iCBT/tCBT	9	0.37	0.15-0.59	29.54	72.92	
Control condition						
CBT vs. WL	6	0.50	0.23-0.77	19.41	74.24	0.3
CBT vs. TAU	13	0.33	0.16-0.51	42.16	71.54	
Quality of studies						
High Quality	14	0.35	0.19-0.52	50.60	74.31	0.5
Lower Quality	5	0.49	0.17-0.81	14.26	71.95	
Medication in CBT group						
Yes	12	0.49	0.30-0.68	38.80	71.65	0.02
No	7	0.19	0.01-0.36	12.91	53.53	
CBT vs. control for QoL						
Delivery Format						
Face-to-face	8	0.45	0.31-0.60	10.62	34.08	0.5
iCBT/tCBT	8	0.37	0.21-0.53	15.73	55.5	
Control Condition						
CBT vs. WL	5	0.53	0.35-0.72	3.03	0.00	0.1
CBT vs. TAU	11	0.36	0.24-0.48	21.02	52.43	
Quality of studies						
High Quality	11	0.44	0.30-0.57	10.31	3.04	0.7
Lower Quality	5	0.36	0.17-0.56	17.33	76.92	
ITT vs. Completers						
ITT	10	0.41	0.25-0.58	24.2	62.82	0.9
Completer Analysis	6	0.42	0.30-0.54	4.13	0.00	

*Note: *The p in this column indicates whether the difference between the effect sizes in this subgroup is significant*

5.2. Collection of empirical evidence for further improvement of treatment effectiveness measurement in depression

The second part of the Results section is dedicated to the collection of empirical evidence for the improvement of the current measurement of treatment effectiveness in depression. This part is designed as a response to all the limitations of the current literature identified in the first part of the thesis. The evidence is collected from a multi-country cross-sectional study, a qualitative study with patients with depression, and an expert survey with representatives from clinical practice. A brief summary of the results from the papers is presented before the articles.

5.2.1. Summary of findings:

- There was a variation in the level of impairment in different functioning domains across countries.
- Gender differences in the impact of functional impairment on quality of life in depression were found
- The most burdensome functional domains were identified
- Clinicians and depressed patients highlighted the importance of both symptoms and functional areas beyond symptoms.
- A set of the most important functional areas in depression, namely mental functions, sleep, energy level, somatic problems, interpersonal relationships and interaction, recreation and daily activities, communication, social participation, daily tasks and demands, work and educational difficulties and personal factors such as self-efficacy, self-esteem or self-awareness was defined.

- Clinicians and patients identified a number of differences regarding the areas improved by psychotherapeutic or pharmacological interventions that were not addressed by the pertinent literature.
- A set of recommendations for future improvement of treatment efficacy measurement was provided

frontiers in Psychology

ORIGINAL RESEARCH
published: 31 August 2016
doi: 10.3389/fpsyg.2016.01342

Which Are the Most Burdensome Functioning Areas in Depression? A Cross-National Study

Kaloyan Kamenov[1,2], Francisco Felix Caballero[1,2,3], Marta Miret[1,2], Matilde Leonardi[4], Päivi Sainio[5], Beata Tobiasz-Adamczyk[6], Josep Maria Haro[7], Somnath Chatterji[8], José Luis Ayuso-Mateos[1,2,3] and Maria Cabello[1,2,3]*

[1] Centro Investigación Biomédica en Red, Instituto de Salud Carlos III, Madrid, Spain, [2] Department of Psychiatry, Universidad Autónoma de Madrid, Madrid, Spain, [3] Instituto de Investigación Sanitaria del Hospital de La Princesa, Hospital Universitario de la Princesa, Madrid, Spain, [4] Neurology, Public Health and Disability Unit, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy, [5] National Institute for Health and Welfare, Helsinki, Finland, [6] Department of Medical Sociology, Jagiellonian University Medical College, Krakow, Poland, [7] Centro de Investigación Biomédica en Red de Salud Mental, Parc Sanitari Sant Joan de Déu, Barcelona, Spain, [8] Department of Health Statistics and Information Systems, World Health Organization, Geneva, Switzerland

Edited by:
Gianluca Castelnuovo,
Catholic University of the Sacred Heart, Italy

Reviewed by:
Michelle Dow Keawphalouk,
Harvard University and Massachusetts Institute of Technology, USA
Andrew Ryder,
Concordia University, Canada

***Correspondence:**
Maria Cabello
maria.cabello@uam.es

Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *24 February 2016*
Accepted: *22 August 2016*
Published: *31 August 2016*

Citation:
Kamenov K, Caballero FF, Miret M, Leonardi M, Sainio P, Tobiasz-Adamczyk B, Haro JM, Chatterji S, Ayuso-Mateos JL and Cabello M (2016) Which Are the Most Burdensome Functioning Areas in Depression? A Cross-National Study. Front. Psychol. 7:1342. doi: 10.3389/fpsyg.2016.01342

Background: The study aimed to identify the most burdensome functioning domains in depression and their differential impact on the quality of life (QoL) of individuals from nine countries in Asia, Africa, Europe, and Latin America.

Materials and Methods: Data from two multi-country projects—the World Health Organization's Study on Global Ageing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE)—were analyzed. Eight functioning domains (pain, mobility, self-care, cognition, interpersonal activities, domestic life, and work, sleep and energy, and affect) and QoL were assessed in 4051 individuals with depression.

Results: The analyses of the pooled sample showed that *affect* (ß = –0.21, $p < 0.001$), *domestic life and work* (ß = –0.16, $p < 0.001$) and *interpersonal activities* (ß = –0.15, $p < 0.001$) were the most affected functioning domains. When the analysis was stratified by gender, women showed similar patterns to the total sample, whereas *mobility*, *self-care*, *cognition* and *pain* were not significant amongst men. The cross-national analysis revealed that difficulties in *affect* and *interpersonal activities* were common across countries, whereas the rest of the domains showed country variability. In addition, being a woman (ß = –0.05), being older (ß = 0.07), being married (ß = 0.05), not having a comorbid condition (ß = –0.03) and having a higher education (ß = 0.04) were all factors associated with higher levels of QoL.

Conclusion: There was a variation in the level of decrements in different functioning domains across countries. This is in line with the growing evidence that reporting functioning sum-scores obscures potential differences among people. Functioning tools should capture the distinctiveness among individuals in order to provide tailored responses.

Keywords: functioning, disability, quality of life, depression, cross-national study

INTRODUCTION

In spite of all evidence based treatments, depression still represents a huge burden to society (Chisholm et al., 2004) due to the disability it causes (Ferrari et al., 2013), its high mortality rates (Cuijpers and Schoevers, 2004), suicide risk (World Health Organization, 2012), and economic impact (Sobocki et al., 2006). The diagnosis of depression is based on a number of symptomatic criteria (World Health Organization, 1992; American Psychiatric Association, 2000, 2013), but it has been argued that this broad diagnosis might lump individuals suffering from different syndromes into one category (Fried and Nesse, 2014). Therefore, there is a growing body of literature suggesting that the depressive symptoms need to be analyzed individually (Lux and Kendler, 2010), shifting the focus from assessing not only the number but also their nature (Lux and Kendler, 2010). Fried and Nesse (2014) analyzed the concurrent effects of individual depressive symptoms on the functional state of depressed individuals and found that the symptoms vary substantially in their associations with impairment. Sad mood and concentration problems were found to be the most debilitating symptoms.

There is also a growing recognition of the importance of improving functioning when treating depression; in fact, normalization of a patient's overall functioning is considered an important criterion for remission (Zimmerman et al., 2006a,b). However, more than 80% of interventional studies published in the last decade have reported only sum-scores of the instruments assessing functioning – e.g., Social Adjustment Scale (Weissman et al., 1978), Sheehan Disability Scale (Sheehan, 1983), WHODAS (Ustun et al., 2010), rather than domain-specific information (Kamenov et al., 2015). These sum-scores do not provide information on the differential impact of each functioning domain on the overall state of a person with depression. Thus, a higher score might indicate either a large number of mildly affected functioning areas or a few domains with marked decrements. It remains unclear whether distinct areas of functioning weight differently in terms of individual burden. The International Classification of Functioning, Disability and Health (ICF) Research Branch of the World Health Organization (WHO) developed an evidence-based Core Set for depression (Cieza et al., 2004) to address the broad spectrum of disability and functioning in depression. Until now the Core Set has not been sufficiently implemented in research studies, perhaps due to the complexity of the model or the large number of categories selected (Alvarezz, 2012). Cieza et al. (2014) proposed a minimal generic set of functioning domains, based on the ICF model, which reflects the experience of individuals with regard to their global health, but the article did not provide any disease-specific information related to depression.

Therefore, the first objective of this study was to identify the most burdensome domains of functioning according to their impact on the quality of life (QoL) of patients with depression. QoL was chosen as an indicator of the overall condition of depressed individuals because it refers to one's satisfaction with life activities and one's appraisal of life in general (IsHak et al., 2002). Moreover, QoL improvement and restoration have been considered the ultimate barometer of treatment success in depression (IsHak et al., 2011).

Furthermore, many studies found cross-national differences in the prevalence and symptom profiles of depression. A population-based study with more than 38000 participants from 10 countries revealed remarkable differences in the lifetime prevalence of depression ranging from 1.5/100 adults in Taiwan to 19.0/100 adults in Beirut (Weissman et al., 1996). The WHO Psychological Problems in General Health Care (PPGHC) study further showed a 15-fold variation in major depression prevalence, from lowest prevalence in Japan and China to highest prevalence in Brazil and Chile (Simon et al., 2002). On the other hand, cross-national differences in symptom profiles were also identified. Loss of energy, insomnia, concentration difficulties and thoughts of death appeared in all countries, whereas weight loss, increased appetite, hypersomnia, retardation, agitation and decrease in sexual interest were determined as country-specific (Weissman et al., 1996). A study by Waza et al. (1999) found that Japanese depressed patients experienced more and different somatic symptoms than American patients. Despite the rich evidence on prevalence and symptom differences in depression, little has been done in regard to potential cross-national differences in functional impairment. Studies have predominantly assessed functioning as a general concept rather than domain-specific. A study by Bromet et al. (2011) based on the World Mental Health survey found that the association between prevalence of depression and functional impairment was positive across high- and low-income countries. Moreover, Simon et al. (2002) showed that depression was universally associated with disability across countries with low, middle, and high prevalence rates of depression.

It is still unknown, however, whether there are cross-national differences in the level of impairment of individual functioning areas in depression. Such information could shed light on the distinctiveness among individuals across countries in order to facilitate the assessment of disability and provide tailored responses. Therefore, the second objective of this paper was to examine the cross-national diversity of the relationship between the functioning domains and QoL of depressed patients in nine countries: Finland, Poland, Spain, China, Ghana, India, Mexico, Russian Federation, and South Africa.

MATERIALS AND METHODS

Sample and Procedure

The study used data obtained from the WHO's Study on Global Ageing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE in Europe), two multi-country projects conducted between 2007 and 2012. The COURAGE survey was conducted in Finland, Poland, and Spain, whereas the SAGE survey was undertaken in China, Ghana, India, Mexico, the Russian Federation, and South Africa. The selected countries represent different geographical locations and levels of socio-economic and demographic status. Both projects collected data on participants aged 18+ years, with an emphasis on people aged 50+ years, from nationally representative samples. The details of the design and methods for Courage in Europe and SAGE are published elsewhere (Kowal et al., 2012; Leonardi et al., 2014).

The sample comprised 4051 non-institutionalized adults (18+) who were currently experiencing an episode of depression from China (296), Ghana (428), India (1522), Mexico (291), Russia (321), South Africa (168), Poland (288), Finland (136) and Spain (601). Trained lay interviewers undertook the face-to-face interviews at the respondents' homes. The interviews in Mexico, Poland, Finland and Spain were completed by computer-assisted personal interview (CAPI), whereas in the remaining countries the researchers used a paper and pencil interview (PAPI). China was the only country where both CAPI and PAPI were used. Quality control procedures were undertaken during the fieldwork (Üstun et al., 2005). Informed consent from all participants was obtained. Ethical approval was obtained from the WHO Ethical Review Committee for SAGE and by Neurological Institute Besta for COURAGE, and by all local ethics research review boards (Helsinki and Uusimaa Hospital District, Finland; Jagiellonian University Medical College, Krakow, Poland; Parc Sanitari Sant Joan de Déu, Barcelona, Spain; La Princesa University Hospital, Madrid, Spain; Shanghai Municipal Centre for Disease Control and Prevention, Shanghai, China; Ghana Medical School, Accra, Ghana; International Institute of Population Sciences, Mumbai, India; National Institute of Public Health, Cuernavaca, Mexico; School of Preventive and Social Medicine, Russian Academy of Medical Sciences, Moscow, Russia; and Human Sciences Research Council, Pretoria, South Africa). The individual response rate ranged from 53% in Finland and Mexico to 93% in China.

Measures

The process of translation and adaptation of instruments aimed to achieve conceptually equivalent versions of all instruments in each of the countries. The first step was a forward translation, where a health professional familiar with the terminology of the specific area translated the instruments from English to the particular language following series of instructions. Then, a bilingual expert panel including health experts and experts with experience in instrument development and translation revised the translation. The third step was a back-translation by an independent translator. Finally, a pre-testing on a target population representative of those who will be administered the questionnaire was done. The whole process was based on a method previously refined in the course of several WHO studies (World Health Organization, 2009).

Depression

Participants who had been diagnosed with depression by a physician and had been receiving treatment during the last 12 months were included in the study. In addition, since there are many cases of undiagnosed persons who actually experience depressive episodes (Sheehan, 2004; Volicer et al., 2011), we assessed depression with a set of symptomatic questions derived from the World Mental Health Survey version of the Composite International Diagnostic Interview (CIDI) for depression (Kessler and Ustun, 2004). The individual items were included in a diagnostic algorithm generating a diagnosis of "depressive episode" according to the criteria specified in the *International Statistical Classification of Diseases and Related Health Problems, 10th revision, Diagnostic Criteria for Research* (World Health Organization, 1992).

Functioning Domains

Functioning was assessed with a multi-domain measure (Salomon et al., 2003) that was developed as an answer to the WHO statement: "functioning and functioning domains constitute the operationalization that best captures our intuitive notion of health" (Cieza et al., 2014). The measure had been previously used in 70 countries from the World Health Survey (Salomon et al., 2003). Participants were asked about the difficulties they had experienced in the last 30 days in each of these domains. The responses to each question were recorded on a 5-point scale ranging from 1 (no difficulty/problem) to 5 (extreme difficulty/inability).

Mobility

The domain of mobility assessed the ability of a person to move and get around. The participants were asked whether in the last 30 days they have had any difficulty in "*vigorous activities,*" "*walking a long distance such as a kilometer (or equivalent),*" "*walking 100 meters,*" "*moving around inside your home,*" "*getting out of your home,*" "*getting where you want to go, using private or public transport if needed,*" "*stooping, kneeling or crouching,*" "*standing up from sitting down,*" "*getting up from lying down,*" "*sitting for long periods,*" "*standing for long periods such as 30 min,*" "*picking up things with your fingers (such as picking up a coin from a table),*" "*extending your arms above your shoulder level*" and "*carrying things (such as carrying grocery bags, water bottles, etc.).*"

Self-Care

This domain measured the capacity of a person to perform self-care activities by answering the following items: "*Overall, in the last 30 days, how much difficulty did you have in: 'taking care of and maintaining your general appearance (for example, grooming, looking neat and tidy),' 'staying by yourself for a few days,' 'washing your whole body,' 'getting dressed,' 'getting to and using the toilet,' 'eating (including cutting up your food).*"

Cognition

This domain measured communication and thinking activities. The two items included *"Concentrating on doing something for 10 min*" and "*learning a new task, for example, learning how to get to a new place.*"

Pain

Pain was assessed with two items: "*How much of bodily aches or pain did you have?*" and "*how much difficulty did you have in your daily life because of your pain?*"

Interpersonal Activities

This domain assessed the ability of individuals to interact with other people through five items: "*Joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can,*" "*personal relationships or participation in* *the community,*" "*dealing with conflicts and tensions with others,*" " *making new friendships*" and "*dealing with people you do not know.*"

Domestic Life and Work

This domain assessed difficulties with day-to-day activities, such as *"taking care of your household responsibilities*" and *"your day-to-day work/school."*

Sleep and Energy

This domain assessed difficulties in sleep patterns ("*sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning*") and energy level ("*not feeling rested and refreshed during the day (for example feeling tired, not having energy).*"

Affect

This domain assessed the emotional functioning of participants. The domain included four items: "*feeling sad, low or depressed,*" "*worry or anxiety,*" "*emotionally affected by your health problems*" and "*how much did these difficulties interfere with your life.*"

Quality of Life

Quality of life was assessed using a short version of the WHO Quality of Life (WHOQOL) instrument (Power, 2003; Skevington et al., 2004). This questionnaire has shown good cross-cultural validity (da Rocha et al., 2012). It was designed as a short and concise instrument of eight items reporting four domains—psychological, social, physical, and environmental, each assessed by two items. The overall QoL score (ranging between 0 and 100) was formed by the sum of the scores of the eight items, with higher scores indicating better quality of life.

Control Variables

Country, age, sex, marital status, presence of comorbid physical chronic conditions (angina, hypertension, asthma, arthritis, or diabetes) and level of education were included in the analysis as control variables.

Statistical Analysis

Descriptive statistics including summary of the socio-demographic data of the participants were obtained.

Factor scores for each functioning domain were obtained and then the scores were transformed into a scale ranging from 0 to 100, with lower scores representing better functioning. Before calculating the factor scores for each of the domains of functioning, confirmatory factor analyses (CFA) were performed to assess the goodness-of-fit of the domains.

To examine the independent contributions of all domains of functioning on QoL, a multiple regression analysis was conducted. Age, sex, country, marital status, comorbidity, and educational level were introduced as covariates to control for potential confounders. In addition, the analysis was carried out on the entire sample of depressed individuals, on men and women and on each country separately. The independent variables were introduced simultaneously in the model because we examined the effect of different domains of functioning on QoL rather than introducing previously established models. The ordinary least squares (OLS) estimation was employed, since it has been shown to yield the best fit of data (Alonso et al., 2011). Standardized (β) coefficients indicated the level of association between the functioning domains and the covariates and QoL, since (β) can be applied as effect size in regression models. Since we conducted multivariate regression models, with several independent variables, the presence of multicollinearity was assessed by means of the Variance Inflation Factor (VIF). Values below 5 were considered adequate (Rogerson, 2001) and providing evidences for little or no multicollinearity in the data. STATA version 11.0 (Stata Corp, 2009) was used to analyze the socio-demographic data, to calculate the factor scores and to conduct the regression models. Amos version 22 (Arbuckle, 2013) was used for the CFA. Confidence intervals (CI) for hypothesis tests were constructed at the 95% confidence level.

RESULTS

Characteristics of the Sample

Socio-demographic and clinical characteristics of the sample in each country are presented in **Table 1**. A total of 4051 people with depression took part in the study. The mean age of the total sample was 60 years ($SD = 14.36$). Women were the majority (66.3%) and 67% of the sample had not completed higher education. Differences could be seen in Russia and Finland, where more than 85% of the sample had completed secondary school. The mean QoL score was 53.59 (16.69).

The Impact of Functioning Areas on Quality of Life

Confirmatory factor analyses were performed to find evidence for unidimensionality and the use of a global score in each domain. In each case, a single-factor model was proposed considering the items assigned to the domain. Then the factor structure was tested. All functional areas presented an acceptable fit according to the goodness-of-fit indices: Comparative Fit Index (CFI) >0.90 and Root Mean Square Error of Approximation (RMSEA) <0.08 in all cases. For the domains that included only two items, Cronbach's alpha value was calculated, being higher than 0.70. Inter-item correlation was also higher than 0.50 in each case, indicating a strong relationship between the two items and also providing evidence of unidimensionality.

The results from the multiple regression analysis (**Table 2**) revealed that *affect* (ß = –0.21, $p < 0.001$), *domestic life and work* (ß = –0.16, $p < 0.001$) and *interpersonal activities* (ß = –0.15, $p < 0.001$) were the most important functioning domains associated with QoL. *Sleep and energy*, *mobility* and *cognition* were also statistically significant, but their effect sizes were smaller compared to the former three. *Pain* ($p = 0.14$) and *self-care* ($p = 0.86$) were the only domains that were not statistically significant.

When the analysis was separated by gender (**Table 2**), women showed similar patterns as the total sample, with the only difference being that *sleep and energy* was only marginally significant (ß = –0.04, $p = 0.06$). *Affect* remained the most important functioning area (ß = –0.24, $p < 0.001$), followed

TABLE 1 | Characteristics of the population by country.

Characteristics	Spain (601)	Poland (288)	Finland (136)	China (296)	Ghana (428)	Mexico (291)	India (1522)	Russia (321)	South Africa (168)
Age mean (*SD*)	62.15 (14.52)	61.4 (15.9)	54.70 (16.03)	61.19 (10.72)	64.75 (12.54)	62.77 (13.12)	56.27 (14.72)	65.56 (12.65)	58.18 (10.28)
Women *n* (%)	434 (72.2)	198 (68.8)	103 (75.7)	191 (64.5)	254 (59.3)	227 (78)	954 (62.7)	244 (76)	107 (63.7)
Men *n* (%)	167 (27.8)	90 (31.3)	33 (24.3)	105 (35.5)	174 (40.7)	64 (22)	568 (37.3)	77 (24)	61 (36.3)
Current marital status *n* (%)									
In a partnership/married	297 (49.4)	120 (41.7)	60 (44.1)	228 (77)	192 (44.9)	179 (61.5)	1113 (73.1)	144 (44.9)	79 (47)
Not in a partnership	304 (50.6)	168 (58.3)	76 (55.9)	68 (23)	233 (54.4)	112 (38.5)	409 (26.9)	176 (54.8)	88 (52.4)
Education									
Less than secondary school *n* (%)	427 (71)	103 (35.8)	13 (9.6)	177 (59.8)	327 (76.4)	230 (79)	1272 (83.6)	45 (14)	127 (75.6)
Secondary school or higher level completed: *n* (%)	174 (29)	185 (64.2)	123 (90.4)	117 (39.5)	90 (21)	61 (21)	249 (16.4)	276 (86)	38 (22.6)
Quality of Life Mean (*SD*)	57.79 (17.42)	50.79 (17.9)	60.89 (17.6)	48.74 (16.98)	52.39 (16.30)	56.36 (14.68)	54.49 (15.28)	46.44 (17.71)	49.5 (16.71)

by *interpersonal activities, domestic life and work, mobility* and *cognition*. *Interpersonal activities* were more strongly associated with their QoL compared to the total sample. Men, however, showed different patterns compared to the total sample and women in particular. *Affect* was still the most fundamental factor, but *sleep and energy* ($ß = -0.13$, $p < 0.001$) appeared to be the second major functioning area for men as opposed to women. *Self-care* was only marginally significant ($ß = -0.08$, $p = 0.06$), whereas *cognition* ($ß = -0.06$, $p = 0.12$), *mobility* ($ß = -0.09$, $p = 0.08$), and *pain* ($ß = 0.001$, $p = 0.84$) were not statistically significant functioning domains in men.

Furthermore, with respect to the control variables, being a woman ($p = 0.001$), being older ($p < 0.001$), being married ($p = 0.001$), not having a comorbid condition ($p = 0.005$), having a higher education ($p = 0.017$) and living in a specific country (compared to China; $p < 0.001$) were associated with higher levels of QoL in people with depression. There were gender differences only in terms of educational level, comorbidity and marital status—the former two not being significant for women and the latter for men. All the variables considered in the analyses had an associated VIF value lower than 5, indicating that the assumption of no perfect multicollinearity can be assumed to conduct the regression model.

Cross-National Differences in the Level of Impairment in Different Functioning Areas

We did a further cross-national analysis, controlling again for sex, age, marital status, level of education and comorbid conditions by exploring the most relevant functioning domains in each of the nine countries. *Affect* was significant in all countries except China. The second most commonly important domain was *interpersonal activities*, significant in all countries except Mexico, China and South Africa. *Pain* was significantly associated with QoL in Spain, Poland, India and Ghana. *Domestic life and work, cognition*, and *sleep and energy* showed statistical significance only in three of the nine countries. *Mobility* ($ß = -0.34$, $p < 0.001$) was the least represented domain across countries, being significant only in Spain. On the other hand, looking at the number of significant areas for each country, in India seven out of eight domains were significant (only *mobility* was not significant), followed by Spain with five (*interpersonal activities, mobility, pain, self-care, and affect*). China was the only country where only one functioning domain was found statistically significant – *sleep and energy* ($ß = -0.15$, $p < 0.05$). Detailed results for each country can be seen in **Figure 1**.

DISCUSSION

The present study examined the differential association of eight functioning domains on QoL in a large and representative sample of 4.051 depressed individuals across nine countries. Our findings suggest that *affect*, *interpersonal activities* and *domestic life and work* had the highest impact on QoL in depression. *Sleep and energy*, *mobility* and *cognition* were also important factors, but their effect was smaller. *Self-care* and *pain* were the only

TABLE 2 | Effect estimates of functioning domains on quality of life using multiple regression analysis.

Variables	Total			Women			Men		
	B (95% *CI*)	***p***	**ß***	**B (95% *CI*)**	***p***	**ß**	**B (95% *CI*)**	***p***	**ß**
Cognition	–0.04 (–0.07–0.01)	**0.001**	–0.07	–0.04 (–0.08–0.01)	**0.007**	–0.07	–0.04 (–0.08–0.01)	0.12	–0.06
Mobility	–0.05 (–0.09–0.01)	**0.007**	–0.08	–0.05 (–0.1–0.001)	**0.046**	–0.07	–0.06 (–0.13–0.01)	0.08	–0.09
Pain	–0.02 (–0.04–0.01)	0.14	–0.03	–0.03 (–0.05–0.004)	0.09	–0.04	0.01 (–0.04–0.04)	0.84	0.01
Self-care	–0.01 (–0.04–0.03)	0.86	0.01	0.02 (–0.02–0.07)	0.32	0.03	–0.07 (–0.13–0.01)	0.06	–0.08
Interpersonal act.	–0.11 (–0.14–0.08)	**<0.001**	–0.15	–0.13 (–0.16–0.10)	**<0.001**	–0.18	–0.07 (–0.12–0.03)	**0.003**	–0.11
Domestic life/Work	–0.09 (–0.12–0.06)	**<0.001**	–0.16	–0.10 (–0.13–0.06)	**<0.001**	–0.17	–0.08 (–0.12–0.03)	**0.001**	–0.13
Sleep and energy	–0.04 (–0.07–0.02)	**<0.001**	–0.07	–0.03 (–0.05–0.01)	0.06	–0.04	–0.08 (–0.11–0.04)	**<0.001**	–0.13
Affect	–0.15 (–0.18–0.12)	**<0.001**	–0.21	–0.17 (–0.20–0.13)	**<0.001**	–0.24	–0.11 (–0.16–0.06)	**<0.001**	–0.16
Controlling variables									
Sex	–1.75 (–2.75–0.75)	**0.001**	–0.05						
Age	0.09 (0.05–0.12)	**<0.001**	0.07	0.09 (0.04–0.14)	**<0.001**	0.08	0.08 (0.01–0.14)	**0.022**	0.06
Educational level	1.41 (0.26–2.56)	**0.017**	0.04	1.05 (–0.46–2.56)	0.17	0.03	1.98 (0.14–3.82)	**0.035**	0.06
Marital status	1.71 (0.71–2.71)	**0.001**	0.05	1.64 (0.42–2.85)	**0.008**	0.05	1.52 (–0.39–3.43)	0.12	0.04
Comorbidity	–1.46 (–2.47–0.45)	**0.005**	–0.03	–0.75 (–2.19–0.3)	0.14	0.03	–2.47 (–4.18–0.76)	**0.005**	–0.07

**Effect size, ß coefficient; Country was introduced as a covariate in the model. * In bold, significant p-values at 95% confidence level.*

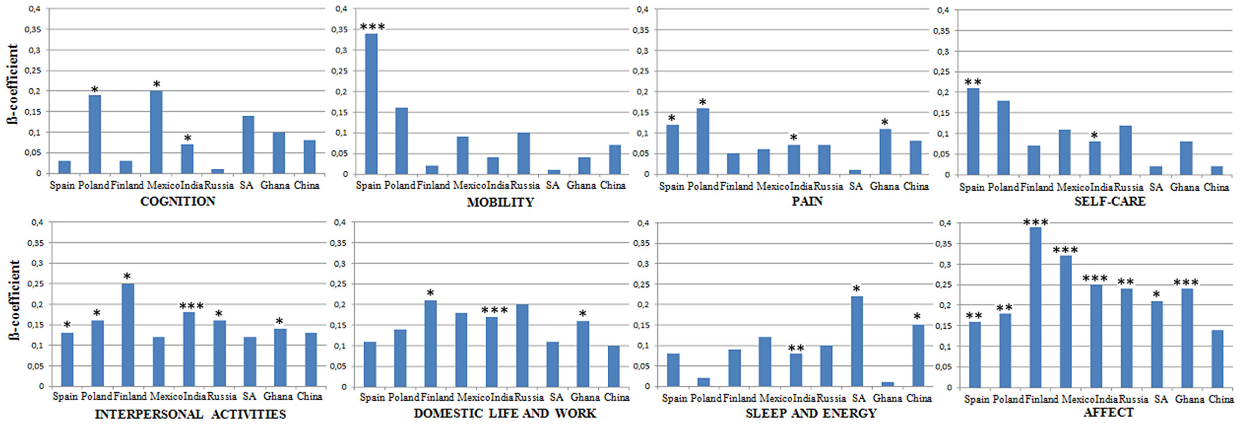


FIGURE 1 | Relationship between functioning domains and quality of life by country. *$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.* Age, sex, marital status, comorbidity, and educational level were introduced as covariates to control for potential confounders. SA, South Africa.

domains that were non-significant for men or women. A possible explanation might be that the participants showed relatively higher levels of self-care and lower levels of pain, and severe decrements in these domains were rare.

Only one study to date has attempted to identify a set of the most relevant functioning domains but does not provide anything disease-specific, but rather general clinical information (Cieza et al., 2014). The authors of the study suggested that *mobility, pain, sleep and energy,* and *affect* were the most important functioning domains associated with the general health of both clinical and general populations. Our study coincides with some of these findings, but the degree of importance varied. *Affect* was the most relevant domain associated with QoL, but *pain* was not significant in our sample. *Interpersonal activities*, however, which was the second most important domain in our study, was not considered in the final set of Cieza et al. (2014). This result is not surprising, as previous studies have already reported that people with depression experience significantly poorer intimate relationships and less satisfying social interactions than individuals with other psychiatric disorders, or the general population (Fredman et al., 1988).

We further examined differences across the included countries. *Affect* was significant in all countries except China. This supports previous evidence that emotional problems, such as low mood, are a core part of the experience of depression (Fried and Nesse, 2014) and chronic physical or mental conditions in general (Weigl et al., 2004). However, most of the generic functioning tools, such as WHODAS-II or SF-36 (Ware and Sherbourne, 1992), do not include affect as a single domain. Difficulties in *interpersonal activities* were also prevailing in most of the countries. However, the rest of the domains were country specific. *Cognition* was associated with QoL in Poland, India and Mexico; *mobility* in Spain; and *sleep and energy* in India, South Africa and China. In India we found a significant positive association between *pain* and QoL ($ß = 0.07$, $p = 0.025$) after controlling for sociodemographic variables and the remaining functioning domains. This finding is counterintuitive, as it indicates that a higher pain is associated with better QoL. In the rest of the countries where *pain* was associated with QoL—Spain, Poland and Ghana—we found a negative relationship between both. We examined the correlation coefficient between QoL and *pain* and found a significant value of $r = -0.340$ ($p < 0.001$). However, after controlling for *affect* we found a non-significant partial correlation coefficient. After we ran the previous regression model without considering *affect* as covariate we did not find any significant association between *pain* and QoL. This suggests that the relationship between *pain* and QoL in India was moderated by *affect*. Similarly, a counterintuitive association was found between *self-care* and QoL in Spain. We found a highly significant correlation between *self-care* and *mobility* in the Spanish sample ($r = 0.764$), which suggested potential multicollinearity in the model. After *mobility* was removed from the regression model, *self-care* was no longer significantly associated with QoL.

The reason why some functioning domains were associated with QoL only in some countries but not in others is unclear, but certain cultural contrasts might be responsible for these variations. For instance, in our study *mobility* was more important for the Spanish population than for any other country. Previous studies evaluating the health status in general population confirm this result, showing that Spanish raters place more importance on *mobility* as a functioning domain compared to other countries due to cultural or lifestyle characteristics (Badia and Alonso, 1995; Badia et al., 2001).

Even though many of the effect sizes associated with the results obtained from the regression models were small or moderate, the results of this study have considerable practical implications. Firstly, in a research perspective, our results boost future changes in the measurement of disability in depression. The study proves that there is a variation in the level of decrements in different functioning domains across countries. Furthermore, it provides a basis for further development of more sensitive, cross-nationally validated and user-friendly instruments weighting the domains according to their importance and providing a better picture on the living experience of depressed individuals. This action is urgent, given the fact that only 5–20% of all clinical trials for depression report functioning outcomes (McKnight and Kashdan, 2009; Kamenov et al., 2015) and to date there is no gold standard tool for measuring functioning in depression (Lam et al., 2015). Symptoms of depression, which are the main focus of clinical trials, provide early signs of treatment response, but the functional outcomes provide an indicator of meaningful change, thus making the inclusion of functional tools in clinical trials a pressing issue (McKnight and Kashdan, 2009). One reason for the lack of comprehensive data on functioning is the complex conceptualization of the term and the lack of disease-specific information on all relevant areas. Another explanation is that they lack comprehensiveness and cultural validity. Therefore, the Canadian Network for Mood and Anxiety Treatments (CANMAT) depicts as a primary aim the development of a scale for measuring functioning outcomes in clinical trials that could be used or adapted for different clinical care settings (Lam et al., 2015). Although several recent trials have attempted to apply newly developed measures designed to capture a more comprehensive array of functioning difficulties, all of them are still in their infancy, do not provide domain-specific information or have not been validated in cross-national samples (Cohen et al., 2013; Zimmerman et al., 2013).

Secondly, the study reveals particular gender differences in the functional impairment of depression. This is an important finding which needs further exploration in other cross-national samples, given the higher prevalence of depression in women compared to men. Different level of impairment in specific functioning areas might be a key to the understanding of these different prevalence rates. Thirdly, our study promotes the need of reporting domain-specific information in studies for better understanding the living experience of depression. Studies predominantly report only the sum-scores of the instruments. These sum-scores do not provide information on the differential impact of each functioning domain on the QoL of individuals. A higher sum-score might indicate either a large number of mildly affected functioning areas or a few domains with marked decrements. Potentially important information on functioning is lost, and a detailed analysis of these functioning domains is likely to reveal important information hidden by the sum-scores. Last, but not least, our study raises the question about the importance of assessing functioning in clinical trials and expanding the diagnostic criteria for depression. Gaining insight on the socio-culturally based differences in the areas of functioning in depression might be the key of promoting future culture-sensitive nosology accounting for functional impairment (Juhasz et al., 2012). At clinical level, with the development of a new instrument for functioning, clinicians experiencing time restraints should be given the opportunity to prioritize and meet the needs of patients promptly. Future studies following our line of research should be able to provide sufficient evidence for implementing national programs focusing on prevention and treatment of functional impairments in depression.

The present study has certain limitations. The data was cross-sectional, thus both QoL and functioning impairment were assessed at the same measurement point. However, our objective was to rank the importance rather than to explore temporal relations or infer causal relationships. Secondly, there were certain variations in the sample size of each country. For this study we selected only participants with depression, but both the COURAGE and SAGE samples were nationally representative. The differences in the number of depressed participants in each country might be due to differences in the prevalence of depression or cross-national differences in reporting in the self-reported instruments (Kessler and Bromet, 2013).

This is the first study to our knowledge to explore the differential impact of functioning domains on QoL in depression across different regions of the world. One of the strengths of the study is its large sample size and geographically and socio-economically diverse participants. Although more than 85% of the world's population lives in low- and middle-income countries, most of the evidence comes from high-income countries

(Saxena et al., 2006). Our paper, however, contributes with data not only from high-income countries, but also low and middle income countries. Our results showed that there was a variation in the importance of different functioning domains across countries. This is in line with the growing evidence that reporting functioning sum-scores blurs potential differences among people. The concealed variability within the concept of functioning has further led to disappointing findings—treatment in depression is only low-to-moderately efficacious for improving functioning (De Silva et al., 2013; Renner et al., 2014). Future research should focus on a more personalized approach to the assessment of functioning.

AUTHOR CONTRIBUTIONS

ML, PS, BT-A, SC, JH, MM, FC, and JA-M conceived, designed and performed the experiments; KK, FC, MC, and MM analyzed the data; KK, MC, MM, and FC wrote the paper; ML, PS, BT-A, SC, JH, JA-M, FC, MM, and MC made critical revisions of the manuscript for important intellectual content.

FUNDING

WHO's Study on Global Ageing and Adult Health (SAGE) is supported by the US National Institute on Aging through Interagency Agreements (OGHA 04034785; YA1323-08-CN-0020; Y1-AG-1005-01) and through research grants (R01-AG034479; 1R21AG034263). The research leading to these results has received funding from European Community's Seventh Framework Programme (grant agreement 223071 - COURAGE in Europe), Instituto de Salud Carlos III (FIS research grants PS09/00295, PS09/01845, PI12/01490, PI13/00059), Spanish Ministry of Economy and Competitiveness ACI-Promociona (ACI2009-1010), European Union Horizon 2020 Framework Programme for Research and Innovation (grant agreement 635316 - ATHLOS), People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013/ under REA grant Agreement n°316795, and Centro de Investigacion Biomedica en Red de Salud Mental. The authors sincerely acknowledge the immense contribution of the research participants from China, Finland, Ghana, India, Mexico, Poland, Russia, South Africa, and Spain, without whom this study would not have been possible. We would also like to acknowledge the principal investigators at the SAGE sites: P. Arokiasamy (India), R. Biritwum (Ghana), Wu Fan (China), R. López Ridaura (Mexico), T. Maximova (Russia) and N. Phaswanamafuya (South Africa). The views expressed in this paper are those of the author(s) and do not necessarily represent the views or policies of the World Health Organization.

REFERENCES

Alonso, J., Petukhova, M., Vilagut, G., Chatterji, S., Heeringa, S., Ustun, T. B., et al. (2011). Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. *Mol. Psychiatry* 16, 1234–1246. doi: 10.1038/mp.2010.101

Alvarezz, A. S. (2012). The application of the international classification of functioning, disability, and health in psychiatry: possible reasons for the lack of implementation. *Am. J. Phys. Med. Rehabil.* 91, S69–S73. doi: 10.1097/PHM.0b013e31823d4f1c

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edn, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association. doi: 10.1176/appi.books.9780890423349

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edn. Arlington, VA: American Psychiatric Publishing.

Arbuckle, J. L. (2013). *IBM SPSS Amos 22 User's Guide*. Crawfordville, FL: Amos Development Corporation.

Badia, X., and Alonso, J. (1995). Re-scaling the Spanish version of the sickness impact profile: an opportunity for the assessment of cross-cultural equivalence. *J. Clin. Epidemiol.* 48, 949–957. doi: 10.1016/0895-4356(94)00197-X

Badia, X., Roset, M., Herdman, M., and Kind, P. (2001). A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. *Med. Decis. Mak.* 21, 7–16. doi: 10.1177/0272989X0102 100102

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., et al. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 9:90. doi: 10.1186/1741-7015-9-90

Chisholm, D., Sanderson, K., Ayuso-Mateos, J. L., and Saxena, S. (2004). Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. *Br. J. Psychiatry* 184, 393–403. doi: 10.1192/bjp.184.5.393

Cieza, A., Chatterji, S., Andersen, C., Cantista, P., Herceg, M., Melvin, J., et al. (2004). ICF Core Sets for depression. *J. Rehabil. Med.* 44(Suppl.), 128–134. doi: 10.1080/16501960410016055

Cieza, A., Oberhauser, C., Bickenbach, J., Chatterji, S., and Stucki, G. (2014). Towards a minimal generic set of domains of functioning and health. *BMC Public Health* 14:218. doi: 10.1186/1471-2458-14-218

Cohen, R. M., Greenberg, J. M., and IsHak, W. W. (2013). Incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life in the individual burden of illness index for depression to measure treatment impact and recovery in MDD. *JAMA Psychiatry* 70, 343–350. doi: 10.1001/jamapsychiatry.2013.286

Cuijpers, P., and Schoevers, R. A. (2004). Increased mortality in depressive disorders: a review. *Curr. Psychiatry Rep.* 6, 430–437. doi: 10.1007/s11920-004-0007-y

da Rocha, N. S., Power, M. J., Bushnell, D. M., and Fleck, M. P. (2012). The EUROHIS-QOL 8-item index: comparative psychometric properties to its parent WHOQOL-BREF. *Value Health* 15, 449–457. doi: 10.1016/j.jval.92011.11.035

De Silva, M. J., Cooper, S., Li, H. L., Lund, C., and Patel, V. (2013). Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. *Br. J. Psychiatry* 202, 253–260. doi: 10.1192/bjp.bp.112.118018

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C.J., et al. (2013). Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med.* 10:e1001547. doi: 10.1371/journal.pmed.1001547

Fredman, L., Weissman, M. M., Leaf, P. J., and Bruce, M. L. (1988). Social functioning in community residents with depression and other psychiatric disorders: results of the new haven epidemiologic catchment area study. *J. Affect. Disord.* 15, 103–112. doi: 10.1016/0165-0327(88)90077-8

Fried, E. I., and Nesse, R. M. (2014). The impact of individual depressive symptoms on impairment of psychosocial functioning. *PLoS ONE* 9:e90311. doi: 10.1371/journal.pone.0090311

IsHak, W., Burt, T., and Sederer, L. E. (2002). *Outcome Measurement in Psychiatry: A Critical Review*. Washington, DC: American Psychiatric Publishing.

IsHak, W. W., Greenberg, J. M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., et al. (2011). Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harv. Rev. Psychiatry* 19, 229–239. doi: 10.3109/10673229.2011.614099

Juhasz, G., Eszlari, N., Pap, D., and Gonda, X. (2012). Cultural differences in the development and characteristics of depression. *Neuropsychopharmacol. Hung.* 14, 259–265. doi: 10.5706/nph201212007

Kamenov, K., Cabello, M., Coenen, M., and Ayuso-Mateos, J. L. (2015). How much do we know about the functional effectiveness of interventions for depression? A systematic review. *J. Affect. Disord.* 188, 89–96. doi: 10.1016/j.jad.2015.08.035

Kessler, R. C., and Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annu. Rev. Public Health* 34, 119–138. doi: 10.1146/annurev-publhealth-031912-114409

Kessler, R. C., and Ustun, T. B. (2004). The World Mental Health (WMH) survey initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int. J. Methods Psychiatr. Res.* 13, 93–121. doi: 10.1002/mpr.168

Kowal, P., Chatterji, S., Naidoo, N., Biritwum, R., Fan, W., Lopez Ridaura, R., et al. (2012). Data resource profile: the World Health Organization Study on global AGEing and adult health (SAGE). *Int. J. Epidemiol.* 41, 1639–1649. doi: 10.1093/ije/dys210

Lam, R. W., Parikh, S. V., Michalak, E. E., Dewa, C. S., and Kennedy, S. H. (2015). Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. *Ann. Clin. Psychiatry* 27, 142–149.

Leonardi, M., Chatterji, S., Koskinen, S., Ayuso-Mateos, J. L., Haro, J. M., Frisoni, G., et al. (2014). Determinants of health and disability in ageing population: the COURAGE in Europe project (collaborative research on ageing in Europe). *Clin. Psychol. Psychother.* 21, 193–198. doi: 10.1002/cpp.1856

Lux, V., and Kendler, K. S. (2010). Deconstructing major depression: a validation study of the DSM-IV symptomatic criteria. *Psychol. Med.* 40, 1679–1690. doi: 10.1017/S0033291709992157

McKnight, P. E., and Kashdan, T. B. (2009). The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. *Clin. Psychol. Rev.* 29, 243–259. doi: 10.1016/j.cpr.2009.01.005

Power, M. (2003). "Development of a common instrument for quality of life," in *EUROHIS: Developing Common Instruments for Health Surveys*. eds A. Nosikov and C. Gudex (Amsterdam: IOS Press), 145–159.

Renner, F., Cuijpers, P., and Huibers, M. J. (2014). The effect of psychotherapy for depression on improvements in social functioning: a meta-analysis. *Psychol. Med.* 44, 2913–2926. doi: 10.1017/S0033291713003152

Rogerson, P. A. (2001). *Statistical Methods for Geography*. London: Sage. doi: 10.4135/9781849209953

Salomon, J., Mathers, C., Chatterji, S., Sadana, R., Üstün, T., and Murray, C. (2003). "Quantifying individual levels of health: definitions, concepts, and measurement levels," in *Health Systems Performance Assessment: Debates, Methods, Empiricism*, eds C. J. L. Murray and D. B. Evans (Geneva: World Health Organization), 301–318.

Saxena, S., Paraje, G., Sharan, P., Karam, G., and Sadana, R. (2006). The 10/90 divide in mental health research: trends over a 10-year period. *Br. J. Psychiatry* 188, 81–82. doi: 10.1192/bjp.bp.105.011221

Sheehan, D. (1983). *The Anxiety Disease*. New York, NY: Scribner's.

Sheehan, D. V. (2004). Depression: underdiagnosed, undertreated, underappreciated. *Manag. Care* 13, 6–8.

Simon, G. E., Goldberg, D. P., Von Korff, M., and Ustun, T. B. (2002). Understanding cross-national differences in depression prevalence. *Psychol. Med.* 32, 585–594. doi: 10.1017/S0033291702005457

Skevington, S. M., Sartorius, N., and Amir, M. (2004). Developing methods for assessing quality of life in different cultural settings. The history of the WHOQOL instruments. *Soc. Psychiatry Psychiatr. Epidemiol.* 39, 1–8. doi: 10.1007/s00127-004-0700-5

Sobocki, P., Jonsson, B., Angst, J., and Rehnberg, C. (2006). Cost of depression in Europe. *J. Ment. Health Policy Econ.* 9, 87–98.

Ustun, T. B., Chatterji, S., Kostanjsek, N., Rehm, J., Kennedy, C., Epping-Jordan, J., et al. (2010). Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull. World Health Organ.* 88, 815–823. doi: 10.2471/BLT.09.067231

Üstun, T. B., Chatterji, S., Mechbal, A., and Murray, C. (2005). "Quality assurance in surveys: standards, guidelines and procedures," in *Household Sample Surveys in Developing and Transition Countries* ed. Department of Economic and Social Affairs Statistics Division of the United Nations (New York, NY: United Nations).

Volicer, L., Frijters, D. H. M., and Van Der Steen, J. T. (2011). Underdiagnosis and undertreatment of depression in nursing home residents. *Eur. Geriatr. Med.* 2, 332–337. doi: 10.1016/j.eurger.2011.08.001

Ware, J. E. Jr., and Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care* 30, 473–483. doi: 10.1097/00005650-199206000-00002

Waza, K., Graham, A. V., Zyzanski, S. J., and Inoue, K. (1999). Comparison of symptoms in Japanese and American depressed primary care patients. *Fam. Pract.* 16, 528–533. doi: 10.1093/fampra/16.5.528

Weigl, M., Cieza, A., Andersen, C., Kollerits, B., Amann, E., and Stucki, G. (2004). Identification of relevant ICF categories in patients with chronic health conditions: a Delphi exercise. *J. Rehabil. Med.* 44(Suppl.), 12–21. doi: 10.1080/16501960410015443

Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., Hwu, H. G., et al. (1996). Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 276, 293–299. doi: 10.1001/jama.1996.03540040037030

Weissman, M. M., Prusoff, B. A., Thompson, W. D., Harding, P. S., and Myers, J. K. (1978). Social adjustment by self-report in a community sample and in psychiatric outpatients. *J. Nerv. Ment. Dis.* 166, 317–326. doi: 10.1097/00005053-197805000-00002

World Health Organization (1992). *International Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10). Geneva: World Health Organization.

World Health Organization (2009). *Process of Translation and Adaptation of Instruments.* Available at: http://www.who.int/substance_abuse/research_tools/translation/en/

World Health Organization (2012). *World Suicide Prevention Day 2012.* Available at: http://www.who.int/mental_health/prevention/en/

Zimmerman, M., Martinez, J. H., Attiullah, N., Friedman, M., Toba, C., Boerescu, D. A., et al. (2013). A new type of scale for determining remission from depression: the remission from depression questionnaire. *J. Psychiatr. Res.* 47, 78–82. doi: 10.1016/j.jpsychires.2012.09.006

Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N., and Boerescu, D. (2006a). How should remission from depression be defined? The depressed patient's perspective. *Am. J. Psychiatry* 163, 148–150. doi: 10.1176/appi.ajp.163.1.148

Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Boerescu, D., and Attiullah, N. (2006b). Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. *Psychiatry Res.* 141, 185–191. doi: 10.1016/j.psychres.2005.05.016

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Submitted to Journal of Affective Disorders

Research recommendations for improving measurement of treatment effectiveness in depression

Kaloyan Kamenov[1, 2], *María Cabello*[1, 2], *Mónica Nieto*[3], *Renaldo Bernard*[4], *Elisabeth Kohls*[5], *Christine Rummel-Kluge*[5], *José Luis Ayuso-Mateos*[1, 2, 3*]

[1] Instituto de Salud Carlos III, Centro Investigación Biomédica en Red, CIBER, Madrid, Spain

[2] Department of Psychiatry, Universidad Autónoma de Madrid, Madrid, Spain

[3] Instituto de Investigación de La Princesa, (IIS-IP), Hospital Universitario de La Princesa, Madrid, Spain

[4] Department of Medical Informatics, Biometry and Epidemiology - IBE, Research Unit for Biopsychosocial Health, Ludwig-Maximilians-Universität München, Munich, Germany

[5] Faculty of Medicine, Department of Psychiatry, Leipzig University, Leipzig, Germany

*Corresponding author
Prof. José Luis Ayuso-Mateos, M.D. Ph.D.
Hospital Universitario de la Princesa
C/ Diego de León 62,
28006 Madrid, SPAIN
Phone: +34 914972716, Fax: +34 914972716
E-mail: joseluis.ayuso@uam.es

Abstract

Background: Despite the steadily escalating psychological and economic burden of depression, there is a lack of evidence for the effectiveness of available interventions on functioning areas beyond symptomatology. Therefore, the main objective of this study was to give an insight into the current measurement of treatment effectiveness in depression and to provide recommendations for its improvement.

Methods: The study was based on a multi-informant approach, comparing data from a systematic literature review, an expert survey with representatives from clinical practice (130), and qualitative interviews with patients (11) experiencing depression.

Results: Current literature places emphasis on symptomatic outcomes and neglects other domains of functioning, whereas clinicians and depressed patients highlight the importance of both. Interpersonal relationships, recreation and daily activities, communication, social participation, work difficulties were identified as being crucial for recovery. Personal factors, neglected by the literature, such as self-efficacy were introduced by experts and patients. Furthermore, clinicians and patients identified a number of differences regarding the areas improved by psychotherapeutic or pharmacological interventions that were not addressed by the pertinent literature.

Limitations: The literature review covered the last ten years of research and qualitative data was obtained from only 11 patients.

Conclusions: Creation of a new cross-nationally applicable measure of psychosocial functioning, broader remission criteria, report of domain-specific information, and a personalized approach in treatment decision-making are the first crucial steps needed for the improvement of the measurement of treatment effectiveness in depression. A better measurement will facilitate the clinical decision making and answer the escalating burden of depression.

Keywords: depression; functioning; intervention; outcome measure; treatment effectiveness

Introduction

Clinical guidelines recommend antidepressant medication (selective serotonin reuptake inhibitors [SSRIs], serotonin–norepinephrine reuptake inhibitors [SNRIs] and tricyclic antidepressants [TCAs]) or psychotherapy (e.g. cognitive behaviour therapy, interpersonal psychotherapy) as first choice treatment options for depression (McAllister-Williams, 2006; Patten et al., 2009). Results from randomized controlled trials and clinical guidelines suggest that internet based treatments and some complementary or alternative therapies, such as exercise or sleep deprivation, are also effective in the short term (Caliyurt and Guducu, 2005; Kvam et al., 2016). There is a large body of research on the effectiveness of these interventions in reducing depressive symptoms. Symptom improvement remains the main focus of clinical trials for depression, and the regulatory approval process for new medications and other interventions is based on symptomatology (Lam et al., 2015).

In spite of the large number of available interventions for depression and the huge evidence base on their effectiveness in terms of reducing symptom severity, the data show that more than 30% of all cases of depression are not adequately solved by first agent treatments (Kohn et al., 2004; National Collaborating Centre for Mental Health, 2010). The meta-analytical evidence of treatment effectiveness is also modest (Cuijpers et al., 2010; Khan and Brown, 2015). Moreover, depression has been ranked as one of the leading causes of burden in the Global Burden of Disease studies since 1990 (Whiteford et al., 2013). Some predictions indicate that it will be the greatest cause of disability worldwide by 2030 (World Health Organization, 2003). According to the World Health Organization (WHO), approximately 1 million people die from suicide every year (World Health Organization, 2003), and the majority of cases occur in the context of depression (Mann et al., 2005). In addition to the psychological burden on individuals, depression also has significant socio-economic costs. The direct and indirect costs of depression in the EU were estimated to be €92 billion in 2010 (Olesen et al., 2012). Nearly half of the costs were the result of productivity losses, indicating the enormous negative impact depression has on the economy.

Even though the lack of early detection and treatment of depression has been considered the main reason for the continuous burden of depression (World Health Organization, 2008), the lack of robust results poses the question of whether the current way of measuring depression is adequate or should be improved. Between 80% and 95% of all areas covered by the outcome measures in interventional studies represent clinical symptomatology (Brockow et al., 2004;

Kamenov et al., 2015; McKnight and Kashdan, 2009). Other relevant areas of functioning beyond symptoms, such as activity limitations or participation restrictions in different domains of life, like social functioning and daily activities (World Health Organization, 2001), are mostly secondary outcomes and often do not account for systematic analyses (Williams et al., 2000). A number of studies state that these areas might more accurately predict the clinical course of depression (Stefos et al., 1996), whereas qualitative research shows that patients have prioritized these functioning outcomes over symptomatic outcomes and determined the return to a normal level of functioning at work, home or school as a major factor for remission in depression (Zimmerman et al., 2006a). Concurrently, some studies provide evidence that these outcomes do not correspond to symptom-based outcomes (Lam et al., 2015). It has been suggested that if symptoms provide early signs of treatment response, functioning outcomes beyond symptoms rather provide an indicator of meaningful change for the patient (McKnight and Kashdan, 2009).

Recently, the Canadian Network for Mood and Anxiety Treatments (CANMAT) highlighted the need for conceptualization and measurement of functioning outcomes in clinical trials (Lam et al., 2015). The lack of gold standard measures for assessing functioning has also been a major critique in recent studies (Lam et al., 2015; Madden et al., 2015). To fill this research gap, the WHO developed an evidence-based Core Set for depression (Cieza et al., 2004) to address the broad spectrum of functioning in depression. However, this tool has not been sufficiently implemented in research studies due to its complexity and large number of categories (Alvarezz, 2012). In addition, two instruments incorporating symptomatic outcomes, functioning, and quality of life were created—the Individual Burden of Illness Index for depression (Cohen et al., 2013) and the Remission from Depression Questionnaire (Zimmerman et al., 2013)—but their validity is still insufficiently researched and therefore prevents broader usage in international research.

Thus, one of the potential reasons for the persisting burden of depression might be the lack of evidence on relevant and meaningful functioning difficulties for this disorder, possibly due to the lack of adequate functioning instruments (as mentioned above) or to the insufficient implementation of measures of functioning in clinical trials in general (Kamenov et al., 2015; Lam et al., 2015; Madden et al., 2015), which can assess comprehensively all areas affected by depression. This research gap was the impetus for the current study, which aimed to provide research recommendations for improving the measurement of treatment effectiveness in depression. More specifically, the study aimed to 1) provide information on the current areas included in the measurement of treatment effectiveness; 2) identify the areas that representatives from clinical practice and patients with depression consider relevant for inclusion in the assessment of psychotherapeutic, pharmacological or other complementary interventions; 3) compare the current status quo in research with the clinician and patient perspectives in order to identify the gaps in the measurement of treatment effectiveness; and 4) provide recommendations for its improvement and integration in future research.

To our knowledge, no previous study has focused on the improvement of treatment effectiveness measurement in depression. Such information would be very important for acquiring policy-relevant information on treatment effectiveness, disability and rehabilitation, as well as for linking the available evidence to the best possible care of depressed patients.

Methods

The present study was based on a comprehensive multi-informant approach, including data from a systematic literature review, expert clinicians in the field of depression, and patients currently diagnosed with depression. The opinion of clinical experts is essential for overcoming the gap between clinical research and the care of individual patients (Tonelli, 1999). However, qualitative research on patients living with a mental disorder was identified as one of the research priorities for public mental health in Europe (Forsman et al., 2015).

1. Systematic literature review

Full details of the systematic literature review are provided elsewhere (Kamenov et al., 2015); a concise description is presented below. An electronic search for studies assessing interventions in depressive disorders was performed using four databases: PsycINFO, PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials. Studies published between 2005 and 2015 were identified by including a set of sensitive MeSH terms and keywords indicative for intervention, depression and functioning. Studies were included if 1) participants were older than 18, 2) the diagnosis of depression was established by a standardized diagnostic tool, and 3) the sample included at least ten participants.

We grouped the treatments into three main categories: psychotherapy, pharmacotherapy and “other” therapies, such as sleep deprivation and exercise therapy (Patten et al., 2009). All primary and secondary outcome measures assessing functioning, quality of life or severity of symptoms that were already validated in depression samples were selected, and all individual items of the selected tools were extracted. The extracted items were analyzed and were linked to the International Classification of Functioning, Disability and Health (ICF) for operationalization purposes by applying the established linking rules (Cieza et al., 2005). The linking process was performed by two researchers. The items were grouped into ten overarching categories based on the ICF classification. A frequency analysis was conducted after all functioning problems were identified to present the percentage of the areas stratified by type of intervention.

2. Expert survey

The survey was available between March 2015 and March 2016. It was designed to collect data from practicing clinicians in the field of depression, assessing interventions used in their daily practice and the psychosocial difficulties addressed by these treatments.The short survey consisted of two questions: 1) “Choose the type of intervention(s) you usually use in your daily practice”; and 2) “List the psychosocial difficulties that this intervention(s) aims to improve in individuals with depression”. Participants could choose up to ten interventions. The aim was to obtain experts’ opinion on the areas that are captured by the specific treatments and that should be included in the assessment of interventions for depression. All answers concerning psychosocial difficulties were linked to the ICF categories according to the existing rules (Cieza et al., 2005). Additionally, some demographic data were collected.

To reflect different opinions and achieve a maximum variation sampling, a wide range of clinicians were approached: psychiatrists, psychotherapists, primary health care doctors and other physicians, social workers, and nurses, amongst others. Clinicians were selected if they had at least two years of clinical expertise in depression. In addition, we searched for the highest possible variability in terms of age, gender, nationality and type of therapy used in daily practice by the clinicians. Potential participants were identified through a number of sources—internal databases of international experts working in depression, heads of psychiatric hospitals and departments, professional websites for clinicians working in depression (e.g. www.commonlanguagepsychotherapy.org) —and through a snowball approach. Experts were sent an email invitation for participation in the survey. We expected a 50-70% non-response rate (Archer, 2008; Horgan and Dimitriou, 2015). Our target was to obtain a sample of 100 experts, and therefore the survey was sent to nearly 250 experts in depression. The study aimed to approach European experts; therefore, the majority of clinicians resided in Europe. However, for comparison purposes, data from non-European experts were also collected.

3. Qualitative interviews with patients with depression

The aim of the present study was to collect data from individuals diagnosed with depression on the treatments they were receiving/had received for depression and the psychosocial difficulties addressed by the interventions. Therefore, qualitative individual interviews with outpatients diagnosed with depression were performed. Participants had to meet the following inclusion criteria: 1) current, or history of, depressive episode in the previous 12 months as main diagnosis (depressive episode [F32], recurrent depressive episode [F33], or currently in partial or total remission [F33.4] according to the International Classification of Diseases) (World Health Organization, 1992); 2) sufficient cognitive capacity to participate in an interview (score > 26 on the mini-mental status examination (MMSE) (Folstein et al., 1975); 3) knowledge of the local language (Spanish); 4) age ≥ 18 years; 5) currently receiving treatment for depression, namely psychotherapy, pharmacotherapy or other treatment prescribed by their mental health professional; and 6) written informed consent. Ethics approval was obtained by the Hospital La Princesa Ethics Committee for Clinical Research in Madrid.

The recruitment of participants and data collection was performed in a public outpatient mental health unit at Hospital La Princesa (Madrid, Spain). Two mental health professionals working in the unit (one psychologist and one psychiatrist) collected the data between September 2015 and March 2016. All patients who met the inclusion criteria were informed about the study and invited to participate. All participants who agreed to participate gave their consent. The study consisted of a face-to-face interview with a research team member and comprised two parts. The first part was a series of demographic and clinical questions, which aimed to collect information on the patients' background (e.g. gender, age, type of depression, number of previous episodes, onset of the disorder and occupation). The second part assessed the type of treatment (psychotherapeutic, pharmacological or other) patients had received or were receiving, and their experience with the respective treatment. During an open personal interview, participants were asked about the psychosocial difficulties they were experiencing or had experienced in the past, and the ones that had or had not improved with the specific treatment they received. Data collection continued until a saturation point was reached, i.e. when the collection of new data did not shed any further light on the investigation we stopped recruiting

(Glaser and Strauss, 1967). More specifically, the major rule for determining saturation was when three consecutive patients in the same group of treatment did not report a new psychosocial difficulty. Participants receiving psychotherapy were allowed to receive additional antidepressant pharmacotherapy when they met the following criteria: no antidepressant dosage change one month prior to the start of the psychotherapeutic sessions or during the psychotherapeutic treatment. As only two patients had been treated with other (alternative or complementary) therapies, no data on "other" therapies is available from this qualitative study.

Recordings of the individual interview sessions were transcribed verbatim. The transcripts were checked by the moderator and the information was extracted and double-checked. All content concerning psychosocial difficulties was translated into English and coded according to ICF categories following the existing ICF linking rules (Cieza et al., 2005). Codification of themes and subthemes for interventions and psychosocial difficulties was double-checked by an independent researcher and analyzed by NVIVO program, version 11. All frequencies were analyzed with SPSS, version 21.

Results

1. Study characteristics

1.1. Literature review

A total of 247 articles, including 71,904 participants, were included in the final synthesis. A total of 66 interventions were identified, all of them grouped into three main categories: psychotherapies, pharmacotherapies or other therapies. The most common intervention within the psychotherapeutic category was CBT. Fluoxetine in particular and the group of SSRIs in general were the most prevalent antidepressants. Among the remaining therapies, St. John's wort was the first agent. A full summary of the study characteristics can be found elsewhere (Kamenov et al., 2015).

1.2. Expert survey

The study was sent to 250 practicing clinicians, with a 52% response rate. 130 clinicians from around the world filled out the survey. 95 were practicing specialists from 21 countries in Europe, and 35 (27%) were residing outside Europe. Among the non-Europeans, there were representatives from all continents, primarily from North and South America, with 15. The average age of the participants was 43 years (SD = 10.5). Males were a slight majority (55%). Experts' characteristics can be seen in Table 1.

Table 1: Characteristics of the experts (N=130) participating in the online survey

Variable	N (%)
Age	
18-34	32 (24.6%)
35-49	65 (50%)
50-64	31 (23.8%)
65+	2 (1.5%)
Females	59 (45%)
Years of experience mean (SD)	14 (10.23)
Non-European experts	35 (27%)
Psychiatrists	73 (56%)
Psychologists	44 (34%)
Others	13 (10%)

1.3.Qualitative interviews with patients

We conducted individual interviews with 11 patients who were receiving/had received in the last 12 months pharmacological or psychological treatment. Patients' diagnoses varied from being in partial remission (N = 4) to experiencing a current moderate episode (N = 5) of a major depressive disorder. The average age of the participants was 58 years (SD = 12), with a higher prevalence of women (73%). Patients' characteristics can be seen in Table 2.

Table 2: Sociodemographic and clinical characteristics of the patients with depression

Case	**Age**	**Gender**	**Occupation**	**Diagnosis**	**Number of previous episodes**	**Age of diagnosis**	**Comorbidity**
1	42	Female	Retired	Mild episode, currently in partial remission	0	40	Fibromyalgia
2	68	Female	Retired	Severe episode, currently in partial remission	1	64	No
3	48	Male	Currently working	Moderate episode, currently in partial remission	0	33	No
4	55	Female	Unemployed	Recurrent depression, currently in partial remission	10	25	Personality disorder
5	62	Female	Housewife	Recurrent depression, current moderate episode	2	55	No
6	86	Female	Retired	Recurrent depression, current moderate episode	No info	No info	No

7	54	Male	Currently working	Moderate episode	0	52	Psoriasis
8	60	Female	Currently working	Moderate episode	0	58	Psoriasis
9	65	Female	Housewife	Mild episode with somatic symptoms	1	53	No
10	48	Male	Unemployed	Moderate episode	2	38	HIV
11	55	Female	Unemployed	Mild episode	3	25	Cancer

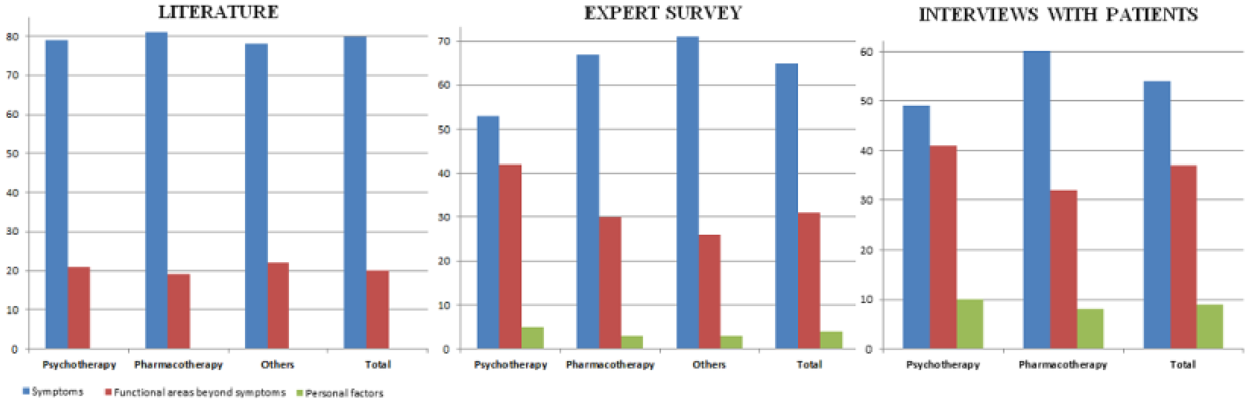
2. Comparison between literature, clinician and patient perspectives on treatment effectiveness

Results from the literature review showed that items related to clinical symptoms—such as global mental functions (confidence, temperament, personality functions), specific mental functions (emotional functions, cognitive functions, body image), energy (energy level, appetite) and sleep functions—accounted for about 65% of the total number of areas addressed within the outcome measures. Body functions representing somatic symptoms (e.g. pain, digestive or sexual problems) accounted for an additional 15–18% across studies. Other areas of functioning beyond symptomatology; such as interpersonal relationships, leisure activities, daily tasks and demands; or major life areas, such as employment or education, represented a very small percentage: 15–20% varying across the categories of interventions. Domains such as social participation or communication represented a negligible percentage.

Unlike results from the literature review, expert clinicians gave minor importance to areas related to clinical symptoms (65%, varying across therapies - from 54% in psychotherapy to 67% in pharmacotherapy). To the contrary, the areas beyond symptomatology had higher importance compared to their role in the literature (from 30% in pharmacotherapy to 43% in psychotherapies). Interpersonal relationships, general tasks and demands, employment and education were pointed out by clinicians as fundamental areas. Communication and social participation represented a major part (up to 10%) of the functioning problems covered by therapies. There were no major differences between the areas identified and the types of therapy used by European and non-European experts.

The qualitative interviews with patients showed patterns similar to those of the expert reports. Patients highlighted the importance of a set of symptoms that represented 54% of all functioning areas. The importance of symptoms such as weight change or change in appetite was underlined by the participants: "*As something that has improved, I can point to my appetite. I* *have an appetite again and have gained weight. I lost five kilos and now I've regained them. I think the reason is that I feel more or less like I did before…*" (P8). However, the areas beyond symptomatology (37% of all areas identified) were also important for patients with depression. Interpersonal relationships were the only domain that was mentioned by all patients: "*Yes, now I go out and meet people. Before when I saw someone in a shop I would turn around and leave because I didn't want him to stop me and talk to me*" (P2). Participants also highlighted problems at work, communication and daily activities as crucial areas. A summary of all relevant areas found in literature, expert and patient reports can be seen in Figure 1.

Figure 1: Comparison between the percentages of functioning areas identified in the literature, the expert survey with clinicians, and individual interviews with patients with depression



In addition, expert clinicians and patients identified a list of personal factors introducing the concept of "self"—self-perception, self-efficacy, self-acceptance, self-awareness, self-help, self-image and self-esteem—as a major part of the treatment process. These personal factors were neglected in the studies included in the systematic review, but constituted a relevant percentage in the answers of clinicians (4%) and patients (9%).

When the analysis was stratified by type of intervention, the literature did not reveal any differences among functioning areas included in studies applying psychotherapy, pharmacotherapy or other interventions. However, such differences were found in the expert reports. Pharmacological treatment appeared to address symptomatic areas much more than psychotherapy (67% vs. 53%), whereas psychotherapy focused more on functioning areas beyond symptoms. Interpersonal relationships and communication constituted 30% of the total number of areas covered by psychotherapies, whereas both had a substantially smaller share in pharmacotherapy (7%) and other therapies (13%). Furthermore, communication represented 13% of the total number of areas covered by psychotherapy, but in pharmacological interventions it constituted only 2%. Likewise, in patient reports, symptomatic areas (54%) were predominantly reported by patients under pharmacological treatment. Lack of motivation for doing things was a salient area on the list of difficulties, with 80% of all patients reporting it as an area improved by medication. , Regarding psychotherapeutic interventions, patients identified interpersonal relationships, communication and emotional difficulties as the three main areas of improvement. More specifically, problems within the family, with an intimate partner or close friends were the most commonly reported improved difficulties: "*Also, I have my family around now. It affects me in a positive way, because it's my family that I'm spending time with; I'm hiking in the mountain with my mother and my aunts. And this makes me happy*" (P4).

Discussion

This study breaks new ground by identifying the drawbacks of the current measurement of treatment effectiveness in depression and by providing research recommendations for its improvement. This was done by comparing a systematic review of the literature, examining the areas of functioning included in the measurement process, and the clinician and patient perspectives on the actual areas addressed by the treatments. Our results showed that current research emphasizes symptomatic outcomes and neglects other domains of functioning, as opposed to the opinion of clinicians and depressed patients, who highlighted the importance of both. The "self" concept (e.g. self-efficacy, self-awareness), which was not considered in the literature, was introduced by experts and patients as a domain that can be improved by treatments and has a huge impact on the overall condition of individuals. Furthermore, clinicians and patients identified a number of differences regarding the areas improved by psychotherapeutic, pharmacological and other treatments. Pharmacological treatments generally improved symptomatic domains to a higher extent. Experts expressed their preference in choosing antidepressants when targeting certain symptomatic difficulties, such as sleep or emotional functioning. Lack of motivation was an important issue for patients and they acknowledged the role of medications in its improvement. On the other hand, psychological treatments were the first choice for patients and experts when areas beyond symptoms were affected. Interpersonal relationships, problems in communication or lack of social participation were areas susceptible to change by psychotherapies. Self-care activities such as eating, dressing, taking care of one's look were also recovered by psychological interventions. Based on the obtained results, the following section provides a summary of recommendations for the improvement of the measurement of treatment effectiveness in depression.

1. *Identification of the most burdensome functioning areas in depression and creation of a new measure of psychosocial functioning*

Our results show that a small percentage of studies apply instruments measuring functioning areas beyond symptoms. The few studies that implement such tools do not provide comprehensive information on functioning, mainly due to the limited number of areas covered by the instruments. All clinicians and patients taking part in the present study identified a number of functioning domains (Table 3) as susceptible to change and crucial for assessment. This list of domains is the first step for the creation of a new instrument, which should include all relevant areas of psychosocial functioning, addressing together symptomatology and areas of functioning beyond symptoms. This unique tool should be comprehensive enough in regard to the health condition, and quick to administer if needed, to be applied in a clinical settings where practitioners have limited time and resources (Wittchen et al., 2001)— something that would provide comparability across studies. The instrument should also take into account differences across groups of patients by weighting the domains according to their importance. Thus, if for a certain group of patients who share similar characteristics, difficulties in communication and daily activities are prominent domains these should be given more weight than the other domains. However, our study is the first to assess this broad spectrum of psychosocial difficulties, and therefore more quantitative and qualitative research is needed to replicate our results and determine the most relevant domains of functioning.

Table 3: Functioning areas identified for inclusion in the measurement of treatment effectiveness

Mental functioning	Global and specific mental functions. Represents symptoms such as emotional functions, rumination, anxiety, anhedonia, feelings of hopelessness and guilt, suicidal ideation, or impaired cognitive functioning
Sleep	Problems in the onset, maintenance and quality of sleep
Energy level	Fatigue, loss of energy and motivation
Somatic functioning	Somatic symptoms, pain or impaired sexual functioning

Interpersonal interactions and relationships	Relationships within the family, intimate relations, relations with friends, or informal social relationships
Recreational and leisure activities	Hobbies, socializing, sports, arts and culture
Communication and social participation	Problems in communication, receiving and producing messages, participation in society, social activities, etc.
General tasks and demands	Problems in daily activities, household responsibilities, self-care, handling stress
Major life areas	Employment, education, economic life
Personal factors	Self-esteem, self-efficacy, self-image, self-awareness

2. A cross-nationally applicable measure of functioning

The majority of studies included in the systematic review provided evidence only from high-income countries. Knowledge on relevant areas in depression from low- and middle-income countries is sparse. The results from the expert survey did not reveal major differences in the answers of European and non-European clinicians; however, these results are not generalizable due to the small number of non-European clinicians. This lack of evidence suggests that a new instrument comprehensively assessing all relevant functioning areas should be also validated in different cross-national samples. Moreover, the instrument should be sensitive to country differences and be validated in different settings. More research from low-, middle-, and high-income countries is needed to provide country-specific functioning information.

3. Broader remission criteria

Remission of depression is currently defined solely in terms of symptom reduction (Zimmerman et al., 2006b) according to cut-off scores on symptom severity scales, such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967), Beck Depression Inventory (BDI) (Beck et al., 1961) or the Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979). A more comprehensive definition of remission is needed to adequately reflect the experience of depressed patients under treatment. Our results show that improvement in functioning areas beyond symptoms is as important as the reduction in symptomatology. One possibility is the creation of a new instrument covering not just symptomatic aspects, but all relevant affected areas. There are already initial steps in this direction. Cohen et al. (Cohen et al., 2013) created an Individual Burden of Illness Index for depression to measure treatment impact and recovery in depression by incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life (QoL). Zimmerman et al. (2014) subsequently validated a new instrument: the Remission from Depression Questionnaire, encompassing different domains of functioning and QoL, along with symptomatology. These authors conclude that their new tool provides a broader perspective on depressed patients' condition than purely symptom-based measures and is more consistent with the biopsychosocial approach in the treatment of depression. However, these tools are still in their infancy and need further validation. Another possibility involves a separate definition of functional remission alongside symptom assessment. An example is a study by Mancini et al. (2012), which applied such criteria, based on the Sheehan Disability Scale (Sheehan, 1983). Future studies should aim to achieve such broader remission criteria.

4. Reporting domain-specific information rather than sum-scores of questionnaires for functioning

Results from the literature review showed that more than 80% of the interventional studies published in the last decade reported only sum-scores of instruments assessing functioning rather than domain-specific information. Despite some methodological and practical advantages of aggregating scores from different domains, these sum-scores also obscure potential differences among people and do not provide detailed information on the differential impact of certain functioning domains on the overall state of depressed persons. A higher sum-score might mean a higher number of less affected functioning areas or a smaller number of domains with marked deterioration. Reporting domain-specific information will potentially reveal differential trajectories in the course of depression, interrelations between distinct domains of functioning, and most importantly, will lead to a more personalized approach in the treatment of depression.

5. ***Personalized approach in treatment decision making***

Current treatment decision making is primarily based on evidence-based medicine. Thus, clinical guidelines recommend psychotherapy and pharmacological agents for all patients as first-line treatments. The regulatory approval process for new medications and other interventions is based primarily on symptomatology. Our results, however, showed that psychotherapeutic and pharmacological interventions targeted the range of functioning difficulties in the population to a different extent. Moreover, patients and experts highlighted the importance of functioning difficulties beyond symptoms in the recovery process. There is a need for a more personalized approach in treatment decision-making that acknowledges specific patient needs and accounts for a more comprehensive array of functioning domains. More research is also needed to explore the effectiveness of the available interventions in each of the relevant functioning areas.

Even though the present study considered all possible perspectives on the measurement of treatment effectiveness, some methodological limitations should be mentioned. First of all, the literature review covered only the last ten years of research, because we aimed to explore the latest trends in assessing treatment effectiveness. Secondly, approximately 70% of the clinicians that took part in the online survey were European. Even though we achieved a representation of non-European experts, wider participation of the latter may have provided different perspectives on the topic. Finally, data was obtained from only 11 patients from Spain. Our approach was the attainment of a saturation point in individuals’ answers, but more patients, with different cultural backgrounds, could have enriched the data.

The present study is the first to our knowledge to provide recommendations for improved treatment measurement using a methodology based on a multi-informant approach. Clinician and patient perspectives are essential for informing the context of clinical research, and overcoming the gap between clinical research and the care of individual patients. We believe that more accurate and comprehensive evidence on the effectiveness of available interventions for depression is needed to answer the steadily escalating societal and economic burden of the disease. Moreover, future research should explore the results of this study further, and apply its recommendations.

References

1. Alvarez, A.S., 2012. The application of the International Classification of Functioning, Disability, and Health in psychiatry: possible reasons for the lack of implementation. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists 91, S69-73.
2. Archer, T.M., 2008. Response rates to expect from Web-based surveys and what to do about it. . Journal of Extension [Online] 46(3)
3. Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of general psychiatry 4, 561-571.
4. Brockow, T., Wohlfahrt, K., Hillert, A., Geyh, S., Weigl, M., Franke, T., Resch, K.L., Cieza, A., 2004. Identifying the concepts contained in outcome measures of clinical trials on depressive disorders using the International Classification of Functioning, Disability and Health as a reference. Journal of rehabilitation medicine, 49-55.
5. Caliyurt, O., Guducu, F., 2005. Partial sleep deprivation therapy combined with sertraline induces more rapid improvements in quality of life items in major depressive disorder. Journal of affective disorders 88, 75-78.
6. Cieza, A., Chatterji, S., Andersen, C., Cantista, P., Herceg, M., Melvin, J., Stucki, G., de Bie, R., 2004. ICF Core Sets for depression. Journal of rehabilitation medicine, 128-134.
7. Cieza, A., Geyh, S., Chatterji, S., Kostanjsek, N., Ustun, B., Stucki, G., 2005. ICF linking rules: an update based on lessons learned. Journal of rehabilitation medicine 37, 212-218.
8. Cohen, R.M., Greenberg, J.M., IsHak, W.W., 2013. Incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life in the Individual Burden of Illness Index for Depression to measure treatment impact and recovery in MDD. JAMA psychiatry 70, 343-350.
9. Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S.D., Andersson, G., 2010. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. Psychological medicine 40, 211-223.
10. Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 12, 189-198.
11. Forsman, A.K., Wahlbeck, K., Aaro, L.E., Alonso, J., Barry, M.M., Brunn, M., Cardoso, G., Cattan, M., de Girolamo, G., Eberhard-Gran, M., Evans-Lacko, S., Fiorillo, A., Hansson, L.,

Haro, J.M., Hazo, J.B., Hegerl, U., Katschnig, H., Knappe, S., Luciano, M., Miret, M., Nordentoft, M., Obradors-Tarrago, C., Pilgrim, D., Ruud, T., Salize, H.J., Stewart-Brown, S.L., Tomasson, K., van der Feltz-Cornelis, C.M., Ventus, D.B., Vuori, J., Varnik, A., 2015. Research priorities for public mental health in Europe: recommendations of the ROAMER project. European journal of public health 25, 249-254.

12. Glaser, B.G., Strauss, A.L., 1967. The Discovery of Grounded Theory: Strategies for Qualitative Research. Chicago, Aldine Publishing Company.

13. Hamilton, M., 1967. Development of a rating scale for primary depressive illness. The British journal of social and clinical psychology 6, 278-296.

14. Horgan, D., Dimitriou, H., 2015. Depression Treatment Survey of Psychiatrists: Outcome and Side Effects. Annals of Psychiatry and Mental Health 3(7): 1048.

15. Kamenov, K., Cabello, M., Coenen, M., Ayuso-Mateos, J.L., 2015. How much do we know about the functional effectiveness of interventions for depression? A systematic review. Journal of affective disorders 188, 89-96.

16. Khan, A., Brown, W.A., 2015. Antidepressants versus placebo in major depression: an overview. World Psychiatry 14, 294-300.

17. Kohn, R., Saxena, S., Levav, I., Saraceno, B., 2004. The treatment gap in mental health care. Bulletin of the World Health Organization 82, 858-866.

18. Kvam, S., Kleppe, C.L., Nordhus, I.H., Hovland, A., 2016. Exercise as a treatment for depression: A meta-analysis. Journal of affective disorders 202, 67-86.

19. Lam, R.W., Parikh, S.V., Michalak, E.E., Dewa, C.S., Kennedy, S.H., 2015. Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists 27, 142-149.

20. Madden, R.H., Glozier, N., Fortune, N., Dyson, M., Gilroy, J., Bundy, A., Llewellyn, G., Salvador-Carulla, L., Lukersmith, S., Mpofu, E., Madden, R., 2015. In search of an integrative measure of functioning. International journal of environmental research and public health 12, 5815-5832.

21. Mancini, M., Sheehan, D.V., Demyttenaere, K., Amore, M., Deberdt, W., Quail, D., Sagman, D., 2012. Evaluation of the effect of duloxetine treatment on functioning as measured

by the Sheehan disability scale: pooled analysis of data from six randomized, double-blind, placebo-controlled clinical studies. International clinical psychopharmacology 27, 298-309.

22. Mann, J.J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., Hegerl, U., Lonnqvist, J., Malone, K., Marusic, A., Mehlum, L., Patton, G., Phillips, M., Rutz, W., Rihmer, Z., Schmidtke, A., Shaffer, D., Silverman, M., Takahashi, Y., Varnik, A., Wasserman, D., Yip, P., Hendin, H., 2005. Suicide prevention strategies: a systematic review. Jama 294, 2064-2074.

23. McAllister-Williams, R.H., 2006. NICE guidelines for the management of depression. Br J Hosp Med (Lond) 67, 60-61.

24. McKnight, P.E., Kashdan, T.B., 2009. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. Clinical psychology review 29, 243-259.

25. Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 134, 382-389.

26. National Collaborating Centre for Mental Health, 2010. Depression: The Treatment and Management of Depression in Adults (Updated Edition), Leicester (UK).

27. Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.U., Jonsson, B., 2012. The economic cost of brain disorders in Europe. European journal of neurology 19, 155-162.

28. Patten, S.B., Kennedy, S.H., Lam, R.W., O'Donovan, C., Filteau, M.J., Parikh, S.V., Ravindran, A.V., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. Journal of affective disorders 117 Suppl 1, S5-14.

29. Sheehan, D., 1983. The Anxiety Disease. Scribner's: New York.

30. Stefos, G., Bauwens, F., Staner, L., Pardoen, D., Mendlewicz, J., 1996. Psychosocial predictors of major affective recurrences in bipolar disorder: a 4-year longitudinal study of patients on prophylactic treatment. Acta psychiatrica Scandinavica 93, 420-426.

31. Tonelli, M.R., 1999. In defense of expert opinion. Academic medicine : journal of the Association of American Medical Colleges 74, 1187-1192.

32. Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575-1586.

33. Williams, J.W., Jr., Mulrow, C.D., Chiquette, E., Noel, P.H., Aguilar, C., Cornell, J., 2000. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Annals of internal medicine 132, 743-756.

34. Wittchen, H.U., Holsboer, F., Jacobi, F., 2001. Met and unmet needs in the management of depressive disorder in the community and primary care: the size and breadth of the problem. The Journal of clinical psychiatry 62 Suppl 26, 23-28.

35. World Health Organization, 1992. International classification of diseases and related health problems, 10th Revision (ICD-10). Geneva: World Health Organization.

36. World Health Organization, 2001. International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization.

37. World Health Organization, 2003. The world health report 2003: Shaping the future.

38. World Health Organization, 2008. mhGAP: Mental Health Gap Action Programme: scaling up care for mental, neurological and substance use disorders.

39. Zimmerman, M., Martinez, J.H., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., 2014. The remission from depression questionnaire as an outcome measure in the treatment of depression. Depression and anxiety 31, 533-538.

40. Zimmerman, M., Martinez, J.H., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., Ragheb, M., 2013. A new type of scale for determining remission from depression: the Remission from Depression Questionnaire. Journal of psychiatric research 47, 78-82.

41. Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Attiullah, N., Boerescu, D., 2006a. How should remission from depression be defined? The depressed patient's perspective. The American journal of psychiatry 163, 148-150.

42. Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Boerescu, D., Attiullah, N., 2006b. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. Psychiatry research 141, 185-191.

6. DISCUSSION

6.1. Evaluation of the current measurement of treatment effectiveness for psychosocial impairment in depression, limitations identified and arguments for creating new evidence

Results from the systematic literature review showed that despite the enormous importance of disability in depression, the effectiveness of all available interventions for depression is still assessed mainly in terms of reduction of clinical symptoms, whereas other areas of functioning are neglected. This was imposingly demonstrated by the fact that every study analyzed in our review applied at least one measure of severity of symptoms, but only less than 20% of the applied questionnaires addressed other areas of functioning. More specifically, QoL measures represented between 14%, and 19% of the overall number of instruments used in studies, whereas tools that measured other areas of functioning (e.g. social functioning) were between 3% and 7.5%.

Similarly, the elaborate content item analysis revealed that around 80% of the areas covered by the outcome measures represented clinical symptomatology. Items related to clinical symptoms like global mental functions (confidence, temperament, and personality functions), specific mental functions (emotional functions, cognitive functions, body image, etc.), energy (e.g. energy level, appetite), sleep functions and body functions representing somatic symptoms (e.g. pain, digestive or sexual problems) were prevailing. Other areas of functioning that were not strictly linked to symptomatology, such as interpersonal relationships (family and partner relationships, informal relationships with friends), leisure activities, daily tasks and demands (daily activities, domestic life, doing housework), or major life areas, such as employment or education, represented a very small percentage.

The meta-analyses that we conducted aimed to reveal the effectiveness of available interventions for depression on psychosocial functioning and to review the process of assessment, the instruments used and the level of evidence provided in literature. The articles provided comprehensive evidence that existing psychological and pharmacological interventions are efficacious for improving psychosocial difficulties. This is a substantial finding considering the importance of these outcomes from patient perspective. There was no robust evidence that one of the groups of interventions was superior, although psychotherapy appeared slightly superior to medication. Both psychotherapeutic and pharmacological interventions and CBT in particular showed better results at reducing symptoms of depression than improving the level of functioning and QoL. This is in line with the current state-of-art of research on depression, focused more on symptom severity rather than functional areas beyond symptoms.

Functional impairment beyond symptoms is seen by current research as a consequence of the health condition and the betterment of symptoms is hence the primary source of improving functioning. However, it might be that the functional instruments used to measure level of functioning are not sensitive and comprehensive enough to reflect the real experience of patients with depression. It has been suggested by researchers (Kamenov et al., 2015; Lam et al., 2015; Madden et al., 2015) that the current functional instruments are somehow limited and do not assess accurately other areas of functioning beyond symptoms.

Another interesting finding comes from the series of meta-regression analyses that we performed, suggesting that functional outcomes beyond symptoms improve when symptom severity improves. However, which is the leading factor is still unknown. Previous research suggests that functional recovery appears later than the symptomatic one and certain level of impairment continues even after the symptomatology is ameliorated. The residual functional impairment has been found to evoke relapse and recurrences (Vittengl et al., 2009); therefore functional outcomes should be directly targeted in the response and remission criteria for a more comprehensive assessment of treatment efficacy.

The meta-analyses revealed several major limitations in the current measurement of treatment effectiveness in depression. Firstly, the effect sizes from all analyzes performed were relatively modest, suggesting that interventions are efficacious for improving psychosocial outcomes, but do not reach out successfully to every patient. One reason for this phenomenon might be the nature of the interventions, which are rather created and designed to alleviate symptom severity than improving functional outcomes beyond symptomatology. Another reason might be the small number of studies applying functional outcomes, which did not allow for generalizability of the results. A third reason might be the inability of functional outcome measures to accurately reflect changes in functional impairment. This suggests that new instruments should be designed to comprehensively assess the effectiveness of different therapies on psychosocial functioning in depression.

A second limitation, as mentioned above, was the very small number of studies that were found to apply outcome measures for functional areas beyond symptoms. The small number of studies did not allow us to perform some analyses, such as a direct comparison of different psychotherapies or antidepressants, and lowered the powered of some of the analyses we conducted. More studies applying functioning and QoL instruments are needed to provide sufficient data for robust conclusions. Secondly, there were a large number of instruments used in the clinical trials, which were heterogeneous in their nature, even though they assessed domains of functioning in general. Some questionnaires assessed general functioning, such as Global Assessment of Functioning (GAF) (Aas, 2010), others assessed only components of psychosocial functioning, such as social functioning (Weissman et al., 1978), mental functioning or work-related functioning (Mundt et al., 2002). Even though the subgroup analyses we performed to analyze the impact of each questionnaire on the general effect of therapies did not reveal any significant difference between the instruments, this lack of coherence in the assessment process suggests further consistency in the selection of instruments and new evidence for a better and more comprehensive outcome measure.

A third major limitation that we detected was the lack of long-term data on the effectiveness of different therapies. Less than one third of the studies reported any follow-up data, which did not allow for separate analysis of long-term effectiveness. Long-term assessment would allow to further investigate the interrelations between different functional outcomes and to capture more comprehensively the changes in the psychosocial functioning of individuals. The last limitation we identified was the sole report of sum-scores of questionnaires. Despite some methodological and practical advantages of aggregating scores from different domains, the sum-scores obscure potential differences among people and do not provide detailed information on the differential impact of certain functioning domains on the overall state of depressed persons. Without knowing how different functional areas react to different therapies, we would not be able to obtain more personalized information on the needs of particular groups of individuals. Personalization of therapies is needed to further explore potential differences among patients. It is possible that the psychological treatments are less effective in some populations, and the added value of pharmacological treatments increases, or the other way around. Future studies should report domain-specific information for better understanding of the trajectories of change in psychosocial functioning in depression.

In conclusion, the findings from the systematic literature review and the two meta-analyses revealed discordance between established research priorities, namely the importance of functional outcomes in depression research, and their actual implementation in literature. This discrepancy poses the question how much do we know about the level of effectiveness of interventions for depression on vital areas of everyday life. Furthermore, it warrants future empirical steps towards improving the current assessment of treatment effectiveness in depression.

6.2. Empirical evidence collected to address the limitations in the current measurement of treatment effectiveness in depression

The best possible way to address the limitations in current research and the need for better assessment of functional effectiveness of interventions for depression is to directly collect empirical evidence. For that purpose we firstly analyzed data from two multi-country projects—the World Health Organization's Study on Global Ageing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE) in order to identify 1) the most burdensome functional domains in depression, 2) gender differences in functional impairment and 3) country variability in psychosocial functioning. This information serves as a basis for further development of more sensitive, cross-nationally validated and user-friendly instrument weighting the domains according to their importance.

Our findings suggest that affect or emotional functioning, interpersonal relationships and domestic life and work had the highest impact on quality of life in depression. Sleep and energy, mobility and cognition were also important factors, but their effect was smaller. Self-care and pain were the only domains that were non-significant for men or women. A possible explanation might be that the participants showed relatively higher levels of self-care and lower levels of pain, and severe decrements in these domains were rare. The importance of emotional functioning has been already determined in previous studies for depression (Cieza et al., 2014). Interpersonal activities, which was the second most important domain in our study, the notion that people with depression experience significantly poorer intimate relationships and less satisfying social interactions than individuals with other psychiatric disorders, or the general population (Fredman et al., 1988).

The study also revealed particular gender differences in the functional impairment of depression. For example, for women affect remained the most important functioning area, followed by interpersonal activities, domestic life and work, mobility and cognition. Men, however, showed different patterns compared to women. Affect was still the most fundamental factor, but sleep and energy appeared to be the second major functioning area. Self-care was only marginally significant, whereas cognition, mobility, and pain were not statistically significant functioning domains in men. This is an important finding which needs further exploration in other cross-national samples, given the higher prevalence of depression in women compared to men. Different level of impairment in specific functioning areas might be a key to the understanding of these different prevalence rates.

We further examined differences across the nine included countries. Affect was significant in all countries except China. This supports previous evidence that emotional problems, such as low mood, are a core part of the experience of depression (Fried and Nesse, 2014) and chronic physical or mental conditions in general (Weigl et al., 2004). However, most of the generic functioning tools, such as WHODAS-II (Ustun et al., 2010), do not include affect as a single domain. Difficulties in interpersonal activities were also prevailing in most of the countries. However, the rest of the domains were country specific. Cognition was associated with QoL in Poland, India and Mexico; mobility in Spain; and sleep and energy in India, South Africa and China. The reason why some functioning domains were associated with QoL only in some countries but not in others is unclear, but certain cultural contrasts might be responsible for these variations. For instance, in our study mobility was more important for the Spanish population than for any other country. Previous studies evaluating the health status in general population confirm this result, showing that Spanish people place more importance on mobility as a functioning domain compared to other countries due to cultural or lifestyle characteristics (Badia and Alonso, 1995; Badia et al., 2001).

In summary, in terms of research, our study raises the question about the importance of assessing functioning in clinical trials and expanding the diagnostic criteria for depression. Gaining insight on the socio-culturally based differences in the areas of functioning in depression might be the key of promoting future culture-sensitive nosology accounting for functional impairment (Juhasz et al., 2012). At clinical level, with the development of a new instrument for functioning, clinicians experiencing time restraints should be given the opportunity to prioritize and meet the needs of patients promptly. Future studies following our line of research should be able to provide sufficient evidence for implementing national programs focusing on prevention and treatment of functional impairments in depression.

Furthermore, we collected information from representatives from clinical practice and patients experiencing depression. Clinical experts opinion was essential for informing the context of clinical research and necessary to overcome the gap between clinical research and the care of individual patients (Tonelli, 1999). On the other hand, qualitative research with patients living with a mental disorder has been identified as one of the research priorities for public mental health in Europe

(Forsman et al., 2015). Obtaining patient perspective provides a fundamental knowledge on the complexity of public mental health and enhanced understanding of the community context.

The results from the expert survey and qualitative interviews highlighted the incongruity between the current research giving emphasis on the symptomatic outcomes and neglecting other domains of functioning beyond depressive symptoms and the opinion of clinicians and depressed patients underlining the importance of both. Interpersonal relationships, recreation and leisure activities, communication and social participation, daily activities, work and educational difficulties were identified by experts and patients as crucial for recovery from depression. Furthermore, some personal factors, such as the “self” concept (self-efficacy, self-awareness, self-image), which was not considered in the literature, was introduced by experts and patients as a domain that can be improved by treatments and has a huge impact on the overall condition of individuals.

Another important contribution of clinicians and patients was the identification of a number of differences regarding the areas improved by different types of interventions – psychotherapeutic or pharmacological. Pharmacological treatments generally improved to higher extent symptomatic domains. Experts expressed their preference in choosing antidepressants when certain symptomatic difficulties such as sleep or emotional functioning should be targeted. Motivation was an important feature for patients and they acknowledged the role of medications for its improvement. On the other hand, psychological treatments were the first choice when other functional areas beyond symptoms were affected. Interpersonal relationships, problems in communication or lack of social participation were areas susceptible to change by psychotherapies. Self-care activities such as eating, dressing, taking care of one's look were also recovered by psychological interventions. Thus, in summary, patients and clinicians acknowledged the entirety of the concept of psychosocial functioning, giving similar importance to both symptoms and areas of functioning beyond symptoms. Findings from the literature, however, showed the total prevalence of depressive symptoms over other areas of psychosocial functioning.

Based on the obtained empirical results, which aimed to address the limitations of the current research, the following section provides a set of recommendations for improving the measurement of treatment effectiveness in depression. These recommendations are an initial step towards more comprehensive and adequate assessment of interventions in depression but do not pretend to be exhaustive. Future studies are needed to replicate our findings or expand our research line.

6.3. Research recommendations for improving the assessment of treatment effectiveness in depression

1. Identification of the most burdensome functioning areas in depression and creation of a new measure of psychosocial functioning

Our results proved that there is a variation in the level of decrements in different functioning domains including symptoms and functional areas beyond symptomatology. The results were validated in nine different countries in Asia, Africa, Europe, and Latin America. On the other hand, literature shows that only a minor percentage of studies apply instruments measuring functional areas beyond symptoms. The few studies that implement such tools do not provide comprehensive information on functioning mainly due to the limited number of areas covered by the instruments. Therefore, based on the data obtained in the present thesis several domains of functioning identified as susceptible to change and crucial for assessment are presented in table 3.

This is the first step for the creation of a new instrument that should include all relevant areas of psychosocial functioning addressing together symptomatology together with other relevant areas of functioning in depression. This unique tool should be comprehensive enough in regard to the health condition and quick to administrate if needed to be applied in a clinical settings where practitioners have limited time and resources (Wittchen et al., 2001). This option would provide comparability across studies. The instrument should also take into account differences across groups of patients by weighting the domains according to their importance. Thus, if for certain groups of patients sharing similar characteristics employment problems and daily activities are prominent domains, they should be given more weight than the rest of the domains. However, our study is the first to assess this broad spectrum of psychosocial difficulties and therefore more quantitative and qualitative research to replicate our results and determine the most relevant domains of functioning is needed.

Table 3. Functional areas identified for inclusion in the measurement of treatment effectiveness

Mental functioning	Global and specific mental functions. Represents symptoms like emotional functions, rumination, anxiety, anhedonia, feelings of hopelessness and guilt, suicidal ideation, or cognitive functioning
Sleep	Problems in the onset, maintenance and quality of sleep
Energy level	Fatigue, loss of energy and motivation
Somatic functioning	Somatic symptoms, pain or sexual functioning
Interpersonal interactions and relationships	Relationships within the family, intimate relations, relations with friends, or informal social relationships
Recreational and leisure activities	Hobbies, socializing, sports, arts and culture
Communication and social participation	Problems in communication, receiving and producing messages, participation in society, social activities, etc.
General tasks and demands	Problems in daily activities, household responsibilities, self-care, handling stress
Major life areas	Employment, education, economic life
Personal factors	Self-esteem, self-efficacy, self-image, self-awareness

2. A cross-nationally applicable measure of functioning in depression

Firstly, the majority of studies included in the systematic review provided evidence from high-income countries. Evidence for relevant areas in depression from low- and middle-income countries was sparse. Secondly, the results from our expert survey did not reveal major differences in the answers of European and non-European clinicians, or in the reports of clinicians working in high-, middle- or low-income countries. However, the representation of non-European experts in our study was not high enough to provide robust results. More research in low- and middle-income countries is warranted. Finally, findings from the two multi-country projects, namely World Health Organization's (WHO) Study on Global Ageing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE in Europe), revealed gender and country specific differences in the importance of several functioning domains in depression. If interpersonal interactions were significant in all countries except Mexico, China and South Africa, physical pain was significantly associated with QoL only in Spain, Poland, India and Ghana. There is a need of a newly developed instrument comprehensively assessing all relevant functioning areas that should be validated in different cross-national samples. Moreover, the instrument should be sensitive to the country differences and provide information that is specific for the particular setting. This can be done by weights in the calculation of the scores. However, more research is needed to assess differences across countries.

3. Broader remission criteria in depression

Remission of depression is currently defined solely in terms of symptom reduction (Zimmerman et al., 2006b) according to cut-off scores on symptom severity scales such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967), Beck Depression Inventory (BDI) (Beck et al., 1961) or the Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979). As our qualitative and expert study underlined, a more comprehensive definition of remission is needed to adequately reflect the experience of depressed patients under treatment. Our results show that improvement in functioning areas other than symptoms is as important as the reduction in functional areas related to symptomatology.

One possibility is the creation of a new instrument covering not just the symptomatic, but all relevant affected areas. There are already initial steps in this direction. Cohen et al. (2013) have created an Individual Burden of Illness Index for depression to measure treatment impact and recovery in depression by incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and QoL. Later on, Zimmerman et al. (2014) validated a new instrument – the Remission from Depression Questionnaire, encompassing different domains of functioning and QoL along with symptomatology. The authors conclude that the new tool provides a broader perspective of depressed patients' condition than purely symptom based measures and is more consistent with the biopsychosocial approach in the treatment of depression. However, these tools are still in their infancy and need further validation. Another possibility involves separate definition of functional remission alongside depressive symptom assessment. An example is a study by Mancini et al. (Mancini et al., 2012), which applied such criteria based on the Sheehan Disability Scale (Sheehan, 1983). Future studies should be designed towards the achievement of such broader remission criteria.

4. Report of domain-specific information

Results of the literature review revealed that more than 80% of the interventional studies published in the last decade reported only sum-scores of instruments assessing global functioning rather than domain-specific information (Kamenov et al., 2015). Despite some methodological and practical advantages of aggregating scores from different domains, the sum-scores obscure potential differences among people and do not provide detailed information on the differential impact of certain functioning domains on the overall state of depressed persons. A higher sum-score might mean a higher number of less affected functioning areas or a smaller number of domains with marked decrements.

Reporting domain-specific information will potentially reveal differential trajectories in the course of depression, interrelations between distinct domains of functioning, and most importantly – will lead to a more personalized approach in the treatment of depression. Some of the findings of this thesis supported the importance of reporting domain-specific information. Findings from the World Health Organization’s (WHO) Study on Global Ageing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE in Europe), two multi-country projects, revealed that different domains of functioning had differential impact on the overall conditions of patients with depression. Moreover, there were certain gender differences in terms of impaired domains. Thus, reporting only a sum-score combining the results of distinct functional domains should obscure valuable and important differences among individuals.

5. *Personalized approach in treatment decision making*

Current treatment decision making is based on evidence-based medicine. Thus, clinical guidelines recommend psychotherapy and pharmacological agents for all patients as first line treatments. The regulatory approval process for new medications and other interventions is based primarily on symptomatology. However, different psychological and pharmacological interventions are also designed to improve other areas of functioning beyond symptoms. This is confirmed by the results obtained from clinician and patient opinions, showing that psychotherapeutic and pharmacological interventions targeted to a different extent the range of functional difficulties in the population. Moreover, patients and experts highlighted the importance of functional difficulties beyond symptoms in the recovery process. There is a need of a more personalized approach in treatment decision making acknowledging specific patient needs and accounting for a more comprehensive array of functional domains. More research is also needed to explore the effectiveness of the available interventions on each of the relevant functioning areas.

6.4. Limitations of the thesis

The present thesis has certain weaknesses which need to be presented. The limitations of each study are listed below.

Systematic literature review

First, the literature search was limited to articles published between 2005 and 2014. This time period was chosen because we intended to analyze the trends in measuring treatment effectiveness in depression after the publication of the last published review of literature on this topic (Brockow et al., 2004). Second, articles were only selected if published in English. This could have left out relevant information published in other languages. Third, because of the wide variety of studies, we analyzed only instruments used in more than three studies included in the review. Thus, we might have omitted a comprehensive outcome measure with a broader scope. Another methodological limitation is the inclusion of trials that did not meet any quality criteria. This was done to avoid any publication bias and capture in a comprehensive way the literature on depression in its current form.

Meta-analyses

The number of studies was relatively small and the results of some of the analyses we performed relied on less than five individual trials. In the meta-analysis assessing the efficacy of CBT on functioning and call we were not even able to perform some of the analyses we intended to. Second, half of the studies did not meet one or more quality criteria. Even though the subgroup analyses did not find statistically significant differences between the high and low quality studies, given their small number, it might be that the effect sizes have been overestimated.

Furthermore, mainly overall improvements in functioning and quality of life were assessed. There was a lack of domain-specific reporting that could have provided information on the effects of interventions on specific areas of functioning and QoL.

Furthermore, the meta-analyses were based on study-level data. Individual patient level meta-analysis based on original datasets of the included studies could have revealed important differences among patients. A further limitation was our inability to analyze long-term outcomes and their interactions, due to the lack of follow-up data. Follow-up data would allow for investigating long-term effects of interventions and temporal relationships among psychosocial areas. Lastly, only articles in English were included. This might have omitted relevant information. In the meta-analysis on CBT only articles published between 2000 and 2015 were included. We selected studies within this search period, as more than 80% of the clinical trials on CBT have been published since year 2000 (Hofmann et al., 2012) and functioning has not been investigated extensively as an outcome of interest before that year (Hirschfeld et al., 2000).

Empirical multi-country study

The data included in this study was cross-sectional, thus both QoL and functioning impairment were assessed at the same measurement point. However, our objective was to rank the importance rather than to explore temporal relations or infer causal relationships. Secondly, there were certain variations in the sample size of each country. For this study we selected only participants with depression, but both the COURAGE and SAGE samples were nationally representative. The differences in the number of depressed participants in each country might be due to differences in the prevalence of depression or cross-national differences in reporting in the self-reported instruments (Kessler and Bromet, 2013).

Study based on data from expert survey and qualitative interviews with patients

Firstly, the way of recruiting experts might not be representative due to the broad, unsystematic invitation to participate in the survey. Around 70% of the clinicians that took part in the online survey were mainly European. Even though we achieved representation of non-European experts, a wider participation of the latter may have provided different perspective on the topic. Furthermore, data from only 11 patients from Spain was obtained. Our approach was the attainment of a saturation point in individuals' answers, but more patients with different cultural backgrounds could have enriched the data.

6.5. Implications and future directions

The aim of this thesis was to provide practical recommendations for improving measurement of treatment effectiveness in depression based on the current limitations in research. Therefore, several implications for research can be drawn out from our findings.

Firstly, our results boost and provide grounds for future changes in the measurement of disability in depression. The study proves that there is a variation in the level of decrements in different functioning domains across countries. Moreover, it shows that literature does not address the areas of functioning mostly impaired in depression and provides a set of domains for further development of more sensitive, cross-nationally validated and user-friendly instruments weighting the domains according to their importance and providing a better picture on the living experience of depressed individuals. This action is urgent, given the fact that only 5% to 20% of all clinical trials for depression report functioning outcomes (Kamenov et al., 2015; McKnight and Kashdan, 2009) and to date there is no gold standard tool for measuring functioning in depression (Lam et al., 2015). Symptoms of depression, which are the main focus of clinical trials, provide early signs of treatment response, but the functional outcomes provide an indicator of meaningful change, thus making the inclusion of functional tools in clinical trials a pressing issue (McKnight and Kashdan, 2009).

Although several recent trials have attempted to apply newly developed measures designed to capture a more comprehensive array of functioning difficulties, all of them are still in their infancy, do not provide domain-specific information or have not been validated in cross-national samples (Cohen et al., 2013; Zimmerman et al., 2013). This gap warrants future studies to continue developing better measures of functioning and clinical trials to provide a more exhaustive measurement of treatment effectiveness.

Secondly, the thesis reveals particular gender differences in the functional impairment of depression. This is an important finding which needs further exploration in other cross-national samples, given the higher prevalence of depression in women compared to men. Different level of impairment in specific functioning areas might be a key to the understanding of these different prevalence rates.

Thirdly, the thesis promotes the need of reporting domain-specific information in studies for better understanding the living experience of depression. Studies predominantly report only the sum-scores of the instruments. These sum-scores do not provide information on the differential impact of each functioning domain on the QoL of individuals. A higher sum-score might indicate either a large number of mildly affected functioning areas or a few domains with marked decrements. Potentially important information on functioning is lost, and a detailed analysis of these functioning domains is likely to reveal important information hidden by the sum-scores.

Fourthly, the thesis raises the question about the importance of assessing functioning in clinical trials and expanding the diagnostic criteria for depression. Gaining insight on the socio-culturally based differences in the areas of functioning in depression might be the key of promoting future culture-sensitive nosology accounting for functional impairment (Juhasz et al., 2012). At clinical level, with the development of a new instrument for functioning, clinicians experiencing time restraints should be given the opportunity to prioritize and meet the needs of patients promptly. Future studies following our line of research should be able to provide sufficient evidence for implementing national programs focusing on prevention and treatment of functional impairments in depression.

The research recommendations that this thesis provides are the first practical step towards improved measurement of treatment effectiveness. The multi-informant approach used in the study, including empirical evidence and data from clinicians and patients is essential for overcoming the gap between clinical research and the care of individual patients. We believe that more accurate and comprehensive evidence on the effectiveness of available interventions for depression is needed to answer the steadily escalating societal and economic burden of the disease.

Besides the implications for research, this thesis has also implications for clinical practice. It was the first to systematically assess the efficacy of the whole spectrum of interventions for psychosocial functioning in depression. The meta-analyses included in the thesis provide comprehensive evidence that existing psychological and pharmacological interventions are efficacious for improving functioning and QoL in depression. There is no robust evidence that one of the interventions is superior, although psychotherapy appears slightly superior to medication. The combination between psychotherapy and medication performs significantly better for both outcomes when compared to each treatment alone. The relatively modest effects, however, suggest that future research should focus on tailoring therapies to better cover the needs of individuals.

7. CONCLUSIONS

The impetus for this thesis was the knowledge gap between the continuously escalating burden of depression and the lack of evidence for the effectiveness of available interventions on important psychosocial areas in depression. To address this gap, the first part of the thesis critically reviewed the current measurement of treatment effectiveness and systematically assessed the effectiveness of all available psychological and pharmacological interventions on psychosocial functioning in depression. Based on the limitations identified in the first part, the second part of the thesis provided empirical data for improving the treatment effectiveness measurement in depression.

Five main recommendations for future improvement of the treatment effectiveness measurement were derived from the research we carried out.

- A new instrument comprehensively assessing all relevant psychosocial difficulties in depression has to be created. This thesis laid the foundations for its design by providing empirical data from nine different countries in Asia, Africa, Europe, and Latin America, and obtained by clinicians and patients, on the areas found to be susceptible to change and crucial for assessment.
- As the results of the thesis revealed gender and country specific differences in the importance of several functioning domains in depression, the new functional tool has to be cross-nationally applicable.
- Report of domain-specific information is needed. Our results show that the vast majority of the interventional studies report only sum-scores of instruments, which, despite some methodological and practical advantages, obscures potential

differences among people. Our results confirmed the differential impact of functioning domains on the overall state of individuals.

- Broader remission criteria for depression including functioning areas beyond symptomatology are needed to adequately reflect the experience of depressed patients under treatment.
- There is a need of a more personalized evidence approach in treatment decision making acknowledging specific patient needs and accounting for a more comprehensive array of functional domains.

With this thesis and the recommendations provided we imply that a more accurate and comprehensive evidence on the effectiveness of available interventions for depression is needed to answer the escalating societal and economic burden of the disease. Future research, however, is warranted to explore further the results of the study and apply the provided recommendations.

7. CONCLUSIONES

El motivo de realización de la presente tesis doctoral se basó en la brecha ente la creciente carga de la depresión y la falta de evidencia sobre la efectividad de las intervenciones psicosociales en áreas importantes de la depresión más allá de los síntomas. En respuesta a dicha brecha, en la primera parte de la tesis se revisó de manera crítica la medición actual de la efectividad de los tratamientos, y se evaluó sistemáticamente la efectividad de las intervenciones psicológicas y farmacológicas en el funcionamiento psicosocial en la depresión. Sobre la base de las limitaciones identificadas en la primera parte, la segunda parte de la tesis doctoral proporcionó datos empíricos y cualitativos para la mejora de la medición de la efectividad de los tratamientos en la depresión.

De la investigación llevada a cabo en esta tesis doctoral, se obtuvieron cinco recomendaciones principales para la futura mejora de la medición de la efectividad de los tratamientos en depresión.

- Existe la necesidad de creación de un nuevo instrumento de evaluación capaz de integrar todas las dificultades psicosociales relevantes en depresión. Esta tesis doctoral sentó las bases de su diseño, proporcionando datos empíricos procedentes de nueve países en Asia, África, Europa y América Latina, y también de médicos y pacientes, sobre las áreas de funcionamiento expuestos a cambios y crucial para la evaluación.
- A medida que los resultados de la tesis revelaron diferencias específicas en términos de sexo y país en la importancia de varios dominios de funcionamiento en la depresión, el nuevo instrumento de funcionamiento a crear tendría que ser aplicable a nivel transnacional.

- Se hace necesaria la creación de un instrumento que recoja información sobre dominios específicos. Nuestros resultados muestran que la gran mayoría de los estudios sólo informan de las puntuaciones totales de los instrumentos, los cuales, a pesar de algunas ventajas metodológicas y prácticas, oscurecen las diferencias potenciales entre las personas. Nuestros resultados confirman el efecto diferencial de los dominios de funcionamiento sobre el estado general de los individuos.
- Se necesitan criterios más amplios de remisión de la depresión, incluyendo áreas de funcionamiento psicosocial diferentes a las de la sintomatología depresiva para reflejar adecuadamente la experiencia de los pacientes deprimidos bajo tratamiento.
- Existe la necesidad de un enfoque basado en evidencia personalizada que ayude la toma de decisiones sobre los tratamientos y que reconozca las necesidades específicas del paciente considerando una gama más amplia de dominios funcionales.

Con esta tesis doctoral y las recomendaciones propuestas, se quiere dar a entender la necesidad de una evidencia más precisa y completa sobre la efectividad de las intervenciones disponibles para la depresión para responder a la creciente carga social y económica de la enfermedad. De todas formas, futuras investigaciones deberán explorar más a fondo los resultados del presente estudio y aplicar las recomendaciones proporcionadas.

8. REFERENCES

1. Aas, I.H., 2010. Global Assessment of Functioning (GAF): properties and frontier of current knowledge. Annals of general psychiatry 9, 20.

2. Alvarezz, A.S., 2012. The application of the International Classification of Functioning, Disability, and Health in psychiatry: possible reasons for the lack of implementation. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists 91, S69-73.

3. American Psychiatric Association, 1980. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association.

4. American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-TR). Washington, DC: American Psychiatric Association.

5. American Psychiatric Association, 1994. Diagnostic and statistical manual of mental disorders, 4th Edition (DSM-IV). Washington, DC: American Psychiatric Association

6. American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders, 4th Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

7. American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association.

8. Andrade, L., Caraveo-Anduaga, J.J., Berglund, P., Bijl, R.V., De Graaf, R., Vollebergh, W., Dragomirecka, E., Kohn, R., Keller, M., Kessler, R.C., Kawakami, N., Kilic, C., Offord, D., Ustun, T.B., Wittchen, H.U., 2003. The epidemiology of major depressive episodes: results

from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. International journal of methods in psychiatric research 12, 3-21.

9. Arbuckle, J.L., 2013. IBM SPSS Amos 22 user's guide. Crawfordville, FL: Amos Development Corporation.

10. Archer, T.M., 2008. Response rates to expect from Web-based surveys and what to do about it. . Journal of Extension [Online] 46(3)

11. Badia, X., Alonso, J., 1995. Re-scaling the Spanish version of the Sickness Impact Profile: an opportunity for the assessment of cross-cultural equivalence. Journal of clinical epidemiology 48, 949-957.

12. Badia, X., Roset, M., Herdman, M., Kind, P., 2001. A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. Medical decision making : an international journal of the Society for Medical Decision Making 21, 7-16.

13. Barth, J., Munder, T., Gerger, H., Nuesch, E., Trelle, S., Znoj, H., Juni, P., Cuijpers, P., 2013. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. PLoS medicine 10, e1001454.

14. Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of general psychiatry 4, 561-571.

15. Bosmans, J.E., van Schaik, D.J., de Bruijne, M.C., van Hout, H.P., van Marwijk, H.W., van Tulder, M.W., Stalman, W.A., 2008. Are psychological treatments for depression in primary care cost-effective? The journal of mental health policy and economics 11, 3-15.

16. Brockow, T., Wohlfahrt, K., Hillert, A., Geyh, S., Weigl, M., Franke, T., Resch, K.L., Cieza, A., 2004. Identifying the concepts contained in outcome measures of clinical trials on depressive disorders using the International Classification of Functioning, Disability and

Health as a reference. Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 49-55.

17. Cabello, M., Mellor-Marsa, B., Sabariego, C., Cieza, A., Bickenbach, J., Ayuso-Mateos, J.L., 2012. Psychosocial features of depression: a systematic literature review. Journal of affective disorders 141, 22-33.

18. Caliyurt, O., Guducu, F., 2005. Partial sleep deprivation therapy combined with sertraline induces more rapid improvements in quality of life items in major depressive disorder. Journal of affective disorders 88, 75-78.

19. Carson, V., 2000. Mental health nursing: the nurse-patient journey. W.B. Saunders.

20. Cashman, J.R., Ghirmai, S., 2009. Inhibition of serotonin and norepinephrine reuptake and inhibition of phosphodiesterase by multi-target inhibitors as potential agents for depression. Bioorganic & medicinal chemistry 17, 6890-6897.

21. Cieza, A., Chatterji, S., Andersen, C., Cantista, P., Herceg, M., Melvin, J., Stucki, G., de Bie, R., 2004. ICF Core Sets for depression. Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 128-134.

22. Cieza, A., Geyh, S., Chatterji, S., Kostanjsek, N., Ustun, B., Stucki, G., 2005. ICF linking rules: an update based on lessons learned. Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine 37, 212-218.

23. Cieza, A., Oberhauser, C., Bickenbach, J., Chatterji, S., Stucki, G., 2014. Towards a minimal generic set of domains of functioning and health. BMC public health 14, 218.

24. Cohen, R.M., Greenberg, J.M., IsHak, W.W., 2013. Incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life in the

Individual Burden of Illness Index for Depression to measure treatment impact and recovery in MDD. JAMA psychiatry 70, 343-350.

25. Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., Klerman, G.L., 1993. The enduring psychosocial consequences of mania and depression. The American journal of psychiatry 150, 720-727.

26. Cuijpers, P., Geraedts, A.S., van Oppen, P., Andersson, G., Markowitz, J.C., van Straten, A., 2011. Interpersonal psychotherapy for depression: a meta-analysis. The American journal of psychiatry 168, 581-592.

27. Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S.D., Andersson, G., 2010. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. Psychological medicine 40, 211-223.

28. Cuijpers, P., van Straten, A., Warmerdam, L., Andersson, G., 2009. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. Depression and anxiety 26, 279-288.

29. Chisholm, D., Sanderson, K., Ayuso-Mateos, J.L., Saxena, S., 2004. Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. The British journal of psychiatry : the journal of mental science 184, 393-403.

30. de Jonghe, F., Hendricksen, M., van Aalst, G., Kool, S., Peen, V., Van, R., van den Eijnden, E., Dekker, J., 2004. Psychotherapy alone and combined with pharmacotherapy in the treatment of depression. The British journal of psychiatry : the journal of mental science 185, 37-45.

31. Deeks, J., Higgins, J., Altman, D.e., 2008. Analysing data and undertaking meta-analyses, in Cochrane Handbook for Systematic Reviews of Interventions. Edited by Higgins JPT, Green S. Chichester. UK, Wiley-Blackwell Chap. 9.

32. DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, R.M., O'Reardon, J.P., Lovett, M.L., Gladis, M.M., Brown, L.L., Gallop, R., 2005. Cognitive therapy vs medications in the treatment of moderate to severe depression. Archives of general psychiatry 62, 409-416.

33. Deshauer, D., 2007. Venlafaxine (Effexor): concerns about increased risk of fatal outcomes in overdose. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 176, 39-40.

34. Duval, S., Tweedie, R., 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455-463.

35. European Pact for Mental Health and Well-being, 2008. EU High Level Conference Brussels, Belgium 12-13th June 2008. (Accessed 15.07.2012 http://ec.europa.eu/health/ph_determinants/life_style/mental/docs/pact_en.pdf)

36. Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., Vos, T., Whiteford, H.A., 2013. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS medicine 10, e1001547.

37. Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 12, 189-198.

38. Forsman, A.K., Wahlbeck, K., Aaro, L.E., Alonso, J., Barry, M.M., Brunn, M., Cardoso, G., Cattan, M., de Girolamo, G., Eberhard-Gran, M., Evans-Lacko, S., Fiorillo, A., Hansson, L., Haro, J.M., Hazo, J.B., Hegerl, U., Katschnig, H., Knappe, S., Luciano, M., Miret, M., Nordentoft, M., Obradors-Tarrago, C., Pilgrim, D., Ruud, T., Salize, H.J., Stewart-Brown, S.L., Tomasson, K., van der Feltz-Cornelis, C.M., Ventus, D.B., Vuori, J., Varnik, A., 2015. Research priorities for public mental health in Europe: recommendations of the ROAMER project. European journal of public health 25, 249-254.

39. Fournier, J.C., DeRubeis, R.J., Hollon, S.D., Dimidjian, S., Amsterdam, J.D., Shelton, R.C., Fawcett, J., 2010. Antidepressant drug effects and depression severity: a patient-level meta-analysis. Jama 303, 47-53.

40. Fredman, L., Weissman, M.M., Leaf, P.J., Bruce, M.L., 1988. Social functioning in community residents with depression and other psychiatric disorders: results of the New Haven Epidemiologic Catchment Area Study. Journal of affective disorders 15, 103-112.

41. Fried, E.I., Nesse, R.M., 2014. The impact of individual depressive symptoms on impairment of psychosocial functioning. PloS one 9, e90311.

42. Furukawa, T.A., Fujita, A., Harai, H., Yoshimura, R., Kitamura, T., Takahashi, K., 2008. Definitions of recovery and outcomes of major depression: results from a 10-year follow-up. Acta psychiatrica Scandinavica 117, 35-40.

43. Glaser, B.G., Strauss, A.L., 1967. The Discovery of Grounded Theory: Strategies for Qualitative Research. Chicago, Aldine Publishing Company.

44. Gloaguen, V., Cottraux, J., Cucherat, M., Blackburn, I.M., 1998. A meta-analysis of the effects of cognitive therapy in depressed patients. Journal of affective disorders 49, 59-72.

45. Hamilton, M., 1967. Development of a rating scale for primary depressive illness. The British journal of social and clinical psychology 6, 278-296.

46. Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.

47. Hirschfeld, R.M., Montgomery, S.A., Keller, M.B., Kasper, S., Schatzberg, A.F., Moller, H.J., Healy, D., Baldwin, D., Humble, M., Versiani, M., Montenegro, R., Bourgeois, M., 2000. Social functioning in depression: a review. The Journal of clinical psychiatry 61, 268-275.

48. Hodgkin, D., Volpe-Vartanian, J., Alegria, M., 2007. Discontinuation of antidepressant medication among Latinos in the USA. The journal of behavioral health services & research 34, 329-342.

49. Hofmann, S.G., Asnaani, A., Vonk, I.J., Sawyer, A.T., Fang, A., 2012. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognitive therapy and research 36, 427-440.

50. Horgan, D., Dimitriou, H., 2015. Depression Treatment Survey of Psychiatrists: Outcome and Side Effects. Annals of Psychiatry and Mental Health 3(7): 1048.

51. Hu, X.Z., Rush, A.J., Charney, D., Wilson, A.F., Sorant, A.J., Papanicolaou, G.J., Fava, M., Trivedi, M.H., Wisniewski, S.R., Laje, G., Paddock, S., McMahon, F.J., Manji, H., Lipsky, R.H., 2007. Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. Archives of general psychiatry 64, 783-792.

52. Hunsley, J., Elliott, K., Therrien, Z., 2013. The efficacy and effectiveness of psychological treatments. Ottawa, Canada: Canadian Psychological Association.

53. IsHak, W., Burt, T., Sederer, L.e., 2002. Outcome measurement in
psychiatry: a critical review. Washington, DC: American Psychiatric
Publishing.

54. IsHak, W.W., Greenberg, J.M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., Fakhry, H., Rapaport, M.H., 2011. Quality of life: the ultimate outcome measure of interventions in major depressive disorder. Harvard review of psychiatry 19, 229-239.

55. Juhasz, G., Eszlari, N., Pap, D., Gonda, X., 2012. Cultural differences in the development and characteristics of depression. Neuropsychopharmacologia Hungarica : a Magyar Pszichofarmakologiai Egyesulet lapja = official journal of the Hungarian Association of Psychopharmacology 14, 259-265.

56. Kamenov, K., Cabello, M., Coenen, M., Ayuso-Mateos, J.L., 2015. How much do we know about the functional effectiveness of interventions for depression? A systematic review. Journal of affective disorders 188, 89-96.

57. Kamenov, K., Mellor-Marsa, B., Leal, I., Ayuso-Mateos, J.L., Cabello, M., 2014. Analysing psychosocial difficulties in depression: a content comparison between systematic literature review and patient perspective. BioMed research international 2014, 319634.

58. Keller, M., 2001. Role of serotonin and noradrenaline in social dysfunction: a review of data on reboxetine and the Social Adaptation Self-evaluation Scale (SASS). General hospital psychiatry 23, 15-19.

59. Keller, M.B., 2003. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. Jama 289, 3152-3160.

60. Keller, M.B., Shapiro, R.W., Lavori, P.W., Wolfe, N., 1982. Recovery in major depressive disorder: analysis with the life table and regression models. Archives of general psychiatry 39, 905-910.

61. Kennedy, N., Foy, K., Sherazi, R., McDonough, M., McKeon, P., 2007. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar disorders 9, 25-37.

62. Kennedy, S.H., Lam, R.W., McIntyre, R.S., Tourjman, S.V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A.J., MacQueen, G.M., McInerney, S.J., McIntosh, D., Milev, R.V., Muller, D.J., Parikh, S.V., Pearson, N.L., Ravindran, A.V., Uher, R., 2016. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Canadian journal of psychiatry. Revue canadienne de psychiatrie 61, 540-560.

63. Kennedy, S.H., Lam, R.W. (Eds.), 2001. Clinical guidelines for the treatment of depressive disorders. Canadian journal of psychiatry. Revue canadienne de psychiatrie 46 Suppl 1, 5S-90S.

64. Kennedy, S.H., Milev, R., Giacobbe, P., Ramasubbu, R., Lam, R.W., Parikh, S.V., Patten, S.B., Ravindran, A.V., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. Journal of affective disorders 117 Suppl 1, S44-53.

65. Kessler, R.C., Bromet, E.J., 2013. The epidemiology of depression across cultures. Annual review of public health 34, 119-138.

66. Kessler, R.C., Ustun, T.B., 2004. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). International journal of methods in psychiatric research 13, 93-121.

67. Khan, A., Brown, W.A., 2015. Antidepressants versus placebo in major depression: an overview. World Psychiatry 14, 294-300.

68. Kirsch, I., Deacon, B.J., Huedo-Medina, T.B., Scoboria, A., Moore, T.J., Johnson, B.T., 2008. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS medicine 5, e45.

69. Kowal, P., Chatterji, S., Naidoo, N., Biritwum, R., Fan, W., Lopez Ridaura, R., Maximova, T., Arokiasamy, P., Phaswana-Mafuya, N., Williams, S., Snodgrass, J.J., Minicuci, N., D'Este, C., Peltzer, K., Boerma, J.T., 2012. Data resource profile: the World Health Organization Study on global AGEing and adult health (SAGE). International journal of epidemiology 41, 1639-1649.

70. Kvam, S., Kleppe, C.L., Nordhus, I.H., Hovland, A., 2016. Exercise as a treatment for depression: A meta-analysis. Journal of affective disorders 202, 67-86.

71. Lam, R.W., Parikh, S.V., Michalak, E.E., Dewa, C.S., Kennedy, S.H., 2015. Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists 27, 142-149.

72. Layard, R., Clark DM, Knapp M, G, M., 2007. Cost-Benefit Analysis of Psychological Therapy- Centre for Economic Performance Report. .

73. Leonardi, M., Chatterji, S., Koskinen, S., Ayuso-Mateos, J.L., Haro, J.M., Frisoni, G., Frattura, L., Martinuzzi, A., Tobiasz-Adamczyk, B., Gmurek, M., Serrano, R., Finocchiaro, C.,

2014. Determinants of health and disability in ageing population: the COURAGE in Europe Project (collaborative research on ageing in Europe). Clinical psychology & psychotherapy 21, 193-198.

74. Linde, K., Kriston, L., Rucker, G., Jamil, S., Schumann, I., Meissner, K., Sigterman, K., Schneider, A., 2015. Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. Annals of family medicine 13, 69-79.

75. Lozano, A.M., Mayberg, H.S., Giacobbe, P., Hamani, C., Craddock, R.C., Kennedy, S.H., 2008. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biological psychiatry 64, 461-467.

76. Luty, S.E., Carter, J.D., McKenzie, J.M., Rae, A.M., Frampton, C.M., Mulder, R.T., Joyce, P.R., 2007. Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. The British journal of psychiatry : the journal of mental science 190, 496-502.

77. Madden, R.H., Glozier, N., Fortune, N., Dyson, M., Gilroy, J., Bundy, A., Llewellyn, G., Salvador-Carulla, L., Lukersmith, S., Mpofu, E., Madden, R., 2015. In search of an integrative measure of functioning. International journal of environmental research and public health 12, 5815-5832.

78. Mancini, M., Sheehan, D.V., Demyttenaere, K., Amore, M., Deberdt, W., Quail, D., Sagman, D., 2012. Evaluation of the effect of duloxetine treatment on functioning as measured by the Sheehan disability scale: pooled analysis of data from six randomized, double-blind, placebo-controlled clinical studies. International clinical psychopharmacology 27, 298-309.

79. Mann, J.J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., Hegerl, U., Lonnqvist, J., Malone, K., Marusic, A., Mehlum, L., Patton, G., Phillips, M., Rutz, W., Rihmer, Z., Schmidtke, A., Shaffer, D., Silverman, M., Takahashi, Y., Varnik, A., Wasserman, D., Yip, P., Hendin, H., 2005. Suicide prevention strategies: a systematic review. Jama 294, 2064-2074.

80. Mayring, P., 2014. Qualitative content analysis: theoretical foundation, basic procedures and software solution.

81. McAllister-Williams, R.H., 2006. NICE guidelines for the management of depression. Br J Hosp Med (Lond) 67, 60-61.

82. McKnight, P.E., Kashdan, T.B., 2009. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. Clinical psychology review 29, 243-259.

83. McHugh, R.K., Whitton, S.W., Peckham, A.D., Welge, J.A., Otto, M.W., 2013. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. The Journal of clinical psychiatry 74, 595-602.

84. Mitchell, P.B., Mitchell, M.S., 1994. The management of depression. Part 2. The place of the new antidepressants. Australian family physician 23, 1771-1773, 1776-1781.

85. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery 8, 336-341.

86. Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 134, 382-389.

87. Mundt, J.C., Marks, I.M., Shear, M.K., Greist, J.H., 2002. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. The British journal of psychiatry : the journal of mental science 180, 461-464.

88. National Collaborating Centre for Mental Health, 2010. Depression: The Treatment and Management of Depression in Adults (Updated Edition), Leicester (UK).

89. Nemeroff, C.B., Thase, M.E., 2007. A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. Journal of psychiatric research 41, 351-359.

90. Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.U., Jonsson, B., 2012. The economic cost of brain disorders in Europe. European journal of neurology 19, 155-162.

91. Olfson, M., Marcus, S.C., Tedeschi, M., Wan, G.J., 2006. Continuity of antidepressant treatment for adults with depression in the United States. The American journal of psychiatry 163, 101-108.

92. Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., Munizza, C., 2004. Combined pharmacotherapy and psychological treatment for depression: a systematic review. Archives of general psychiatry 61, 714-719.

93. Papakostas, G.I., Thase, M.E., Fava, M., Nelson, J.C., Shelton, R.C., 2007. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biological psychiatry 62, 1217-1227.

94. Parikh, S.V., Quilty, L.C., Ravitz, P., Rosenbluth, M., Pavlova, B., Grigoriadis, S., Velyvis, V., Kennedy, S.H., Lam, R.W., MacQueen, G.M., Milev, R.V., Ravindran, A.V., Uher, R., 2016. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016

Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 2. Psychological Treatments. Canadian journal of psychiatry. Revue canadienne de psychiatrie 61, 524-539.

95. Patten, S.B., Kennedy, S.H., Lam, R.W., O'Donovan, C., Filteau, M.J., Parikh, S.V., Ravindran, A.V., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. Journal of affective disorders 117 Suppl 1, S5-14.

96. Pies, R., 2010. Antidepressants work, sort of--our system of care does not. Journal of clinical psychopharmacology 30, 101-104.

97. Power, M., 2003. Development of a common instrument for quality of life. In Nosikov A, Gudex C. (toim.). EUROHIS: Developing Common Instruments for Health Surveys. IOS Press, Amsterdam, Netherlands. pp. 145–159.

98. Preskorn, S., Ross, R., Stanga, C., 2004. Selective Serotonin Reuptake Inhibitors. In Sheldon H. Preskorn, Hohn P. Feighner, Christina Y. Stanga, Ruth Ross. Antidepressants: Past, Present and Future. Berlin: Springer, pp. 241–262.

99. Ravindran, A.V., Lam, R.W., Filteau, M.J., Lesperance, F., Kennedy, S.H., Parikh, S.V., Patten, S.B., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. Journal of affective disorders 117 Suppl 1, S54-64.

100. Ro, E., Clark, L.A., 2009. Psychosocial functioning in the context of diagnosis: assessment and theoretical issues. Psychological assessment 21, 313-324.

101. Rush, A.J., Fava, M., Wisniewski, S.R., Lavori, P.W., Trivedi, M.H., Sackeim, H.A., Thase, M.E., Nierenberg, A.A., Quitkin, F.M., Kashner, T.M., Kupfer, D.J., Rosenbaum, J.F., Alpert, J., Stewart, J.W., McGrath, P.J., Biggs, M.M., Shores-Wilson, K., Lebowitz, B.D., Ritz, L., Niederehe, G., 2004. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Controlled clinical trials 25, 119-142.

102. Salomon, J., Mathers, C., Chatterji, S., Sadana, R., Üstün, T., Murray, C., 2003. Quantifying individual levels of health: definitions, concepts, and measurement levels. In: Murray CJL, Evans DB, editors. Health systems performance assessment: debates, methods, empiricism. Geneva: World Health Organization; pp. 301–18.

103. Shah, A., Wadoo, O., Latoo, J., 2010. Psychological Distress in Carers of People with Mental Disorders. Psychological Distress in Carers of People with Mental Disorders 3.

104. Sheehan, D., 1983. The Anxiety Disease. Scribner's: New York.

105. Sheehan, D.V., 2004. Depression: underdiagnosed, undertreated, underappreciated. Manag Care 13, 6-8.

106. Simon, G.E., Goldberg, D.P., Von Korff, M., Ustun, T.B., 2002. Understanding cross-national differences in depression prevalence. Psychological medicine 32, 585-594.

107. Skevington, S.M., Sartorius, N., Amir, M., 2004. Developing methods for assessing quality of life in different cultural settings. The history of the WHOQOL instruments. Social psychiatry and psychiatric epidemiology 39, 1-8.

108. Taylor, M.J., Rudkin, L., Hawton, K., 2005. Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. Journal of affective disorders 88, 241-254.

109. Thase, M.E., Friedman, E.S., Biggs, M.M., Wisniewski, S.R., Trivedi, M.H., Luther, J.F., Fava, M., Nierenberg, A.A., McGrath, P.J., Warden, D., Niederehe, G., Hollon, S.D., Rush, A.J., 2007. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. The American journal of psychiatry 164, 739-752.

110. Tonelli, M.R., 1999. In defense of expert opinion. Academic medicine : journal of the Association of American Medical Colleges 74, 1187-1192.

111. Trindade, E., Menon, D., Topfer, L.A., Coloma, C., 1998. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 159, 1245-1252.

112. Trompenaars, F.J., Masthoff, E.D., Van Heck, G.L., Hodiamont, P.P., De Vries, J., 2006. Relationship between mood related disorders and quality of life in a population of Dutch adult psychiatric outpatients. Depression and anxiety 23, 353-363.

113. Tyrer, P., 1993. What is social function? In P. Tyrer & P. Casey (Eds.), Social function in psychiatry: The hidden axis of classification exposed (pp. 1–10). Petersfield, Hampshire, England: Wrightson.

114. Ustun, T.B., Chatterji, S., Kostanjsek, N., Rehm, J., Kennedy, C., Epping-Jordan, J., Saxena, S., von Korff, M., Pull, C., 2010. Developing the World Health Organization Disability Assessment Schedule 2.0. Bulletin of the World Health Organization 88, 815-823.

115. Vittengl, J.R., Clark, L.A., Dunn, T.W., Jarrett, R.B., 2007. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. Journal of consulting and clinical psychology 75, 475-488.

116. Vittengl, J.R., Clark, L.A., Jarrett, R.B., 2009. Deterioration in psychosocial functioning predicts relapse/recurrence after cognitive therapy for depression. Journal of affective disorders 112, 135-143.

117. Volicer, L., Frijters, D. H. M., & Van Der Steen, J. T, 2011. Underdiagnosis and undertreatment of depression in nursing home residents. European Geriatric Medicine, 2(6), 332-337.

118. Weigl, M., Cieza, A., Andersen, C., Kollerits, B., Amann, E., Stucki, G., 2004. Identification of relevant ICF categories in patients with chronic health conditions: a Delphi exercise. Journal of rehabilitation medicine, 12-21.

119. Weissman, M.M., Bland, R.C., Canino, G.J., Faravelli, C., Greenwald, S., Hwu, H.G., Joyce, P.R., Karam, E.G., Lee, C.K., Lellouch, J., Lepine, J.P., Newman, S.C., Rubio-Stipec, M., Wells, J.E., Wickramaratne, P.J., Wittchen, H., Yeh, E.K., 1996. Cross-national epidemiology of major depression and bipolar disorder. Jama 276, 293-299.

120. Weissman, M.M., Prusoff, B.A., Thompson, W.D., Harding, P.S., Myers, J.K., 1978. Social adjustment by self-report in a community sample and in psychiatric outpatients. The Journal of nervous and mental disease 166, 317-326.

121. Weissman, M.M., Sholomskas, D., John, K., 1981. The assessment of social adjustment. An update. Archives of general psychiatry 38, 1250-1258.

122. Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575-1586.

123. Whoqol Group, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychological medicine 28, 551-558.

124. Wittchen, H.U., Holsboer, F., Jacobi, F., 2001. Met and unmet needs in the management of depressive disorder in the community and primary care: the size and breadth of the problem. The Journal of clinical psychiatry 62 Suppl 26, 23-28.

125. World Health Organization, 1992. International classification of diseases and related health problems, 10th Revision (ICD-10). Geneva: World Health Organization.

126. World Health Organization, 2001. International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization.

127. World Health Organization, 2003. The world health report 2003: Shaping the future.

128. World Health Organization, 2010. mhGAP Intervention Guide for Mental, Neurological and Substance Use Disorders in Non-Specialized Health Settings: Mental Health Gap Action Programme (mhGAP), Geneva.

129. World Health Organization Quality of Life Group, 1997. Measuring quality of life. http://www.who.int/mental_health/media/68.pdf.

130. Zimmerman, M., Martinez, J.H., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., 2014. The remission from depression questionnaire as an outcome measure in the treatment of depression. Depression and anxiety 31, 533-538.

131. Zimmerman, M., Martinez, J.H., Attiullah, N., Friedman, M., Toba, C., Boerescu, D.A., Ragheb, M., 2013. A new type of scale for determining remission from depression: the Remission from Depression Questionnaire. Journal of psychiatric research 47, 78-82.

132. Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Attiullah, N., Boerescu, D., 2006a. How should remission from depression be defined? The depressed patient's perspective. The American journal of psychiatry 163, 148-150.

133. Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Boerescu, D., Attiullah, N., 2006b. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. Psychiatry research 141, 185-191.