Health technology assessment of antidepressant pharmacotherapies and cognitive behavioral therapies in treatment of major depressive disorder

Scoping document for a Health Technology Assessment

29 April 2020

Tala Ballouz, Henock G Yebyo, Yuki Tomonaga, Dominik Menges, Arjun Bhadhuri, Matthias Schwenkglenks, Milo A Puhan

The Swiss Medical Board (SMB) is planning a project addressing the value of antidepressants within a Health Technology Assessment (HTA) framework in collaboration with Epidemiology, Biostatistics, and Prevention Institute at the University of Zurich and the Institute of Pharmaceutical Medicine at the University of Basel. As discussed during the first expert meeting held on 10.12.2019, we performed a preliminary literature search on the available evidence and potential gaps to establish a research question. Findings were summarized in the first version of the scoping document. Following stakeholder feedback received on 20.03.2020, the document was revised and the research question was further refined.

Considering inputs by the following stakeholders:

Dr. Hanspeter Conrad, Swiss Mental Healthcare

Prof. Dr.med Drahomir Aujesky, Schweizerische Gesellschaft für Allgemeine Innere Medizin (SGAIM)

Dr. med. Regula Capaul, Schweizerische Gesellschaft für Allgemeine Innere Medizin (SGAIM)

Prof. Dr.med. Susanne Walitza, SGKJPP – Schweizerische Fachgesellschaft für Kinder- und Jugendpsychiatrie und -psychotherapie

Markus Gnaegi, santésuisse

Dr. Markus Wolf, University of Zurich, Department of Psychology, Clinical Psychology and Psychotherapy Research

Prof. Dr. Birgit Watzke, University of Zurich, Department of Psychology, Clinical Psychology and Psychotherapy Research

Andreas Daurù, Stiftung Pro Mente Sana

Prof. Dr. Erich Seifritz,, SGPP – Schweizerische Gesellschaft für Psychiatrie und Psychotherapie

Dr. Pierre Vallon, SGPP – Schweizerische Gesellschaft für Psychiatrie und Psychotherapie

Markus Ziegler, Interpharma

Table of Contents

Summary of the key findings of the scoping process

- The reported beneficial effects of antidepressants in trials and meta-analyses and their clinical significance have been questioned by many in the field due to:
    1. highly selected populations in trials limiting the generalizability of the findings (i.e. unclear if the beneficial and harmful effects are similar in real world patients)
    2. most participants in trials had moderate to severe depression, while in clinical practice mild depression is more commonly encountered
    3. assessment of only short-term outcomes in most trials (up to eight weeks), while antidepressants are commonly prescribed for months
    4. antidepressants have been studied in these trials in isolation and not as one component of chronic disease management of patients with depression
    5. long-term adverse effects of antidepressants less detected due to the short-term follow up of trials
    6. inclusion of low-quality trials in systematic reviews
- Some meta-analyses of individual participant data from short-term trials have shown a possible differential effect of antidepressants by severity of baseline depression, while others showed no differences.
- Combination of psychotherapy and antidepressants mostly seems to be superior to both monotherapies in short-term trials.
- Inconsistent findings regarding cost-effectiveness of antidepressants compared to non-pharmacologic therapies.
- The systematic inclusion of values and patient preferences regarding antidepressant treatments in guideline development is often neglected.
- Quantitative assessments of the benefit-harm balance of antidepressant treatments are scarce.

Background

Major depressive disorder (MDD)– or unipolar major depression– is the most commonly diagnosed depressive disorder. It is characterized by a history of at least one major depressive episode that lasted at least two weeks. The depressive episode manifests itself with five or more of the symptoms listed in **Table 1,** one of which must be either depressed mood or loss of interest as described by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)[1]. However, none of these symptoms are pathognomonic for MDD and may occur frequently in other psychiatric or general medical illnesses. Additionally, each episode of MDD may be characterized by a different combination of symptoms, thus episodes may vary within an individual and across individuals.

Table 1. Symptoms of a depressive episode (DSM-5)[1]

○ Depressed mood most of the day, nearly every day
○ Loss of interest or pleasure in most or all activities, nearly every day
○ Insomnia or hypersomnia nearly every day
○ Significant weight loss or weight gain (e.g., 5 percent within a month) or decrease or increase in appetite nearly every day
○ Psychomotor retardation or agitation nearly every day that is observable by others
○ Fatigue or low energy, nearly every day
○ Decreased ability to concentrate, think, or make decisions, nearly every day
○ Thoughts of worthlessness or excessive or inappropriate guilt, nearly every day
○ Recurrent thoughts of death or suicidal ideation, or a suicide attempt

For improved diagnostic specificity, DSM-5 further classifies MDD into 8 different subtypes such as peripartum, anxiety, melancholic, and catatonic. However, these subtypes are not mutually exclusive and a depressive episode may have features of more than one subtype[1]. DSM-5 also includes a severity specifier for MDD (i.e. mild, moderate or severe) depending on the number and severity of symptoms and the degree of functional disability[1].

The lifetime prevalence of MDD varies across countries[2]. It is estimated to be around 12.8% and 20.6% in Europe and the United States (US), respectively [3,4]. In Switzerland, MDD, which accounts for 2% of the total disability-adjusted life years[5], has a lifetime prevalence of approximately 16.7%[6]. Across all settings, women are affected twice more than men. The prevalence of MDD peaks in the second and third decades of life and again, but to a lesser extent in the fifth and sixth decades [7]. The severity, frequency and duration of symptoms varies between individuals. Individuals may experience a single episode of MDD in their lifetime, have a highly recurrent course with full resolution of symptoms between each episode, or have persistently fluctuating depressive symptoms. For most individuals, the typical course is recurrent with 50% of individuals recovering from the first MDD episode experiencing at least one recurrent episode in their lifetime. The likelihood of recurrence increases with each

subsequent episode, with the greatest risk of recurrence being in the first few months after recovery from the last depressive episode[8]. In some cases, MDD episodes may not respond satisfactorily to antidepressant treatment. Those that do not respond to two consecutive treatments of antidepressants given at an adequate dosage for a sufficient time are labeled as "treatment-resistant depression"[9]. The enormous variation in the presentation and course of MDD is reflected in the breadth of explanations for the pathophysiological and etiological mechanisms underlying depression. The exact mechanisms are not fully understood, however available evidence argues for a complex interaction between neurobiological (e.g. brain neurotransmitters, changes in receptor functions and glucocorticoid production), psychosocial (e.g. early life trauma, stressors, social isolation) and genetic factors[10–12] .

1. Treatment of major depressive disorder

Numerous treatment strategies for MDD are available. These include psychotherapy (such as cognitive behavioral therapy or interpersonal therapy) and/or pharmacotherapy with the aim of achieving symptoms remission and restoring a normal level of psychosocial functioning as needed for a satisfactory personal and working life and social participation. An example of an approach to the management of MDD adapted from the Swiss Guidelines- Schweizerische Gesellschaft für Psychiatrie und Psychotherapie (SGPP) is illustrated in the figure below (**Figure 1**)[14,15].

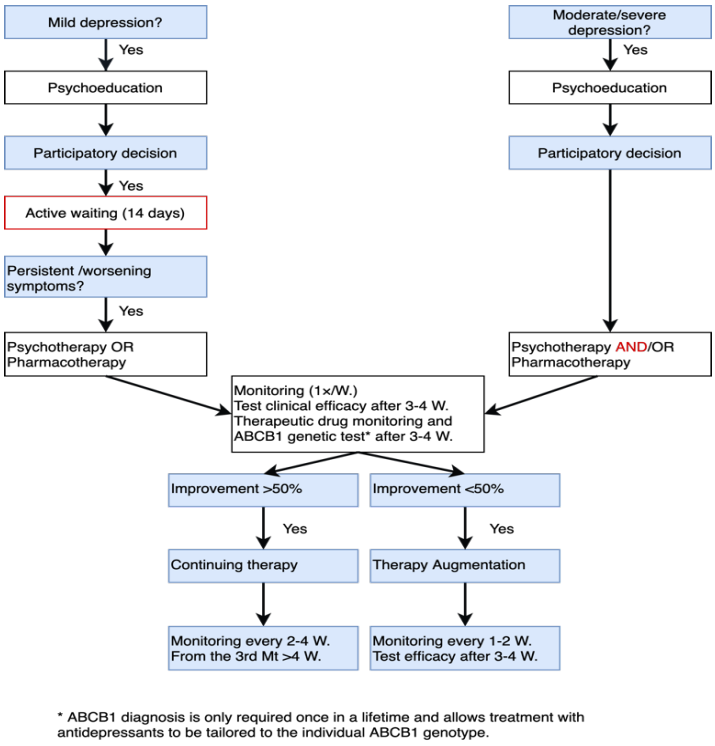

Figure 1. Treatment algorithm for MDD as by the Swiss Guidelines SGPP (adapted and translated)

The management of MDD can be divided into three phases[14–17]:

1- **Acute phase** (6-12 weeks) during which the treatment goal is symptom improvement until remission has been achieved and psychosocial functioning has been restored.

2- **Continuation phase** (4-9 months) where treatment is continued, and remission is sustained. The main aim of this phase is to reduce the risk of experiencing a relapse since discontinuation of treatment of an acute episode of MDD may be associated with a higher risk of relapse even if the depressive symptoms have largely subsided.
3- **Maintenance phase** (≥1 year) to prevent recurrent depressive episodes in those at a higher risk of recurrence of MDD and/or those with risk factors and diminished coping resources that may trigger recurrent episodes or contribute to it becoming a chronic condition.

The choice of initial treatment depends on multiple factors such as patient preference, costs, comorbid conditions, prior treatment experience, drug-drug interactions, anticipated side effects and the severity of symptoms.

A. Psychotherapy

Psychotherapy is defined 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"[18]. Several types of psychotherapies are used for the treatment of MDD and several meta-analyses have shown their efficacy with none of the psychotherapies showing superior efficacy over another[19–22]. **Table 2** lists the major types of psychotherapies used in major depression. The choice of psychotherapy is usually based on the availability of treatment and patient preferences. Most often, cognitive behavioral therapy (CBT) and interpersonal psychotherapy are used as they are the most frequently studied types of psychotherapy in major depression.

Table 2. Types of psychotherapy used in major depression

○ Cognitive behavioral therapy
○ Interpersonal psychotherapy
○ Psychodynamic therapy
○ Supportive psychotherapy
○ Behavioral activation
○ Family and couples therapy
○ Life review therapy

The efficacy of psychotherapies has been demonstrated in numerous RCTs. In a meta-analysis of 304 studies comparing 15 specific types of psychotherapy to control conditions (e.g. waiting list) in adult depression, Cuijpers et al. reported significant moderate to large effects of psychotherapies[23]. However, such meta-analyses are thought to overinflate the effect of psychotherapy due to inclusion of low quality studies and publication bias[24–26]. While some randomized controlled trials (RCTs) on psychotherapy are rigorous in design and implementation including the use of comparators that control for the non-specific

effects of psychotherapy, others are suboptimal (open-label trials, inadequate blinding of outcome rating etc).

The most frequently used and studied psychotherapy is cognitive-behavioral therapy (CBT) which is considered a "family" of related therapies. CBT is defined as "a form of psychotherapy that integrates theories of cognition and learning with treatment techniques derived from cognitive therapy and behavior therapy. CBT assumes that cognitive, emotional, and behavioral variables are functionally interrelated. Treatment is aimed at identifying and modifying the client's maladaptive thought processes and problematic behaviors through cognitive restructuring and behavioral techniques to achieve change". Categories and delivery formats of CBT are briefly described in **Table 3**[27–30]. As access to face-to-face CBT may be limited by distance, time, cost and stigma, internet-based CBT offers potential advantages when it coming to increasing access to care while being equally effective as traditional CBT[31].

Table 3. Cognitive behavioral therapy (CBT)

Types	○ Cognitive therapy ○ Problem-solving therapy ○ Rational-emotive behavior therapy ○ Third wave therapies (e.g., mindfulness-based CBTs, acceptance and commitment therapy, dialectical behavior therapy)
Delivery formats	○ Face to face (Individual or group-based) ○ Internet-based CBT (iCBT) (guided or unguided self-help)

B. Antidepressants

Several classes of antidepressants exist **(Table 4),** with selective serotonin reuptake inhibitors (SSRIs) being most commonly used as first-line treatments.

Table 4. Classes of antidepressants

	Classes of antidepressants	**Examples**
1st generation antidepressants	Monoamine oxidase inhibitors (MAOIs)	Tranylcypromine, phenelzine, seligiline
	Tricyclic antidepressants (TCA)	Amitriptyline, amoxapine, clomipramine, imipramine, nortriptyline
2nd generation antidepressants	Selective serotonin reuptake inhibitors (SSRI)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
	Serotonin-norepinephrine reuptake inhibitors (SNRI)	Venlafaxine, duloxetine, desvenlofaxine, levomilnacipran
	Atypical antidepressants	Mirtazapine, agomelatine, bupropion

Many guidelines, such as the American Psychiatric Association (APA) and European Psychiatric Association (EPA) guidelines recommend the use of antidepressants as first line therapy in

depression[16,32]. On the other hand, in contrast to other guidelines, NICE recommends against the use of antidepressants in those with mild depression based on the judgement that their benefit-harm balance does not justify their use[33]. Similarly, both the Swiss SGPP- and German S-3 guidelines[17] recommend withholding antidepressants in mild depression based on patient preferences and/or if the symptoms are expected to resolve without treatment[17].

Efficacy of antidepressants

An exploratory screening of the literature was conducted to identify existing systematic reviews and Health Technology Assessment (HTA) documents assessing outcomes related to antidepressants. The search resulted in the list of systematic reviews and meta-analyses illustrated in the appendix (Appendix-Table 1). A full systematic literature review of the effectiveness and safety of antidepressants will be undertaken as described later in the document.

i. Antidepressants vs. placebo

Multiple systematic reviews have examined the effects of antidepressants compared to placebo, all of which found a significant effect of antidepressants on depressive symptoms. The most comprehensive systematic review to date includes a network meta-analysis of 522 RCTs comprising 116,477 individuals and assessed the short-term efficacy and acceptability of 21 antidepressants. Both placebo-controlled and head-to-head trials were included and short-term outcomes (at 8 weeks) were assessed. Most patients had moderate-severe depression. Similar to previous systematic reviews, results showed that antidepressants were effective in reducing the symptoms of depression and achieving remission[34]. However, the clinical significance of these findings has been debated. Hengartner et al. transformed the effect size (d=0.3) reported by Cipriani et al. into mean-point differences on the HDRS-17 scale. The effect size corresponded to approximately 2 points on the scale and the authors considered it to be clinically irrelevant as drug-placebo differences below 3 points are undetectable by clinicians[35]. Interestingly, in a previously published systematic review and meta-analysis of 131 RCTs comparing SSRIs and placebo, authors found effect sizes similar to those reported by Cipriani et al. As these effect sizes were below predefined clinical threshold criteria (defined by NICE) set by the authors, they also questioned the clinical relevance of their results[36]. Additional limitations to the available evidence include the high or unclear risk of bias of most trials and low generalizability of results due to the high selectivity of included patients in trials. Most trials recruited participants through advertisement and excluded those with comorbid conditions. Thus, evidence from these trials may not be based on people that are commonly seen in real world clinical practice settings as demonstrated by the STAR*D trial[37,38]. This trial was designed to evaluate treatment outcomes in representative outpatients and enrolled 4,041 participants based on broadly inclusive selection criteria. Authors estimated that more than 77% of those participants would have been excluded from a conventional phase III clinical trial[37,38].

Differences in the effectiveness of antidepressants as a function of severity of depression is controversial. A few individual participant data (IPD) meta-analyses have examined the influence of baseline severity on the efficacy of antidepressants with contradicting results. Khan et al. reported an increasing benefit of antidepressants with increased severity of depression symptoms compared to placebo in a study including 329 patients [39]. Fournier et al. reported similar findings and attributed their findings to decreased responsiveness to placebo among the more severe patients rather than increased responsiveness to medications[40]. Contrarily and in larger IPD meta-analyses, Furukawa et al., Gibbons et al., and Rabinowitz et al. did not show any significant drug-placebo difference as a function of initial depression severity[41–43].

ii. Antidepressants vs. psychotherapy alone or in combination with psychotherapy

Studies indicate that antidepressants and psychotherapy have comparable efficacy; however, some have suggested that the two therapies have differential long-term effects. In contrast to antidepressants, where the benefits may be lost after discontinuation, the effects of psychotherapy may persist up to 15 months after completion of therapy[44,45].

The combination of antidepressants and psychotherapy has been well established as superior to either monotherapies. Cuijpers et al. recently examined the relative effects (treatment response, remission and acceptability) of psychotherapies, pharmacotherapies and their combination in a systematic review that included a network meta-analysis of 101 studies with 11,910 patients included[46]. Most participants in this systematic review had moderate to severe depression and most trials had high risk of bias. Overall, combined treatment was more effective than either therapy alone in achieving response at the end of treatment course. Combined psychotherapy or psychotherapy alone were more acceptable than antidepressants alone. Combination treatment was also more effective than antidepressants in two separate network meta-analyses limited to studies assessing moderate or severe depression. There were too few studies on patients with mild depression to be able to assess the relative effects of treatments[46].

C. Effects of treatment beyond the acute management phase

The effectiveness of antidepressants has been largely based on short-term RCTs with systematic reviews and meta-analyses combining data on outcomes spanning 4-12 weeks. However, as antidepressants are usually continued for several months after initial remission as continuation or maintenance therapy to prevent relapse[16], an examination of effects beyond the acute phase is essential. Results from long-term RCTs and observational studies suggest that antidepressants may not produce beneficial effects in the long-term but may in fact increase the risk of relapse or other harmful effects[35,47–50]. For example, in a 9-year observational study in the US, patients with depression treated with medications were more likely to experience recurrence of symptoms than those treated without medications, regardless of the MDD severity[50]. Results from a systematic review and meta-analyses of 27 RCTs with 3037 patients followed up for a median of 16.6 months included a higher likelihood of relapse with increased duration of

treatment[51]. Cuijpers et al. reported better efficacy of combination therapy in achieving treatment response than both psychotherapy and pharmacotherapy alone and better efficacy with psychotherapy than pharmacotherapy at 6 and 12 months[46]. These results were in line with previous systematic reviews [44,52,53].

D. Harms of treatment

Since the US Food and Drug Administration (FDA) issued a black warning regarding the increased risk of suicidal behavior in children and adolescents on SSRIs[54], the safety of antidepressants has been increasingly questioned. The assessment of the harms of antidepressants has been limited by highly selected trial populations and the short-term nature of follow-up, thereby potentially limiting the detection of long-term harmful effects. Despite the general tolerability of antidepressants, in particular SSRIs compared to TCAs or MAOs, they are not without harmful effects[36,55–57]. A systematic review examining the risks and benefits of 2nd generation antidepressants reported that 63% of patients in efficacy trials experienced at least one adverse event during treatment with gastrointestinal disturbances being the most common[55]. On the short term, these adverse effects, such as nausea and headache, are often transient and resolve after several days or weeks[58]. Adverse event reports on long-term use of antidepressants included sexual dysfunction, bleeding, withdrawal effects, weight gain and osteoporotic fractures[56,57]. These effects may be more pronounced in older and comorbid populations. A recently published systematic umbrella review of 45 systematic reviews of 4,471 observational studies showed evidence of several adverse effects including high risk of osteoporotic fractures, stroke and gastrointestinal tract bleeding particularly in those over the age of 65 years. Authors also found evidence suggestive of increased risk of neonatal and maternal adverse events in pregnant women using antidepressants[59]. However, after accounting for confounding by indication, the authors reported that none of the associations with adverse outcomes were supported by convincing evidence[59]. In older people, the link between dementia and antidepressants has been examined with conflicting results. While some studies proposed that antidepressants reduce the risk of dementia[60], other longitudinal studies have suggested the contrary[61]. In a systematic review of 18 longitudinal studies, Chan et al. concluded that antidepressants are indeed associated with a greater risk of dementia[62].

Such findings suggest the need for a benefit-harm assessment to justify the net benefit of the use of antidepressants. Such an assessment would also include the possible harms of psychotherapies as an alternative to antidepressants. These harms have been largely neglected and have not been systematically reviewed[63]. Meister et al. reported that only one out of 9 psychotherapy trials on persistent depressive disorder published information on adverse events as compared to 39 out of 42 drug trials[63]. Additionally, as of yet there isn't a generally accepted definition of side effects of psychotherapy and the distinction between the main effects and side effects of psychotherapy often may not be very clear[64]. However, it has been suggested that psychotherapies could potentially lead to deterioration of depression

during therapy, non-response, symptom substitution and suicidal ideations in about 5-20% of patients[65,66].

E. Patient preferences

Evidence-informed decision-making does not only involve the best available evidence on the effectiveness and efficacy of interventions, but also patient perspectives and preferences. In depression, the importance of patient preferences in particular have been emphasized in some treatment guidelines (e.g., German S-3 and Swiss SGPP guidelines)[14–17]. Additionally, since some of the available treatments have demonstrated equivalent efficacy, some authors suggest that patient preferences can be important in choosing a treatment option[67]. For example, surveys exploring the attitudes of individuals towards different treatments found that their main concern was the side effects of antidepressants, whereas concerns towards psychotherapy were more related to time commitments and costs involved. In terms of acceptability, a meta-analysis suggested a 3-fold preference for psychological treatment over pharmacological treatment in psychiatric disorders including depression[68]. In a survey of 641 patients from primary care practices in Germany, 58% reported that they are likely or very likely to consider psychotherapy as a treatment option for depression. In a subgroup analysis, patients with moderate depression showed higher preference for antidepressants as a treatment option than patients with mild depression[69]. Taking into consideration these patient preferences during doctor-patient consultations may play an important role in treatment adherence and may lead to better health outcomes. Furthermore, patient preferences are rarely taken into account explicitly and systematically in guideline development. However, using systematic methods to explore the preference-sensitivity of treatment decisions may be of significant value. For instance, it is possible to incorporate patient preferences in the benefit-harm assessments of antidepressants at guideline level.

F. Cost-effectiveness of depression treatments

Costs of antidepressants and psychotherapy may influence the choice of treatment and may impose significant additional economic burdens. Studies assessing the cost-effectiveness of different modalities had conflicting results[70–72]. Recently, Ross and colleagues used a decision analytic model to evaluate the cost-effectiveness of CBT versus second generation antidepressants in the US. Neither treatment was found to be consistently more cost-effective than the other. At 1 year, there was a 70% likelihood that second generation antidepressants would be the preferable treatment. However, at 5 years there was 75% likelihood that CBT would be preferable, reflecting the potential for long-term cost savings. Most of the uncertainty of these findings came from the lack of evidence on the relative rates of relapse as long-term trials are generally lacking[73].

2. Swiss Context

According to the Swiss Health Survey conducted in 2017, 8.6% of the population surveyed had symptoms of moderate to severe depression, which is comparable to the rest of Europe. More women than men are diagnosed with depression and the highest prevalence appears to be in people aged 15-24 years[74]. A longitudinal assessment of the development of MDD in 18-19 year old individuals in Zurich followed up to the age of 50 years revealed a cumulative incidence of 32.5%[75]. The burden associated with depression in Switzerland has been assessed by Tomonaga et al. and estimated to be around €8 billion per year, related mainly to hospitalization costs and workdays lost [76].

Data on the management of depression in Switzerland is scarce. Data from the Swiss Health Surveys seems to indicate that many patients are treated with medications. Using a health claims database (Helsana), Haller et al. recently estimated that 8.7% of the population were prescribed antidepressants over one year, which is higher than antidepressant prescription prevalence in other European countries[77]. Women and older people were more likely to receive antidepressants and most of the patients were prescribed the medications by general practitioners[78]. A drug report published in 2019 by Helsana revealed that antidepressants were ranked as the 5th most expensive and purchased class of drugs. Additionally, purchases have increased since 2015 and 2017 by 21.5% and 13.3% respectively[79]. **Appendix 2** lists the available antidepressant drugs in Switzerland by class and active ingredient according to the Swiss "Spezialitätenliste".

Objectives

The HTA aims to assess the effectiveness, safety, benefit-harm balance, and health economic properties of antidepressant pharmacotherapy alone, CBT alone, or antidepressant pharmacotherapy in combination with CBT, beyond the acute management phase in adults with MDD.

Specific objectives will include the following:

- To determine the clinical effectiveness and safety of different antidepressant pharmacotherapies and CBT alone or in combination (Table 6), beyond the acute phase
- To quantitatively assess the benefit-harm balance of the different antidepressant interventions when administered beyond the acute phase
- To evaluate the cost-effectiveness and budget impact of the different antidepressant interventions beyond the acute phase

Table 5. MDD treatment Interventions and comparators

Interventions		Comparators
AD	⟷	Usual care/placebo
AD	⟷	AD
AD	⟷	CBT
AD plus CBT	⟷	Usual care/placebo
AD plus CBT	⟷	AD
AD plus CBT	⟷	CBT

AD: Antidepressant; CBT: Cognitive Behavioral Therapy

Population, intervention, comparator, and outcomes (PICOs)

i. Population

The target population of the HTA will be adult patients (18 years or older), diagnosed with MDD using validated diagnostic instruments, such as DSM-3, DSM-4, DSM-5 and ICD-10. Patients with treatment resistant depression, persistent depressive disorders, seasonal affective disorders, bipolar depression, psychotic depression, substance/medication induced depressive disorder, and perinatal depression are not considered part of the target population as they constitute categories of depression that are distinct from major depressive disorder and need their own treatment approaches. However, some studies may have included mixed populations of these other depression types. In this case, we will consider studies if the MDD cases covered at least 90% of the participants. We will include studies that reported on concurrent mental disorders in addition to MDD and we will assess the impact of including such populations on the overall effect in sensitivity analyses. We will exclude studies that focus exclusively on patients with MDD with a specific comorbid mental disorder as the type of intervention studied would be targeting the comorbid mental disorder rather than MDD alone..

ii. Intervention

We will consider studies that have administered any of the following interventions for at least 12 weeks:

1. Antidepressants
    - SSRIs (escitalopram, citalopram, paroxetine, fluvoxamine, fluoxetine, sertraline)
    - SNRIs (duloxetine, reboxetin, venlafaxine)
    - TCAs (clomipramine, amitryptiline, trimipramine, doxepin)
    - Atypical antidepressants (mirtazapine , agomelatine, bupropion)
    - MAOIs (moclobemide)
    - Serotonin modulators (vortioxetine, trazodone)
    - Tetracyclic antidepressant (mianserin)
2. CBTs, including face-to-face (individual or group-based) and internet-based CBTs (guided or unguided self-help)

3. Combination of ADs and CBTs

iii. Comparators

We will include the following comparators:

- Control conditions (e.g., placebo, waiting list, treatment as usual)
- Antidepressant pharmacotherapy or CBT as monotherapy

iv. Outcomes

a. Clinical efficacy or effectiveness outcomes:

- Response rates: typically defined as 50% improvement between baseline and endpoint using (i) standardized clinician-rated scales (e.g. Hamilton Rating Scale of Depression (HDRS or HAM-D), Montgomery–Asberg Depression Rating Scale (MADRS)) or (ii) self-report measures (such as Patient Health Questionnaire-9 (PHQ-9), Beck Depression Inventory (BDI), and BDI-II) or any other depression scale used by the authors.
- Remission rates
- Relapse rates
- Improvement in social function or activities of daily life (functional capacity) as reported by authors
- Quality of life (as measured by SF-36 Health Survey, WHO quality of life-BRFE or any other instrument)
- Patient adherence

b. Safety or harm outcomes:

- Acceptability (defined as study drop-out for any reason)
- Specific adverse events (e.g. hyponatremia, seizures, suicidal ideas or behaviors, hepatotoxicity, weight gain, gastrointestinal symptoms, sexual side effects)
- Withdrawals because of specific adverse events
- Treatment burden

c. Health economic outcomes:

- Short-term and long-term costs
- Direct and indirect costs
- Quality-adjusted life years (QALYs)
- Cost-effectiveness (costs per QALY gained)
- Budget impact

Subgroups

The following subgroups will be treated separately in the case of expected possible sources of heterogeneity and differential effects:

- Baseline severity of the MDD: mild , moderate and severe
- Dosing schedule of antidepressants (fixed or flexible)
- Delivery format of CBT
- Type of scale rating (clinician rated versus self-reported)
- Age: 18-41 years, 42-65 years, ≥65 years
- Treatment duration: Less than 12 weeks, 12 weeks to 6 months, >6 months to 12 months, >12 months to 24 months, and >24 months after randomization
- Studies in settings similar to Switzerland compared to others (i.e. industrialized versus non-industrialized).
- Type of setting: inpatient vs. outpatient and specialized vs. primary care settings

The data sources, search strategy, and analysis for the clinical assessment and cost-effectiveness evaluation are as follows.

Part 1: Systematic review of comparative effectiveness and safety of ADs and CBTs in the treatment of MDD

Information sources

We will focus on RCTs that meet the above PICOs to address the question of effectiveness and safety of ADs and CBTs.

Search strategy

We will adopt our approach used previously in various areas (including the rehabilitation–ICU project commissioned by the SMB) to follow a two-step systematic search process[80]. That is, although the aims could differ (e.g., sometimes they focus on AD or CBT monotherapy or on acute treatment phase only, mixed populations, etc.), there have already been several published systematic reviews of antidepressant/CBT interventions. We expect the potentially eligible RCTs for our aim to be identified reliably by the most recently published high-quality systematic reviews. We will thus first identify the existing high-quality systematic reviews on MDD interventions and we will further conduct a follow-up research to identify more recently published studies following the systematic reviews.

(i) In the first step, we will conduct a systematic search in the Medline (PubMed) and Cochrane Library databases for systematic reviews on MDD interventions published in the last 4 years (i.e.2018-2020). Search terms for ADs will include "antidepressant", "antidepressant drug therapy",

'antidepressant pharmacologic therapy' as well as individual generic names and broad terms related to second-generation antidepressants in conjunction with "systematic reviews", "meta-analysis" and "network meta-analysis". For the CBTs, terms such as "psychotherapy", "cognitive therapy" and "cognitive-behavioral therapy" will be used. Two independent reviewers will read the titles and abstracts of the identified systematic reviews to assess eligibility. We will then evaluate the eligibility of the systematic reviews based on full-text and further assess their quality using the "Assessing the Methodological Quality of Systematic Reviews" (AMSTAR) 2 checklist[81]. Since we will use the systematic reviews for retrospective extraction of individual RCTs for our HTA, we will emphasize the AMSTAR-2 criteria that deemed relevant for our aim, such as those that focus on the PICOs, the quality of the literature search (completeness, selection, extraction strategies), more precisely on the AMSTAR-2 criteria 1 and 4–9. Systematic reviews meeting these criteria will be considered to be of good quality and will be used to extract potential sources of RCTs eligible for our analysis (i.e., all studies identified in- and excluded in each systematic review will be considered).

(ii) In the second step, we will conduct a follow-up search of studies that may be published in periods following the publication of the selected high-quality systematic reviews. The databases used will include Medline (PubMed), EMBASE, PsycInfo and Cochrane Library. For the follow-up research, we will use the same search strategies that were used in the selected high-quality systematic reviews to ensure consistency. In addition, bibliographies of the included studies will be searched for additional studies. We will exclude studies that were conducted prior to 1 January 1995. We chose this date based on the date of introduction of the last major class of antidepressants (SNRIs) into the market. It is likely that the landscape of MDD treatment before 1995 differed from what it is now. On the other, we anticipate no major changes in MDD management since then. We will also search for unpublished studies in Clinical Trials.gov, Drugs@FDA, the European Medicines Agency, the National Institute of Mental Health website, the American Psychological Association website, Scopus, the conference proceedings citation index, and reference lists of relevant reviews and included trials. Studies published in English, German, French or Italian will be considered.

Study selection and data management

Individual RCTs that will be identified from the selected high-quality systematic reviews (step 1 above) and follow-up research (step 2 above) will be reviewed in full text to determine their eligibility for our analysis. See Figure 1 for the selection process of the studies. In the case of multiple publications from the same RCT, we will include all publications if they provide complementary information; otherwise we will include only those with the most informative and complete data. We will use CADIMA (https://www.cadima.info)– an online platform– for conducting the study screening and data extraction. The extracted data will be exported to an excel which will then be used for analysis in R. Two independent reviewers will be involved in the full-text assessment to select eligible RCTs for our

analysis. Disagreements between reviewers will be resolved by consensus between the two reviewers and with the involvement of an experienced senior reviewer.

Data collection

We will extract information from the selected RCTs regarding study (setting, design, randomization, concealment, blinding, year of publication), demographic and other characteristics of study participants (age, severity of disease), details of the intervention and comparators (type, dose, mode of delivery), and measured outcomes (see outcomes above). The same reviewers will collect the necessary data independently in consultation with a senior reviewer for any disagreement or clarification. Where deemed necessary, trial authors will be contacted by e-mail up to three times for additional or rectifying unclear information.

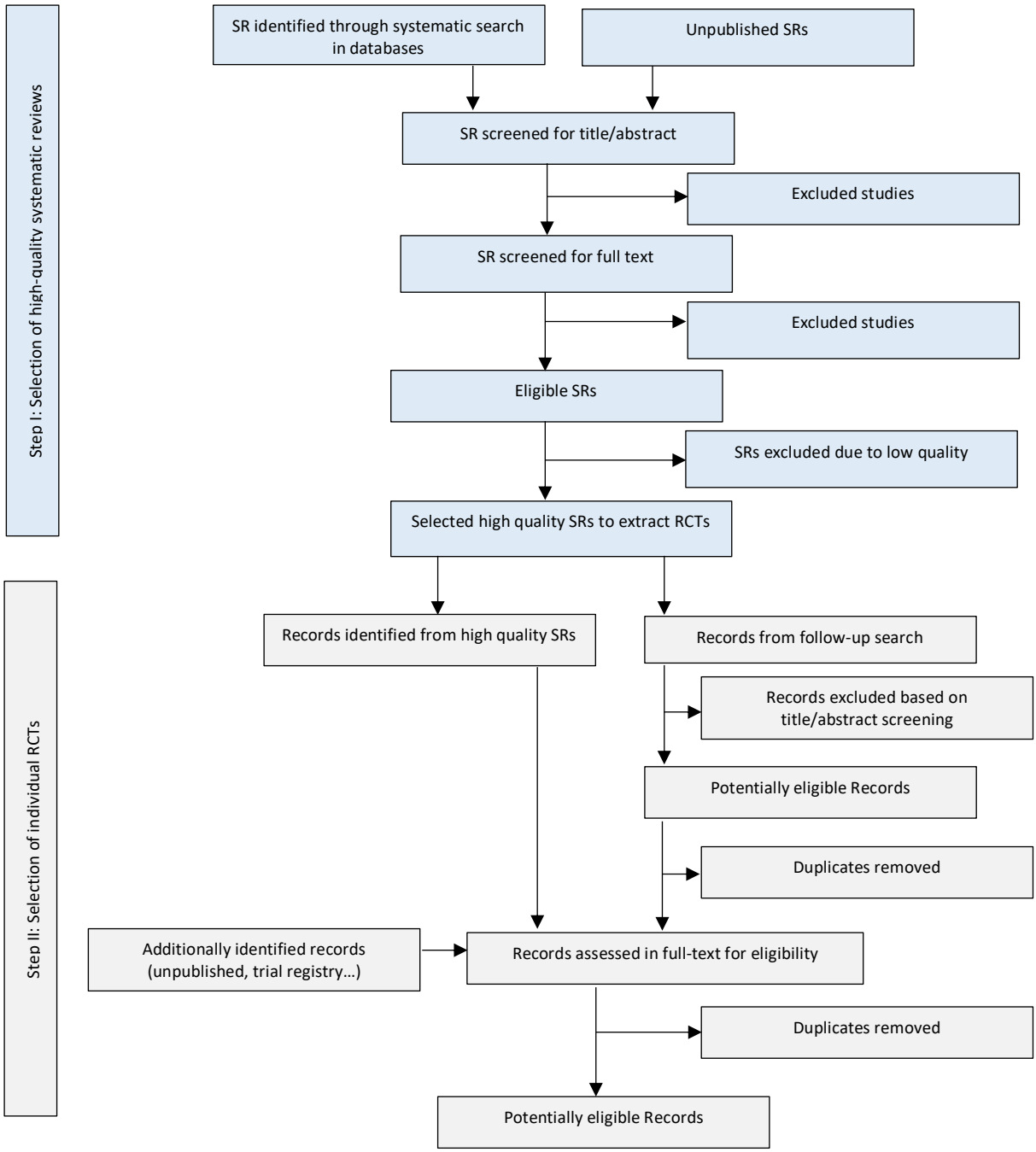

Figure 2. A dummy flowchart for study selection

SR: Systematic review

Risk of bias (methodological quality) assessment

For all selected RCTs, we will assess study-level risk of bias on the different domains in accordance to the Cochrane Handbook[82], including random sequence generation, concealment of allocation, blinding (participant, staff and outcome evaluation), differential loss of follow-up, and selective reporting and other factors such as sponsorship bias. The same investigators involved in the review will independently rate the risk of bias. If the raters disagree, the final rating will be made by consensus or with the involvement of another member of the review group.

Data synthesis

We will perform descriptive statistics for the included RCTs regarding the PICOs and additional characteristics such as study settings, year of publication, and sponsorship. The comparisons will be presented in the network diagram, showing all available comparisons, number of participants, level of variance, average risk of bias in each comparison. Primary analysis will be done by intervention type (e.g. antidepressants versus CBT). Further analyses may include analysis by class (e.g. SSRI, face-to-face CBT) and by individual treatment (e.g. sertraline, group CBT).

Pairwise meta-analyses

We will perform a pairwise meta-analysis with random-effect model for the pairwise comparisons to obtain a summary of standardized mean differences (SMD, Cohen's d) for the continuous outcomes or odds ratio (OR) for the dichotomous outcomes with their 95% confidence intervals (CIs)[83]. The heterogeneity for the placebo-controlled and the active head-to-head comparisons will be visually inspected using forest plots and the heterogeneity will be statistically quantified using I^2 statistic with its 95% CI.

Assessment of the transitivity assumption

The epidemiological and clinical plausibility of the transitivity assumption will be assessed[84]. We will look more closely at whether distributions of possible effect modifiers are similar across comparisons. Some clinical features, such as bipolarity, psychotic and subthreshold depression, may moderate efficacy; and thus, we will ensure the transitivity in our network meta-analysis with regard to these variables by limiting our samples to participants with non-psychotic unipolar major depression. We will examine if other variables (e.g., age, depression severity, doses, mode of delivery, etc.) are similarly distributed across studies grouped by comparison. The inclusion of placebo and concerns about its potential to violate the transitivity assumption will be examined carefully.

Network meta-analyses

We will estimate the indirect and mixed effects using a frequentist, multivariate, random-effect meta-analysis model[85]. The estimation will use binomial probability for dichotomous outcomes and normal probability for continuous outcomes and takes into account correlations in multi-arm RCTs. The heterogeneity variance in the random effect distribution will be considered to measure the extent of treatment effect variability across the studies and within the comparisons. We will assume a single heterogeneity parameter for each network. Finally, we will rank the different antidepressant treatments' efficacy and safety based on the surface under the cumulative ranking curve (SUCRA).

Assessment of inconsistency

While the conceptual evaluation of the transitivity assumption determines the justifiability of conducting network meta-analysis, we will also evaluate the consistency of direct and indirect evidence on the observed data using a consistency test statistic. The consistency test often has a low power, which tends to lead to a false negative for the presence of inconsistency and should therefore be interpreted with caution. We will calculate the Inconsistency Factor with its 95% CIs for the closed loops available using the node-splitting method[86], which tests the direct estimate of a comparison with the indirect estimate coming from the entire network, unlike the loop-specific approach that compares with the indirect estimate pooled from a specific loop[87]. We will also evaluate consistency across the entire network by calculating the I^2 for network heterogeneity, inconsistency, and for both[88,89].

All analyses will be carried out in R.

Publication bias

We will use the comparison-adjusted funnel plots to investigate whether the results in imprecise studies differ from those in more precise studies[90]. We will also perform network meta-regression model to identify relationships between study size and effect size[91].

Confidence of evidence

We will assess the quality or confidence of the direct estimates using the standard Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach based on the five domains (risk-of-bias[92], inconsistency[93], indirectness[94], imprecision[95], and publication bias[96]). For the network estimates, particularly of the indirect and mixed effects, we will adopt the GRADE approach with the extension for network meta-analysis[97].

Part 2: Quantitative benefit-harm assessment

In this analysis, we will simultaneously consider all outcomes relating to benefits and harms associated with antidepressant interventions in order to quantitatively assess the benefit-harm balance. We will use the approach by Gail et al.[98], which we have previously demonstrated in various decision contexts, including statins[99], roflumilast[100], aspirin[101], and target blood pressure[102]. The approach uses an exponential model to estimate the absolute events of benefit and harm in MDD patients who have taken the antidepressant interventions over a period of time compared to their counterparts without the antidepressant interventions. The resulting absolute events for each outcome will be adjusted according to patient preference to produce events on a common scale. Each of the preference-adjusted events will be summed over the outcomes to produce a benefit-harm balance index. This index will be used to assess whether the benefit outweighs the harm or vice versa. The analysis will be performed stochastically with

10,000 (could be more depending on the converging success) simulations taking the distribution–i.e., considering the statistical uncertainty– of the input parameters, including treatment effects, baseline incidence and patient preferences. The results will then be a distribution of the benefit-harm balance index. We will calculate the probability (or proportion of simulations) that patient subgroups would be more likely to experience net benefit from the antidepressant interventions.

The probability that the net benefit equals the net harm (i.e., zero net benefit, on average) is 0.5, where patients and clinicians would be in equipoise. Although it is not clear at what level above the equipoise the treatments should be initiated, we will adopt a previously used threshold probability of 0.6, which ensures a certain absolute net benefit[99–102]. A probability of net benefit between 0.4 and 0.6 indicates uncertain benefit-harm balance, suggesting that initiation of antidepressant treatments should be conditional on the patients' risk profile and treatment goals and values. Any probability value below 0.4 suggests that the antidepressant interventions are less likely to provide net benefit.

Evidence for the BHA will include findings from the systematic review that addresses the comparative clinical effectiveness and safety of ADs and CBTs **(Part 1).** In addition, the quantitative benefit-harm assessment needs multiple parameters on top of the treatment effects from the systematic reviews. Briefly, the minimal parameters needed to conduct the benefit-harm balance assessment include treatment/intervention estimates, baseline incidence of benefit and harm outcomes without the use of antidepressant treatments, and patient preference (or relative importance) of outcomes. Therefore, besides the outputs of our systematic review, we will additionally search for valid, precise, and relevant data from observational, registry or health insurance data specifically to find the baseline risks of the selected benefit and harm outcomes, which will allow us to estimate the absolute effect of antidepressant interventions. Similarly, we will assess the availability of patient preferences on the benefit and harm outcomes. Where possible, we will explore better data sources for baseline risks and preferences that would apply specifically to the Swiss context.

Part 3: Health Economic Evaluation

Approach to health economic assessment

1. Systematic review of economic literature

In a systematic literature search, literature on the cost-effectiveness of antidepressant pharmacotherapy alone, CBT alone, or antidepressant pharmacotherapy in combination with CBT in patients with MDD will be identified. This search will be based on the search strategy used for the clinical effectiveness assessment and adapted for the health economic evaluation by removing the RCT filter and adding a health economic filter.

The identified economic studies will be critically assessed. As one tool, the "Consolidated health economic evaluation reporting standards" (CHEERS) checklist will be used[103]. Plausibility of the results and the transferability of international results to Switzerland will be critically considered. Transferability will be assessed through a multistep approach based on previously published procedures[104–107]. To the extent that they are transferable, costs and incremental cost-effectiveness ratios (ICERs) may be adapted to Switzerland by taking into account differences in healthcare resource utilization and purchasing power parities[108,109]. Change of healthcare costs over time will be used in this case to extrapolate all cost estimations to the same year (presumably 2018)[110]. The aim of the cost adaptation would be to make international cost-effectiveness results more comparable and to achieve a rough indication of the possible magnitude of ICERs for Switzerland. It will not be possible to directly interpret resulting estimates as "ICERS for Switzerland", where practice patterns and effects may differ from those published internationally.

Results will be summarized in tabular and/or graphical formats and synthesized narratively.

2. Cost-effectiveness analysis

The range and complexity of the cost-effectiveness part will depend on the results of the systematic review of the economic literature, and on the results of the clinical part. Only after assessing the quantity and quality of the available information, it will be possible to decide if a detailed *de novo* cost-effectiveness analysis is sensible to perform.

Ideally, a *de novo* cost-effectiveness analysis will be conducted for Switzerland including all treatments listed in the PICO. To correctly compare the selected interventions, this would require to apply a uniform horizon. However, it is not yet known whether a longer-term analysis will be feasible with the available data.

Depending on the available literature and on the results of the network meta-analysis conducted, one of the following approaches may be pursued:

- Markov model with long time horizon based on the data available for all interventions
- Markov model with long time horizon based on the short-term data available plus mid/long-term modelling based on extrapolation of long-term estimates
- Markov model with short time horizon based on the data available for all interventions
- Alternative approaches may include health economic evaluation based on other models, depending on the type of evaluation judged more adequate for the decision context and better comparable to other health economic studies in the context.

In case a cost-effectiveness analysis is not sensibly feasible given the available data, we will develop a cost or cost-minimization model. The model will be suitable to accommodate new evidence as it arises and link different levels of effectiveness of AD treatments to cost impact and economic performance.

3. Budget impact analysis

The actual expenditure for the treatment of MDD patients and the impact on the Swiss healthcare system will also be investigated in a budget impact analysis, considering the available information for Switzerland. Several scenarios assuming different MDD treatments (out of AD, CBT, and usual care/placebo alone) will be compared to scenarios including different combination of the investigated treatments (assuming different market shares, like for example 50% AD alone, 25% AD plus CBT, and 25% CBT alone).

4. Perspective

Costs will be assessed from a health insurance law (KVG) perspective and, if possible, from a societal perspective.

5. Additional data sources

In addition to the published literature, the following sources of information may be used for the cost and budget impact analyses:

- Swiss specialty list: will be used for the drug prices[111]
- Swiss Hospital Statistics 2017/2018: hospitalized MDD patients may be identified through relevant treatments (e.g. CHOP codes), diagnostic codes (i.e. ICD-10 codes), and hospitalization codes (i.e., SwissDRG codes)[112]
- Diagnosis-related case cost statistics (Statistik diagnosebezogener Fallkosten) of the Swiss Federal Office of Statistics: this statistic may be used to estimate the hospitalization cost per patient according to their SwissDRG (i.e., according to their diagnoses and treatment combinations received)[113]
- Swiss tariff framework for ambulatory care (TARMED): TARMED positions may be used to estimate costs of outpatient consultations, services and interventions provided[114]

Further sources may be identified and added at a later point in time.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. 5th ed. Arlington, VA: American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596. Accessed January 14, 2020.

2. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Sci Rep*. 2018;8(1):1-10. doi:10.1038/s41598-018-21243-x

3. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*. 2018;75(4):336-346. doi:10.1001/jamapsychiatry.2017.4602

4. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl*. 2004;(420):21-27. doi:10.1111/j.1600-0047.2004.00327.x

5. Global Health Data Exchange | GHDx. http://ghdx.healthdata.org/. Accessed January 20, 2020.

6. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593-602. doi:10.1001/archpsyc.62.6.593

7. Malhi GS, Mann JJ. Depression. *The Lancet*. 2018;392(10161):2299-2312. doi:10.1016/S0140-6736(18)31948-2

8. Solomon DA, Keller MB, Leon AC, et al. Multiple Recurrences of Major Depressive Disorder. *AJP*. 2000;157(2):229-233. doi:10.1176/appi.ajp.157.2.229

9. Gaynes BN, Lux L, Gartlehner G, et al. Defining treatment-resistant depression. *Depression and Anxiety*. 2020;37(2):134-145. doi:10.1002/da.22968

10. Sullivan PF, Neale MC, Kendler KS. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *AJP*. 2000;157(10):1552-1562. doi:10.1176/appi.ajp.157.10.1552

11. Teo AR, Choi H, Valenstein M. Social Relationships and Depression: Ten-Year Follow-Up from a Nationally Representative Study. *PLoS One*. 2013;8(4). doi:10.1371/journal.pone.0062396

12. aan het Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. *CMAJ*. 2009;180(3):305-313. doi:10.1503/cmaj.080697

13. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? *World Psychiatry*. 2010;9(3):155-161.

14. Holsboer-Trachsler E, Hättenschwiler JA, Beck J, et al. Erhaltungstherapie und Rezidiv-prophylaxe unipolarer depressiver Störungen. *Swiss Med Forum*. 2016;16(36). doi:10.4414/smf.2016.02705

15. Holsboer-Trachsler E, Hättenschwiler JA, Beck J, et al. Die Akutbehandlung depressiver Episoden. *Swiss Med Forum*. 2016;16(35). doi:10.4414/smf.2016.02704

16. American Psychiatric Association. *Practice Guideline for The Treatment of Patients With Major Depressive Disorder (3rd Ed.)*.; 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed April 6, 2020.

17. DGPPN. S3-Leitlinie/Nationale Versorgungsleitlinie Unipolare Depression - Langfassung, 2. Auflage, 5. Version; 2015. doi:https://doi.org/10.6101/AZQ/000364.

18. Recognition of Psychotherapy Effectiveness. https://www.apa.org. https://www.apa.org/about/policy/resolution-psychotherapy. Accessed January 15, 2020.

19. Cuijpers P, van Straten A, van Oppen P, Andersson G. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. *J Clin Psychiatry*. 2008;69(11):1675-1685; quiz 1839-1841. doi:10.4088/jcp.v69n1102

20. Barth J, Munder T, Gerger H, et al. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. *PLoS Med*. 2013;10(5):e1001454. doi:10.1371/journal.pmed.1001454

21. Shinohara K, Honyashiki M, Imai H, et al. Behavioural therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews*. 2013;(10). doi:10.1002/14651858.CD008696.pub2

22. Cuijpers P, Karyotaki E, Wit L de, Ebert DD. The effects of fifteen evidence-supported therapies for adult depression: A meta-analytic review. *Psychotherapy Research*. 2020;30(3):279-293. doi:10.1080/10503307.2019.1649732

23. Cuijpers P, Karyotaki E, Wit L de, Ebert DD. The effects of fifteen evidence-supported therapies for adult depression: A meta-analytic review. *Psychotherapy Research*. 2020;30(3):279-293. doi:10.1080/10503307.2019.1649732

24. Cuijpers P, Karyotaki E, Reijnders M, Ebert DD. Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. *Epidemiology and Psychiatric Sciences*. 2019;28(1):21-30. doi:10.1017/S2045796018000057

25. Cuijpers P, van Straten A, Bohlmeijer E, Hollon SD, Andersson G. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychol Med*. 2010;40(2):211-223. doi:10.1017/S0033291709006114

26. Driessen E, Hollon SD, Bockting CLH, Cuijpers P, Turner EH. Does Publication Bias Inflate the Apparent Efficacy of Psychological Treatment for Major Depressive Disorder? A Systematic Review and Meta-Analysis of US National Institutes of Health-Funded Trials. *PLoS ONE*. 2015;10(9):e0137864. doi:10.1371/journal.pone.0137864

27. Hayes SC, Hofmann SG. The third wave of cognitive behavioral therapy and the rise of process-based care. *World Psychiatry*. 2017;16(3):245-246. doi:10.1002/wps.20442

28. Gaudiano BA. Cognitive-Behavioral Therapies: Achievements and Challenges. *Evid Based Ment Health*. 2008;11(1):5-7. doi:10.1136/ebmh.11.1.5

29. Kahl K, Winter L, Schweiger U. The third wave of cognitive behavioural therapies: what is new and what is effective? *Current Opinion in Psychiatry*. 2012;25(6):522-528. doi:10.1097/YCO.0b013e328358e531

30. American Psychiatric Association. Cognitive Behaivor Therapy. https://dictionary.apa.org/cognitive-behavior-therapy. Accessed April 8, 2020.

31. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. *Cogn Behav Ther*. 2018;47(1):1-18. doi:10.1080/16506073.2017.1401115

32. Möller H-J, Bitter I, Bobes J, Fountoulakis K, Höschl C, Kasper S. Position statement of the European Psychiatric Association (EPA) on the value of antidepressants in the treatment of unipolar depression. *European Psychiatry*. 2012;27(2):114-128. doi:10.1016/j.eurpsy.2011.08.002

33. National Collaborating Centre for Mental Health. *Depression: The NICE Guideline on the Treatment and Management of Depressionin Adults.* Leicester: The British Psychological Society and The Royal College of Psychiatrists; 2018. https://www.nice.org.uk/guidance/cg90/evidence/full-guidline-pdf-4840934509. Accessed January 13, 2020.

34. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet*. 2018;391(10128):1357-1366. doi:10.1016/S0140-6736(17)32802-7

35. Hengartner MP, Angst J, Rössler W. Antidepressant Use Prospectively Relates to a Poorer Long-Term Outcome of Depression: Results from a Prospective Community Cohort Study over 30 Years. *Psychother Psychosom*. 2018;87(3):181-183. doi:10.1159/000488802

36. Jakobsen JC, Katakam KK, Schou A, et al. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry*. 2017;17(1):58. doi:10.1186/s12888-016-1173-2

37. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. *AJP*. 2006;163(1):28-40. doi:10.1176/appi.ajp.163.1.28

38. Zimmerman M, Chelminski I, Posternak MA. Generalizability of Antidepressant Efficacy Trials: Differences Between Depressed Psychiatric Outpatients Who Would or Would Not Qualify for an Efficacy Trial. *AJP*. 2005;162(7):1370-1372. doi:10.1176/appi.ajp.162.7.1370

39. Khan A, Brodhead AE, Kolts RL, Brown WA. Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. *Journal of Psychiatric Research*. 2005;39(2):145-150. doi:10.1016/j.jpsychires.2004.06.005

40. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303(1):47-53. doi:10.1001/jama.2009.1943

41. Furukawa TA, Maruo K, Noma H, et al. Initial severity of major depression and efficacy of new generation antidepressants: individual participant data meta-analysis. *Acta Psychiatr Scand*. 2018;137(6):450-458. doi:10.1111/acps.12886

42. Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. *Arch Gen Psychiatry*. 2012;69(6):572-579. doi:10.1001/archgenpsychiatry.2011.2044

43. Rabinowitz J, Werbeloff N, Mandel FS, Menard F, Marangell L, Kapur S. Initial depression severity and response to antidepressants v. placebo: patient-level data analysis from 34 randomised controlled trials. *The British Journal of Psychiatry*. 2016;209(5):427-428. doi:10.1192/bjp.bp.115.173906

44. Cuijpers P, Hollon SD, van Straten A, Bockting C, Berking M, Andersson G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open*. 2013;3(4). doi:10.1136/bmjopen-2012-002542

45. Imel ZE, Malterer MB, McKay KM, Wampold BE. A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia. *Journal of Affective Disorders*. 2008;110(3):197-206. doi:10.1016/j.jad.2008.03.018

46. Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry*. 2020;19(1):92-107. doi:10.1002/wps.20701

47. Goldberg D, Privett M, Ustun B, Simon G, Linden M. The effects of detection and treatment on the outcome of major depression in primary care: a naturalistic study in 15 cities. *Br J Gen Pract*. 1998;48(437):1840-1844.

48. Gardarsdottir H, Egberts TC, Stolker JJ, Heerdink ER. Duration of Antidepressant Drug Treatment and Its Influence on Risk of Relapse/Recurrence: Immortal and Neglected Time Bias. *Am J Epidemiol*. 2009;170(3):280-285. doi:10.1093/aje/kwp142

49. Hengartner MP, Passalacqua S, Andreae A, et al. Antidepressant Use During Acute Inpatient Care Is Associated With an Increased Risk of Psychiatric Rehospitalisation Over a 12-Month Follow-Up After Discharge. *Front Psychiatry*. 2019;10. doi:10.3389/fpsyt.2019.00079

50. Vittengl JR. Poorer Long-Term Outcomes among Persons with Major Depressive Disorder Treated with Medication. *PPS*. 2017;86(5):302-304. doi:10.1159/000479162

51. Viguera AC, Baldessarini RJ, Friedberg J. Discontinuing Antidepressant Treatment in Major Depression. *Harv Rev Psychiatry*. 1998;5(6):293-306. doi:10.3109/10673229809003578

52. Karyotaki E, Smit Y, Holdt Henningsen K, et al. Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. *Journal of Affective Disorders*. 2016;194:144-152. doi:10.1016/j.jad.2016.01.036

53. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. *BMJ*. 2015;351. doi:10.1136/bmj.h6019

54. U.S. Food and Drug Administration. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications. FDA. http://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications. Published November 3, 2018. Accessed January 20, 2020.

55. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder: An Updated Meta-analysis. *Ann Intern Med*. 2011;155(11):772. doi:10.7326/0003-4819-155-11-201112060-00009

56. Moret C, Isaac M, Briley M. Problems associated with long-term treatment with selective serotonin reuptake inhibitors. *J Psychopharmacol (Oxford)*. 2009;23(8):967-974. doi:10.1177/0269881108093582

57. Cartwright C, Gibson K, Read J, Cowan O, Dehar T. Long-term antidepressant use: patient perspectives of benefits and adverse effects. *Patient Prefer Adherence*. 2016;10:1401-1407. doi:10.2147/PPA.S110632

58. Uher R, Farmer A, Henigsberg N, et al. Adverse reactions to antidepressants. *The British Journal of Psychiatry*. 2009;195(3):202-210. doi:10.1192/bjp.bp.108.061960

59. Dragioti E, Solmi M, Favaro A, et al. Association of Antidepressant Use With Adverse Health Outcomes: A Systematic Umbrella Review. *JAMA Psychiatry*. 2019;76(12):1241-1255. doi:10.1001/jamapsychiatry.2019.2859

60. Burke SL, Maramaldi P, Cadet T, Kukull W. Decreasing hazards of Alzheimer's disease with the use of antidepressants: mitigating the risk of depression and apolipoprotein E. *International Journal of Geriatric Psychiatry*. 2018;33(1):200-211. doi:10.1002/gps.4709

61. Then C-K, Chi N-F, Chung K-H, et al. Risk analysis of use of different classes of antidepressants on subsequent dementia: A nationwide cohort study in Taiwan. *PLOS ONE*. 2017;12(4):e0175187. doi:10.1371/journal.pone.0175187

62. Chan JYC, Yiu KKL, Kwok TCY, Wong SYS, Tsoi KKF. Depression and Antidepressants as Potential Risk Factors in Dementia: A Systematic Review and Meta-analysis of 18 Longitudinal Studies. *Journal of the American Medical Directors Association*. 2019;20(3):279-286.e1. doi:10.1016/j.jamda.2018.12.004

63. Meister R, von Wolff A, Mohr H, et al. Adverse event methods were heterogeneous and insufficiently reported in randomized trials on persistent depressive disorder. *J Clin Epidemiol*. 2016;71:97-108. doi:10.1016/j.jclinepi.2015.10.007

64. Linden M, Strauß B, Scholten S, Nestoriuc Y, Brakemeier E-L, Wasilewski J. Definition und Entscheidungsschritte in der Bestimmung und Erfassung von Nebenwirkungen von Psychotherapie. *Psychother Psych Med*. 2018;68(9/10):377-382. doi:10.1055/a-0619-5949

65. Linden M, Schermuly-Haupt M-L. Definition, assessment and rate of psychotherapy side effects. *World Psychiatry*. 2014;13(3):306-309. doi:10.1002/wps.20153

66. Lilienfeld SO. Psychological Treatments That Cause Harm. *Perspect Psychol Sci*. 2007;2(1):53-70. doi:10.1111/j.1745-6916.2007.00029.x

67. Winter SE, Barber JP. Should treatment for depression be based more on patient preference? *Patient Prefer Adherence*. 2013;7:1047-1057. doi:10.2147/PPA.S52746

68. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry*. 2013;74(6):595-602. doi:10.4088/JCP.12r07757

69. Dorow M, Löbner M, Pabst A, Stein J, Riedel-Heller SG. Preferences for Depression Treatment Including Internet-Based Interventions: Results From a Large Sample of Primary Care Patients. *Front Psychiatry*. 2018;9. doi:10.3389/fpsyt.2018.00181

70. Barrett B, Byford S, Knapp M. Evidence of cost-effective treatments for depression: a systematic review. *Journal of Affective Disorders*. 2005;84(1):1-13. doi:10.1016/j.jad.2004.10.003

71. Brettschneider C, Djadran H, Härter M, Löwe B, Riedel-Heller S, König H-H. Cost-Utility Analyses of Cognitive-Behavioural Therapy of Depression: A Systematic Review. *PPS*. 2015;84(1):6-21. doi:10.1159/000365150

72. Gajic-Veljanoski O, Sanyal C, McMartin K, et al. Economic evaluations of commonly used structured psychotherapies for major depressive disorder and generalized anxiety disorder: A systematic review. *Canadian Psychology/Psychologie canadienne*. 2018;59(4):301-314. doi:10.1037/cap0000155

73. Ross EL, Vijan S, Miller EM, Valenstein M, Zivin K. The Cost-Effectiveness of Cognitive Behavioral Therapy Versus Second-Generation Antidepressants for Initial Treatment of Major Depressive Disorder in the United States: A Decision Analytic Model. *Ann Intern Med*. 2019;171(11):785. doi:10.7326/M18-1480

74. Statistik B für. Gesundheitsstatistik 2019. Bundesamt für Statistik. https://www.bfs.admin.ch/bfs/de/home/aktuell/neue-veroeffentlichungen.gnpdetail.2019-0201.html. Published October 29, 2019. Accessed January 14, 2020.

75. Angst J, Paksarian D, Cui L, et al. The epidemiology of common mental disorders from age 20 to 50: results from the prospective Zurich cohort Study. *Epidemiology and Psychiatric Sciences*. 2016;25(1):24-32. doi:10.1017/S204579601500027X

76. Tomonaga Y, Haettenschwiler J, Hatzinger M, et al. The economic burden of depression in Switzerland. *Pharmacoeconomics*. 2013;31(3):237-250. doi:10.1007/s40273-013-0026-9

77. Lewer D, O'Reilly C, Mojtabai R, Evans-Lacko S. Antidepressant use in 27 European countries: Associations with sociodemographic, cultural and economic factors. *The British Journal of Psychiatry*. 2015;207(3):221-226. doi:10.1192/bjp.bp.114.156786

78. Haller E, Watzke B, Blozik E, et al. Antidepressant prescription practice and related factors in Switzerland: a cross-sectional analysis of health claims data. *BMC Psychiatry*. 2019;19(1):196. doi:10.1186/s12888-019-2178-4

79. Helsana drug report 2019. https://www.helsana.ch/en/helsana-group/about-our-company/health-sciences/drug-report. Accessed January 14, 2020.

80. Yebyo HG, Aschmann HE, Kaufmann M, Puhan MA. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. *American Heart Journal*. 2019;210:18-28. doi:10.1016/j.ahj.2018.12.007

81. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358. doi:10.1136/bmj.j4008

82. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343. doi:10.1136/bmj.d5928

83. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

84. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods*. 2012;3(2):80-97. doi:10.1002/jrsm.1037

85. Multivariate Random-effects Meta-regression: Updates to Mvmeta - Ian R. White, 2011. https://journals.sagepub.com/doi/10.1177/1536867X1101100206. Accessed April 9, 2020.

86. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*. 2010;29(7-8):932-944. doi:10.1002/sim.3767

87. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol*. 2013;42(1):332-345. doi:10.1093/ije/dys222

88. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods*. 2012;3(2):98-110. doi:10.1002/jrsm.1044

89. Jackson D, Barrett JK, Rice S, White IR, Higgins JPT. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine*. 2014;33(21):3639-3654. doi:10.1002/sim.6188

90. Furukawa TA, Miura T, Chaimani A, et al. Using the contribution matrix to evaluate complex study limitations in a network meta-analysis: a case study of bipolar maintenance pharmacotherapy review. *BMC Research Notes*. 2016;9(1):218. doi:10.1186/s13104-016-2019-1

91. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods*. 2012;3(2):161-176. doi:10.1002/jrsm.57

92. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *Journal of Clinical Epidemiology*. 2011;64(4):407-415. doi:10.1016/j.jclinepi.2010.07.017

93. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *Journal of Clinical Epidemiology*. 2011;64(12):1294-1302. doi:10.1016/j.jclinepi.2011.03.017

94. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *Journal of Clinical Epidemiology*. 2011;64(12):1303-1310. doi:10.1016/j.jclinepi.2011.04.014

95. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *Journal of Clinical Epidemiology*. 2011;64(12):1283-1293. doi:10.1016/j.jclinepi.2011.01.012

96. GRADE guidelines: 5. Rating the quality of evidence—publication bias - Journal of Clinical Epidemiology. https://www.jclinepi.com/article/S0895-4356(11)00181-8/fulltext. Accessed April 9, 2020.

97. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014;349. doi:10.1136/bmj.g5630

98. Gail MH, Costantino JP, Bryant J, et al. Weighing the Risks and Benefits of Tamoxifen Treatment for Preventing Breast Cancer. *J Natl Cancer Inst*. 1999;91(21):1829-1846. doi:10.1093/jnci/91.21.1829

99. Yebyo HG, Aschmann HE, Puhan MA. Finding the Balance Between Benefits and Harms When Using Statins for Primary Prevention of Cardiovascular Disease: A Modeling Study. *Ann Intern Med*. 2019;170(1):1-10. doi:10.7326/M18-1279

100. Puhan MA, Yu T, Boyd CM, Ter Riet G. Quantitative benefit-harm assessment for setting research priorities: the example of roflumilast for patients with COPD. *BMC Med*. 2015;13:157. doi:10.1186/s12916-015-0398-0

101. Stegeman I, Bossuyt PM, Yu T, Boyd C, Puhan MA. Aspirin for Primary Prevention of Cardiovascular Disease and Cancer. A Benefit and Harm Analysis. *PLOS ONE*. 2015;10(7):e0127194. doi:10.1371/journal.pone.0127194

102. Aschmann HE, Puhan MA, Robbins CW, et al. Outcome preferences of older people with multiple chronic conditions and hypertension: a cross-sectional survey using best-worst scaling. *Health and Quality of Life Outcomes*. 2019;17(1):186. doi:10.1186/s12955-019-1250-6

103. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *International Journal of Technology Assessment in Health Care*. 2013;29(2):117-122. doi:10.1017/S0266462313000160

104. Drummond M, Barbieri M, Cook J, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Health*. 2009;12(4):409-418. doi:10.1111/j.1524-4733.2008.00489.x

105. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride J-E. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. *Curr Med Res Opin*. 2007;23(4):671-682. doi:10.1185/030079906x167327

106. O'Brien BJ. A tale of two (or more) cities: geographic transferability of pharmacoeconomic data. *Am J Manag Care*. 1997;3 Suppl:S33-39.

107. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. *Pharmacoeconomics*. 2004;22(13):857-876. doi:10.2165/00019053-200422130-00004

108. OECD Data. Health spending. theOECD. http://data.oecd.org/healthres/health-spending.htm. Accessed April 11, 2020.

109. OECD Data. Purchasing power parities (PPP). theOECD. http://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. Accessed April 11, 2020.

110. Swiss Federal Statistical Office (SFSO). Kosten und Finanzierung des Gesundheitswesens. https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/kosten-finanzierung.html. Accessed April 11, 2020.

111. Arzneimittel-Kompendium der Schweiz. https://compendium.ch./. Accessed April 11, 2020.

112. Swiss Federal Statistical Office (SFSO). Swiss Hospital Statistic. Bundesamt für Statistik. /content/bfs/de/home/statistiken/kataloge-datenbanken/tabellen.assetdetail.3722888.html. Published November 27, 2017. Accessed April 11, 2020.

113. Swiss Federal Statistical Office (SFSO). Swiss diagnosis-related group (SwissDRG) case costs statistics (Statistik diagnosebezogener Fallkosten). https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/erhebungen/fks.html. Accessed April 11, 2020.

114. Swiss tariff framework for ambulatory care (TARMED). https://www.tarmed-browser.ch/de. Accessed April 11, 2020.

115. Noma H, Furukawa TA, Maruo K, et al. Exploratory analyses of effect modifiers in the antidepressant treatment of major depression: Individual-participant data meta-analysis of 2803 participants in seven placebo-controlled randomized trials. *Journal of Affective Disorders*. 2019;250:419-424. doi:10.1016/j.jad.2019.03.031

116. Chen C, Shan W. Pharmacological and non-pharmacological treatments for major depressive disorder in adults: A systematic review and network meta-analysis. *Psychiatry Research*. 2019;281:112595. doi:10.1016/j.psychres.2019.112595

117. Krause M, Gutsmiedl K, Bighelli I, Schneider-Thoma J, Chaimani A, Leucht S. Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: A systematic review, pairwise and network meta-analysis. *European Neuropsychopharmacology*. 2019;29(9):1003-1022. doi:10.1016/j.euroneuro.2019.07.130

118. Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder: Results from a Systematic Review with Network Meta-Analysis. *Drug Saf*. 2014;37(1):19-31. doi:10.1007/s40264-013-0129-4

119. Koeser L, Donisi V, Goldberg DP, McCrone P. Modelling the cost-effectiveness of pharmacotherapy compared with cognitive–behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK. *Psychological Medicine*. 2015;45(14):3019-3031. doi:10.1017/S0033291715000951

120. Henssler J, Kurschus M, Franklin J, Bschor T, Baethge C. Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. *J Clin Psychiatry*. 2018;79(1). doi:10.4088/JCP.15r10545

121. Gartlehner G, Wagner G, Matyas N, et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. *BMJ Open*. 2017;7(6):e014912. doi:10.1136/bmjopen-2016-014912

122. Ramsberg J, Asseburg C, Henriksson M. Effectiveness and Cost-Effectiveness of Antidepressants in Primary Care: A Multiple Treatment Comparison Meta-Analysis and Cost-Effectiveness Model. *PLoS One*. 2012;7(8). doi:10.1371/journal.pone.0042003

123. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. *JAMA Psychiatry*. 2016;73(6):565-574. doi:10.1001/jamapsychiatry.2016.0076

124. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry*. 2014;13(1):56-67. doi:10.1002/wps.20089

125. Serretti A, Mandelli L, M L, elli. Antidepressants and Body Weight: A Comprehensive Review and Meta-Analysis. *J Clin Psychiatry*. 2010;71(10):1259-1272. doi:10.4088/JCP.09r05346blu

126. Gartlehner G, Gaynes BN, Amick HR, et al. Comparative Benefits and Harms of Antidepressant, Psychological, Complementary, and Exercise Treatments for Major Depression: An Evidence Report for a Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. 2016;164(5):331-341. doi:10.7326/M15-1813

127. Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA. A Systematic Review of Comparative Efficacy of Treatments and Controls for Depression. *PLoS One*. 2012;7(7). doi:10.1371/journal.pone.0041778

128. Serretti A, Chiesa A. Treatment-Emergent Sexual Dysfunction Related to Antidepressants: A Meta-Analysis. *Journal of Clinical Psychopharmacology*. 2009;29(3):259-266. doi:10.1097/JCP.0b013e3181a5233f

129. Arroll B, Macgillivray S, Ogston S, et al. Efficacy and Tolerability of Tricyclic Antidepressants and SSRIs Compared With Placebo for Treatment of Depression in Primary Care: A Meta-Analysis. *Ann Fam Med*. 2005;3(5):449-456. doi:10.1370/afm.349

130. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008;5(2):e45. doi:10.1371/journal.pmed.0050045

131. Guaiana G, Gupta S, Chiodo D, Davies SJ, Haederle K, Koesters M. Agomelatine versus other antidepressive agents for major depression. *Cochrane Database of Systematic Reviews*. 2013;(12). doi:10.1002/14651858.CD008851.pub2

132. Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *BMJ*. 2002;325(7371):991. doi:10.1136/bmj.325.7371.991

133. Williams N, Simpson AN, Simpson K, Nahas Z. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. *Human Psychopharmacology: Clinical and Experimental*. 2009;24(5):401-408. doi:10.1002/hup.1033

134. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-758. doi:10.1016/S0140-6736(09)60046-5

135. Deshauer D, Moher D, Fergusson D, Moher E, Sampson M, Grimshaw J. Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. *CMAJ*. 2008;178(10):1293-1301. doi:10.1503/cmaj.071068

136. Cipriani A, La Ferla T, Furukawa TA, et al. Sertraline versus other antidepressive agents for depression. *Cochrane Database Syst Rev*. 2009;(2):CD006117. doi:10.1002/14651858.CD006117.pub2

Appendix I

Identified systematic reviews and pairwise (or network) meta-analyses

Clinical effectiveness			Studies that reported safety outcomes	Stdies that reported Cost-effectiveness evaluation	Studies that used IPD	Long-term outcomes
AD vs. placebo/other AD	**AD vs. psychotherapies**	**AD vs. combination of AD and pyschotherapy**				
Cuijpers 2020[46]	Cuijpers 2020[46]	Cuijpers 2020[46]	Jakobsen 2017[36]	Brettschneider 2015[71]	Noma 2019[115]	Cuijpers 2020[46]
Cipriani 2018[34]	Chen 2019[116]	Krause 2019[117]	Reichenpfader 2014[118]	Koeser 2015[119]	Rabinowitz 2016[43]	Henssler 2018[120]
Chen 2019[116]	Krause 2019[117]	Gartlehner 2017[121]	Gartlehner 2011[55]	Ramsberg 2012[122]	Kuyken 2016[123]	Karyotaki 2016[52]
Krause 2019[117]	Gartlehner 2017[121]	Cuijpers 2014[124]	Serretti 2010	Barret 2005[70]	Gibbons 2012[42]	Amick 2015[53]
Gartlehner 2017[121]	Gartlehner 2016[126]	Khan 2012[127]	Serretti 2009[128]		Fournier 2010[40]	Cuijpers 2014
Jakobsen 2017[36]	Cuijpers 2013[44]		Arroll 2005[129]		Kirsch 2008[130]	Cuijpers 2013[44]
Guaiana 2013[131]	Khan 2012[127]		Furukuwa 2002[132]		Cuijpers 2008[19]	Williams 2009[133]
Khan 2012[127]	Cuijpers 2008[19]					Imel 2008[45]
Cipriani 2009[134]	Imel 2008[45]					Deshauer 2008[135]
Cipriani 2009[136]						
Furukuwa 2002[132]						

AD: antidepressant, IPD: individual participant data; Colors or highlights indicate same studies; IPD: Individual patient data (while the other studies used study-level aggregated data)

Appendix II

List of available antidepressants by class and drug in Switzerland*

Class	Drug	Brand name (Company)
SSRI	Escitalopram	Cipralex (Lundbeck)
	Citalopram	Citalopram Helvepharm (Helvepharm) Citalopram Mepha (Mepha Pharma) Citalopram Sandoz (Sandoz Pharmaceuticals) Citalopram Streuli (Streuli Pharma) Claropram (Axapharm) Claropram Spirig HC (Spirig HealthCare) Seropram (Lundbeck)
	Paroxetine	Deroxat (GlaxoSmithKline) Paronex ((Sandoz Pharmaceuticals)) Paroxetin Helvepharm (Helvepharm) Paroxetin Mepha (Mepha Pharma) Paroxetin Spirig (Spirig HealthCare)
	Fluvoxamine	Floxyfral (Mylan Pharma)
	Fluoxetine	Fluctine (Eli Lilly) Fluoxetin Axapharm(Axapharm) Fluoxetin Helvepharm (Helvepharm) Fluoxetin Mepha (Mepha Pharma) Fluoxetin Sandoz (Sandoz Pharmaceuticals) Fluoxetin Spirig (Spirig HealthCare)
	Sertraline	Seralin Mepha ((Mepha Pharma)) Sertragen (Streuli Pharma) Sertralin Helvepharm (Helvepharm) Sertralin Pfizer (Pfizer) Sertralin Sandoz eco (Sandoz Pharmaceuticals) Sertralin Spirig HC (Spirig HealthCare) Zoloft (Pfizer)
SNRI	Duloxetine	Cymbalta (Eli Lilly) Duloxetin Axapharm (Axapharm) Duloxetin Mepha (Mepha Pharma) Duloxetin NOBEL (NOBEL Pharma) Duloxetin Sandoz (Sandoz Pharmaceuticals) Duloxetin Zentiva (Helvepharm) Duloxetin Spirig HC (Spirig HealthCare)
	Reboxetin	Edronax (Pfizer)
	Venlafaxine	Efexor ER (Pfizer) Venlafaxin ER Sandoz (Sandoz Pharmaceuticals) Venlafaxin Mepha ER (Mepha Pharma) Venlafaxin Pfizer ER (Pfizer) Venlafaxin (Helvepharm) Venlafaxin Spirig HC (Spirig HealthCare) Venlax ER (Drossapharm)
TCA	Clomipramine	Anafranil (Novartis)
	Amitriptyline	Saroten (Lundbeck)
	Doxepin	Sinquan (Pfizer)
	Trimipramine	Surmontil (Sanofi-Aventis) Trimipramin Sandoz (Sandoz Pharmaceuticals) Trimipramine Zentiva (Helvepharm)
Atypical antidepressants	Mirtazapine	Mirtazapin Helvepharm (Helvepharm) Mirtazapin Mepha (Mepha Pharma) Mirtazapin Sandoz eco (Sandoz Pharmaceuticals) Mirtazapin Spirig HC (Spirig HealthCare) Mirtazapin Streuli (Streuli Pharma) Remeron (MSD Merck Sharp & Dohme)
	Agomelatine	Valdoxan (Servier)
	Bupropion	Wellbutrin X, Zyban (GlaxoSmithKline)
MAOIs	Moclobemide	Aurorix (MEDA Pharma)
Serotonin modulators	Vortioxetine	Brintellix (Lundbeck)
	Trazodone	Trazodon Sandoz (Sandoz Pharmaceuticals) Trittico (Vifor)
Tetracyclic antidepressant	Mianserin	Mianserin Mepha 30 (Mepha Pharma)

SSRI: Selective serotonin reuptake inhibitors, SNRI: Serotonin-norepinephrine reuptake inhibitors, TCA: Tricyclic antidepressants, MAOI: Monoamine oxidase inhibitors

*as listed on http://www.xn--spezialittenliste-yqb.ch/