Antidepressants and cognitive behavioural therapy interventions for major depressive disorder beyond the acute management phase

Report of the Appraisal Committee of the Swiss Medical Board

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Impressum

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1 Executive Summary

Major depressive disorder (MDD) is one of the most frequent mental health disorders and is associated with a substantial societal and health-economic burden. Around one in three people over age 15 in Switzerland experience mild, moderate or severe MDD during their lifetime. MDD is most often managed using psychotherapy (most commonly cognitive behavioural therapies, CBT) and/or antidepressant medication (ADM). The goals of therapy are remission of depressive symptoms, restoration of normal psychosocial functioning, and prevention of relapse. The management of MDD proceeds over three phases: the acute phase, lasting 6 to 12 weeks, aiming at achieving remission, the continuation phase, lasting 4 to 9 months, aiming at preventing relapse, and the maintenance phase, which may last years, aiming at preventing recurrence or chronic depression. Patients may initially respond to the therapy partially (response) or fully (remission), may subsequently remain in remission (recovery), may suffer a relapse shortly after achieving a response/remission, or may experience a recurrence of MDD. Current treatment recommendations are largely based on short-term randomized controlled trials (RCTs) focused on the acute management phase. Little is known about the benefits and harms of ADM and CBT beyond 12 weeks of treatment.

The Swiss Medical Board evaluated the evidence from RCTs regarding the clinical efficacy, safety and health economic impact of ADM and CBT alone or in combination, in patients over 18 years of age with MDD who were treated beyond the acute management phase. The assessment was based on standard methods for systematic reviews and health economic analysis. Based on this assessment, this Appraisal Report was drafted using the Evidence-to-Decision (EtD) framework.

For the assessment of clinical efficacy and safety, 42 RCTs were identified. Random-effects pairwise meta-analyses and frequentist multivariable random-effects network meta-analyses were conducted when possible, but most data were synthesised using descriptive analysis. Data was not available for many outcomes, comparisons or time periods. The evidence was judged overall to be of low quality. Both ADM and CBT appear to be clinically effective compared to placebo or usual care beyond the acute phase of treatment, however neither was clearly superior to the other. Given that reporting of adverse events was very limited in trials of CBT, much uncertainty remained regarding the safety and differences in the potential benefits and potential harms of ADM compared with CBT. The Appraisal Committee concluded that both ADM and CBT have desirable but variable clinical effects, but the relative effects are unknown. The therapeutic safety and differences between desirable and undesirable effects of ADM and CBT remain unknown.

The health economic analysis included a systematic review of 33 cost-effectiveness analyses of ADMs and CBT from high income western countries, a cost-adaptation to Switzerland based on 29 of the identified studies, and a budget impact analysis from the Swiss healthcare payer's perspective. The

Appraisal Committee determined that the overall cost of treatment for MDD to the Swiss healthcare payer is high, although around 80 percent of the costs are related to hospitalizations. The impact of ADM or CBT on hospitalizations beyond the acute phase of treatment for MDD is not known. Given potential similar clinical effectiveness and higher costs of CBT, if all patients with MDD were to be treated with generic ADM compared with CBT there might be moderate savings for the Swiss healthcare payer. The choice of therapy may however be significantly impacted by multiple factors including severity of symptoms, patient preference, cost, availability and acceptability. As the current distribution of CBT and ADM as therapies for MDD in Switzerland are not known, the actual budget impact of these therapies remains unknown.

The Appraisal Committee concluded that given the burden of MDD there is probably no important uncertainty or variability in how stakeholders value the effects of ADM and CBT. Based on the evidence available, for patients with MDD beyond the acute management phase, the Appraisal Committee issued a recommendation for ADM and a conditional recommendation for CBT +/- ADM, although with the caveat that outcomes and safety data beyond 12 months are particularly scarce.

2 Abbreviations and definitions

ACT*	Acceptance and commitment therapy
ADM	Antidepressant medication
ADRDA	Alzheimer's Disease and Related Disorders Association
AD-SUS	Adult Service Use Schedule
AE	Adverse Effect
BA*	Behavioural activation
BCBT*	Blended cognitive behavioural therapy
BDI-II	Beck Depression Inventory-II
BHA	Benefit harm assessment
BIA	Budget impact analysis
CBA	Cost-Benefit Analysis
CBASP*	Cognitive behavioural analysis system of psychotherapy
CBT*	Cognitive behavioural therapy
CBTe*	Cognitive behavioural therapy with exercise
CBTm*	Cognitive behavioural therapy with mindfulness
CCBT*	Computerized CBT
CCDAN	Cochrane Collaboration Depression, Anxiety and Neurosis Review Group
CEA	Cost effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	Confidence Interval
C-QIDS-SR	Quick inventory of depressive symptomatology
CRD	Centre for Review and Dissemination
CSDD	Cornell Scale for Depression in Dementia
CT*	Cognitive Therapy
DBT*	Dialectical behaviour therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
e.g.	exempli gratia (lat., = for example)
EUROHIS	European Health Information System Quality of Life index
EQ5D (5D/3L)	Evaluates mobility, self-care, usual activities, pain/discomfort, anxiety/depression
GAF	Global Assessment of Functioning
GRADE	Grading of Recommendations Assessment, Development, and Evaluation

HAM-D	Hamilton Depression Rating Scale
HDRS	Hamilton Depression Rating Scale
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IQR	Interquartile Range
KVG	Swiss health insurance law (“Krankenversicherungsgesetz”)
LIFE	Longitudinal Interval Follow-up Evaluation
MADRS	Montgomery–Asberg Depression Rating Scale
MBCL*	Mindfulness-based compassionate living
MD	Mean Difference
MDD	Major Depressive Disorder
MID	Minimal Important Difference
NMA	Network meta-analysis
NR	Not Reported
OECD	Organization for Economic Co-operation and Development
PHQ-9	Patient Health Questionnaire 9 item
PICO	Population, Intervention, Comparator, Outcome
PST*	Problem solving therapy
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QOLIE-89	Quality of Life in Epilepsy Inventory-89
RCT*	Randomised Controlled Trial
REBT*	Rational-emotive behaviour therapy
REML	Restricted Maximum-Likelihood Estimator
RR	Risk Ratio
SASS	Social Adaptation Self-evaluation Scale
SCBT*	Standard cognitive behavioural therapy
SD	Standard Deviation
SDS	Sheehan Disability Scale
SFOPH	Swiss Federal Office of Public Health
SF-36	Short-Form-36 Questionnaire
SMD	Standardized mean difference
SSRI	Selective serotonin reuptake inhibitor
ST	Standard Therapy

TAU	Treatment As Usual
UK	United Kingdom
USA	United States of America
USD	United States Dollars
VAS	Visual Analogue Scale
vs.	Versus
WHO-5	WHO (Five) Well-being Index
WL	Waiting list
WSAS	Work and Social Adjustment Scale

*forms of cognitive behavioural therapy (CBT)

Classes of Antidepressants

Class	Examples
Atypical antidepressants	bupropion, mirtazipine
Selective Serotonin Re-uptake Inhibitors (SSRI)	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, reboxetine , sertraline
Serotonin-norepinephrine reuptake inhibitors	duloxetine, venlafaxine,
Melatonergic-serotonergic	agomelatine
Tricyclic antidepressant	amitriptyline, clomipramine

Definitions

Dominated strategy (in CEA): Strategy with higher costs and lower QALYs

Health systems perspective (in CEA): costs to the health payers

Societal perspective (in CEA): includes heath system and societal costs e.g. loss of income/ productivity.

NMA: Network meta-analysis comparing three or more interventions simultaneously in one analysis by combining both direct evidence (of relative effects from within one study) and indirect evidence (of relative effects from different studies) across a network of studies.[1]

Transitivity: Applies to the validity of an indirect comparison of treatment effects of different interventions across different randomized trial datasets where these effects are not directly compared but are on average similar in all other relevant factors.[1]

SMD (standardized mean difference): Summary statistics from a meta-analysis when the studies assess the same outcome but are using different scales/metrics.

3 Background

Major depressive disorder (MDD) is one of the most frequent mental health disorders and is associated with a substantial societal and health-economic burden.[2,3] Over a life course, MDD affects more than one in five people[4-6] and often has a recurrent and fluctuating course.[7,8] MDD is commonly classified as mild, moderate or severe.[9] According to the Swiss Health Survey of 2017, 26% of the Swiss population over 15 years of age had mild MDD, 6% had moderate MDD and almost 3% had severe MDD.[10] The proportion of the population with moderate to severe MDD increased from 6.5% to 8.6% between 2012 and 2017[10] and may have risen further during the COVID-19 pandemic. Of concern, among 19 to 34 year olds in Switzerland, suicide, a potential consequence of MDD, is the most common cause of death.[11] In 2013, the economic burden associated with depression in Switzerland was estimated at around €8 billion per year.[3] MDD remains therefore an important clinical and public health concern in Switzerland.

MDD may be treated with various strategies, the most common being antidepressant medication (ADM) or psychotherapeutic approaches (most commonly cognitive behavioural therapies, CBT).[9] There are multiple classes of ADMs and multiple individual medications within each class, usually in the form of oral tablets. CBT involves learning to change behaviour or thought patterns.[12], and comprises a set of therapeutic strategies, which can be conducted in person, online or digitally. The frequency of CBT sessions may vary from a single intervention to multiple times per week. Both ADM and CBT continue for weeks, months or years, and may be used alone or in combination. The therapeutic modalities and strategies for MDD are therefore very broad.

The goals of MDD therapy are to achieve remission from depressive symptoms, restore normal psychosocial functioning, and prevent relapse. Patients may initially respond to the therapy partially (response) or fully (remission). Subsequently they may remain in remission (recovery), may suffer a relapse shortly after achieving a response/remission, or may experience a recurrence of MDD. The choice of treatment strategy depends on severity of symptoms and on other factors, including patient preference, monetary cost, availability and acceptability of the treatment options, and potential adverse effects. The management of MDD proceeds over three phases: The first phase (acute phase) generally ranges from 6 to 12 weeks, where initial treatment is focused on achieving remission of symptoms. Therapy is then continued over the ensuing 4 to 9 months (continuation phase) to prevent relapse, after which treatment may continue for a year or more (maintenance phase), in order to prevent recurrence or chronic depression. Multiple outcomes are therefore possible after or during therapy for MDD.

Several guidelines recommend psychotherapy as the initial treatment modality for mild to moderate depression, and the combination of ADM and psychotherapy for moderate to severe symptoms.[9,13,14]

Current recommendations are largely based on short-term randomized controlled trials (RCTs) covering the acute management phase (up to 12 weeks). Despite the magnitude of the clinical problem, there is little, and even conflicting, evidence as to the benefits of ADM and psychotherapy beyond 12 weeks of treatment.[15-17] Also, given the mostly only short-term follow-up reported in the available studies, the potential harms of treatments of these therapies have not been systematically examined.[18,19]

To address this knowledge gap, the commissioned Health Technology Assessment [HTA] aimed at evaluating the clinical efficacy and safety, benefit-harm balance and health economic characteristics of ADM and CBT, alone or in combination, in patients with MDD who were treated beyond the acute management phase (i.e. >12 weeks), within the context of Switzerland, from the healthcare payer and societal perspectives.

4 Methods

In the formal scoping process, the PICO (population, intervention, comparison, outcome) questions were defined in consultation with stakeholders. Evidence of clinical effectiveness and safety as well as health economic evidence were assessed using the methods described in detail in the corresponding Assessment Report.

The population of interest included adult patients (≥18 years) diagnosed with MDD, defined using validated diagnostic instruments (e.g., *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-3, DSM-4, and DSM-5 or the International Classification of Diseases (ICD)-10). Treatment resistant depression, persistent depressive disorders, seasonal affective disorders, bipolar depression, psychotic depression, substance/medication induced depressive disorder, and perinatal depression were excluded.

In the main analyses, ADM and CBT were considered as therapeutic groups, compared to each other individually or in combination, and to control conditions (placebo, waiting list [WL], treatment as usual [TAU]). Treatment phases of interest were defined as the continuation phase (13 to 24 weeks from the start of treatment) and the maintenance phase (≥25 weeks from the start of treatment). Analyses reporting outcomes concerning individual medications or specific forms of CBT are included in the Appendices of the accompanying Appraisal Report. The most frequently studies classes of ADM were selective serotonin reuptake inhibitors (SSRI e.g. escitalopram, fluoxetine) and atypical antidepressants (e.g. mirtazapine). The most frequently assessed form of CBT was cognitive therapy (CT).

First, a two-step approach systematic literature review was carried out to identify relevant RCTs. Random-effects pairwise meta-analyses and frequentist multivariable random-effects network meta-

analyses were conducted when possible. When not possible, data were synthesised using descriptive analysis. Forty-three studies based on 42 RCTs were included in the quantitative analyses, of which 29 reported data on the continuation phase (13 to 24 weeks) and 14 reported on the maintenance phase (≥25 weeks). Observation periods varied between 13 and 168 weeks and studies included between 30 and 1088 subjects.

Sixteen studies each evaluated ADMs head-to-head or ADM *versus* placebo, 8 studies evaluated ADM *versus* CBT, 6 studies compared different CBTs, 4 studies evaluated ADM *versus* ADM + CBT; 2 studies tested CBT *versus* placebo, 2 studies evaluated ADM *versus* TAU, and 1 study each evaluated CBT *versus* TAU, CBT *versus* WL, or CBT *versus* ADM + CBT.

Sixteen studies included subjects with any severity level MDD; 4 studies included subjects with mild to moderate MDD; 22 studies included subjects with moderate to severe MDD; and 2 studies included subjects with severe MDD. Three studies included only elderly adults, 7 studies included subjects with diverse co-morbid medical conditions (diabetes mellitus, end stage renal disease on haemodialysis, heart failure, acute coronary syndrome, multiple sclerosis, Alzheimer's disease, and epilepsy).

Data were extracted based on the intention-to-treat [ITT] principle. Clinical efficacy outcomes of interest included relapse, recurrence, quality of life (QoL), social functioning, response, and remission. Safety outcomes included assessment of acceptability, worsening of depression, mortality, specific adverse effects, and tolerability.

Second, in addition to the analysis of adverse events (AE) reported in the included RCTs, a novel Benefit-Harm Assessment (BHA) was performed to evaluate the relative effects of each therapy over a time horizon of 12 months. The methods applied are described in detail in the Assessment Report. Given the novelty of this approach and that BHA has thus far not been incorporated into the HTAs completed by the Swiss Medical Board, the BHA results are briefly described here but were not considered in the final assessment.

Third, the health economic assessment comprised a systematic health economic literature review, a cost-effectiveness analysis (CEA) and a budget impact analysis (BIA). A de novo CEA was not conducted as this was considered redundant given existing relevant literature from other European countries. Thirty-three CEAs were included into the systematic review and findings from 29 of these were transferable for adaptation to Switzerland. Detailed methods and assumptions are outlined in the corresponding Health Economic Assessment Report. The systematic review and CEA variably reported the healthcare payer and the societal perspectives. The BIA was conducted from the Swiss healthcare payer perspective with a time horizon of 1 year.

The Appraisal Committee discussed the results of the assessment in a meeting held in November 2021 using the Evidence-to-Decision (EtD) framework.[20] Recommendations were formulated based on the available evidence and additional considerations including feedback from stakeholders. All recommendations apply to subjects over 18 years with MDD, and apply to the therapeutic groups of ADMs and CBT, and not to individual therapies. The EtD framework considers several domains such as the balance between desirable and undesirable effects, quality of evidence, cost-utility/resource requirements, patient values, health equity, and acceptability/feasibility of the intervention. Differences in desirable and undesirable effects were categorized as large, moderate, small, or trivial. The resulting recommendations were formulated as in favour of a given intervention, in favour of either the intervention or comparator, or against the intervention. Recommendations were supplemented by considerations regarding subgroups, implementation aspects, monitoring and evaluation, and research priorities.

5 Results of the appraisal

Given the permutations of comparisons and the stratification by treatment phase the results of clinical efficacy and safety outcomes are summarized for simplicity and clarity in Table 1. Studies comparing different medications (ADM vs. ADM) or different forms of CBT (CBT vs. CBT) were not included in the main analyses but are reported in the appendix of the Appraisal Report.

5.1 Evidence of clinical effectiveness and harm

5.1.1 Desirable effects

5.1.1.1 Evidence from randomized studies

Primary clinical outcomes included relapse, recurrence, improvement in QoL, improvement in social functioning.

Relapse, defined as the proportion of patients experiencing depression relapse during the continuation/maintenance phases, was investigated in 9 studies (3 continuation, 6 maintenance phases). This was most often assessed using the Hamilton Rating Scale of Depression (HAM-D) score. Overall, a statistically significant reduction in relapse was only observed with ADM vs. placebo in the continuation phase (Table 1). Pairwise meta-analysis of 2 studies evaluating relapse risk in the maintenance phase did not find a significant reduction in relapse with ADM vs. placebo overall; however, a post-hoc analysis did find a significant reduction in risk among patients with severe MDD (21% with ADM vs. 31% with placebo). A non-significant trend towards fewer relapses was observed for CBT vs. ADM, CBT vs. placebo and CBT + ADM vs. ADM, predominantly in the maintenance phase. Direct and indirect estimates from the network meta-analysis of relapse risk in the maintenance

phase of treatment did not find any significant difference between comparators where data were available.

Recurrence, defined as the proportion of patients experiencing recurrent depressive episodes during the continuation/maintenance phases, was only reported in 1 study comparing ADM vs. ADM + CBT in the maintenance phase (Table 1). No difference was observed over 3 years of follow-up in a cohort of patients who had achieved recovery in the acute phase of treatment. For all other comparisons data was either not available or comparisons were non-significant

Improvement in quality of life was examined in 6 studies (4 continuation, 2 maintenance phases). Changes in QoL were assessed by various scales across the studies [EUROHIS, EQ5D, EQ5D3L (EuroQoL 5-Dimension 5-Level Questionnaire), QOLIE-89 (Quality of Life in Epilepsy Inventory-89), Visual Analogue Scale (VAS), and WHO-5 (WHO well-being index)]. QoL improved significantly among subjects with diabetes mellitus and moderate to severe MDD who received ADM vs. TAU (diabetes therapy) in the continuation phase. Among subjects with epilepsy and MDD treated with ADM or CBT, QoL had improved similarly in both groups at 16 weeks. The standardized mean difference (SMD) tended to favour ADM over CBT. For all other comparisons data was either not available or comparisons were non-significant (Table 1).

Improvement in social functioning was assessed in 7 studies using the SDS, SASS and GAF scales. Social functioning (assessed by the SDS score) improved significantly across all sub-scores at 24 weeks (continuation phase) in subjects with moderate to severe MDD who received ADM vs. placebo. In 2 studies examining the maintenance phase, there was no difference in functional impairment between subjects receiving ADM or placebo at 9 months when assessed by the HAM-D or SDS scales, although SASS scores improved significantly among those receiving ADM vs. placebo. For all other comparisons data were either not available or comparisons were non-significant, although the SMDs tended to favour ADM over ADM + CBT or placebo, and to favour CBT over ADM, CBT + ADM and TAU (Table 1).

Secondary clinical outcomes of interest included response and remission.

Response refers to the proportion of participants responding to treatment, typically defined as a 50% improvement between baseline and the follow-up timepoint using standardized scales [e.g., Hamilton Depression Rating Scale (HDRS or HAM-D), Montgomery–Asberg Depression Rating Scale (MADRS), PHQ-9 (Patient Health Questionnaire 9 item)]. Response was evaluated in 17 studies (14 continuation, 3 maintenance phase). Network meta-analysis (NMA) found that both ADM and CBT were associated with a significantly greater response to therapy compared to placebo in the continuation phase (Table 1). Pairwise meta-analysis of 3 studies comparing ADM vs. CBT found a

significantly better response to therapy with CBT in the continuation phase, however this effect was not seen in the NMA. For all other comparisons, data were either not available or comparisons were non-significant, although CBT tended to be superior to ADM. In specific drug level analyses, behavioural analysis (BA) and cognitive therapy (CT) were superior to ADMs, and standard CBT was better than tri-cyclic antidepressants (TCA) and atypical antidepressants in the continuation phase. No differences were observed in the maintenance phase.

Remission was defined variably by investigators, using threshold values in the HAM-D, MADRS, PHQ-9 and C-QIDS-SR (Quick Inventory of Depressive Symptomatology) scores in 21 studies (17 continuation, 4 maintenance) (Table 1). In the continuation phase, in pairwise meta-analyses and NMA, ADM and CBT alone were superior to placebo, and CBT alone or in combination with ADM was superior to ADM alone.

5.1.1.2 Additional considerations

Overall, the available evidence suggests that for the primary clinical outcomes, ADM and CBT are likely to be effective in reducing the risk of relapse; however, there appears to be no clear statistical evidence for the superiority of one treatment over the other. Similarly, while there was an improvement in QoL over time with both ADM and CBT, and improvements in social functioning were observed in subjects receiving ADM, CBT or their combination, there was no clear evidence that either was more effective than the other. Regarding the secondary outcomes of response and remission, ADM and CBT were both effective compared to placebo, and CBT alone or in combination with ADM may be more effective than ADM alone.

Given the paucity of studies, the high heterogeneity between studies, and the largely descriptive synthesis of the data in the Assessment Report, the findings are suggestive, rather than conclusive for most analyses. In many studies, subjects with varying severities of MDD, and /or underlying co-morbidities were enrolled and compared, making data interpretation with regard to severity difficult in most cases. Subgroup analyses were rarely reported. The important lack of data on the maintenance phase precludes robust conclusions on the long-term efficacy of ADM and/or CBT as therapy for MDD.

5.1.1.3 Judgment

The Appraisal Committee concluded that in subjects with MDD receiving treatment beyond the acute management phase, the desirable effects of ADM and CBT compared with placebo are positive but variable. The desirable effects of ADM compared with CBT alone, or either ADM or CBT compared with the combination of both, remain unknown.

5.1.2 Safety

5.1.2.1 Evidence from randomized studies

Primary safety outcomes with regards to safety included acceptability, worsening of depression and mortality.

Acceptability, defined as the proportion of participants who left the trial for any reason prior to the end of the study, was reported in 33 studies (25 continuation, 9 maintenance phase). In the continuation phase, acceptability of the combination of ADM + CBT was significantly superior to either therapy alone (Table 1). Results of pooled analyses of ADM vs. placebo in the continuation phase were divergent, depending on study design and sensitivity analysis. In the NMA, acceptability of CBT tended to be superior to ADM and to placebo. For all other comparisons and for the maintenance phase data was either not available or comparisons were divergent or non-significant.

Worsening of depression symptoms was reported in 2 studies, both from the continuation phase. No difference was observed for CBT vs. either ADM or WL. For all other comparisons and for the maintenance phase, no data were available.

Mortality, including all-cause death, was reported in 14 studies (10 continuation, 4 maintenance phase). In the continuation phase, 2 deaths were reported overall. In one study of ADM vs. placebo, the one death reported may have been a medication-related cardiac death. In the maintenance phase, in 2 studies of ADM vs. placebo there were more deaths (10 vs. 5 deaths) in subjects randomized to ADM by 39 weeks of follow-up. No other studies were available for the other comparisons.

Secondary safety outcomes with regard to safety include specific adverse effects and tolerability.

Specific adverse effects included all available data on AEs, classified by organ system, in accordance with the "System Organ Class (SOC)" Medical dictionary for regulatory activities (MedDRA) classification of the European Medicines Agency [EMA]. The risk of any AEs was significantly higher with ADMs compared to placebo and CBT. There were no differences between the groups with regards to serious adverse effects. During the Continuation phase, the frequency of any adverse effect was 61.7% (59.5 – 63.9) for ADM; 33.3% (27.1 – 40.2) for placebo; and 1.3% (0.3 – 5.5) for CBT; no data were reported for ADM + CBT. Frequencies of serious adverse effects were 4.4% (3. – 5.4) for ADM; 5.0% (3.4 – 7.2) for placebo; 9.7% (5.8 – 15.6) for CBT; no data were reported for ADM + CBT. During the maintenance phase, the frequencies of any adverse effect were 39.7% (37.4 – 42.0) for ADM; 46.8% (41.3 – 52.5) for placebo; CBT not reported; 18.1% (13.6 – 23.6) for ADM + CBT. Frequencies of serious effects were 7.9% (6.0 – 10.3) for ADM; 1.4% (0.3 – 7.8) for placebo; 1.2% (0.2 – 6.3) for CBT; 22.4% (14.8 – 32.3) for ADM + CBT.

Most frequent adverse effects reported for ADMs during the continuation phase included gastrointestinal (32%), nervous system (31%), general (12%), psychiatric (12%) and cardiac (9%) events, and during the maintenance phase included reproductive (21%), gastrointestinal (20%) nervous system (19%), and cardiac (13%) events. Adverse effects were less frequently described in CBT studies, the most frequently reported AEs during the continuation phase included nervous system (21%), general (12%), and musculoskeletal (10%) events.

Tolerability was defined as the proportion of participants who left a study due to AEs. Drop-outs due to AEs were reported in 25 studies and ranged from 0.8% for CBT to 9.2% for ADM in the continuation phase and from 7.1% for placebo to 9.6% for ADM in the maintenance phase. One study reported better tolerability of CBT vs. ADM at 16 weeks. In pairwise meta-analysis, tolerability of ADM was less than placebo in the continuation phase but not different in the maintenance phase.

5.1.2.2 Additional considerations

Details on specific AEs are included in Table 13 in the Assessment Report. The relative severity of the listed AEs is difficult to assess from the report. It is likely that AEs are more frequently identified and reported with ADM use than with CBT. Reporting of AEs was inconsistent across trials, and was especially limited in those evaluating CBT. AEs such as emotional discomfort or distress, interdependence between client and therapist may tend to be underreported due to detection, information and courtesy bias. In RCTs where AEs were reported, a high proportion of subjects experienced adverse effects, particularly those receiving ADM. The relative impact of ADM or CBT on hospitalization was not included into the clinical systematic review, which could have a significant impact on cost-effectiveness of the therapies.

Overall, regarding safety, CBT and ADM + CBT were generally more accepted and tolerated by study subjects compared to ADM alone. The risk of bias including predominant pharmaceutical sponsorship of ADM trials and investigator sponsorship and lack of placebo in CBT trials must be considered.

5.1.2.3 Judgment

The Appraisal Committee concluded that the differences in undesirable effects between ADM, CBT or combination therapy in patients with MDD receiving these treatments beyond the acute management phase are not known.

5.1.3 Certainty of evidence

Overall, the certainty of the evidence included in the Assessment Report is low. Most studies were judged to have a high risk of bias (relapse: 8 of 9 studies; recurrence: 1 of 1; QoL: 3 of 6; social functioning: 2 of 7; mortality: 3 of 14), all other studies had significant concerns. The GRADE assessments of the data for the various comparisons are included in Table 1. These assessments

were not estimable for most comparisons. The certainty of the evidence was considered moderate for comparisons of ADM vs. placebo for the outcomes relapse, improvement in social functioning and acceptability, as well as for worsening of depression with CBT vs. WL. The quality of evidence for ADM vs. CBT for relapse, acceptability, worsening of depression and mortality was considered low. Certainty of evidence for all other comparisons where estimable was either low, or more commonly very low.

Sensitivity analyses

Subjects were rarely stratified by severity of depression. Thus, pre-specified subgroup analyses were not possible. Measurement of QoL and social functioning focused on changes between baseline and endpoints at end of follow-up, but differences between intervention and comparator were rarely analysed or interpreted in the context of detecting a minimally important difference. Therefore, the clinical relevance remains unknown.

5.1.3.1 Additional considerations

The important uncertainty about the data stems from multiple methodological issues. The high heterogeneity between study designs, interventions and study populations limits pairwise and network meta-analyses. Trial durations were short (few lasted more than 1 year) and only 1 study reported a 3-year follow up. Data on long-term outcomes were therefore largely lacking. Duration of remission/response was not reported. The exclusive inclusion of RCTs may have enriched the data for highly selected populations with more severe MDD, who may have been more at risk of relapse. The frequently used “enrichment design” – i.e. randomization only of subjects who had responded to treatment during the acute phase for the longer-term follow-up in the continuation and maintenance phases, is somewhat artificial and is unlikely to reflect the clinical reality. This may have increased the number of responders to therapy in the study populations. The methods of evaluating AEs across studies were heterogeneous, and rarely described in detail; objective, structured instruments were very rarely used. AEs were rarely reported in CBT trials. Reasons for study drop-outs were not reported.

Further uncertainty arises because of an underlying assumption that interventions within treatment groups (i.e., all ADMs and all forms of CBT) were similar. The merging of such treatments may have violated transitivity of studies. Analysis at the overall treatment level may have missed within group differences and may have underestimated the efficacy of some interventions. Dosing adequacy of ADMs and the number of CBT sessions may have impacted outcomes but were not assessed. In addition, studies of ADM and CBT are inherently different. ADM studies were usually double-blinded and placebo controlled, whereas blinding is not possible for CBT and the choice of placebo for CBT is difficult. While CBT studies were most often investigator-initiated, 18 trials which assessed ADMs

were sponsored by industry, such that the risk of bias through principal investigator or sponsor allegiance may exist.

The evidence regarding the comparative clinical efficacy and safety of ADM and CBT on outcomes beyond the acute phase of therapy therefore remains largely inconsistent and inconclusive.

5.1.3.2 Judgment

The Appraisal Committee concluded that the overall certainty of evidence regarding the effects of ADM, CBT or combination therapy in patients with MDD receiving these treatments beyond the acute management phase is very low.

5.1.4 Stakeholder values

For the outcome Improvement in Social Functioning, using the threshold cut-off a total SDS score of ≤6 for functional remission, 53% of subjects who received ADM achieved functional remission compared to 28% who received placebo, which is a meaningful clinical difference. Similar findings were also found in the subgroup analysis of individuals with severe MDD. However, differences in outcomes between interventions and comparators were overall rarely analysed or interpreted in the context of detecting a minimally important difference. Therefore, the actual clinical impact, beyond statistical significance, remains unknown for most comparisons.

5.1.4.1 Additional considerations

It appears reasonable to presume that treatment for MDD is of value to the individual and to society. Depressive symptoms and QoL are intrinsically intertwined for the individual. Society would value less depression as this would translate into improved productivity, better social functioning etc. Given the shortage of psychiatrists/psychologists[21], medication is valuable and a more scalable alternative than current forms of CBT (digital technologies may improve scalability of CBT in the future). It is possible however that AEs are more frequent with ADMs. Treatment for MDD may be accompanied by stigma. How this would impact an individual's choice of ADM or CBT may be relevant to the success of their therapy. Acceptability may be highest for ADM + CBT. Reasons for study drop-outs were not reported. It is possible that certain treatment discontinuations may have occurred because of intolerance to the ADM or CBT, while others may have been associated with stigma or cost, and some may have been because subjects felt well enough to stop therapy. These factors can only be speculated upon, but further investigation would be relevant to understand stakeholder values.

5.1.4.2 Judgment

The Appraisal Committee concluded that there is probably no important uncertainty or variability in how stakeholders value the effects of ADM, CBT or combination therapy in patients with MDD receiving these treatments beyond the acute management phase.

5.1.5 Balance between desirable and undesirable effects

From the main assessment, the balance of benefit vs. harm is not clear. Overall, the data are too sparse and heterogeneous for rigorous comparisons and the true clinical significance and long-term outcomes beyond the acute phase remain unknown. The lack of detail in terms of severity of MDD, subgroup analysis, ADM dosing, and frequency of CBT sessions limit interpretation of potential benefits. The large risks of bias (measurability, reporting, courtesy bias) in reporting of AEs between ADM and CBT precludes robust interpretation of potential harms.

5.1.5.1 Additional considerations

In an attempt to objectively assess the relative benefits and harms, a formal benefit-harm analysis (BHA) was conducted in addition to the systematic review with a time horizon of 12 months. Details of this analysis are outlined in the corresponding Assessment Report. The overall net clinical benefit was determined as a composite of both the reduction in relapse and the increase in harm outcomes with additional adjustment by preference weights. The net clinical benefit can be interpreted as number of death-equivalents averted without experiencing any harmful events, or can be converted to averted relapse-equivalents by dividing the net index by the preference weight of relapse.

The findings of the BHA strongly favour CBT or CBT + ADM compared with ADM alone, but there are many important caveats that must be considered in interpretation of this conclusion:

- i) any AE was considered as harm;
- ii) AEs were rarely reported in CBT studies, producing bias against ADM;
- iii) thresholds for net clinical benefit were rarely reported or analysed;
- iv) generic preference weights that have been applied in other decision contexts were assigned on a scale of 0 to 1; the relevance to MDD is unknown;
- v) the analysis assumed the probability of benefit or risk of harm was constant over time;
- vi) net clinical benefit was arbitrarily assumed for a probability > 60%, harm was presumed for a probability of net clinical benefit < 40%; the validity of these assumptions is unknown
- vii) subgroup analysis was not possible;
- viii) follow-up in most studies was too short, therefore outcomes were extrapolated to 12 months.

This BHA is among the first to be conducted in the context of MDD, and there is little evidence for comparison. The BHA is based on multiple assumptions, therefore, the results should be interpreted with caution and must be considered in light of the significant limitations of the studies analysed, which include the lack of detailed AE data and the lack of known empirical preference weights from patient preference surveys. The conclusions from the BHA were therefore not considered for inclusion in the judgements in this HTA.

5.1.5.2 Judgment

The Appraisal Committee concluded that the balance of desirable and undesirable effects of ADM, CBT or combination therapy in patients with MDD receiving these treatments beyond the acute management phase is not known.

5.2 Considerations regarding resource requirements and cost-effectiveness

The health economic analysis consisted of 3 components, a health economic literature review, a cost-effectiveness analysis (CEA), and a budget impact analysis (BIA) for Switzerland. The systematic review and CEA variably reported from the healthcare payer and the societal perspectives. The BIA was conducted from the Swiss healthcare payer perspective with a time horizon of 1 year. Detailed methods and assumptions are outlined in the corresponding Health Economic Assessment Report.

5.2.1 Evidence

5.2.1.1 Health economic literature review

The systematic review included cost effectiveness/utility analyses comparing quality adjusted life years/disability adjusted life years (QALYs/DALYs) published from 2006 onwards. Eligible subjects were those with MDD diagnosed with a validated tool, who were treated with an ADM for at least 12 weeks or received CBT for at least 4 weeks. Eligible comparators included different ADMs, non-CBT-based psychological interventions, or unspecified usual care. Outcomes of interest included incremental cost per QALY gained, incremental cost per DALY avoided, and net monetary benefit based on QALYs or DALYs. Studies were excluded if they were from low- and middle-income countries or Asia given the differences in health systems compared with Switzerland, or if they included co-morbid populations.

Thirty-three studies from 12 high income western countries met inclusion criteria for the systematic review. Fourteen studies assessed ADM as the intervention (10 ADM vs. ADM, 4 ADM vs. placebo/supportive care) and 19 studies assessed CBT as the intervention (12 CBT vs. usual care; 5 CBT vs. ADM; 2 CBT vs. behavioral activation or website information). Two studies included subjects with recurrent depression, 16 were within-trial analyses, and 17 were model-based. The time horizon across the studies varied from 6 weeks to 60 months. Studies are outlined in detail in Table 18 of the Assessment Report.

Antidepressant medication

Of the 14 studies (5 UK, 3 Sweden, 5 Europe, 1 US) assessing cost-effectiveness of ADMs, all except one had a duration of 12 months or less. Cost and utility inputs were variable.

Six CEAs tested *escitalopram* as intervention vs. other ADMs/combinations/groups. All were model-based, 5 of 6 were funded by pharmaceutical industry (Belgium, Scotland, Italy, Sweden, Netherlands). In all studies escitalopram dominated or produced lower incremental cost-effectiveness ratios (ICERs) than the comparator and was therefore deemed highly cost-effective. In one study where escitalopram was used as the comparator it was dominated by agomelatine (Greece).

Two CEAs evaluated *venlafaxine* as a first-line or a maintenance intervention. In both studies, venlafaxine was considered cost effective with an ICER of GBP 7,215/QALY (vs. combinations of venlafaxine, fluoxetine, amitriptyline, UK) and USD 18,548/QALY (vs. placebo, Sweden). Seven CEAs evaluated venlafaxine as the comparator intervention. In 5 studies (4 pharma-funded), escitalopram was considered more cost-effective. The single non-industry funded study reported an ICER for escitalopram of Euro 3,723/QALY (Sweden). Two further CEA found that duloxetine dominated venlafaxine (Scotland) and that agomelatine was more cost-effective than generic venlafaxine with an ICER of Euro 1,446/QALY (Greece).

In one government-funded CEA, *sertraline* was found to dominate placebo when tested as the intervention [17]. In contrast, when used as a comparator, sertraline was dominated by escitalopram in 4 studies (Belgium, USA, Italy, Sweden) and by agomelatine in 1 study (Greece). One industry-funded CEA found duloxetine to be cost-effective compared to venlafaxine, mirtazapine, or SSRIs as a group with ICERS of GBP 6,304/QALY or better (Scotland). Three CEAs -evaluated duloxetine as a comparator and in all 3 duloxetine was dominated by escitalopram (Belgium Italy, Sweden).

Three CEAs, conducted within trials and from the healthcare perspective, evaluated *SSRI*s as a group vs. tricyclic ADMs or usual care. In all 3 analyses, SSRIs were found to be cost-effective vs. usual care (ICER GBP 14,854/QALY, UK), vs. tricyclic ADM (ICER GBP 2,692/QALY, UK) and vs. active monitoring (ICER Euro 6,142/QALY, Spain).

Agomelatine was compared with other ADMs (escitalopram, generic venlafaxine, fluoxetine, sertraline) in an industry-funded study and was found to be cost-effective with an ICER of Euro 3.303/QALY or better (Greece).

When other ADMs were evaluated as comparator strategies (e.g., paroxetine, mirtazapine, fluoxetine, citalopram, amitriptyline, fluvoxamine, reboxetine), most were found to have

unfavourable cost-effectiveness profiles relative to the intervention ADM (e.g. escitalopram, venlafaxine, duloxetine, sertraline, or agomelatine).

Cognitive behavioural therapy

Nineteen CEAs (8 UK, 4 Netherlands, 1 Germany, 1 Canada, 2 Sweden, 1 Spain, 1 USA, 1 Australia) evaluated the cost-effectiveness of CBT. All studies were funded by public sector organizations. Costs included and utility inputs were variable. CBT was found to be cost-effective compared to the comparator, below the relevant country thresholds in 8 of the 19 studies. In 5 within-trial CEAs however, CBT was dominated by the comparator. The cost-effectiveness of CBT was uncertain or neutral in the remaining 6 analyses. CBT was found to be cost-effective in 3 of 6 studies which took a societal perspective and in 4 of 11 studies which took a healthcare system perspective.

5.2.1.2 Cost-effectiveness analysis

A de novo CEA was not conducted as this was considered redundant given existing relevant literature from other European countries. Of the 33 studies included in the systematic review, 29 were considered transferrable to Switzerland. Adaptation of the findings to Switzerland included corrections for i) resource utilization (quantity correction – Swiss patients are known to receive more treatment); ii) prices ("price correction" for Switzerland); iii) change in resource utilization/prices over time, based on yearly growth rates of Swiss healthcare expenditures. Importantly, however, this process *cannot* be interpreted as achieving realistic ICERs for Switzerland. The adaptation however intended to achieve a certain approximation.

Antidepressant medications

The literature provides no information about the cost-effectiveness of ADM vs. usual care or TAU. A conclusive health economic appraisal of ADM based on published studies is not possible.

Among the ADMs, numerical adaptation for Switzerland rendered *escitalopram* the dominant strategy in most cases. Two studies report a trade-off between escitalopram and venlafaxine from a healthcare perspective, with ICERs estimated to be below CHF 15,000 per QALY gained. When using a societal perspective, the same authors concluded that escitalopram was a dominant strategy if compared to venlafaxine It is remarkable that despite methodological differences, all studies concluded that escitalopram was highly cost-effective. At the same time, it is noteworthy that five out of six cost-effectiveness analyses evaluating escitalopram were funded by a pharmaceutical company which produces escitalopram.

Venlafaxine was assessed in 7 studies and was dominated by escitalopram in most analyses, or was less expensive but less effective. Venlafaxine generally dominated other ADMs (e.g. citalopram, duloxetine, fluoxetine, paroxetine, sertraline)

The cost-effectiveness of *sertraline* was assessed in 6 studies. Sertraline was found to be a dominant strategy compared with citalopram (from both healthcare and societal perspectives), and with fluvoxamine or placebo (from the healthcare perspective). In comparisons with paroxetine or fluoxetine, sertraline was dominant or dominated in different studies. Compared with duloxetine, sertraline, often being less expensive but also less effective and was dominated in 1 study. Sertraline was dominated compared with escitalopram, venlafaxine, and agomelatine from both healthcare and societal perspectives.

The cost effectiveness of *duloxetine* was assessed in 4 studies. In 3 studies, duloxetine was dominated by escitalopram from the healthcare and societal perspectives. Comparison with venlafaxine yielded discordant results. In 3 studies, duloxetine was dominated by venlafaxine (healthcare and societal perspectives) but in another study duloxetine was less expensive and more effective than venlafaxine (healthcare perspective).

Cognitive behavioural therapy

The cost-effectiveness of face-to-face CBT versus ADM was assessed in 4 studies and was variable. CBT was dominated by ADM from the societal and healthcare system perspectives when assessed over a 12 month time horizon, but dominated ADM when assessed over a 60 month horizon. In other studies, analysis of CBT vs. ADM and CBT + ADM vs. ADM yielded a broad range of ICERs including over CHF 100,000 per QALY gained, depending on the time horizon and severity of MDD. CBT (10-12 sessions) was dominated by usual care from a societal perspective (1 study, time horizon of 36 months). CBT (20 sessions over 16 weeks) was dominated by behavioural activation (1 study, time horizon of 18 months, healthcare perspective)

Ten studies evaluated the cost-effectiveness of internet-based CBT compared with usual care. The results were discordant. Three studies from the societal perspective found that internet-based CBT may be dominant vs. usual care, however 5 studies estimated internet-based CBT to be more expensive and more effective than usual care. Two further studies found internet-based CBT to be less expensive but also less effective than usual care, and in 1 study found usual care to be dominant.

5.2.1.3 Budget impact analysis

For the BIA, the number of patients aged 15 years or older with MDD in Switzerland were extrapolated from the prevalence data reported in the Swiss Health Survey of 2017 to the Swiss population in 2020. Calculations were based on a total of around 2.56 million people, including 1,918,786 with mild MDD (25.9%), 434,012 people with moderate MDD (5.9%) and 204,424 people with severe MDD (2.8%). Costs calculated for 1 year included hospitalization, physician visits, psychotherapy and ADMs. Cost of laboratory tests, additional medications and loss of productivity

were not included. The BIA was performed from the healthcare perspective and is based on multiple assumptions and extrapolations.

Eligible patients for inclusion in the BIA were those reporting being treated for mental health issues or who reported ADM use. A total of 449,555 patients were presumed to be treated, of whom 334,835 were assumed to receive ADMs. The presumed distribution of ADM use among patients was 50% for severe MDD (167,417 patients), 40% for moderate MDD (133,934 patients) and 10% for mild MDD (33,483 patients)**.** Furthermore, an estimated 31.9% of the MDD patients may require hospitalisation, with a mean duration of 18.4 days (mild MDD, 3.1 days at a cost of CHF 942/day; moderate MDD, 16.9 days at a cost of CHF 678/day; severe MDD, 31.1 days at a cost of CHF 650/day). The estimated number of physician visits were 5.81 for mild MDD, 6.52 for moderate MDD and 7.39 for severe MDD. The costs of a physician visit were conservatively estimated at CHF 100 per visit were assumed to remain the same for all treatments.

Prior data from Switzerland found that most patients treated for MDD underwent psychotherapy (87.5%), and a smaller proportion received ADMs, although this increased with severity of MDD[3]. Treatment costs varied according to the treatment distribution assumptions (i.e. psychotherapy, ADM, or a combination of both) and type of ADM**.** Multiple combinations of these therapies were modelled in the BIA. For psychotherapy, 12 sessions per year were assumed at a cost of CHF 150 per session. The lowest and highest costs per dose of the ADMs were extracted from the Swiss compendium and multiplied by the number of doses required per year. Escitalopram was taken to be the most cost-effective drug based on the CEA. For the analysis it was presumed that all patients received escitalopram.

Treatment costs (ADM and/or psychotherapy) amounted to CHF 114 million if all patients received Escitalopram only, CHF 603 million if all patients received psychotherapy alone, and CHF 716 million if all patients were to receive psychotherapy + ADM. Total costs for hospitalization amounted to 5,016 million CHF (mild MDD: 98; moderate MDD: 1,534; severe MDD: 3,384). Total costs for physician visits amounted to CHF 231 million (mild MDD: 19; moderate MDD: 87; severe MDD: 124). The total costs for hospital stay and physician visits of CHF 5,246 million were assumed to remain the same for all treatments, independently of the chosen treatment option. Total direct medical costs therefore ranged from CHF 5,330 million if all MDD patients received the least expensive ADM alone, to CHF 6,032 million if all patients received psychotherapy and the most expensive ADM. Hospitalizations accounted for 80% of total direct medical costs. Considering the fixed costs for hospital stay and physician visits, the range in the variable budget is between CHF 84 million and 854 million. But given that the current usual treatment of MDD in Switzerland is unknown, the budget impact of ADM prescription and CBT cannot be calculated.

5.2.1.4 Additional considerations

In summary, for Switzerland, it appears that escitalopram may be the most cost-effective ADMs, followed by venlafaxine, sertraline, and duloxetine. The CEAs of CBT or internet-based CBT compared with ADMs or usual care yielded discordant results. The high heterogeneity in the results of the CBT studies suggest that the cost-effectiveness may depend on how CBT is provided (e.g. number of sessions, treatment duration, setting). Given that the bulk of the costs associated with treatment of MDD from the healthcare payer perspective is hospitalizations, treatment that would successfully reduce hospitalization, even if considered expensive, may ultimately reduce overall costs.

5.2.1.5 Judgment

The Appraisal Committee concluded that from the perspective of the Swiss healthcare payer, the resources required for the treatment of MDD are large. With all else being equal, there might be moderate savings if all patients with MDD were treated with ADM compared to CBT beyond the acute management phase, however many unknowns remain. The overall budget impact for the Swiss healthcare payer for treatment of patients with MDD beyond the acute management phase is unknown.

5.2.2 Certainty of evidence with regard to resource requirements

Strengths of the health economic literature review and the CEA adapted to Switzerland include that a broad spectrum of interventions and comparators were evaluated and that the majority of the eligible studies were indeed transferrable to Switzerland. Important limitations however include the high heterogeneity across studies in terms of populations, interventions, comparators, time horizons, types of costs captured and health system structure. In addition, costs and QALYs gained over the long term remain largely unknown. Most CEAs investigating the ADMs were sponsored by industry and most CBT studies were susceptible to bias through researcher allegiance, therefore the potential for bias is present in both cases. Finally, no direct Swiss data was available, and the adaptation process cannot be interpreted as achieving realistic ICERs for Switzerland. The various permutations of therapy for MDD, including ADM, CBT or combination therapy, as well as how and by whom these therapies can be administered are likely to impact their cost-effectiveness. These have not been captured by the current CEAs but are likely relevant to clinical practice.

A strength of the BIA is that it is based on Swiss numbers of potential patients affected, costs of hospitalization and of medication, however there are significant limitations. Multiple assumptions were made in terms of use of ADMs, which ADMs were used, costs of physician visits and psychotherapy (which are likely significantly underestimated), the number of visits for CBT required. The severity distribution of MDD was extrapolated from US data. Information of treatment distribution in Switzerland is not available. The exclusion of costs of diagnostic tests and other

medications likely led to significant underestimation of the costs especially for ADMs. The relative rates of hospitalization among patients receiving ADM or CBT are not known. The representativeness of the presumption of one year of CBT is not known. The cost-effectiveness could change if e.g. a limited number of sessions was found to have a long-term positive impact. The societal perspective and indirect costs were not considered which arguably are highly relevant for mental health.

5.2.2.1 Judgment

The Appraisal Committee concluded that the certainty of evidence regarding resources required to treat patients with MDD with ADM and/or CBT beyond the acute management phase is moderate.

5.3 Health equity

A search of published evidence of health equity impact of ADM and/or CBT was not part of the assessment. The HTA did not consider social, legal, or logistical implications of these therapies. The BIA presumed that around 1 in 5 Swiss people with MDD are treated. Decision-making regarding treatment choices is likely being made on an individual basis given the doctors' and patients' time, preferences, and the financial resources available. How potential stigma of MDD and /or its treatment may impact equity is not known. In terms of treatment, given the likely cost-effectiveness and affordability of ADMs, as well as the fact that they can be prescribed by non-mental health specialists (internists, family physicians etc.), equitable access to treatment for MDD is likely increased by ADMs. Given the time and expertise required for CBT, potential language or cultural barriers, concerns about privacy and confidentiality and that there would likely never be enough therapists in Switzerland to provide CBT to all who could benefit, as well as the high cost per session, access to CBT may be inequitable. Access to the combination of ADMs + CBT may be more equitable than CBT alone if the CBT component were required less frequently.

5.3.1 Judgment

The Appraisal Committee concluded that the impact on health equity of ADM, CBT or combination therapy for patients with MDD with beyond the acute management phase varies.

5.4 Acceptability

Given their wide-spread use, both CBT and ADM are generally accepted by all relevant stakeholders. In the systematic review, where study "drop-out" was used as a surrogate for acceptability, CBT may be more acceptable than ADM, however the reasons for drop-outs were not clear. AEs are easier to monitor with medication and were not often monitored in CBT studies. Various forms of therapy may be acceptable to different people who may have different causes/precipitators of MDD and different indications for ADMs or CBT. Potential stigma, immigration status, culture, gender, language may impact whether an individual is willing to accept any therapy, ADMs or CBT for MDD. Delivery of CBT

may be modifiable, e.g. online to meet more diverse needs. CBT may be less acceptable to health insurers if they restrict the number of covered CBT sessions.

5.4.1 Judgment

The Appraisal Committee concluded that the acceptability of ADM, CBT or combination therapy for patients with MDD beyond the acute management phase varies among key stakeholders.

5.5 Feasibility

Both ADMs and CBTs are feasible as therapies, however the shortage of mental health practitioners in Switzerland may make CBT less practically implementable compared with ADMs which are more scalable. CBT may also be less feasible if required urgently, for individuals with tight work schedules, or language barriers, and cultural differences may exist. Online CBT may be feasible if individuals have access to the internet although privacy concerns must be prioritized. Use of both forms of therapies requires follow-up and monitoring.

5.5.1 Judgment

The Appraisal Committee concluded that the feasibility of ADM, CBT or combination therapy for patients with MDD with beyond the acute management phase varies.

6 Recommendations

For patients with MDD beyond the acute management phase, the Appraisal Committee issued a recommendation for ADM and a conditional recommendation for CBT +/- ADM. Outcome and safety data beyond 12 months are particularly scarce

Justification

From the systematic review, where data was available, both ADM and CBT had a clear benefit over placebo or TAU for the treatment of MDD in terms of relapse, improvement in QoL, improvement in social functioning, response and remission, predominantly for the continuation phase. There was, however, no clear superiority of ADM or CBT over each other. Acceptability and the experience of AEs was difficult to assess given risk of bias, but may favor CBT or CBT + ADM. In contrast, ADMs were clearly more cost-effective than CBT over 1 year and from a budget perspective, CBT costs could be five-fold those for ADMs. Overall, therefore, for similar clinical efficacy, but greater cost-effectiveness the recommendation for ADMs is stronger. The recommendation for CBT remains conditional as this form of therapy is effective, but possibly less feasible than ADMs, and the cost-effectiveness may be significantly impacted by how it is implemented. It is also important to

recognize that in Swiss practice it is likely that most people who receive ADMs do also receive some form of CBT.

Subgroup considerations

There were no robust subgroup analyses performed in this HTA. Specifically, a highly relevant stratification would be by severity of MDD as therapeutic strategies may be different for the 3 grades of MDD. The absence of this data is important in interpretation of the Assessment Report findings.

Implementation considerations

Given that MDD is highly prevalent in the Swiss population, in order to optimize equitable access to treatment when needed, the treatment options must be feasible and implementable at scale. Both ADMs and CBT are technically feasible, however given the logistical barrier of the lack of mental health practitioners, other social/structural barriers, and the high costs of CBT, CBT may not be realizable at scale in its current forms. ADMs in contrast are often generic, affordable and can be administered at scale. The clinical monitoring required with ADM use, including AEs and potential drug-interactions, was however largely not addressed in this HTA and requires resources and skills. A likely individual barrier to implementation of either therapy is stigma associated with MDD which may impact health-care seeking or the choice of ADM or CBT.

Monitoring and evaluation

Given the paucity of data beyond the acute phase, monitoring and evaluation should extend to the continuation and maintenance phases in research and quality assurance activities regarding management strategies for MDD.

Research priorities

One of the main conclusions of this HTA is that the data is sparse, existing studies are highly heterogeneous, are at risk of significant bias, and do not provide data on long term outcomes of clinical and practical interest. Given the prevalence of MDD and the high budgetary impact it is imperative that large, well designed, impartial studies are conducted to understand the long-term implications of ADMs and CBT as therapeutic strategies for patients with MDD beyond the acute

management phase. AEs must be clearly documented for all therapeutic options. Cost-effectiveness analysis must include the societal perspective.

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