SMB Expertenrat, Evidence-to-Decision Table (version 01/11/21)

Adapted from GRADEpro GDT: https://gradepro.org/

QUESTION

Antidepressants and cognitive behavioural therapy interventions for major depressive disorder: Evaluating the clinical efficacy and safety, benefit-harm balance and health economic characteristics of ADM and CBT interventions, alone or in combination, in patients with MDD and receiving these treatments beyond the acute management phase (i.e., >12 weeks) within the context of Switzerland.	
POPULATION:	Adult patients (≥18 years) diagnosed with Major Depressive Disorder (MDD)
INTERVENTION:	1. Antidepressant Medication (ADM) • Escitalopram, citalopram, paroxetine, fluvoxamine, fluoxetine, sertraline, duloxetine, reboxetine, venlafaxine, clomipramine, amitriptyline, trimipramine, doxepin, mirtazapine , agomelatine, bupropion, moclobemide, vortioxetine, trazodone, and mianserin. 2. Cognitive behavioural therapies (CBT) • BA: behavioural activation; CT: cognitive therapy; REBT: rational emotive behaviour therapy; DBT: dialectical behaviour therapy; ACT: acceptance and commitment therapy; CBASP: cognitive behavioural analysis system of psychotherapy; MBCL: mindfulness-based compassionate living; PST: problem solving therapy.
COMPARISON:	1. ADM or CBTs as monotherapy 2. Combination of ADM and CBTs 3. Control conditions (placebo, waiting list, treatment as usual)
MAIN OUTCOMES:	1. Clinical efficacy outcomes: • Primary: relapse, recurrence, quality of life (QoL), social functioning • Secondary: response, remission 2. Safety outcomes: • Primary: acceptability (i.e., proportion of participants who withdrew from the study for any reason), worsening of depression, mortality • Secondary: specific adverse effects, tolerability (i.e., proportion of participants who withdrew from the study due to adverse effects) 3. Health economic outcomes: costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs)
SETTING:	Psychiatry, psychology practice in Switzerland
PERSPECTIVE:	Variable, Swiss health care payer and societal perspectives
BACKGROUND:	Major depressive disorder (MDD) is one of the most frequent mental health disorders with a substantial societal and economic burden. MDD is mainly treated by antidepressant medications (ADM) or psychotherapy, of which cognitive behavioural therapy (CBT) is the most frequent form. The choice of initial treatment depends on multiple factors including the severity of depression symptoms, costs, and patient preferences. Treatment is often continued for several months to achieve remission and prevent relapse and may be maintained for up to three years in patients at risk of recurrence. Current understanding of the efficacy of the different interventions is largely based on short-term randomized controlled trials (RCTs) encompassing the acute management phase (up to 12 weeks). Longer term efficacy is uncertain. Furthermore, due to the short-term nature of the studies, little is known about the persistence and development of adverse effects (AE). This lack of evidence has so far hindered an adequate evaluation of the risk-benefit ratios of MDD therapies. This Health Technology Assessment (HTA), therefore aimed at evaluating the clinical efficacy and safety, benefit-harm balance and health economic characteristics of ADM and CBT interventions, alone or in combination, in patients with MDD who received these treatments beyond the acute management phase (i.e., >12 weeks), within the context of Switzerland.
CONFLICT OF INTERESTS:	None identified

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Assessment of the clinical efficacy and safety of the different MDD treatments was divided into three periods - acute phase: ≤12 weeks - continuation phase: 13 to 24 weeks - maintenance phase: ≥25 weeks - outcomes assessed at >12 weeks deemed to be mid- to long-term - MDD diagnosed 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) *The appendix had individual comparisons between drugs/types of CBT etc. NOT included here, far too detailed and not the aim of the assessment, beyond the limited capacity for this HTA - makes no sense unless comprehensive and too much data missing overall* **Two step approach systematic literature review with random-effects pairwise meta-analysis and frequentist multivariable random-effects network meta-analyses when possible, or descriptive analysis** - 988 unique records identified in 1st step -> Included 2 high quality RCTs (published between 2018-2020) - 623 + 7799 (8422, published since 1995) additional records identified from the 2 RCTs and follow-up search in 2nd step - 43 studies (42 trials) included in quantitative synthesis (see Fig 3. In Assessment Report – not clear how numbers add up) - 8 studies evaluating ADM versus CBT - 4 studies evaluating ADM versus ADM plus CBT - 1 study evaluating CBT versus ADM plus CBT - 16 studies assessed either ADM versus placebo - 2 studied assessed CBT versus placebo - 2 studies assessed ADM versus TAU - 1 study assessed CBT versus TAU - 1 study assessed CBT versus waiting list - 16 studies evaluated different ADM head to head - 6 studies compared different CBTs - 29 studies at 13 to 24 weeks (continuation phase) - 14 studies at ≥25 weeks (maintenance phase) - duration 13 to 168 weeks - Sample sizes of participants ranged from 30 to 1088 **EFFECT ESTIMATES:** **Clinical efficacy** ***Primary outcomes***	• Excluded populations: treatment resistant depression, persistent depressive disorders, seasonal affective disorders, bipolar depression, psychotic depression, substance/medication induced depressive disorder, and perinatal depression. • The clinical efficacy, safety, and cost effectiveness outcomes were agreed on in consultation with the experts and stakeholders during the scoping process • Evidence from RCTs, including multi-arm and multistage trials, with 3 types of study design: • Design I: usual two- or multi-arm parallel RCTs • Design II: enrichment or discontinuation trials - participants receive open label treatment for the acute phase, those responding are subsequently randomly allocated to continue the treatment or to receive the comparator (placebo or active control) and followed up. • Design III: similar to Design I but only participants responding to the acute phase treatment are maintained on treatment and followed up. • data extracted based on the intention-to-treat (ITT) • where the trial assessed different dosages of an ADM, data extracted from arm using current recommended dosage • most frequently used classes of ADM were SSRIs and atypicals • most frequently assessed CBT was CT. • 13 studies had an extension/continuation phase for 12 up to 32 weeks. • 22 studies assessed any of the outcomes at ≤12 weeks • **Severity of MDD studies**: • 16 - any severity level MDD • 4 - mild to moderate MDD • 22 -moderate to severe MDD • 2 - severe MDD • 3 - elderly adults (56–58) • 7 - co-morbid medical condition (diabetes mellitus, end stage renal disease on haemodialysis, heart failure, acute coronary syndrome, multiple sclerosis, Alzheimer's disease, and epilepsy).

	RELAPSE: proportion of patients experiencing depression relapse during the continuation/maintenance phases, as defined by each of the studies (Table 2 Assessment report) - 9 studies: o 3 continuation phase o 6 maintenance phase - Pairwise meta-analysis only possible for ADM vs. placebo *ADM vs CBT*: - <u>Continuation phase</u> (n=1): (ref 67) o higher but non-significant risk of relapse among those receiving ADM (RR = 2.48, 95% CI= 0.69 to 8.87) - <u>Maintenance phase</u> (n=2): (ref 66, 68). o Both studies found no difference: at 96 (RR= 1.19 , 95% CI = 0.50 to 2.80), or at 44 weeks (RR= 0.86, 95% CI = 0.31 to 2.40) *ADM vs. ADM + CBT:* - <u>Continuation phase</u> – no studies - <u>Maintenance phase</u> (n=1): o 66 relapses in 44 patients (ADM+CBT) vs. 80 relapses in 49 patients (ADM), respectively, not significant. ADM vs. Placebo: - <u>Continuation phase</u> (n=2, descriptive) o <u>lower risk of relapse with ADM</u> (agomelatine (AGM) vs. placebo (21% versus 41%, RR= 0.49, 95% CI= 0.34 to 0.68) at 24 weeks. o <u>lower risk of relapse with ADM</u> in severe MDD subgroup (22% versus 45%; RR= 0.49, 95% CI= 0.33 to 0.71) o <u>lower proportion of relapse</u> in patients with single or recurrent MDD who had responded to 6 weeks of ADM (AGM and fluoxetine, FXT) treatment in the acute phase (14% in AGM and 18% in FXT groups; RR 0.49, 95% CI= 0.29 to 0.83). - <u>Maintenance phase</u> (n = 2, pairwise M-A) o no difference in the risk of relapse between ADM and placebo (RR= 0.84, 95% CI= 0.44 to 1.59) o estimates from the 2 studies were inconsistent, substantial heterogeneity (I^2= 66%, 95% CI= 0.0% to 92.3%; Q= 2.94, p= 0.09) o post-hoc analysis in 1 study <u>lower proportion of relapse with ADM vs. placebo</u> in more severe patients (with HAM-D > 25 and CGI-S≥5) (21% versus 31%) *CBT vs. placebo:* - <u>Continuation phase</u> – no studies - <u>Maintenance phase</u> (n=1): o Non-significant lower risk of relapse with CBT group (CT) (n= 14/86, 16%) compared to placebo (n = 17/69, 25%) after 44 weeks *CBT vs. treatment as usual (TAU):* no studies *ADM vs. TAU:* no studies *CBT vs. waiting list (WL):* no studies *ADM vs. WL:* no studies ***Network meta-analysis and ranking of treatment regarding relapse*** - <u>Maintenance phase</u> *(Figure 6 Assessment report)*:	• Longer term studies are done in those who initially responded to therapy

	○ No difference in the effects of any of the treatments in either Design I or Design II studies ○ no significant differences between the different drug classes in maintenance phase - P score analysis Design 1: CBT > ADM + CBT > ADM - P score analysis Design 2: CBT> ADM > Placebo	• Not totally clear which phases these apply to
	RECURRENCE: proportion of patients experiencing recurrent depressive episodes during the continuation/maintenance phases, as defined by each of the studies (Table 5 Assessment Report) *ADM vs. ADM + CBT:* - Continuation phase – no studies - Maintenance phase (n=1): • phase 1 of trial, patients randomized to ADM monotherapy or ADM plus CBT -> *those who achieved recovery in phase 1* were randomized to receive either maintenance or withdrawal of ADM with a 3-year follow-up • no difference in recurrence between the ADM monotherapy vs. ADM plus CBT groups at three years (RR= 0.99, 95% = CI 0.69 to 1.41) - *No studies identified for other comparisons*	• Many longer term studies are done in those who initially responded to therapy -> "enriched"
	IMPROVEMENT IN QOL *(Table 6 Assessment report)* - 6 studies (report says 7, table has 6 studies, 6 references): • 4 continuation phase • 2 maintenance phase - Narrative synthesis - 4 studies ADM vs ADM or CBT vs CBT *ADM vs. CBT* - Acute phase – no studies (report not assessing acute phase? Unclear why this is reported) - Continuation phase (n=1): • adults with epilepsy and MDD randomized to ADM (Sertraline, SRT) or CBT (CBT) for 16 weeks • total QOLIE-89 scores improved from baseline to the follow-up in both groups (ADM= 51±14.9 to 66.1±17.7 and CBT= 50.1 ±13.6 to 63.0 ±18.4) -> no significant difference - Maintenance phase: no studies	• QoL using the Quality of Life in Epilepsy Inventory-89 (QOLIE-89)
	ADM vs. TAU: - Acute phase (n=1 treatment continued for 6 months, evaluated at 3 and 6): • patients with DM and severe MDD randomized to receive ADM (SRT) or TAU (diabetes only medications) for six months. • At three months, mean scores increased from 43.5±0.54 at baseline to 64±0.22 (ADM) and from 43.8±0.58 to 56±0.39 (TAU) -> no significant difference - Continuation phase (n=1) • At 6 months significant improvement in those receiving ADM compared to TAU (88.0±0.26 versus 64±0.48) - Maintenance phase: no studies - *No studies identified for other comparisons*	• QoL was evaluated at three and six months using the WHO-5 (wellbeing index)

	IMPROVEMENT IN SOCIAL FUNCTIONING OR ACTIVITIES OF DAILY LIFE (ADL) *(Table 7 Assessment Report)* - 7 studies: • 5 continuation phase • 2 maintenance phase - Narrative synthesis *ADM vs. CBT* - Acute phase (n = 1) • At three months, no significant differences between ADM and CBT in patients with moderate to severe MDD - Continuation phase (n=1): • No significant differences between between ADM and CBT in patients with moderate to severe MDD (ADM: change from 23.3±9.6 to 9.9±9.4 at 6 months; CBT: 19.1±9.4 to 8.6±8.7 at 6 months) - Maintenance phase: no studies *ADM vs. ADM + CBT* - Acute phase (n = 1) • At three months, no significant differences between ADM and CBT in patients with moderate to severe MDD (ADM: change from 23.3±9.6 to 13.1±11.1 at month 3; ADM plus CBT: 24.6±7.0 to 15.6±9.8 at month 3) - Continuation phase (n=1): • No significant differences between ADM and CBT in patients with moderate to severe MDD (ADM: change from 23.3±9.6 to 9.9±9.4 at month 6; ADM plus CBT: 24.6±7.0 to 11.1±2.0 at month 6) - Maintenance phase: no studies *CBT vs. ADM + CBT* - Acute phase (n = 1) • At three months, no significant differences between ADM and CBT in patients with moderate to severe MDD (CBT: change from 19.1±9.4 to 12±8.4 ADM plus CBT: 24.6±7.0 to 15.6±9.8 at month 3). - Continuation phase (n=1): • No significant differences between between ADM and CBT in patients with moderate to severe MDD (CBT: change from 19.1±9.4 to 8.6±8.7; ADM plus CBT: 24.6±7.0 to 11.1±2.0 at month 6) - Maintenance phase: no studies *ADM vs. placebo* - Acute phase (n = 2) • ADM (Duloxetine, DLX) versus placebo on the functional impairment of patients with moderate to severe MDD • HAMD work/activities item - inconsistent results • trial II -> difference between the two groups at week 12 • in both trials majority of participants still had depressive symptoms related to social functioning. • SASS total score, in both trials ADM -> significant improvement at week 12 (mean change of ADM versus placebo- trial I: 7.18±0.62 vs 3.40±0.99, p=0.001; trial II: 7.54±0.61 versus 4.52±0.92, p=0.006)	• social functioning was evaluated using the Work and Social Adjustment Scale (WSAS) • outcome measured using the HAMD work/activities item and two patient rated scales: Social Adjustment Scale (SASS) with an increase in the outcome measurement signifying improvement and Sheehan Disability Scale (SDS) where a decrease in the score means less functional impairment

	• SDS scores, only Oakes trial II found a significant difference in the scores between the two groups (mean change of ADM versus placebo- trial I: -8.32±0.53 vs -6.84±0.87, p=0.142; trial II: -7.70±0.52 vs -4.94±0.84, p=0.005). - Continuation phase (n=1): • After receiving ADM (AGM) or placebo in the acute phase, only responders entered the extension period -> social functioning assessed at week 24 using SDS • mean decreases in the total SDS score (improvement in social functioning) - significantly greater in the ADM vs. placebo, mean differences reaching 7.25±1.14 points. • Within the scale, decreases in all the sub-scores (i.e., work/school, social life, family life/home responsibilities) were greater in the ADM vs. placebo • threshold cut-off total score of ≤6 for functional remission -> 53% of ADM achieved functional remission vs. 28% in the placebo group. • Similar findings in subgroup with severe MDD. - Maintenance phase (n = 1): • reducing the functional impairment: in patients with moderate to severe MDD at 9 months -> no differences in changes of the HAMD work/activities item and SDS scores between ADM (DLX) vs placebo at 9 months • Trial II detected significant improvement in SASS scores at month 9 from baseline in the ADM vs. placebo (13.81±1.04 vs 9.28±1.92, p=0.04). *CBT vs. TAU* - Acute phase (n = 1) • social functioning: no differences (CBT: change in WSAS score from 19.1±9.4 to 12±8.4; TAU: 21.9±11.5 to 13.1±9.3 at month 3). - Continuation phase (n=1): • No difference between (CBT: change in WSAS score from 19.1±9.4 8.6±8.7 at month 6; TAU: 21.9±11.5 to 10.3±10.3 at month 6) - Maintenance phase: no studies - *no studies identified for other comparisons* ***Secondary outcomes*** **RESPONSE**: proportion of participants responding to treatment which is typically defined as a 50% improvement between baseline and the follow-up timepoint using standardized scales (e.g., Hamilton Rating Scale of Depression (HDRS or HAM-D), Montgomery–Asberg Depression Rating Scale (MADRS)) • 23 studies • Acute phase - 16 • Continuation phase - 14 • Maintenance phase - 3 *ADM vs CBT* - Acute phase - no studies - Continuation phase (n=3, Figure 20 Assessment report): • Pooled at 13 to 24 weeks resulted in an RR of 0.79 (95% CI= 0.65 to 0.95) favouring CBT - Maintenance phase: (n = 1) • no difference was between the two groups (RR= 1.27, 95% CI= 0.63 to 2.55)	**Summary:** - most studies evaluated ADM vs placebo - Better response and remission with ADM vs placebo in acute phase consistent with literature - Varying rates of acceptability and worse tolerability of ADM in acute phase - Efficacy of ADM or CBT during continuation and maintenance phases **evaluated in 8 studies** - Large uncertainty - Methodological shortcomings - Most at high risk of bias - GRADE -> general quality of evidence was low - CBT trials blinding not possible - Trail durations short, few > 1 year, 1 had 3 year follow up - Trial designs problematic – follow only responders, switch to placebo after open label treatment etc. - Duration of remission not evaluated - Variable patient groups some with comorbidities only -Relapse: 1 study (ADM vs CBT) in the continuation phase -> higher non-significant risk of relapse among those receiving ADM. Maintenance phase ADM vs CBT comparable Non-significant, lower risk of relapse with ADM + CBT vs ADM Lower relapse with ADM vs placebo in continuation but not maintenance phase Less relapse with CBT vs placebo in maintenance phase (1 study) Recurrence: similar between ADM or ADM + CBT combination by three years (1 study) Results similar to some other reviews, different from others where ADM+CBT was better than ADM alone Response and remission rates favour ADM + CBT in continuation and maintenance phases QOL improved with both ADM and CBT at 16 weeks Social functioning improved with both ADM and CBT or combination up to 6 months Acceptability was higher with ADM +CBT than ADM or CBT, higher with CBT than ADM Side effects common, reporting inconsistent **Overall:**

	ADM vs placebo - Acute phase (n = 6, Figure 21 Assessment report) • pooled analysis -> better response with ADM vs placebo (RR= 1.24, 95% CI= 1.00 to 1.54). Heterogeneity 80%. • Omission of 2 studies with less severe MDD -> RR of 1.44 (95% CI= 1.23 to 1.70) favouring ADM, heterogeneity reduced to 52% - Continuation phase (n=5, Figure 21 Assessment report): • better response with ADM compared to placebo: ▪ design I (RR= 1.57, 95% CI= 0.94 to 2.62) ▪ design III (RR= 1.65, 95% CI= 1.27 to 2.14) - Maintenance phase: no studies ***Network meta-analysis*** - Continuation phase (Figure 22 Assessment report): • Response non-significantly better for CBT vs ADM (RR= 0.75, 95% CI= 0.52 to 1.08) • better for ADM vs placebo (RR= 1.60, 95% CI= 1.08 to 2.36) • better for CBT vs placebo (RR= 2.13, 95% CI= 1.30 to 2.47) • Similar findings on the individual drug level analysis with significantly better response for both BA and CT compared to ADMs. • In the class level analysis: ▪ better response with standard CBT compared to TCA and atypical ADMs ▪ No differences between CBT and 3rd wave CBT. - Maintenance phase (Figure 22) • no difference between any of the comparisons ***Treatment rankings*** - Continuation phase: CBT > ADM > placebo > WL. - Maintenance phase: ADM + CBT > ADM > CBT **REMISSION**: proportion of participants with remission, as defined by authors • 26 studies • Acute phase - 15 • Continuation phase - 17 • Maintenance phase - 4 *ADM vs CBT* - Acute phase - no studies - Continuation phase (n=5, Figure 23 Assessment report): • Pooled analysis favouring CBT -> RR of 0.76 (95% CI= 0.59 to 0.98) - Maintenance phase: (n = 1) • no difference (RR= 0.69, 95% CI= 0.29 to 1.67) *ADM vs ADM + CBT* - Acute phase - no studies - Continuation phase (n=2, Figure 24 Assessment report): • pooled analysis favouring ADM+CBT (RR=0.40, 95% CI= 0.40 to 0.92) - Maintenance phase: (n = 1) • no difference at 1 year (RR= 0.95, 95% CI= 0.87 to 1.05). *ADM vs placebo* - Acute phase (n = 6, Figure 25 Assessment report)	• available evidence suggests both ADM and CBT are effective in reducing the risk of relapse and recurrence. • ->no statistical evidence of the superiority of one treatment over the other • while there was an improvement in QoL over time with both ADM and CBT -> no significant difference between the two. • there were improvements in the social functioning of patients receiving ADM, CBT or their combination. • -> no evidence that either was more effective than the other. R • regarding safety CBT and ADM plus CBT were generally more accepted and tolerated by patients compared to ADM alone. • reporting of AEs was inconsistent across trials, especially scarce in those evaluating CBT • In RCTs who reported AEs, a high proportion experienced adverse effects, particularly hose receiving ADM. • Important limitations large heterogeneity of studies as well, risk of bias arising from the lack of blinding in CBT trials

	• pooled analysis favouring ADM -> RR of 1.52 (95% CI= 1.34 to 1.72) - Continuation phase (n = 3, Figure 25 Assessment report): • better remission with ADM vs placebo (RR= 1.93, 95% CI= 1.38 to 2.69). Heterogeneity 0%. - Maintenance phase: no studies ***Network meta-analysis*** - Continuation phase: • remission significantly better for ADM + CBT vs ADM (RR=0.55, 95% CI= 0.36 to 0.84) • remission significantly better for CBT vs ADM (RR= 0.66, 95% CI= 0.49 to 0.89) • remission significantly better for ADM vs placebo (RR= 1.98, 95% CI= 1.39 to 2.82) • remission significantly better CBT vs placebo (RR= 3.01, 95% CI= 1.95 to 4.67) • no difference was found for the remaining comparisons - Maintenance phase: • No difference between any of the comparisons	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small o Trivial o Varies o Don't know	**Safety** ***Primary outcomes*** **ACCEPTABILITY**: proportion of participants who left the trial for any reason prior to the end of the study (Table 8 Assessment Report) - 35 studies (there are 33 studies in the table): • 25 continuation phase • 9 maintenance phase *ADM vs CBT* - Acute phase (n = 2, Figure 10 Assessment report) • pairwise meta-analysis, -> no difference between ADM and CBT (RR= 1.17, 95% CI = 0.49 to 2.80). - Continuation phase (n=6, Figure 11 Assessment Report): • pooled meta-analysis -> no difference between the two groups (RR= 1.57, 95% CI= 0.94 to 2.62) - Maintenance phase: (n=2) • Divergent results: 1 study - no difference between the drop-out rates in the two groups by 96 weeks (RR= 1.21, 95 % CI= 0.87 to 1.68), 2nd study -> lower dropout with ADM vs CBT at 44 weeks (RR= 0.62, 95 % CI= 0.41 to 0.93) *ADM vs ADM + CBT* - Acute phase (n = 1) • no difference at 12 weeks (RR=1.22, 95% CI= 0.77 to 1.92). - Continuation phase (n=1): • significantly higher dropout rate in the ADM group vs ADM + CBT group at 24 weeks (58% vs 28%, RR= 2.06, 95 % CI= 1.31 to 3.25). - Maintenance phase: (n=2, Figure 12 in Assessment report) • pooled analysis for longer than 24 weeks -> no difference (RR= 1.23, 95 % CI: 0.92 to 1.65)	• CAVE: 18 trials which assessed an ADM compared to placebo or another ADM, were sponsored by the pharmaceutical industry. • CAVE: researcher allegiance in CBT studies

	CBT vs ADM + CBT - Acute phase - no studies - Continuation phase (n=1): • higher acceptability of ADM plus CBT vs CBT alone at 24 weeks (60% vs 28%; RR= 2.12, 95 % CI= 1.29 to 3.48) - Maintenance phase: no studies *ADM vs placebo* - Acute phase (n = 4, Figure 13 Assessment Report) • pooled analysis -> overall higher acceptability rate for ADM (RR= 0.79, 95% CI = 0.67 to 0.94). [results consistent, no heterogeneity] - Continuation phase (n=8): • no significant difference ADM vs placebo across all studies with design I, pooled estimate of RR=1.41 (95%= 0.93 to 2.14), moderate heterogeneity (54%) (**Error! Reference source not found.** Assessment Report) • better acceptability of placebo when study with older participants omitted (RR= 1.69, 95% CI= 1.07 to 2.69), heterogeneity was reduced to 20% (**Error! Reference source not found.**) • pooled analysis of studies with design III -> better acceptability for ADM vs placebo (RR= 0.71, 95% CI= 0.57 to 0.89) (**Error! Reference source not found.** Assessment report), no heterogeneity - Maintenance phase: (n=5, the text says 6, but only 5 studies are included) • design I (n = 3, Figure 16 Assessment Report): no difference between ADM and placebo (pooled RR estimate= 0.96, 95 % CI= 0.85 to 1.07), heterogeneity 28% • design II (n = 2, Figure 17 Assessment Report): overall pooled estimate -> no difference between the two groups (RR= 0.72, 95% CI= 0.40 to 1.29). Substantial heterogeneity (82%) *CBT vs placebo* - Acute phase - no studies - Continuation phase (n=1): • Non-significant difference in acceptability between the two groups at 16 weeks (15% versus 22%; RR= 0.65, 95 % CI= 0.32 to 1.32) - Maintenance phase: no studies *CBT vs TAU* - Acute phase - no studies - Continuation phase (n=1): • no difference at the 24 weeks(RR= 1.29, 95% CI= 0.80 to 2.08) - Maintenance phase: no studies *ADM vs TAU* - Acute phase - no studies - Continuation phase (n=1): • no difference at week 24 (RR= 1.11, 95 % CI = 0.78 to 1.60). - Maintenance phase: no studies - *No studies on ADM or CBT vs. WL* ***Network meta-analysis and treatment ranking***	• Design I: two trials were consistent with each other a third was not - could potentially be due to the selective (patients with Alzheimer's disease) and older population (as reflected by mean age of participants) in 3rd study. Pooled analysis after omitting the 3rd study -> similar results with no heterogeneity • Design II: high heterogeneity: I^2 = 82%, 95% CI= 26.0% to 95.8%; Q=5.68, p=0.02) which could possibly be related to the different treatments given in the open label phase of the two studies (CBT in 1 study, ADM in 2nd study), as well as the different efficacy and side effects of the two ADMs used in the trials (AGM and FXT). • There was evidence of inconsistency in one of the seven loops in the continuation phase network of studies with design I.

	- Acute phase: acceptability significantly better for ADM vs placebo (RR= 0.79, 95 % CI= 0.67 to 0.94 - Continuation phase: acceptability was lower for • ADM vs CBT (RR= 1.41, 95% CI= 0.90 to 2.21) and • ADM vs CBT + ADM (RR= 2.45, 95% CI= 1.12 to 5.35) • Design I: • AGM and PAR had higher dropout than placebo • Different CBT had lower dropout than placebo (range from an RR of 0.68 (for CT) to 0.86 (for REBT)) • Different CBT had lower dropout than ADM (RR ranging from 0.15 to 0.80) • class level analysis • standard CBT and 3rd wave CBT were comparable to each other • standard CBT and 3rd wave CBT had lower drop-out rates than SSRI and NARI classes - Maintenance phase: no significant differences between any of the comparisons ***Treatment rankings***: - Acute phase: ADM + CBT > CBT > ADM > placebo - Continuation phase: ADM + CBT > TAU > CBT > placebo > ADM - Maintenance phase: • design I: ADM + CBT > CBT > ADM > placebo • design II: ADM > CBT > placebo third **WORSENING OF DEPRESSION SYMPTOMS** - 2 studies (Table 10 Assessment Report) - Both continuation phase *ADM vs CBT* - Acute phase – no studies - Continuation phase (n=1): • ADM (SRT) vs CBT (SCBT) -> no difference at week 16 (7% in ADM versus 8% in CBT, RR= 1.13, 95% CI= 0.36 to 3.54) - Maintenance phase: no studies *CBT vs WL* - Acute phase – no studies - Continuation phase (n=1): • no difference at week 16 (8% versus 9%, respectively; RR= 0.86, 95% CI= 0.27 to 2.76) - Maintenance phase: no studies - *no studies identified for other comparisons* **MORTALITY** (all-cause death) - 14 studies (Table 11 Assessment Report) • 3 acute phase • 10 continuation phase • 4 maintenance phase *ADM vs CBT* - Acute phase – no studies	• There was no evidence of inconsistency in the maintenance phase networks.

- Continuation phase (n=1):
  - 1 unrelated death by 16 weeks
- Maintenance phase: no studies

ADM vs placebo
- Acute phase (n = 1)
  - 2 deaths, questionable if related
- Continuation phase (n= 3):
  - 2 studies – no deaths
  - 1 study possible related cardiac death
- Maintenance phase: (n=2)
  - higher number of deaths in the ADM vs placebo (10 versus 5 deaths) by week 39

- *no studies identified for other comparisons*

Secondary outcomes

SPECIFIC AES: 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) (Table 13 Assessment Report)

Side effects
- significantly higher risk of any adverse effects (as reported by studies) in ADMs compared to placebo and CBT
- no differences between the groups with regards to serious adverse effects
- ADM vs placebo: higher risk of gastrointestinal and nervous system AEs with ADMs compared to placebo in both the acute and continuation phases.
- ADM vs CBT: increased the risk of gastrointestinal and nervous system AEs in the continuation phase.

- Acute phase:
  - Any side effect: ADM 47.2% (43.2 – 51.4), Placebo 36.6% (26.4 – 48.2), CBT not reported, ADM + CBT not reported
  - Serious side effect: not reported
- Continuation phase:
  - Any side effect: ADM 61.7% (59.5 – 63.9), Placebo 33.3% (27.1 – 40.2), CBT 1.3% (0.3 – 5.5), ADM + CBT not reported
  - Serious side effect: ADM 4.4% (3. – 5.4), Placebo 5.0% (3.4 – 7.2), CBT 9.7% (5.8 – 15.6), ADM + CBT not reported
- Maintenance phase:
  - Any side effect: ADM 39.7% (37.4 – 42.0), Placebo 46.8% (41.3 – 52.5), CBT not reported, ADM + CBT 18.1% (13.6 – 23.6)
  - Serious effect: ADM 7.9% (6.0 – 10.3), Placebo 1.4% (0.3 – 7.8), CBT 1.2% (0.2 – 6.3), ADM + CBT 22.4% (14.8 – 32.3),

ADM
- Acute phase: Most frequent: gastrointestinal (34%) and nervous system (18%), general (12%), psychiatric (6%)
- Continuation phase: Most frequent: gastrointestinal (32%), nervous system (31%),general (12%), psychiatric (12%), cardiac (9%)

	- Maintenance phase: Most frequent: reproductive (21%), gastrointestinal (20%) nervous system (19%), cardiac (13%) AEs *CBT* - Adverse effects less frequently described - continuation phase: nervous system (21%), general (12%), and musculoskeletal (10%) **TOLERABILITY**: proportion of participants who left the study due to AEs - Drop-outs due to adverse effects were reported in 25 studies • Acute phase range: 5.3% for placebo to 7.7% for ADM • Continuation phase range: 0.8% for CBT to 9.2% for ADM • Maintenance phase range: 7.1% for placebo to 9.6% for ADM *ADM vs CBT* (n = 1) - 9% in the ADM group dropped vs 0% in the CBT group by week 16 *ADM vs Placebo (n =* **Error! Reference source not found.** in assessment report) - Acute phase (n = 5): pairwise meta-analyses -> no difference - Continuation phase (n = 6): pairwise meta-analyses -> ADM less tolerable than placebo (RR= 3.46, 95% CI= 1.65 to 7.25) - Maintenance phase (n = 2): pairwise meta-analyses -> no difference	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	**Primary outcomes:** **Relapse studies**: • 8/9 HIGH risk of bias • Network meta-analysis maintenance phase : substantial heterogeneity (I^2= 66%, 95% CI= 0.0% to 92.3%; Q=2.94, p= 0.09) **Recurrence studies**: • 1/1 HIGH risk of bias **QOL studies**: • Large heterogeneity • 3/6 HIGH risk of bias • 3/6: some concerns about the evidence **Social functioning & ADL studies**: • 2/7 HIGH risk of bias • 5/7 some concerns about the evidence **GRADE Assessment for quality of evidence regarding RELAPSE in continuation phase** (Table 4 Assessment Report)**:** • ADM vs CBT: low • ADM vs. placebo: moderate • effect not estimable for other comparisons **GRADE Assessment for quality of evidence regarding RECURRENCE in continuation phase**	**Strengths:** - Comprehensive search process, similar to others (disputed to some degree by stakeholders) - Topics relevant to clinical practice - Covered multiple trial designs - Attempt to answer unknown clinical questions (long etrm outcomes) **Limitations** - Heterogenous populations – limit pairwise and network meta-analyses - Assumption that interventions were similar - Many different classes of ADM lumped together - Wide range of CBT lumped together - May be violation of transitivity as treatments may have been merged - ADT – usually double blinded placebo controlled - Blinding not possible for CBT - Choice of placebo for CBT is difficult - Hard to estimate placebo effect of ADM and CBT - Analysis at overall treatment level -> miss within group difference, may underestimate efficacy of some interventions - Did not evaluate adequacy of dosing of ADM - Number of CBT sessions and duration often not clear - Analyzed outcomes at study level, not individual patient level

	• not possible **GRADE Assessment for quality of evidence regarding QOL in <u>continuation</u> phase** • ADM vs CBT: very low • ADM vs TAU: very low **GRADE Assessment for quality of evidence regarding social functioning and ADL in <u>continuation</u> phase** • ADM vs CBT: very low • ADM vs ADM + CBT: very low • CBT vs ADM + CBT: very low • CBT vs TAU: very low • ADM vs placebo: moderate. **Acceptability** • Risk of bias - not assessed *ADM vs. CBT* <u>Continuation phase</u>: Heterogeneity across 5 studies was substantial with I^2 of 52% (95% CI= 0.0% to 82.4%; Q=10.52, p= 0.062) -> reduced to 0% (Q= 0.68 , p=0.41) when restricted to 2 studies including only moderate to severe MDD (**Error! Reference source not found.** Assessment Report). *ADM vs placebo*: <u>Acute phase</u>: Results were consistent across studies with no heterogeneity (I^2=0%, Q=1.80, p=0.62) **GRADE assessment for the different comparisons regarding acceptability in the <u>continuation phase</u>** (**Error! Reference source not found.** Assessment Report) • ADM vs CBT: low • ADM vs ADM + CBT: low • CBT vs ADM + CBT: low • ADM vs placebo: moderate • ADM vs TAU: low • CBT vs placebo: low • CBT vs TAU: low **Worsening of depression symptoms**: • Risk of bias: some concerns overall regarding the evidence **GRADE assessment for the different comparisons regarding worsening of symptoms in the continuation phase** (table 4 Assessment report) • ADM vs CBT: low • CBT vs WL: moderate **Mortality** • Risk of bias: 3 studies high risk of bias, some concerns for the remaining 11 studies **GRADE assessment for the different comparisons regarding mortality in the continuation phase** (**Error! Reference source not found.** Assessment report) • ADM vs CBT: low • ADM vs placebo: low	- Restricted inclusion criteria - Did not obtain missing information - ***Most ADM trials sponsored by industry*** - ***CBT trials – bias by PI allegiance*** - 1995 – 2020 is a long time - Publication bias, selective reporting - Data scare for longer term outcomes - Largely narrative synthesis - Pooled analyses limited by few studies and methodological issues - unable to do pre-specified subgroup analyses - no stratification by severity of depression (which is included in guidelines) - only included RCTs = highly selected populations, may have more severe MDD and be more at risk of relapse etc - often "enrichment design" – patients had responded previously, not real life - inadequate assessment of AEs, especially in CBT trials, mostly not reported - The methods of evaluating adverse effects across studies were heterogeneous, rarely described in detail and objective, structured instruments were very rarely used. - Quality of life and social functioning. Measurement focused on changes between baseline and endpoints, differences between intervention and comparator and results were almost never analysed or interpreted in the context of detecting a minimally important difference **Conclusion:** *"The evidence regarding the comparative clinical efficacy and safety of antidepressants and cognitive behavioural therapy on the mid- to long-term remains largely inconsistent and inconclusive"*

	Adverse effects Assessment and reporting of adverse effects was inconsistent across studies and data regarding adverse effects, in particular those related to CBT and ADM plus CBT, was scarce	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**IMPROVEMENT IN SOCIAL FUNCTIONING OR ACTIVITIES OF DAILY LIFE (ADL)** *ADM vs, placebo:* - Acute phase: SASS scores in the ADM groups of both trials were ≥35 which indicated that the patients achieved normal social functioning, while the placebo groups fell short of the cut-off score. - Continuation phase: SDS Score threshold cut-off total score of ≤6 for functional remission -> 53% of ADM achieved functional remission vs. 28% in the placebo group. - Presume being treated for depression is of value - Depression symptoms and QOL are intrinsically entwined - Society would value less depression -> more productivity, harmony etc - Given shortage of psychiatrists/psychologists, medication is valuable - Drop outs are interesting – do people feel well enough to stop medication, or are they so bothered by side-effects that they stop despite feeling psychologically better, or do they stop because they feel the medication is not working +/- side effects? Other reasons, stigma etc?	Differences between intervention and comparator and results were almost never analysed or interpreted in the context of detecting a minimally important difference

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ *Favors the comparison* ○ *Probably favors the comparison* ○ *Does not favor either the intervention or the comparison* ○ *Probably favors the intervention* ○ *Favors the intervention* ○ *Varies* ○ *Don't know*	**From main assessment report the balance of benefit vs. harm is not clear** - data too sparse and heterogeneous and lack of detail/reporting/large risks of bias especially for AEs with ADM vs CBT ***Benefit Harm Analysis*** • Benefit outcomes: reduction of relapse, recovery, recurrence • Harm outcomes: all AES, all-cause drop-out • 12 month horizon • Net benefit -> total "death equivalents" avoided Looking at Fig 27 in the Assessment reports, there is large overlap between ABM, CBT and combinations ***Probability of net clinical benefit preventing relapse*** *(Table 15 Assessment report, Figure 27):* • CBT vs ADM -> 91.8% considering specific harms • CBT vs ADM -> 98.2% when all-cause drop-out considered *Using only RCTs ≥ 25 weeks (and all-cause dropout)* • probability of net clinical benefit CBT vs ADM - 77.1% -> decrease in net clinical benefit over time • CBT + ADM vs ADM -> increased net clinical benefit to 96.7% (unclear if for > 25 weeks or all?)	Drop outs are interesting – do people feel well enough to stop medication, or are they so bothered by side-effects that they stop despite feeling psychologically better, or do they stop because they feel the medication is not working +/- side effects? Other reasons, stigma etc? **BHA analysis** – recommendations of PROTECT group and modified Gail approach • Considered: CBT vs ADM or CBT + ADM vs vs CBT or CBT + ADM vs ADM • Evidence for input limited • Treatment efficacy based on pair-wise meta-analysis • Incidence rates based on RCTs as no population data available Assumptions: • Preference weights non-existent -> generics values assigned • Gail approach combines outcomes (not time dependent) • Benefit assumed for probability > 60% • Harm presumed for probability < 40% • Neither benefit or harm 40 – 60% • Most follow up too short -> extrapolated to 12 months

	• CBT+ADM vs. CBT -> increased net clinical benefit to 80.3 % (text states 80.3, Table states 72.0, unclear of this is for 6 months or > 25 month studies) ***Absolute expected events*** *(Table 15 Assessment report):* • Based on effects of RCTs with follow-up < 6 mo -> no. of relapse equivalents avoided over 12 months ○ 346 in 1000 MDD patients with CBT vs. ADM • Based on effects of RCTs with follow-up > 6 mo -> no. of relapse equivalents avoided over 12 months ○ 126 in 1000 MDD p patients with CBT vs ADM ○ 228 in 1000 MDD patients for CBT + ADM vs ADM ○ 125 in 1000 DDD patients for CBT + ADM vs CBT ***Sensitivity analysis*** • TIME: Probability of net clinical benefit over 24 month horizon (Table 16 Assessment Report, Figure 28) ○ CBT vs ADM -> 95.5% (extrapolated from RCTS with < 6mo fu) ○ CBT vs ADM - >70.1% ○ CBT + ADM vs ADM -> 77.6% ○ CBT+ADM vs. CBT -> 74% • RISK: relative rates of relapse and dropout were higher in MDD patients treated with ADM than with CBT -> CBT was superior at all relapse risk levels ○ likelihood of net benefit of CBT vs ADM ranged from 84.0% to 92% for relapse risks of 5% (or 4/1000 person-months) and 50% risk over one year (58/1000 person-months), respectively ○ similar results when different specific harms substituted for all-cause dropout • PREFERENCE WEIGHTS: net clinical benefit for CBT compared with ADM, regardless of any preference weights for both outcomes- CBT was protective for both relapse and dropouts compared with ADM. ○ probabilities of net benefit and absolute net clinical benefit increased as the preference weights for the outcomes increased. • *Net clinical benefit similar if all-cause drop out or AEs were used, suggests most drop-outs were likely due to AES*	• Assume consistent AEs or drop-outs over 12 months • Selective recording of AEs • Selective recruitment of study subjects • Mid-long-term BHA beyond scope here Sensitivity analyses • Extended horizon to 24 months • varied spectrum of relapse from 5% to 50% over 1 year • Varied preference weights • Class level BHA- data sparse • CT/REBT -> greater net clinical benefit than SSRIs, with probabilities of 98.8% and 99.4% for models considering specific harms and dropout **Conclusion:** "relatively high probability for a mid- to long-term net clinical benefit with CBT compared to ADM, or dual therapy with CBT plus ADM compared to a monotherapy" "*Obtaining more detailed data on relevant outcomes, such as recovery and recurrence, and harm outcomes would allow to better explore the mid- to long-term benefit-harm balance of interventions for MDD."*

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	**Budget Impact Analysis** • Costs calculated for 1 year • Healthcare perspective <u>Assumptions</u>**:** • Only patients that reported consuming ADMs (with or without sedatives/narcoleptics) are considered eligible • assumed among the patients taking ADM -> severe MDD (50%), moderate MDD (40%), mild MDD (10**%)** • estimated that 31.9% of the MDD patients may require a hospitalisation, with a mean duration of 18.4 days o mild: 3.1 days o moderate: 16.9 days o severe: 31.1 days • estimated number of physician visits (from study published in 2013, CH) o mild: 5.81 o moderate: 6.52 o severe 7.39 • most patients (87.5%) suffering from MDD undergo psychotherapy (CH, 2013); use of ADMs is less frequent • costs of hospitalisations and physician visits were assumed to remain the same for all treatments (no data) • treatment costs varied according to the treatment distribution assumptions (i.e. psychotherapy, ADM, or a combination of both) and type of ADM • <u>Costs included:</u> • hospitalisations, physician visits, psychotherapy, and ADM. • Costs related to laboratory tests, additional medications, or productivity loss (in terms of disability or workdays lost) were not included • Used costs for 2020 • The daily base price can differ across different types of hospitals and regions -> Federal Office of Statistics -> mean daily base price in Switzerland in 2018 was CHF 681.2 • Assumed daily hospitalisation costs of: o CHF 2,923 for mild MDD (3.1 days x CHF 942/day) o CHF 11,454 for moderate MDD (16.9 days x CHF 678/day) o CHF 20,211 for severe MDD (31.1 days x CHF 650/day) • conservatively assumed costs of CHF 100 per physician visit • assumed psychotherapy cots of CGF 150 per session, 12 sessions per year • costs for ASMs from Compendium, assumed all took same drug <u>Prevalence of MDD in Switzerland</u> (Swiss Health Survey 2017): proportion of population aged ≥ 15 years: • Mild 25.9% (1,918,786 people) • Moderate 5.9% (434,012 people) • Severe 2.8% (204,424 people) • Total: approx.. 2.6 million people <u>Estimated number of patients treated:</u>	Advantage of assumption: • patients' selection is restricted to those who are effectively treated for depression (assuming that ADM are mainly prescribed to depressive patients) Disadvantage of assumption: • detailed information of disease severity distribution is not available. • Not all MDD patients are treated with ADMs (before starting ADM, psychotherapy is usually advised). • total number of eligible patients may be underestimated • likely marked under estimation of cost of physician visits • what about psychologists? Sensitivity analyses: - varied proportion of population eligible by +/- 30% - varied LOS by +/- 30% - varied number physician visits +/- 30% - varied costs for psychotherapy form CHF 100 – 250 - varied psychotherapy visits from 6 to 40 - costs ADM varied from lowest to highest Strengths: - Swiss numbers Limitations - Multiple assumptions - Estimation of eligible patients -> not all with mental health issues have MDD, severity distribution extrapolated form US - Information of treatment in Switzerland not available - Extrapolations of costs, LOS - Exclusion of diagnostic tests, other medications - Societal perspective missing - 2014 study -> direct costs 6.349 million, indirect costs 10.639 for mental health in CH

	• For mental issues – 449,555 • With ADMs - 334,835 ○ Mild: 33,483 ○ Moderate: 133,934 ○ Severe: 167,417 <u>Total costs for hospitalizations</u> (mio CHF): • Mild : 97,87 • Moderate: 1,534.08 • Severe: 3,383.67 • Total: 5,015.62 <u>Total costs for physician visits</u> (mio CHF): • Mild: 19,45 • Moderate: 87,32 • Severe: 123,72 • Total: 230,50 <u>Costs ADM +/-/or Psychotherapy</u> (Table 33 Assessment Report) • 100% psychotherapy: CHF 602.70 mio • 100% ADM: CHF 113.66 mio • 100% psychotherapy + ADM: CHF 716.36 mio (687-801) • Costs for ADM only range from CHF 84 million (all on fluoxetine) to CHF 198 million (all on sertraline) – Table 34 Assessment Report **Total direct costs MDD:** • **Range CHF 5,330 mio (100% least expensive ADM) to CHF 6,032 mio (100% psychotherapy + most expensive ADM)** • Hospitalization costs -> 80% of costs (82 – 92% dep. on assumptions)	- sensitivity analyses in Table 35 Assessment report

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	**HEALTH ECONOMIC ASSESSMENT** • Systematic literature review • Adaptation of cost-effectiveness data to Switzerland • Budget impact analysis (BIA) Population: • People with MDD measured by a questionnaire such as the PHQ-9 (Patient Health Questionnaire 9 item) or the CES-D (Center for Epidemiologic Studies Depression Scale) Interventions: • ADM ≥ 12 weeks (individual drugs) • CBT ≥ 4 weeks Comparators • Different ADM to intervention • Non-CBT-based psychological intervention • Usual care (non-specific)	• Given the large amount of published literature, including several studies from European countries, a new cost-effectiveness analysis was considered redundant **BIA limitations:** - Estimation of eligible patients -> not all with mental health issues have MDD, severity distribution extrapolated form US - Information of treatment in Switzerland not available - Extrapolations of costs, LOS - Exclusion of diagnostic tests, other medications - Societal perspective missing

Outcomes:

- Incremental cost per QALY gained
- Incremental cost per DALY avoided
- Net monetary benefit based on QALYs or DALYs

Study designs:

- Cost effectiveness/utility analysis comparing QALY/DALYs
- Form 2006 onwards
- Excluded LMIC, ASIA, conference proceedings, co-morbid populations

- CHEERS Checklist
- Assessed transferability
- Adaptation to Switzerland
  - Correction for resource utilization (quantity correction – CH pts receive more Rx)
  - Prices ("price correction")
  - Change in resource utilization/prices over time -> based on yearly growth rates of Swiss health care expenditures

Systematic review:

- 2088 citations identified -> 33 met inclusion criteria (Table 18 Assessment report) -> 29 fulfilled transferability criteria to Switzerland
  - 14 assessed ADM as intervention
    - 10 vs another ADM
    - 4 vs placebo/supportive care
  - 19 assessed CBT as intervention
    - 12 vs usual care
    - 5 vs ADM
    - 2 vs behavioral activation or website information
  - Countries: UK (13), Sweden (5), Netherlands (5), Belgium (1), Scotland (1), USA (1), Italy (1), Greece (1), Spain (2), Germany (1), Canada (1), Australia (1)
  - 2 -> recurrent depression
  - 16 within-trial analyses
  - 17 model-based
  - Time horizon 6 weeks – 60 months

ADMs

- 14 CEAs from 2006 – 2019
- Most ≤ 12 months, 1 x 2 years
- 5 UK, 3 Sweden, 5 Europe, 1 USA

Costs included:

- 14/14 included medication costs and outpatient healthcare costs
- 12/14 included inpatient costs were also included in the majority of the analyses
- 4/14 included costs of specific laboratory tests
- 6/6 from societal perspective included productivity costs
- 0/6 included out-of-pocket costs
- Cost estimated from the published literature (6), primary resource use data (2), combining patient self-reporting and medical practice records (2)

Clinical inputs:

- 6/14 -> positive data for escitalopram

	• 1/14 assumed equivalent remission rates for agomelatine, escitalopram, venlafaxine • 1/14 estimated better rates for duloxetine and venlafaxine vs SSRIs (group) Utility inputs - variable **CBT** • 19 CEAs from 2006 – 2019 • All funded by public sector • 12 within trial, 7 model-based • 8 UK, 4 Netherlands, 7 other • Time horizon 6 weeks – 36 months • 11 public sector perspective, 6 societal perspective, 1 employer perspective, 1 unclear • Varying diagnostic criteria used: the patient health questionnaire (PHQ-9), the BDI-II, DSM-IV, MADRS-S and the CES-D, others ○ 5 mild-moderate MDD ○ 2 moderate – severe MDD ○ 1 recurrent MDD (≥3 prior episodes) • Interventions: ○ 11 digital/computerized ○ 8 unspecified/face-to-face ○ Number of sessions variable (5 – 18) • Comparator: ○ 12 usual care ○ 5 ADM ○ 2non-CBT-based psychological intervention Costs included: • 16/19 included intervention costs • 19/19 included outpatient costs • 17/19 included medication costs • 12/19 included inpatient costs • 7/8 adopting a societal perspective included productivity costs • 4/8 included out-of-pocket costs to patients. • 3/12 within-trial CEAs used the Trimbos and iMTA Questionnaire on Costs Associated with Psychiatric Illness (TIC-P) to estimate healthcare resource use, 2/12 used the Adult Service Use Schedule, 2/12 used the Client Service Receipt Inventory • 4/7 model-based CEAS estimated costs based on the published literature • 3/7 defined resource use estimates by combining data from the published literature with a range of assumptions Clinical inputs: • 4/7 model-based -> CBT more favorable • 2 trial-based -> CBT more favorable • 1 found response higher with CBT vs usual care but lower probability of recovery with CBT Utility inputs - variable	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**COST EFFECTIVENESS LITERATURE REVIEW** **ADMs** ***Escitalopram***: • 6 CEAs tested escitalopram as intervention vs another ADM s/combinations/groups (all model-based) ○ 5/6 funded by pharma, 1 investigator-funded ○ 6/6 -> escitalopram dominated or produced lower ICER than comparator (highly cost-effective) • 1 CEA used escitalopram as comparator -> dominated by agomelatine (based on assumptions of equivalent remission rates) ***Venlafaxine***: • 2 CEAs – as 1st line or maintenance intervention ○ Both -> Venlafaxine was cost effective ▪ ICER UK: GBP 7,215/QALY (vs. combinations of venlafaxine, fluoxetine, amitriptyline) ▪ ICER Sweden: USD 18,548/QALY (vs placebo) • 7 CEAs -> venlafaxine as comparator ○ 4 pharma funded -> escitalopram more cost-effective than venlafaxine ○ 1 non-industry funded -> escitalopram more cost-effective than venlafaxine ▪ ICER: Euro 3,723/QALY ○ 1 duloxetine more cost-effective than venlafaxine (dominant) ○ 1 agomelatine more cost-effective than generic venlafaxine ▪ ICER: Euro 1,446/QALY ***Sertraline*** • 1 government funded (UK) sertraline vs placebo ○ Sertraline -> dominant • 5 CEAs used sertraline as comparator ○ 4/5 sertraline dominated by escitalopram ○ 1/5 sertraline dominated by agomelatine ***Duloxetine*** • Industry-funded CEA (UK) duloxetine vs venlafaxine, mirtazapine, SSRI group ○ ICERS: GBP 6,304/QALY or better dep. on comparator -> duloxetine cost- effective • 3 CEAs -> duloxetine as comparator ○ In 3/3 dominated by escitalopram ***SSRIs*** • 3 CEAs, within trial, healthcare perspective -> SSRI vs. tricyclic ADM or usual care ○ 3/3 SSRI cost-effective ▪ SSRI vs usual care (UK, 26 weeks): ICER GBP 14,854/QALY ▪ SSRI vs tricyclic ADM (UK, 12 months): ICER GBP 2,692/QALY ▪ SSRI vs active monitoring (Spain, 12 months): ICER Euro 6,142/QALY ***Other ADMs*** • Agomelatine vs other ADMs (escitalopram, generic venlafaxine, fluoxetine, sertraline), industry funded (Greece) ○ ICER Euro 3.303/QALY or better, dep. on comparator (based on assumptions of equivalent remission rates) -> agomelatine cost-effective • Other ADMs were evaluated as comparator strategies (e.g. paroxetine, mirtazapine, fluoxetine, citalopram, amitriptyline, fluvoxamine, reboxetine) -> most had unfavourable cost-effectiveness	**Strengths:** - Broad spectrum of interventions and comparators - Adaptation to Switzerland **Limitations** - High heterogeneity across studies: populations, interventions comparators, time horizons, types of costs captured - No study with long-term horizon reported costs and QALYs gained - Most studies -> acute phase - Most CEAs sponsored by pharma - CBT researcher allegiance

profile relative to another antidepressant (e.g. escitalopram, venlafaxine, duloxetine, sertraline, or agomelatine).

CBT

Analysis:

- 8/19 -> CBT cost effective
- 5/19 (witin trial) -> CBT was dominated by comparator
- 6/19 – uncertain/neutral
- Societal perspective
  - 3/6 -> CBT cost effective
- Health systems perspective
  - 4/11 -> CBT cost effective

ADAPTATION TO SWITZERLAND

- process **cannot** be interpreted as achieving realistic ICERs for Switzerland (intends to achieve a certain approximation)

ADMs

Escitalopram *(n = 6, Table 20 Assessment Report)*:

- healthcare perspective: costs ranged from CHF 1,336 (time horizon 6 months, USA) to CHF 5,963 (time horizon 12 months, Italy)
- societal perspective: costs ranged from CHF 2,144 (time horizon 12 months, Sweden) to CHF 40,290 in (time horizon 26 weeks, Netherlands)
- cost saving in all comparisons except two (cost savings ranged form CHF 3 to CHF 4,634)
  - Belgium: escitalopram was more expensive (cost difference CHF 40) and more effective (QALY difference 0.003) than venlafaxine ->ICER CHF 13,477 per QALY gained (12-month time horizon, healthcare perspective
  - Sweden: escitalopram more expensive (cost difference CHF 4) and more effective (QALY difference 0.0036) than venlafaxine -> ICER CHF 1,130 per QALY gained (12-month time horizon, societal perspective).

Venlafaxine (n = 7, Table 21 Assessment Report)

- in most cases venlafaxine was dominated by escitalopram , or less expensive but less effective
- compared to other ADMs (e.g. citalopram, duloxetine, fluoxetine, paroxetine, sertraline), venlafaxine was generally dominant
- UK: venlafaxine followed by fluoxetine -> ICER of CHF 2,801/QALY vs fluoxetine followed by venlafaxine
- UK: venlafaxine dominant if compared to other treatment combinations (healthcare perspective).
- Scotland: venlafaxine -> ICER of CHF 31,601/QALY vs mirtazapine
- Scotland: venlafaxine -> ICER of CHF 58,296/QALY vs SSRIs

Sertraline (n=6, Table 22 Assessment Report)

- Sertraline -> dominant strategy vs citalopram (healthcare and societal perspectives).
- Italy, UK: sertraline dominant strategy vs fluvoxamine and placebo (healthcare perspective)
- comparisons with paroxetine or fluoxetine -> discordant results (sertraline dominant/dominated in different studies).
- sertraline vs duloxetine -> often less expensive but also less effective (dominated by duloxetine in 1)
- sertraline dominated vs escitalopram, venlafaxine, and agomelatine (healthcare and societal perspectives).

	Duloxetine (n=4, Table 23 Assessment Report) • 3 studies -> duloxetine was dominated by escitalopram (healthcare and societal perspectives) • comparison with venlafaxine -> discordant results: ○ Belgium, Italy, Sweden -> duloxetine was dominated by venlafaxine (healthcare and societal perspectives) ○ Scotland -> duloxetine was less expensive and more effective than venlafaxine (healthcare perspective) • duloxetine vs citalopram -> had ICERs from CHF 484 to CHF 13,031/QALY (healthcare perspective). • duloxetine vs citalopram -> dominant strategy or had a ICER of CHF 7,581/ QALY (societal perspective) ***Other antidepressants*** (Table 24 Assessment Report) • Scotland: SSRIs dominant vs mirtazapine • Scotland: SSRIs -> ICERs of CHF 26,106 and CHF 58,296 per QALY vs. duloxetine and venlafaxine, (healthcare perspective). • Greece: agomelatine dominant strategy when combined with sertraline, escitalopram, fluoxetine (societal perspective with non-generic prices). I • Greece: agomelatine vs venlafaxine -> ICER of CHF 3,244/QALY **CBT** ***CBT versus ADM*** (n = 4) • UK: CBT (12 months, 8 weekly sessions plus 4 sessions every 3 months) dominated by ADM (societal and healthcare system perspectives). I • Germany (15 months), UK (3 months): CBT vs ADM -> ICERs around CHF 50,000 – CHF 70,000/QALY • USA: CBT vs ADM -> ICERs > CHF 100,000/QALY gained (time horizon and treatment duration of 12 months, healthcare and societal perspectives) • USA: CBT vs ADM -> dominant strategy with a time horizon and treatment duration of 60 months (healthcare and societal perspectives) ***CBT +ADM versus ADM*** (n=2) • Germany: CBT + ADM (15 months) vs ADM -> ICER of CHF 94,049/QALY gained (time horizon 27 months, healthcare perspective) • UK: CBT + ADM (3 months) vs ADM -> ICER of CHF 69,351/QALY for moderate depression, CHF 31,523/QALY for severe depression (time horizon of 15 months, healthcare perspective) ***CBT versus usual care*** *(n=1)* • Netherlands: CBT (10-12 sessions) was dominated by usual care from a societal perspective (time horizon of 36 months) ***CBT versus behavioural activation*** (n=1) • UK: CBT (20 sessions over 16 weeks) was dominated by behavioural activation [simple psychological treatment conducted by junior mental health workers with no professional training]. (time horizon of 18 months, healthcare perspective) ***Internet-based CBT versus usual care*** (n=10) • very discordant results • 3 studies (Netherlands, Australian, Spain)-> internet-based CBT may be dominant vs usual care (variable: 6 weekly lessons, 10 modules, 12 weeks) - all used time horizon of 12 months and societal perspective	**CBT:** • time horizons of the analyses ranged from 3 to 60 months, • treatment durations ranged from 2 to 60 months. • Independent of the adopted perspective (healthcare or societal), it was not possible to identify any specific trend according to time horizon or treatment duration (i.e. CBT or the comparators were not more frequently dominant or cost-effective for a specific time horizon or treatment duration). **Summary for Switzerland:** • escitalopram may be the most cost-effective ADMs, followed by venlafaxine, sertraline, and duloxetine. • CEAs of CBT or internet-based CBT vs ADMs or usual care -> discordant results. • 2 studies of CBT + ADM versus ADM alone -> ICERs ranging between CHF 30,000 and CHF 95,000/QALY gained • high heterogeneity in the results of the CBT studies suggest that the cost-effectiveness ion may depend on how CBT is provided (e.g. number of sessions, treatment duration, setting).

	• 5 studies (Canada, UK, Sweden, Netherlands, Spain) -> internet-based CBT estimated to be more expensive and more effective than usual care -> ICERs ranging from CHF 2,224 and CHF 71,599/QALY gained. (variation in the assumed treatment duration, from 6-8 weekly modules to 12 weeks and time horizon from 3 to 12 months). • 2 studies (Netherlands, Sweden) -> internet-based CBT was less expensive but also less effective than usual care (• 1 study (UK) -> usual care was dominant	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	• no study reported on equity • considerations o stigma CBT vs. ADM o costs CBT vs. ADM (relative OOP?) o time requited for CBT o lack of appointments with therapists (acute shortfall) o language/cultural barriers greater for CBT o privacy, confidentiality	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes o Yes o Varies o Don't know	• Using “drop outs” as surrogate for acceptability, CBT may be more acceptable, but reason for dropouts not clear • Various forms of therapy may be acceptable to different people • CBT and ADM generally accepted • Online CBT may be more acceptable if concerns of stigma etc.	• are there Limitations set by health insurance for number for CBT sessions?

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes o Yes o Varies o Don’t know	• acute shortage of mental health practitioners in CH • both treatments are feasible • CBT may be less feasible if language barriers, cultural differences, working 100%, etc. • Online CBT may be feasible if IT literate, have access to internet etc. • Privacy could be an issue	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings (ADM)**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention (ADM)**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention (CBT +/- ADM)**	**Recommendation for the intervention (ADM)**
○	○	○	○	○

CONCLUSIONS

Recommendation

Justification

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities