

Economic evidence tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 137: Economic evidence table for computerised cognitive behavioural therapy with support following inadequate response to antidepressants

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Phillips 2014 UK Cost effectiveness and cost-utility analysis	Interventions: Computerised CBT (MoodGYM) comprising 5 1hr modules, usually taken weekly, plus support in the form of telephone interviews (cCBT) Attention control (five websites with general information about mental health)	Adults with depressive symptoms, as measured by PHQ-9 responses, identified via occupational health settings Pragmatic RCT (Phillips 2014, N=637) Source of efficacy and resource use data: RCT (for clinical analysis: completion 56% at 6 weeks; 36% at 12 weeks; for cost analysis: completion rates not reported) Source of unit costs: national sources	Costs: hospital (inpatient and outpatient care), community services, staff time (GP, psychiatrist, district nurse, counsellor, occupational health providers, other providers), medication Intervention cost appears to have been omitted from analysis Productivity losses considered in societal perspective Mean total NHS cost per person (SD): cCBT: £29 (£110); Control: £38 (£125) Outcome measures: Work and Social Adjustment Scale (WSAS); QALYs estimated based on EQ-5D (UK tariff) Outcome results: WSAS difference: -0.470 (95% CI -1.837 to 0.897) QALY: cCBT: 0.082; control: 0.083 at 6 weeks cCBT: 0.167; control: 0.170 at 12 weeks	ICER of control vs cCBT: £3,667/QALY	Perspective: NHS (and societal) Currency: GBP£ Cost year: likely 2010 Time horizon: 12 weeks for outcomes; 6 weeks for costs Discounting: NA Applicability: directly applicable Quality: very serious limitations

Table 138: Economic evidence tables for cognitive therapy or cognitive behavioural therapy in addition to antidepressants versus antidepressants alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Scott 2003 UK Cost effectiveness analysis	Interventions: Cognitive therapy (16 sessions in 20 weeks plus 2 booster sessions) in addition to antidepressants (minimum dose equivalent to \geq 125mg of amitryptiline) and clinical management (30-min appointments with a psychiatrist every 4 weeks during 20 weeks and every 8 weeks during the 48-week follow-up) (CT & AD) Antidepressants and clinical management alone (AD)	Outpatients 21-65 years that met DSM-III-R criteria for major depression, who were in an episode within the past 18 months but not in the past 2 months. At randomisation they had residual symptoms over at least 8 weeks with HAMD \geq 8 and BDI \geq 9. Exclusion criteria: past history of bipolar disorder; current history of significant Axis I or II comorbidity; currently receiving formal psychotherapy; having previously received CT for > 5 sessions. RCT (Paykel 1999/Scott 2000, N=158) Source of efficacy data: RCT (N=158) Source of resource use data: RCT (full data for 65% of participants) Source of unit costs: national & local inpatient cost data	Costs: CT, medication, clinical management, inpatient care, day hospital, GP, social worker, community psychiatric nurse, therapist/counsellor, group therapy, marital therapy. Mean cost per person: CT & AD: £1898 AD: £1119 Cost difference: £779 (95% CI £387 to £1170) Primary outcome measure: percentage of relapses Cumulative relapse rates: CT & AD: 29% AD: 47% Adjusted HR 0.51 (95% CI 0.32-0.93)	ICER of CT & AD vs AD: £4328 per relapse prevented £4667 using mean imputation £5028 using non-parametric multiple imputation £7056 using only the 65% of subjects in the complete case analysis Probability of CT & AD being cost-effective 0.60 and 0.80 at WTP of £6000 and £8500 per relapse prevented, respectively Probability sensitive to method of missing data imputation	Perspective: NHS/PSS Currency: GBP£ Cost year: 1999 Time horizon: 17 months Discounting: 6% Applicability: partially applicable Quality: minor limitations
Hollingshurst 2014 UK Cost consequence	Interventions: Cognitive behavioural therapy comprising 12-18 sessions lasting	Adults aged 18-75 years with major depression, who had adhered to antidepressant medication for at least 6 weeks in	Costs: medication, primary and community mental and general health care, specialist (secondary) mental health care, personal out-of-pocket expenditure such as travel costs, use of private	AT 12 MONTHS ICER of CBT vs. TAU £14,911/QALY Probability of CBT being cost-effective	Perspective: NHS/PSS for cost-utility analysis; health and

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
and cost-utility analysis	<p>about an hour each, taking place at a GP surgery or a similar location, in addition to treatment as usual (CBT)</p> <p>Treatment as usual alone, comprising GP care, including antidepressant treatment as judged appropriate by the person's GP or a referral as required (TAU)</p>	<p>primary care, but who continued to have significant depressive symptoms; people had a BDI-II score of at least 14 or more and an ICD-10 diagnosis of depression using the Revised Clinical Interview Schedule (CIS-R)</p> <p>RCT (Wiles 2013/2016, N=469)</p> <p>Source of efficacy data and resource use data: RCT (NHS and PSS cost and QALY data available for n=368 at 12 months; follow-up data available for n=248)</p> <p>Source of unit costs: national sources</p>	<p>therapies and over-the-counter medications; productivity losses</p> <p>AT 12 MONTHS</p> <p>Mean total cost per person (SD): NHS/PSS cost: CBT £1614 (£1100); TAU £763 (£697); difference: £850 (95%CI £683 to £1017)</p> <p>Personal expenditure: CBT £80 (£12), TAU £127 (£35); difference -£47 (95%CI -£120 to £25)</p> <p>Out-of-pocket expenses: CBT £694 (£4,824), TAU £517 (£2,464); difference £176 (95%CI -£662 to £1014)</p> <p>Lost productivity: CBT £1,067 (£3,887), TAU £1,102 (£3,529); difference -£36 (95%CI -£797 to £726)</p> <p>AT 3-5 YEARS</p> <p>Mean annual NHS/PSS cost (SD): CBT £885 (£938); TAU £604 (£904); difference: £281 (95%CI £32 to £531)</p> <p>Outcome measures: response (reduction of at least 50% in BDI-II score); BDI-II score; remission (BDI-II <10; SF-12 mental and physical subscales; EQ-5D; QALYs estimated using EQ-5D & SF-6D ratings (latter in sensitivity analysis) (UK tariff)</p> <p>AT 12 MONTHS</p> <p>Response: CBT 55.3%, TAU %31.3; OR 2.89 (95%CI 2.03 to 4.10)</p> <p>BDI-II score (mean, SD): CBT 17.0 (14.0), TAU 21.7 (12.9); difference -5.1 (-7.1 to -3.1)</p>	<p>0.74 and 0.91 at WTP of £20,000/QALY and £30,000/QALY, respectively</p> <p>Results robust to changes in psychologist unit costs and exclusion of hospitalisation costs.</p> <p>Results sensitive to use of SF-6D instead of EQ-5D, with ICER rising at £29,626/QALY</p> <p>Analysis of completers' data (instead of imputation of missing data): ICER £18,361/QALY</p> <p>AT 3-5 YEARS</p> <p>ICER of CBT vs. TAU £5,374/QALY</p> <p>Probability of CBT being cost-effective at a WTP of £20,000/QALY and £30,000/QALY: 0.92 and 0.95, respectively</p>	<p>social care provider for cost consequence analysis, with service user expenses and productivity losses assessed in additional analyses</p> <p>Currency: GBP£</p> <p>Cost year: 2010 for endpoint data; 2013 for follow-up data</p> <p>Time horizon: 12 months; follow-up analysis 3-5 years (median 45.5 months, interquartile range 42.5 to 51.1)</p> <p>Discounting: 3.5% annually</p> <p>Applicability: directly applicable</p> <p>Quality: minor limitations</p>

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			<p>Remission: CBT 39.6%, TAU 18.2%; OR 2.74 (95%CI 1.82 to 4.13)</p> <p>SF-12 mental sub-scale (mean, SD): CBT 39.1 (14.6), TAU 35.4 (12.8); difference 4.8 (2.7 to 6.9)</p> <p>SF-12 physical sub-scale (mean, SD): CBT 44.6 (13.2), TAU 41.1 (13.5); difference -0.7 (95%CI -2.1 to 0.8)</p> <p>QALYs: CBT 0.62 (0.22), TAU 0.56 (0.25); difference 0.053 (95%CI 0.019 to 0.087)</p> <p>AT 3-5 YEARS</p> <p>Response: CBT 43%, TAU 27%; OR 2.09 (95%CI 1.19 to 3.67)</p> <p>BDI-II score (mean, SD): CBT 19.2 (13.8), TAU 23.4 (13.2); difference -3.6 (-6.6 to -0.6)</p> <p>Remission: CBT 28%, TAU 18%; OR 1.77 (95%CI 0.93 to 3.39)</p> <p>SF-12 mental sub-scale (mean, SD): CBT 38.7 (12.1), TAU 34.6 (11.8); difference 3.5 (0.7 to 6.3)</p> <p>SF-12 physical sub-scale (mean, SD): CBT 42.2 (13.8), TAU 39.2 (13.5); difference 0.9 (95%CI -0.2 to 3.8)</p> <p>Mean annual QALYs: CBT 0.60 (0.17), TAU 0.54 (0.20); difference 0.052 (95%CI 0.003 to 0.102)</p>		

Table 139: Economic evidence tables for intensive short-term psychodynamic psychotherapy versus treatment as usual (TAU)

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Town 2017/2020 Canada Cost-utility analysis	Interventions: Intensive short-term psychodynamic psychotherapy (STPP) Treatment as usual in secondary care, comprising community mental health teams delivering pharmacotherapy and clinical management, supportive or structured activities focused around symptom management and in some cases individual or group psychotherapy (TAU)	Adults (aged 18-65 years) with depression who were non-remitting following at least one antidepressant treatment course RCT (Town 2017/2020, N=60) Source of efficacy and resource use data: RCT (N=60) Source of unit costs: national cost data	Costs (only mental health related): intervention, physician visits, inpatient care, outpatient care, medication, A&D, out of pocket Mean cost per person: STPP: \$4,674; TAU \$5,178 Primary outcome measure: QALY based on SF-6D collected from SF-12 (UK tariff) Mean QALY per person: STPP: 0.90; TAU: 0.87	As reported by authors: STPP dominant When high volume service users were removed from analysis: ICER of STPP vs TAU: Can\$19,015/QALY STPP cost-saving in 2.5% of iterations Probability of STPP being cost-effective 0.65 at WTP of \$25,000/QALY	Perspective: mental health payer Currency: Canadian\$ Cost year: 2017 Time horizon: 18 months Discounting: 1.5% Applicability: partially applicable Quality: potentially serious limitations

Table 140: Economic evidence table for mirtazapine as an adjunct treatment to SSRIs or SNRIs

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kessler 2018a/2018b UK Cost-utility analysis	Interventions: Mirtazapine in addition to SSRI or SNRI treatment	Adults (aged ≥18 years) with a BDI score of ≥14 and a diagnosis of depression according to ICD-10, who had	Costs: mirtazapine, other medication, hospital care related to depression or mental health (inpatient care, A&E attendances, outpatient care), primary and community care (GP or nurse contacts at the surgery, by telephone or at home, counselling or other talking therapies, face-to-face	INMB of mirtazapine vs. placebo: £398 (-£914 to £1709) [completer analysis] £92 (-£106 to £290) [imputed data analysis]	Perspective: NHS/PSS (personal costs and productivity losses)

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	Pill placebo in addition to SSRI or SNRI treatment	used an SSRI or SNRI for at least six weeks but were still depressed. RCT (Kessler 2018a/2018b, N=480) Source of efficacy data: RCT (N=368) Source of resource use data: RCT (N=369) Source of unit costs: national sources	or computerised CBT, mental health clinic attendances, prescribed exercise programmes, NHS Direct or 111, NHS walk-in centres), personal social services (mental health nurse home visits, occupational therapy, social worker, day centre use, self-help groups run by social services, home care worker visits, other) Costs to people with depression & their carers and productivity costs estimated separately Mean cost per person (SD): mirtazapine: £261 (£52); placebo £192 (£49) Difference: £69 (£71) Primary outcome measure: QALY based on EQ-5D-5L (UK tariff) Mean QALYs per person (SD): mirtazapine 0.734 (0.009); placebo 0.724 (0.009). Difference: 0.009 (0.013)	Probability of mirtazapine being cost-effective 0.69 and 0.71 at WTP of £20,000 and £30,000 per QALY, respectively.	considered in additional analysis) Currency: GBP£ Cost year: 2016 Time horizon: 12 months Discounting: NA Applicability: directly applicable Quality: minor limitations

Table 141: Economic evidence table for continuation of current treatment (citalopram) versus switching to another antidepressant (venlafaxine, sertraline) or augmentation with bupropion

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Olgati 2013 US Cost-utility analysis	Interventions: Different strategies for non-remitters: A. Continuation of current treatment (citalopram) for 13 weeks B. Choice to:	Adult outpatients with chronic depression, with a HAMD17 \geq 14, who were treated with citalopram for 13 weeks and received 2nd line treatment following no remission; exclusion criteria: indications for hospital treatment such as psychotic symptoms, suicidal risk or inpatient detoxification	Costs: medication, primary care, outpatient visits, community mental health services Mean total cost per person: Strategy A: \$724 Strategy B: \$800 Strategy Ba: \$809 Strategy Bb: \$849	ICER of strategy B versus strategy A: Deterministic analysis: \$11,481/QALY Probabilistic analysis: \$10,665/QALY (95%CI: \$6,498 to \$14,832)	Perspective: 3rd party payer Currency: US\$ Cost year: 2011 Time horizon: 26 weeks Discounting: NA Applicability: partially applicable

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	a. switch to sertraline or venlafaxine for 13 weeks or b. augment with bupropion for 13 weeks Remitters (HAMD17<7) continued treatment with citalopram for another 13 weeks	for alcohol / substance dependence; obsessive compulsive disorder, eating disorder Decision-analytic modelling Source of efficacy data: data for A taken from a non-RCT (Wade 2006); data for B taken from a study comprising series of RCTs (Rush2006), thus breaking randomisation rules Source of resource use data: expert opinion Source of unit costs: national sources	Outcome measure: QALY estimated based on service Canadian/US users' preferences for vignettes Incremental number of QALYs per person: Strategy B vs strategy A: 0.007 Strategy Ba vs strategy A: 0.006 Strategy Bb vs strategy A: 0.008	ICER of strategy Ba versus strategy A: \$14,738/QALY ICER of strategy Bb versus strategy A: \$15,458/QALY Results robust to changes in utility scores and the probability of remission after 3 months of citalopram (strategy A)	Quality: very serious limitations

Table 142: Economic evidence table for sertraline versus venlafaxine versus bupropion

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Singh 2017 US Cost-effectiveness analysis	Interventions: Sertraline Venlafaxine Bupropion	People who require further treatment after inadequate response to a SSRI RCT (Rush 2006; N=727) Source of efficacy and resource use data: RCT Source of unit costs: national sources	Costs: medication, outpatient and A&E visits, hospitalisation Mean cost per person (SD): Sertraline: \$2,232 (\$3,248) Venlafaxine: \$2,416 (\$2,176) Bupropion: \$1,972 (\$1,629) Outcome measures: response and remission Response: Sertraline: 27%; Venlafaxine: 28%; Bupropion: 26% Remission: Sertraline: 27%; Venlafaxine: 25%; Bupropion: 26%	At a WTP of \$30,000 / unit of effectiveness, venlafaxine had the highest net health benefit in terms of response and a probability of being the most cost-effective option around 40%; sertraline had the highest net health benefit in terms of remission and a probability of being the	Perspective: payer Currency: US\$ Cost year: 2014 Time horizon: 9 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				most cost-effective option around 45%	
Soini 2017 Finland Cost-utility analysis	Interventions: Sertraline Venlafaxine Bupropion [and vortioxetine, agomelatine, which were not included in review question]	People who require further treatment after inadequate response to a SSRI Decision-analytic modelling Source of efficacy data: RCT (Rush 2006; N=727) Source of resource use data: published evidence and expert opinion Source of unit costs: national sources	Costs: medication, GP visits, psychiatrist, psychotherapist or counsellor, psychiatric ward, outpatient visit Mean cost per person: Sertraline: €3070; Venlafaxine: €2943; Bupropion: €2961 Primary outcome measure: QALY based on EQ-5D (Finnish VAS scale) Mean QALYs per person: Sertraline: 0.7247; Venlafaxine: 0.7272; Bupropion: 0.7356	Sertraline dominated by both venlafaxine and bupropion ICER of bupropion vs venlafaxine: €2,235/QALY Probability of cost-effectiveness not possible to estimate, as analysis included options not relevant to review question	Perspective: payer Currency: Euro (€) Cost year: 2013 Time horizon: 12 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 143: Economic evidence table for duloxetine versus venlafaxine versus mirtazapine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Benedict 2010 UK Cost-utility analysis	Interventions: Duloxetine Venlafaxine Mirtazapine	Adults with severe major depression defined by a HAMD17 score ≥ 25 , who failed previous SSRI treatment and were referred to mental health specialists in secondary care Decision-analytic modelling Source of efficacy data: meta-analyses of clinical trials -randomisation possibly broken Source of resource use data: expert opinion	Costs: medication, A&E Visits, GPs, psychiatrists, hospitalisation Mean total cost per person: Duloxetine £1,622 Venlafaxine £1,667 Mirtazapine £1,640 Outcome measure: QALY estimated based on EQ-5D ratings (UK tariff) Number of QALYs per person: Duloxetine 0.637 Venlafaxine XR 0.632 Mirtazapine 0.629	Duloxetine dominates venlafaxine XR and mirtazapine Probability of duloxetine being cost-effective at WTP £20,000/QALY: approximately 0.80 Results robust to sensitivity analysis	Perspective: Scottish NHS Currency: GBP£ Cost year: likely 2003 Time horizon: 48 weeks Discounting: NA Applicability: directly applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit costs: national sources			

Table 144: Economic evidence table for escitalopram versus duloxetine versus venlafaxine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Nordström 2010 Sweden Cost effectiveness and cost-utility analysis	Interventions: Escitalopram Duloxetine Venlafaxine	Adults with major depression who initiated treatment with one of the assessed interventions in primary care, who had had a history of treatment with another antidepressant within the previous 6 months Decision-analytic modelling Source of efficacy data: pooled analysis of trial data, including only participants who had already received antidepressant therapy prior to randomisation – data for duloxetine and venlafaxine pooled together Source of resource use data: cohort study conducted in 56 primary care centres in Sweden over 6 months Source of unit costs: national sources	Costs: medication, staff time (GP, psychiatrist, other doctors e.g. neurologist, cardiologist, psychotherapist, counsellor, psychologist, nurse), hospitalisation, treatment of side effects, indirect costs (sick leave) Mean total healthcare cost per person: Escitalopram €973 Duloxetine €990 Venlafaxine €1,014 Outcome measures: probability of remission (defined as a MADRS total score ≤ 12) achieved after 8 weeks of treatment and sustained until the end of 6 months; QALY estimated based on EQ-5D ratings (UK tariff) Probability of remission: Escitalopram: 50.1% Duloxetine: 33.6% Venlafaxine: 33.6% Mean QALYs per person: Escitalopram 0.322 Duloxetine 0.297 Venlafaxine 0.298	Escitalopram dominant over duloxetine and venlafaxine Considering healthcare costs only: probability of escitalopram being cost-effective at WTP £20,000/QALY (€22,080/QALY) 0.981 and 0.985 compared with duloxetine and venlafaxine, respectively Results robust to changes in remission rates, relapse rates, number of GP visits, or incidence of nausea	Perspective: societal; healthcare costs reported separately Currency: Euros(€) Cost year: 2009 Time horizon: 6 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 145: Economic evidence table for generic SSRIs (citalopram, fluoxetine, paroxetine) versus escitalopram versus paroxetine controlled release versus sertraline versus venlafaxine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Malone 2007 US Cost effectiveness analysis	Interventions: Generic SSRIs (citalopram, fluoxetine, paroxetine, weighted according to market share) Escitalopram Paroxetine controlled release [CR] Sertraline Venlafaxine extended release [XR]	Adults with major depression who failed to achieve remission with SSRIs Decision-analytic modelling Source of efficacy data: review of published trial data and further assumptions – synthesis by naïve addition of data (leading to breaking of randomisation) Source of resource use data: analysis of 1,814 persons enrolled in 10 antidepressant studies Source of unit costs: medication costs from national sources; other unit costs taken from other studies, unclear whether these were national or local	Costs: medication, physician visits, laboratory tests, inpatient mental health care Mean total healthcare cost per person: Generic SSRIs \$3,095 Escitalopram \$3,127 Paroxetine CR \$3,206 Sertraline \$3,178 Venlafaxine \$3,172 Outcome measure: probability of remission (defined as a HDRS score ≤ 7 or a MADRS total score ≤ 10) Probability of remission: Generic SSRIs 18.5% (weighted average) Escitalopram 19.4% Paroxetine CR 17.7% Sertraline 19.5% Venlafaxine XR 22.2%	Paroxetine CR and sertraline dominated by other options ICER of venlafaxine XR vs. generic SSRIs \$2,073 per person achieving remission ICER of escitalopram vs. generic SSRIs \$3,566 / additional person remitting [extendedly dominated] Results of sensitivity analysis reported using primarily each intervention's CER and not ICERs.	Perspective: 3rd party payer Currency: US\$ Cost year: not reported, likely 2005 Time horizon: 6 months Discounting: NA Applicability: partially applicable Quality: very serious limitations

Table 146: Economic evidence table for atypical antipsychotics adjunct to a SSRI versus lithium adjunct to a SSRI

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Edwards 2013 UK Cost-utility analysis	Interventions: An atypical antipsychotic drug (AAP)	Adults with treatment-resistant depression (TRD) defined as failure to respond to at least 2 previous antidepressants in the current episode of depression	Costs: medication (weighted costs according to expert opinion; it was estimated that AAP comprises 30% aripiprazole, 30% olanzapine,	Augmentation with lithium dominates augmentation with AAP Probability of lithium being dominant 1	Perspective: NHS/PSS Currency: GBP£ Cost year: 2011

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	as an adjunct to an SSRI Lithium as an adjunct to an SSRI	Decision-analytic modelling Source of efficacy data: systematic review and indirect comparison using 6 RCTs comparing olanzapine + fluoxetine vs. fluoxetine alone in people with TRD and 1 RCT comparing lithium + fluoxetine vs. fluoxetine alone in people who had failed at least one antidepressant; a common class effect was assumed for the SSRIs and the AAPs. Data on lithium taken from population that had failed to respond to 1 previous SSRI (so not a TRD population) Source of resource use data: mainly clinical expert opinion, length of hospitalisation taken from national hospital episode statistics Source of unit costs: national sources	20% quetiapine, and 20% risperidone; and an SSRI comprises 20% citalopram, 20% escitalopram, 30% fluoxetine, and 30% sertraline), healthcare professional time (GP, CMHT, CRHTT), hospitalisation and monitoring (laboratory testing) Mean total cost per person: AAP £5,644; Lithium £4,739 Outcome measure: QALYs estimated using EQ-5D ratings (UK tariff) Mean QALYs per person: AAP 1.225; Lithium 1.253	Results sensitive to efficacy of augmentation strategies and discontinuation rates; robust under different assumptions regarding resource use, as well as under changes in remission and relapse risk at follow-up	Time horizon: 12 months Discounting: NA Applicability: directly applicable Quality: potentially serious limitations Other comments: a fixed baseline MADRS score was assumed; change in MADRS scores at endpoint assumed to have a normal distribution in order to estimate proportions of people in response, no response, and remission states

Table 147: Economic evidence table for aripiprazole adjunct to an antidepressant versus bupropion adjunct to an antidepressant versus switching to bupropion

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Yoon 2018 US Cost-effectiveness and cost-utility analysis	Interventions: Aripiprazole adjunct to an antidepressant Bupropion adjunct to an antidepressant	Adult veterans with treatment-resistant depression (TRD) defined as failure to respond to at least 2 previous antidepressants in	Costs: medication, mental health care (inpatient, outpatient) Mean total cost per person: Aripiprazole adjunct: \$2,273; Bupropion adjunct: \$2,171; Bupropion switch: \$2,201 Outcome measures: Remission, defined as QIDS-C score of ≤5 in 2 consecutive	On remission outcome: Bupropion switch dominated by bupropion adjunct ICER of aripiprazole adjunct vs bupropion adjunct: \$5,094/remission On QALY outcome:	Perspective: healthcare Currency: US\$ Cost year: likely 2016 Time horizon: 12 weeks Discounting: NA

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	Switching to bupropion	the current episode of depression RCT (Mohamed 2017; N=1522) Source of efficacy data & resource use data: RCT (completers n=1131) Source of unit costs: national sources	follow-up visits; QALYs estimated using EQ-5D, no further details reported (e.g. if it was VAS or TTO, and, if the latter, which tariff was used). Remission: Aripiprazole adjunct: 29%; Bupropion adjunct: 27%; Bupropion switch: 22% Mean QALYs per person: Aripiprazole adjunct: 0.15; Bupropion adjunct: 0.14; Bupropion switch: 0.15	ICER of aripiprazole adjunct vs bupropion switch \$468,126/QALY ICER of bupropion switch vs bupropion adjunct: \$29,039/QALY At WTP \$20,000/remission, probability of cost-effectiveness: aripiprazole adjunct 76%; bupropion adjunct 23%; bupropion switch: 1%	Applicability: partially applicable Quality: potentially serious limitations

Table 148: Economic evidence table for aripiprazole versus quetiapine versus olanzapine/fluoxetine (all adjunct to antidepressant treatment) versus antidepressant treatment alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Taneja 2012 US Cost effectiveness analysis	Interventions: Aripiprazole 2-20 mg /day and antidepressant therapy (ARI) Quetiapine 150 mg /day or 300 mg /day and antidepressant therapy (QUE) Fixed-dose combination of olanzapine 6, 12, or 18 mg /day with fluoxetine 50 mg /day (OLZ/FLUO)	Adults with major depression who responded inadequately to previous antidepressant therapy Decision-analytic modelling Source of efficacy data: meta-analysis of published phase III clinical trials and indirect comparison using placebo as baseline comparator Source of resource use data: administrative databases and assumptions Source of unit costs: national sources	Costs: medication, outpatient care for depression, treatment of adverse events Mean total healthcare cost per person: ARI \$847 QUE 150 mg/day \$541 QUE 300 mg/day \$672 OLZ/FLUO \$791; AD \$192 Outcome measure: probability of response (defined as at least 50% reduction in MADRS total score) Probability of response: ARI 49% QUE 150 mg/day 34% QUE 300 mg/day 38% OLZ/FLUO 45%; AD 30%	QUE 150 & 300 mg/day and OLZ/FLUO extendedly dominated ICER of ARI vs. AD \$3,447 per person responding Results sensitive to changes in relative effectiveness	Perspective: healthcare system Currency: US\$ Cost year: 2011 Time horizon: 6 weeks Discounting: NA Applicability: partially applicable Quality: very serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	Antidepressant therapy alone (AD)				

Table 149: Economic evidence table for brexpiprazole versus quetiapine versus olanzapine/fluoxetine (all adjunct to antidepressant treatment) versus antidepressant treatment alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Sussman 2017 US Cost-effectiveness analysis	Interventions: Brexpiprazole adjunct to antidepressants [BREX] Quetiapine XR 300mg/day adjunct to antidepressants [QUET300] Quetiapine XR 150mg/day adjunct to antidepressants [QUET150] Olanzapine/fluoxetine adjunct to antidepressants [OLZ/FLUO] Antidepressants alone [AD]	Adults aged 18–65 years with single or recurrent non-psychotic major depressive episode and inadequate response after an adequate trial of 1–3 antidepressants Decision-analytic modelling Source of efficacy data: various trials and meta-analyses, using indirect comparisons for evidence synthesis Source of resource use data: published literature Source of unit costs: published evidence and national sources	Costs: medication, standard healthcare for depression, healthcare costs relating to response, remission, relapse, treatment discontinuation, management of adverse events Mean total cost per person: BREX \$11,511; QUET300 \$10,072; QUET150 \$9,082; OLZ/FLUO \$8,256; AD \$7255 Outcome measures: response and remission (different definitions across trials informing the analysis) Response / Remission: BREX 48.4% / 22.4% QUET300 41.1% / 17.1% QUET150 37.8% / 14.6% OLZ/FLUO 41.8% / 17.9% AD 32.5% / 10.4%	QUET150 and QUET300 dominated by OLZ/FLUO using both response and remission as outcomes ICER of BREX vs OLZ/FLUO: \$48,745/responder and \$71,839/remitter ICER of OLZ/FLUO vs AD: \$10,720/responder and \$13,293/remitter	Perspective: payer Currency: US\$ Cost year: unclear; likely 2015 Time horizon: 48 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 150: Economic evidence table for electroconvulsive therapy versus antidepressants (TCAs, SSRIs, SNRIs, and lithium augmentation) or psychotherapy

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Greenhalgh 2005 UK Cost-utility analysis	Interventions: Electroconvulsive therapy (ECT), TCAs, SSRIs, SNRIs and lithium augmentation (Li) combined in 8 strategies of 3 lines of therapy plus maintenance therapy of SSRI unless otherwise specified: 1. SNRI, SSRI, Li 2. ECT, SSRI, Li; ECT maintenance in ECT 3. ECT, SSRI, Li; Lithium & TCA maintenance in ECT 4. SNRI, ECT, Li; Lithium & TCA maintenance in ECT 5. ECT, SSRI, Li 6. SNRI, SSRI, ECT; Lithium & TCA maintenance in ECT 7. SNRI, ECT, Li; ECT maintenance in ECT 8. SNRI, SSRI, ECT; ECT maintenance in ECT	Adults with major depressive disorder who require hospitalisation Decision-analytic modelling (decision tree) Source of efficacy data: systematic literature review of RCTs and published meta-analyses, and further assumptions. Source of resource use data: published literature and expert opinion Source of unit costs: national sources	Costs: intervention (ECT, medication, hospitalisation), continued care for non-responders (nursing home placement with psychiatric provision), maintenance treatment (laboratory testing, contacts with GP, psychiatrist and psychiatric nurse) Mean total cost per person (95% CI): Strategy 1. £11,400 (£9,349 to £13,718) Strategy 2. £15,354 (£13,445 to £17,361) Strategy 3. £10,997 (£9,080 to £13,045) Strategy 4. £10,592 (£8,874 to £12,435) Strategy 5. £11,022 (£9,016 to £13,069) Strategy 6. £13,939 (£11,161 to £17,049) Strategy 7. £12,591 (£10,678 to £14,497) Strategy 8. £14,548 (£11,680 to £17,717) Primary outcome measure: QALYs estimated based on preferences for vignettes using the McSad health state classification system valued by service users with previous depression in Canada using SG Mean total QALYs per person (95% CI): Strategy 1. 0.490 (0.453 to 0.526) Strategy 2. 0.458 (0.422 to 0.493) Strategy 3. 0.424 (0.389 to 0.459) Strategy 4. 0.470 (0.431 to 0.508) Strategy 5. 0.539 (0.498 to 0.579) Strategy 6. 0.489 (0.452 to 0.524) Strategy 7. 0.486 (0.449 to 0.522) Strategy 8. 0.494 (0.459 to 0.529)	Strategies 1, 2, 3, 6, 7, and 8 were dominated ICER of Strategy 5 vs. strategy 4: £6,232/QALY Results modestly sensitive to use of alternative utility values; results robust to small changes in costs and suicide rates	Perspective: NHS Currency: GBP£ Cost year: 2001 Time horizon: 12 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
<p>Ross 2018 US Cost-utility analysis</p>	<p>Interventions: Electroconvulsive therapy (ECT) as 1st, 2nd, 3rd, 4th, 5, 6th line of treatment, following 0-5 lines of antidepressants and/or psychotherapy No ECT</p>	<p>Adults with treatment-resistant depression Decision-analytic modelling Source of efficacy data: meta-analyses, RCTs, observational studies and further assumptions. No comparative data used and no evidence synthesis of available data undertaken. Source of resource use data: published literature Source of unit costs: published literature and national sources</p>	<p>Costs: ECT, medication, outpatient and inpatient care, laboratory testing Mean total cost per person: 1st line ECT \$54,520, 2nd line ECT \$52,000, 3rd line ECT \$49,830, 4th line ECT \$50,900, 5th line ECT \$49,850, 6th line ECT \$50,080, no ECT \$42,490 Primary outcome measure: QALYs estimated based on published utility data, which are derived from RQ-5D (UK tariff) Mean total QALYs per person: 1st line ECT 2.78, 2nd line ECT 2.77, 3rd line ECT 2.77, 4th line ECT 2.76, 5th line ECT 2.76, 6th line ECT 2.75, no ECT 2.63</p>	<p>4th, 5th, and 6th line ECT dominated ICER of 3rd line ECT vs no ECT \$54,000/QALY ICER of 2nd vs 3rd line ECT \$564,000/QALY ICER of 1st vs 2nd line ECT \$815,000/QALY At WTP \$100,000/QALY, probability that at least 1 ECT strategy is cost-effective: 74-78%; probability of cost-effectiveness of 3rd line ECT: 56-58%. Results at the WTP robust under alternative scenarios tested</p>	<p>Perspective: healthcare Currency: US\$ Cost year: 2013 Time horizon: 4 years Discounting: 3% annually Applicability: partially applicable Quality: very serious limitations</p>