APPENDIX 32: HEALTH ECONOMICS – EVIDENCE TABLES

Abbreviations

Ari	aripiprazole
Car	carbamazepine
CBT	cognitive behavioural therapy
CI	confidence interval
CPN	community psychiatric nurse
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EPA	eicosapentaenoic acid
GP	general practitioner
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
Imi	imipramine
Lam	lamotrigine
Li	lithium
MDQ	Mood Disorder Questionnaire
MRS	Mania Rating Scale
MS	mood stabiliser
NA	not applicable
NHS	National Health Service
Olz	olanzapine
QALY	quality-adjusted life year
Que	quetiapine
RCT	randomised controlled trial
SD	standard deviation
SHO	senior house officer
Val	valproate
Ven	venlafaxine
WTP	willingness to pay
YMRS	Young Mania Rating Scale
XR	extended release

1.1 CASE IDENTIFICATION AND ASSESSMENT OF ADULTS WITH BIPOLAR DISORDER

Reference to included study:

Menzin J, Sussman M, Tafesse E, Duczakowski C, Neumann P, Friedman M. A model of the economic impact of a bipolar disorder screening program in primary care. Journal of Clinical Psychiatry. 2009;70:1230-06.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: Description and values** **Outcomes: Description and values**	**Results: Cost-effectiveness**	**Comments**
Menzin and colleagues (2009) US Cost-effectiveness analysis	Interventions: Screening with one-time administration of the Mood Disorder Questionnaire (MDQ) followed by referral to psychiatrists for people screened positive No screening	Population: Adults presenting for the first time with symptoms of major depressive disorder in primary care Study design: Decision analytic modelling Source of effectiveness data: Literature review and further assumptions Source of costs (resource use data combined with unit costs): Published literature	Costs: *Direct medical:* administration of MDQ by nurse and physician, referral to psychiatrists, inpatient care, outpatient care, medication Cost per person: *MDQ:* $34,107 *No screening:* $36,044 Primary outcome: Number of people correctly diagnosed with bipolar disorder or unipolar depression Number of correctly diagnosed people (per 1000 people screened): *MDQ:* 440 *No screening:* 402	MDQ is dominant versus no screening Probability of MDQ being cost-saving: 76% Results robust under various alternative scenarios considering different prevalence of bipolar disorder, sensitivity/specificity, time horizon, treatment costs, and so on	Perspective: Third-party payer Currency: US$ Cost year: 2006 Time horizon: 5 years Discounting: 3% annually Applicability: Partially applicable Quality: Potentially serious limitations

1.2 PHARMACOLOGICAL INTERVENTIONS FOR MANIA, HYPOMANIA AND MIXED EPISODES IN ADULTS WITH BIPOLAR DISORDER

References to included studies:

1. Bridle C, Palmer S, Bagnall AM, Darba J, Duffy S, Sculpher M, et al. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Health Technology Assessment. 2004;8.
2. Caro JJ, Huybrechts KF, Xenakis JG, O'Brien JA, Rajagopalan K, Lee K. Budgetary impact of treating acute bipolar mania in hospitalized patients with quetiapine: an economic analysis of clinical trials. Current Medical Research and Opinion. 2006;22:2233-42.
3. Revicki DA, Paramore LC, Sommerville KW, Swann AC, Zajecka JM, for the Depakote Comparator Study Group. Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. Journal of Clinical Psychiatry. 2003;64:288-94.
4. Zhu B, Tunis SL, Zhao Z, Baker RW, Lage MJ, Shi L, Tohen M. Service utilization and costs of olanzapine versus divalproex treatment for acute mania: results from a randomized, 47-week clinical trial. Current Medical Research and Opinion. 2005;21:555-64.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Bridle and colleagues (2004) UK Cost-effectiveness analysis	Interventions: Quetiapine 619.2 mg/day Olanzapine 16.2 mg/day Valproate semisodium 1,513.5 mg/day Lithium 1,417 mg/day Haloperidol 10.4 mg/day	Population: Adults with bipolar disorder experiencing an acute manic episode Study design: Decision analytic modelling Source of effectiveness data: Systematic literature review and network meta-analysis (seven studies included) Source of resource use data: Expert opinion, information from manufacturers and further assumptions Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation, drug acquisition, specific diagnostic and laboratory tests required for monitoring; costs of adverse events excluded Cost per person: *Quetiapine:* £3,165 *Olanzapine:* £3,161 *Valproate semisodium:* £3,139 *Lithium:* £3,162 *Haloperidol:* £3,047 Primary outcome: Response rates according to a ≥ 50% improvement in people's baseline manic symptoms, measured using the Young Mania Rating Scale (YMRS) Mean response rates (95% CI): *Quetiapine:* 0.47 (0.38–0.55) *Olanzapine:* 0.54 (0.46–0.62) *Valproate semisodium:* 0.45 (0.37–0.54) *Lithium:* 0.50 (0.39–0.60) *Haloperidol:* 0.52 (0.41–0.62)	Lithium, valproate semisodium and quetiapine dominated by haloperidol ICER of olanzapine compared with haloperidol: £7,179 per additional responder Probability of cost effectiveness at WTP £20,000 per additional responder: *Olanzapine:* 0.44 *Haloperidol:* 0.37 *Lithium:* 0.16 *Quetiapine:* 0.02 *Valproate semisodium:* 0.01 Results robust under alternative scenarios including hospitalisation beyond 3 weeks for non-responders, treatment of non-responders with second- and third-line drugs, reductions in diagnostic and laboratory costs, inclusion of effectiveness data for people initially excluded from analysis according to a modified intention-to-treat approach, and inclusion of treatment costs for extrapyramidal symptoms due to haloperidol use	Perspective: NHS Currency: UK£ Cost year: 2001–2002 Time horizon: 3 weeks Discounting: NA. All patients assumed to be hospitalised during the total 3 weeks of time horizon examined Applicability: Partially applicable Quality: Potentially serious limitations Quetiapine and olanzapine are now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Caro and colleagues (2006) US Cost consequence analysis	Intervention: Quetiapine Comparator: Usual care comprising 45% monotherapy with lithium, 25% lithium plus risperidone, 25% lithium plus olanzapine, and 5% lithium plus quetiapine	Population: Adults with bipolar I disorder, in acute manic episode Study design: Decision analytic modelling (discrete event simulation) Source of effectiveness data: Literature review Source of resource use data: Administrative databases Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation and physician fees, emergency room and intensive care units, routine physician and psychiatrist visits, laboratory tests, medication, management of side effects Cost results (mean ± half width 95%CI) *Total cost per person:* *Quetiapine:* $5,525 ± $21 *Usual care:* $6,912 ± $20 Outcomes: Percentage of people responding at 21 days and remitting at 84 days Percentage of people responding at 21 days (mean ± half width 95%CI): *Quetiapine:* 54% ± 0.29 *Usual care:* 43% ± 0.39 Percentage of people remitting at 84 days (mean ± half width 95%CI): *Quetiapine:* 80% ± 0.33% *Usual care:* 74% ± 0.33%	Quetiapine dominates usual care Results sensitive to drug prices, discharge criteria and side-effect management costs	Perspective: Third party payer Currency: US$ Cost year: 2004 Time horizon: 100 days Discounting: NA Applicability: Partially applicable Quality: Potentially serious limitations Quetiapine is now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Revicki and colleagues (2003) US Cost consequence analysis	Intervention: Valproate semisodium; initiated at 20 mg/kg/day, could be increased by 500 mg/day on days 3 and 6 if clinically important symptoms or mania persisted. *Maximum dose allowed:* 1000 mg/day Comparator: Olanzapine; initiated at 10 mg/day, could be increased by 5 mg/day on days 3 and 6 if manic symptoms persisted. *Maximum dose allowed:* 20 mg/day	Population: Adults with bipolar I disorder between 18–65 years old, experiencing an acute manic episode Study design: Double-blind, multi-centre RCT (21 US sites, n = 120) (ZAJECKA2002) Source of effectiveness data: RCT Source of resource use data: RCT (n = 52) and further assumptions Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation; physicians' fee; emergency room; psychiatric, physician, psychologist or other mental health provider visits; home health service visits; medication Mean (SD) total medical costs: *Valproate semisodium:* $13,703 ($8,708) *Olanzapine:* $15,180 ($16,780) (p = 0.88) Outcomes: Clinical improvement based on Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia-Change Version and the Hamilton Rating Scale for Depression; health-related quality of life (HRQoL) based on the Quality of Life Enjoyment and Satisfaction Questionnaire and restricted activity days Changes in MRS scores at 3 weeks: *Valproate semisodium:* -14.9 (baseline 30.8) *Olanzapine:* -16.6 (baseline 32.3) (p = 0.368) Changes in Quality of Life Enjoyment and Satisfaction Questionnaire scores (subjective feelings) at 12 weeks: *Valproate semisodium:* -4.4 *Olanzapine:* -4.7 (p = 0.95) No statistically significant differences in other outcomes	Non-applicable	Perspective: Third party payer Currency: US$ Cost year: Not stated Time horizon: 12 weeks Discounting: NA. Participants discontinued treatment if not improved after 3 weeks, but data still collected for 12 weeks; HRQoL and resource-use data collected via telephone interviews Applicability: Partially applicable Quality: Potentially serious limitations Olanzapine is now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Zhu and colleagues (2005) US Cost consequence analysis	Intervention: Olanzapine 5–20 mg/day Comparator: Valproate semisodium 500–2,500 mg/day	Population: Adults with bipolar I disorder aged 18–75 years, hospitalised for an acute manic or mixed episode and with a YMRS total score of ≥ 20 at both screening and baseline Study design: Double-blind, multi-centre RCT (48 US sites, acute phase 0-3 weeks n = 251; maintenance phase 3–47 weeks n = 147) (TOHEN2002) Source of effectiveness data: RCT (n = 251) Source of resource use data: Participants who entered the maintenance phase of the RCT (n = 147) Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation (full/partial), outpatient psychiatric physician and other mental health provider visits, emergency room visits, home visits by healthcare professionals, medication, laboratory tests Average annual total costs per person: *Olanzapine:* $14,967 *Valproate semisodium:* $15,801 (no statistically significant difference) Outcomes: Clinical improvement based on YMRS and rate of symptom remission (defined as YMRS score ≤ 12) at 3 weeks (acute phase); median time to remission of manic symptoms Improvement in manic symptoms at 3 weeks: Significantly greater for olanzapine Percentage of symptom remission: *Olanzapine:* 54.4% *Valproate semisodium:* 42.3% ($p < 0.05$) Median time to remission: *Olanzapine:* 14 days *Valproate semisodium:* 62 days	Non-applicable	Perspective: Third party payer Currency: US$ Cost year: 1999-2000 Time horizon: 47 weeks Discounting: NA Applicability: Partially applicable Quality: Potentially serious limitations

1.3 PHARMACOLOGICAL INTERVENTIONS FOR ACUTE DEPRESSION IN ADULTS WITH BIPOLAR DISORDER

Reference to included study:

Ekman M, Lindgren P, Miltenburger C, Meier G, Locklear JC, Chatterton ML. Cost effectiveness of quetiapine in patients with acute bipolar depression and in maintenance treatment after an acute depressive episode. PharmacoEconomics. 2012;30:513-30.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Ekman and colleagues (2012) UK Cost-utility analysis	Interventions: Quetiapine (Que) Quetiapine and mood stabiliser (lithium [Li] or divalproex) (Que and MS) Olanzapine (Olz) Olz and Li, Olz replaced by venlafaxine (Ven) in acute depression (Olz and Li 1) Olz and Li, Olz replaced by paroxetine in acute depression (Olz and Li 2) Aripiprazole, replaced by Olz and Ven in acute depression (Ari)	Population: Adults aged 40 years with bipolar disorder (I or II) experiencing an acute depressive episode or being in remission Study design: Decision analytic modelling (discrete event simulation) Source of effectiveness data: RCTs and meta-analyses Source of resource use data: Published data based on expert opinion Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation, outpatient care, crisis teams, staff costs including senior house officer (SHO), general practitioner (GP), community psychiatric nurse (CPN), practice nurse and dietician, drug acquisition, laboratory tests, costs of adverse events included; indirect costs considered in sensitivity analysis Primary outcome: QALY Costs and QALYs per 1000 people starting in acute depression: *Que:* £21,874; 3.497 *Que and MS:* £21,324; 3.524 *Olz:* £21,551; 3.460 *Olz and Li 1:* £22,425; 3.495 *Olz and Li 2:* £22,073; 3.489 *Ari:* £24,657; 3.472 *Mixed:* £21,618; 3.484	Start in acute depression: Que and MS dominates all; Que dominates all except Olz and Mixed ICER of Que versus Olz: 8,591/QALY ICER of Que versus Mixed: £18,570/QALY Compared with Olz, probability of Que being cost-effective at WTP 0 and £30,000/QALY: 21%; 90% Results (quetiapine versus olanzapine) robust under several alternative scenarios but moderately sensitive to inclusion of indirect costs, time horizon, treatment duration and dosages	Perspective: NHS Currency: UK£ Cost year: 2011 Time horizon: 5 years Discounting: 3.5% Applicability: Directly applicable Quality: Very serious limitations; evidence synthesis methods inappropriate as populations, phase of disorder and outcome measures differed across RCTs used for indirect comparisons Quetiapine and olanzapine are now available in generic form

	Mixed scenario: risperidone in mania, Ven and Li in depression, Olz in maintenance (Mixed)				

1.4 SERVICES FOR ADULTS WITH BIPOLAR DISORDER – MOOD DISORDER CLINICS

Reference to included study:

Kessing LV, Hansen HV, Hvenegaard A, Christensen EM, Dam H, Gluud C, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. British Journal of Psychiatry. 2013;202:212-9.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Kessing and colleagues (2013) Denmark Cost-effectiveness analysis	Interventions: Specialised outpatient mood disorder clinic Standard decentralised psychiatric treatment	Population: Adults with recently diagnosed bipolar disorder (following discharge from one of their first three psychiatric hospital admissions for a manic episode) Study design: RCT (N = 158) (KESSING2013) Source of effectiveness data: RCT Source of resource use data: RCT, published literature and assumptions Source of unit costs: National published data	Costs: *Direct medical:* intervention, mental health centre, private psychiatrist, outpatient treatment at the local psychiatric hospital, drugs, inpatient care Cost per person: *Mood disorder clinic:* €25,953 *Standard care:* €29,147 Primary outcome: Rate of first readmission to hospital Percentage of first readmission to hospital: *Mood disorder clinic:* 36.1% *Standard care:* 54.7% (p = 0.034)	Mood disorder clinic dominates standard care Cost results sensitive to intervention costs and length of hospital re-admission	Perspective: Health service Currency: Euros (€) Cost year: Likely 2012 Time horizon: 2 years Discounting: NA Applicability: Partially applicable Quality: Potentially serious limitations

1.5 PHARMACOLOGICAL INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF ADULTS WITH BIPOLAR DISORDER

References to included studies:

1. Calvert NW, Burch SP, Fu AZ, Reeves P, Thompson TR. The cost-effectiveness of lamotrigine in the maintenance treatment of adults with bipolar I disorder. Journal of Managed Care Pharmacy. 2006;12:322-30.
2. Ekman M, Lindgren P, Miltenburger C, Meier G, Locklear JC, Chatterton ML. Cost-effectiveness of quetiapine in patients with acute bipolar depression and in maintenance treatment after an acute depressive episode. PharmacoEconomics. 2012;30:513-30.
3. Fajutrao L, Paulsson B, Liu S, Locklear J. Cost-effectiveness of quetiapine plus mood stabilizers compared with mood stabilizers alone in the maintenance therapy of bipolar I disorder: Results of a Markov model analysis. Clinical Therapeutics. 2009;3:1456-68.
4. McKendrick J, Cerri KH, Lloyd A, D'Ausilio A, Dando S, Chinn C. Cost effectiveness of olanzapine in prevention of affective episodes in bipolar disorder in the United Kingdom. Journal of Psychopharmacology. 2007;21:588-96.
5. NCCMH (2006) Bipolar Disorder: the Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists.
6. Revicki DA, Hirschfeld RM, Ahearn EP, Weisler RH, Palmer C, Keck PE Jr. Effectiveness and medical costs of divalproex versus lithium in the treatment of bipolar disorder: results of a naturalistic clinical trial. Journal of Affective Disorders. 2005;86:183-93.
7. Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technology Assessment. 2007;11.
8. Woodward TC, Tafesse E, Quon P, Kim J, Lazarus A. Cost-effectiveness of quetiapine with lithium or divalproex for maintenance treatment of bipolar I disorder. Journal of Medical Economics 2009;12:259-68.
9. Woodward TC, Tafesse E, Quon P, Lazarus A. Cost effectiveness of adjunctive quetiapine fumarate extended-release tablets with mood stabilizers in the maintenance treatment of bipolar I disorder. PharmacoEconomics. 2010;28:751-64.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Calvert and colleagues (2006) US Cost-effectiveness and cost-utility analysis	Interventions: Lamotrigine Lithium Olanzapine No maintenance treatment	Population: Adults with bipolar disorder I stabilised after resolution of a mixed/manic episode Study design: Decision analytic modelling Source of effectiveness data: Double-blind placebo-controlled RCTs (BOWDEN2003, CALABRESE2003) Source of resource use data: Published data, clinical guidelines and a physician survey Source of unit cost data: Published national sources	Costs: *Direct medical:* physician time, medication, laboratory tests, hospitalisation; costs of side effects not considered Total annual cost per person: *Lamotrigine:* $6,503 *Lithium:* $5,806 *Olanzapine:* $7,395 *No treatment:* $10,722 Primary outcomes: • Number of acute episodes avoided • Number of euthymic days achieved • QALYs Annual number of acute episodes avoided: *Lamotrigine:* 1.64 *Lithiun:* 1.34 *Olanzapine:* 1.37 *No treatment:* 0 Annual number of euthymic days per person: *Lamotrigine:* 309 *Lithium:* 286 *Olanzapine:* 294 *No treatment:* 227 Annual number of QALYs per person: *Lamotrigine:* 0.762 *Lithium:* 0.735 *Olanzapine:* 0.739	No treatment is dominated by all drugs Lamotrigine dominates olanzapine for all three outcome measures ICER of lamotrigine versus lithium: • $2,400 per acute episode avoided • $30 per extra euthymic day • $26,000 per QALY Results most sensitive to transition probabilities and utility values	Perspective: Direct payer Currency: US$ Cost year: 2004 Time horizon: 18 months Discounting: NA Applicability: Partly applicable Quality: Very serious limitations; indirect comparisons using RCTs with different study designs and populations so method of analysis was inappropriate Lamotrigine and olanzapine are now available in generic form

			No treatment: 0.692		
Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Ekman and colleagues (2012) UK Cost-utility analysis	Interventions: Quetiapine Quetiapine and mood stabiliser (lithium or divalproex) (Que and MS) Olanzapine (Olz) Olanzapine and lithium, olanzapine replaced by venlafaxine (Ven) in acute depression (Olz and Li 1) Olanzapine and lithium, olanzapine replaced by paroxetine in acute depression (Olz and Li 2) Aripiprazole, replaced by olanzapine and venlafaxine in acute depression (Ari) *Mixed scenario:* risperidone in mania, venlafaxine and lithium in depression, olanzapine in maintenance (Mixed)	Population: Adults aged 40 years with bipolar disorder (I or II) experiencing an acute depressive episode or being in remission Study design: Decision analytic modelling Source of effectiveness data: RCTs and meta-analyses Source of resource use data: published data based on expert opinion Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation, outpatient care, crisis teams, staff costs including senior house officer (SHO), general practitioner (GP), community psychiatric nurse (CPN), practice nurse and dietician, drug acquisition, laboratory tests, costs of adverse events included; indirect costs considered in sensitivity analysis Primary outcome: QALY Costs and QALYs per 1000 people starting in remission: *Que:* £18,928; 3.551 *Que and MS:* £16,534; 3.570 *Olz:* £18,209; 3.525 *Olz and Li 1:* £19,371; 3.537 *Olz and Li 2:* £19,197; 3.536 *Ari:* £22,062; 3.528 *Mixed:* £18,189; 3.534	Start in remission: Que and MS dominates all Que dominates all except Olz and Mixed *ICER of Que versus Olz:* £27,437/QALY *ICER of Que versus Mixed:* £41,691/QALY *Compared with Olz, probability of Que being cost-effective at WTP 0 and £30,000/QALY:* 29%; 92% Results robust under several alternative scenarios but moderately sensitive to inclusion of indirect costs, time horizon, treatment duration and dosages	Perspective: NHS Currency: UK£ Cost year: 2011 Time horizon: 5 years Discounting: 3.5% Applicability: Directly applicable Quality: Very serious limitations; evidence synthesis methods inappropriate as populations, phase of disorder and outcome measures differed across RCTs used for indirect comparisons Quetiapine and olanzapine are now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Fajutrao and colleagues (2009) UK Cost-effectiveness and cost-utility analysis	Interventions: Quetiapine adjunctive to mood stabiliser (lithium or valproate) (Que + MS) Mood stabiliser (lithium or valproate) alone (MS)	Population: Adults with bipolar disorder I newly stabilised with a combination of Que and MS Study design: Decision analytic modelling Source of effectiveness data: Two double-blind placebo-controlled RCTs Source of resource use data: Clinical guidelines mainly based on expert opinion Source of unit cost data: National sources	Costs: *Direct medical:* staff time (psychiatrist, senior house officer, general practitioner, community psychiatric nurse, laboratory nurse), medication, laboratory tests, hospitalisation, crisis resolution and home treatment teams; costs of side effects not considered Total cost per person: *Que + MS:* £9,130 *MS:* £9,637 Primary outcomes: • Number of acute episodes • Percentage of people hospitalised due to acute episodes • QALYs Number of acute episodes per person: *Que + MS:* 0.84 *MS:* 1.84 Percentage of people hospitalised due to acute episodes: *Que + MS:* 0.30 *MS:* 0.42 QALYs: *Que + MS:* 1.57 *MS:* 1.50	Que + MS dominant Results most sensitive to risk and length of hospitalisation, cost of hospital stay, and quetiapine acquisition cost	Perspective: NHS Currency: UK£ Cost year: 2007 Time horizon: 24 months Discounting: 3.5% Applicability: Directly applicable Quality: Potentially serious limitations Quetiapine and olanzapine (administered in mania) are now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
McKendrick and colleagues (2007) UK Cost-effectiveness analysis	Interventions: Olanzapine Lithium	Population: Adults with bipolar disorder I newly stabilised following response to olanzapine and lithium combination therapy for mania Study design: Decision analytic modelling Source of effectiveness data: Double-blind RCT Source of resource use data: UK chart review and other published sources Source of unit cost data: National sources	Costs: *Direct medical:* physician time, medication, laboratory tests, hospitalisation, outpatient care, home visits; costs of side effects not considered Total cost per person: *Olanzapine:* £3,619 (95% CI £2,941 to £4,385) *Lithium:* £4,419 (95% CI £3,537 to £5,563) Primary outcome: Number of acute episodes Number of acute episodes per person: *Olanzapine:* 0.58 (95% CI, 0.53 to 0.64) *Lithium:* 0.81 (95% CI, 0.71 to 0.91)	Olanzapine dominates lithium Sensitivity analysis: Results most sensitive to risk and length of hospitalisation for mania, cost of hospitalisation, and time horizon Results ranging from olanzapine being dominant to ICER of olanzapine versus lithium £367 per acute episode avoided	Perspective: NHS Currency: UK£ Cost year: 2003 Time horizon: 12 months Discounting: NA Applicability: Directly applicable Quality: Potentially serious limitations Olanzapine is now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
NCCMH (2006) UK Cost-effectiveness and cost-utility analysis	Interventions: Olanzapine Valproate semisodium Lithium No drug treatment	Population: Adults with bipolar I disorder in a stable state following an acute episode (that is, in a sub-acute or euthymic state). *Three sub-groups assessed:* men, women without child-bearing potential, and women with child-bearing potential. Study design: Decision analytic modelling Source of effectiveness data: Indirect comparisons using double-blind RCTs Source of resource use data: Expert opinion and published sources Source of unit cost data: National sources	Costs: *Direct medical:* drug acquisition, visits to consultant psychiatrists, senior house officers (SHOs), general practitioners (GPs), community psychiatric nurses (CPNs), laboratory testing, treatment of acute episodes (hospitalisation, crisis teams, enhanced outpatient treatment, additional medication); costs of side effects not considered Total cost per person: ***Men:*** *Olanzapine:* £17,346 *Valproate:* £15,550 *Lithium:* £12,902 *No treatment:* £14,077 ***Women:*** *Olanzapine:* £17,461 *Valproate:* £15,652 *Lithium:* £12,931 *No treatment:* £14,175 Primary outcomes: • Number of acute episodes averted • Number of days free from acute episode • Number of QALYs Number of acute episodes averted per person: ***Men:*** *Olanzapine:* 295 *Valproate:* 777 *Lithium:* 626 *No treatment:* 0 ***Women:*** *Olanzapine:* 297	(Relevant options not reported are dominated by absolute or extended dominance) Men: ***A. Outcome – acute episodes averted or days free from episode:*** *ICER of valproate versus lithium:* £17,564/episode averted; £148/day free from episode ***B. Outcome – QALY:*** *Olanzapine versus lithium:* £11,810/QALY Women without child-bearing potential: ***A. Outcome – acute episodes averted or days free from episode:*** *ICER of valproate versus lithium:* £16,529/acute episode averted; £104/day free from episode ***B. Outcome – QALY:*** *Olanzapine versus lithium:* £11,419/QALY Women with child-bearing potential: *A. Outcome – acute episodes averted or days free from episode:* Lithium is dominant *B. Outcome – QALY:* Olanzapine versus lithium: £11,419/QALY Results sensitive to efficacy data, baseline rate of manic to depressive episodes and baseline risk of relapse *Probability of olanzapine being cost-effective at WTP £20,000/QALY:* 90-92%	Perspective: NHS Currency: UK£ Cost year: 2006 Time horizon: 5 years Discounting: 3.5% Applicability: Partially applicable Quality: Very serious limitations; indirect comparisons using RCTs with different study designs and populations so method of analysis was inappropriate Olanzapine is now available in generic form

			Valproate: 783 *Lithium:* 618 *No treatment:* 0 <u>Number of days free from episode per person:</u> ***Men:*** *Olanzapine:* 1,468 *Valproate:* 1,527 *Lithium:* 1,509 *No treatment:* 1,455 ***Women:*** *Olanzapine:* 1,480 *Valproate:* 1,539 *Lithium:* 1,513 *No treatment:* 1,467 <u>QALYs per person:</u> ***Men:*** *Olanzapine:* 3.57 *Valproate:* 3.27 *Lithium:* 3.19 *No treatment:* 3.26 ***Women:*** *Olanzapine:* 3.64 *Valproate:* 3.32 *Lithium:* 3.19 *No treatment:* 3.29		

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Revicki and colleagues (2005) US Cost consequence analysis	Intervention: Valproate semisodium added to usual psychiatric care (including other medications); initiated at 15–20 mg/kg/day or based on usual psychiatric practice Comparator: Lithium added to usual psychiatric care (including other medications); dosed up to 1,800 mg/day during mania, between 900–1,200 mg/day for maintenance therapy	Population: Adults with bipolar I disorder, following discharge after hospitalisation for an acute manic or mixed episode Study design: Pragmatic, multicentre clinical trial, maintenance phase (33 US sites, n = 201) Source of effectiveness data: Pragmatic trial Source of resource use data: Pragmatic trial and further assumptions Source of unit cost data: National sources	Costs: *Direct medical:* hospitalisation; outpatient psychiatric, physician, psychologist and other mental health provider visits; emergency room visits; home health service visits; medication Mean (standard error) total medical costs per person: *Valproate semisodium:* $28,911 ($3,599) *Lithium:* $30,666 ($7,364) (p = 0.693) Outcomes: Number of months without manic or depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); participant functioning and quality of life measured using the mental component summary and physical component summary scores of the Short From Health Survey 36, the Mental Health Index and a questionnaire on disability days; adverse events and continuation rates ***Number of months without DSM-IV mania or depression (mean, SD):*** *Valproate semisodium:* 5.3 (4.6) *Lithium:* 5.4 (4.4) (p = 0.814) Non-significant differences in any other outcomes between groups	Non-applicable	Perspective: Third party payer Currency: US$ Cost year: 1997 Time horizon: 1 year following hospital discharge Discounting: NA HRQoL and resource use data collected via telephone interviews Applicability: Partially applicable Quality: Potentially serious limitations

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Soares-Weiser and colleagues (2007) UK Cost-utility analysis	Interventions: Carbamazepine (Car) Imipramine (Imi) Lamotrigine (Lam) Lithium (Li) Lithium plus imipramine (Li + Imi) Olanzapine (Olz) Valproate (Val)	Population: Adults with stabilised bipolar disorder I; separate analysis for adults with a recent depressive episode and those with a recent manic episode Study design: Decision analytic modelling Source of effectiveness data: Systematic review and network meta-analysis Source of resource use data: National guidelines based on expert opinion, published data and further assumptions Source of unit cost data: National sources	Costs: *Direct medical:* medication, laboratory tests, hospitalisation, staff time (psychiatric consultant, senior house officer, GP, community psychiatric nurse, practice nurse), crisis resolution and home treatment teams; costs of side effects not considered Total cost per person: recent depressive episode / recent manic episode: *Car:* £96,951 / £103,503 *Imi:* £83,314 / £98,961 *Lam:* £64,117 / £70,964 *Li:* £62,649 / £58,657 *Li + Imi:* £64,602 / £72,954 *Olz:* £65,659 / £50,347 *Val:* £56,233 / £57,320 Primary outcome: QALY QALYs gained per person: recent depressive episode / recent manic episode: *Car:* 13.95 / 14.24 *Imi:* 14.47 / 14.57 *Lam:* 14.66 / 14.86 *Li:* 15.34 / 15.72 *Li + Imi:* 15.43 / 15.62 *Olz:* 14.39 / 14.99 *Val:* 14.73 / 14.98	Recent depressive episode: Car, Imi, Lam and Olz dominated by other treatment options *ICER of Li versus Val:* £10,409/QALY *ICER of Li + Imi versus Li:* £21,370/QALY Probability(%) of cost effectiveness at willingness-to-pay £20,000/QALY: *Car:* 0.04 *Imi:* 0.04 *Lam:* 4.72 *Li:* 35.74 *Li + Imi:* 47.41 *Olz:* 0.09 *Val:* 11.96 Recent manic episode: *Car, Imi, Lam, Li + Imi and Val dominated by other treatment options* *ICER of Li versus Olz:* £11,359/QALY Probability(%) of cost effectiveness at willingness-to-pay £20,000/QALY: *Car:* 0.29 *Imi:* 0.00 *Lam:* 0.21 *Li:* 77.04 *Li + Imi:* 8.94 *Olz:* 11.12 *Val:* 2.40 Results sensitive to the assumption that lithium reduces mortality	Perspective: NHS Currency: UK£ Cost year: 2004-5 Time horizon: Over lifetime Discounting: 3% Applicability: Directly applicable Quality: Very serious limitations; network meta-analysis inappropriate as included RCTs had different study designs Olanzapine and lamotrigine are now available in generic form Distinction between people with a previous manic versus depressive episode and differential data based on very limited evidence

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectivenes**	**Comments**
Woodward and colleagues (2009) US Cost-effectiveness and cost-utility analysis	Interventions: Quetiapine adjunctive to mood stabiliser (lithium or valproate) (Que + MS) Mood stabiliser (lithium or valproate) alone (MS)	Population: Adults with bipolar disorder I stabilised with Que + MS Study design: Decision analytic modelling Source of effectiveness data: Pooled data from two double-blind RCTs Source of resource use data and unit costs: Published literature, national unit costs and further assumptions	Costs: *Direct medical:* physician time, medication, laboratory tests, hospitalisation; costs of side effects not considered Total cost per person: *Que + MS:* £12,930 *MS:* £12,937 Primary outcomes: • Number of acute episodes • Percentage of people hospitalised due to acute episodes • QALYs Number of acute episodes per person: *Que + MS:* 1.5 *MS:* 2.6 Percentage of people hospitalised due to acute episodes *Que + MS:* 0.43 *MS:* 0.77 QALYs per person *Que + MS:* 1.491 *MS:* 1.440	Que + MS dominant Results most sensitive to cost of quetiapine, risk and length of hospitalisation for acute episodes (especially manic), cost of inpatient treatment for a manic episode	Perspective: Third-party payer Currency: US$ Cost year: 2007 Time horizon: 2 years Discounting: 3% Applicability: Partially applicable Quality: Potentially serious limitations Quetiapine is now available in generic form

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Woodward and colleagues (2010) US Cost-effectiveness and cost-utility analysis	Interventions: Quetiapine fumarate XR adjunctive to mood stabiliser (lithium or valproate) (Que XR + MS) Mood stabiliser (lithium or valproate) alone (MS) Lithium (Li) Lamotrigine (Lam) Olanzapine (Olz) Aripiprazole (Ari) No maintenance treatment	Population: Adults with stabilised bipolar disorder I Study design: Decision analytic modelling Source of effectiveness data: Pooled data from two double-blind RCTs evaluating Que +MS versus MS (but NO Que XR) and other published literature identified via a non-systematic review Source of resource use data and unit costs: Published literature, national unit costs and further assumptions	Costs: *Direct medical:* physician time, medication, laboratory tests, hospitalisation; for societal perspective: loss of productivity. Costs of side effects not considered. Total healthcare (societal) cost per person: *Que XR + MS:* $14,878 ($16,351) *MS:* $13,697 ($16,356) *Li:* $10,086 ($12,444) *Lam:* $16,449 ($18,731) *Olz:* $15,300 ($18,169) *Ari:* $15,893 ($18,055) *No treatment:* $15,608 ($19,689) Primary outcomes: • Number of acute episodes • Number of hospitalisations due to acute episodes • QALYs Number of acute episodes (hospitalisations due to acute episodes) per person: *Que XR + MS:* 1.50 (0.43) *MS:* 2.63 (0.77) *Li:* 2.37 (0.66) *Lam:* 2.29 (0.70) *Olz:* 2.86 (0.71) *Ari:* 2.16 (0.58) *No treatment:* 3.99 (1.13) QALYs per person: *Que XR + MS:* 1.49 *MS:* 1.44 *Li:* 1.44 *Lam:* 1.47	Direct medical costs only: Que XR + MS dominates Lam, Olz, Ari and no treatment. *ICER of Que XR+ MS versus MS:* $22,959/QALY *ICER of Que XR+ MS versus Li:* $100,235/QALY *Societal perspective:* Que XR + MS dominates MS, Lam, Olz, Ari and no treatment *ICER of Que XR + MS versus Li:* $81,712/QALY Results most sensitive to efficacy, utility for the euthymia state, cost of quetiapine XR, risk and length of hospitalisation for manic episodes, and cost of inpatient treatment for a manic episode Probability of cost effectiveness at willingness-to-pay $100,000/QALY: *Que XR + MS:* 50% *Li:* 50%	Perspective: Third-party payer and societal perspectives Currency: US$ Cost year: 2009 Time horizon: 2 years Discounting: 3% Applicability: Partially applicable Quality: Very serious limitations Olanzapine and lamotrigine are now available in generic form. Effectiveness data taken from RCTs assessing quetiapine and not quetiapine XR RCTs synthesised for all comparisons other than that between Que XR and MS versus MS had different designs and populations, so method of synthesis inappropriate

			Olz: 1.39 *Ari:* 1.45 *No treatment:* 1.36		

1.6 NUTRITIONAL INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF ADULTS WITH BIPOLAR DISORDER

Reference to included study:

Cheema N, Frangou S, McCrone P. Cost-effectiveness of ethyleicosapentaenoic acid in the treatment of bipolar disorder. Therapeutic Advances in Psychopharmacology. 2013;3:73-81.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Cheema and colleagues (2013) UK Cost-utility analysis	Interventions: Ethyl-eicosapentaenoic acid adjunctive to mood stabilisers (ethyl-EPA) Placebo adjunctive to mood stabilisers	Population: Adults with bipolar I disorder in a stable (euthymic) state Study design: Decision analytic modelling Source of effectiveness data: Double-blind placebo-controlled RCT (FRANGOU2006) and further assumptions Source of resource use data: RCT and further assumptions Source of unit cost data: Published national sources	Costs: *Direct medical:* inpatient and outpatient care (psychiatric and non-psychiatric), emergency clinic, accident and emergency, day centre, day hospital, depot clinic, physician, psychologist, community psychiatric nurse, community nurse, GP, occupational therapist, social worker, sheltered workshop, work rehabilitation, home help, befriender, informal carer, ethyl-EPA Primary outcome: QALYs Costs and outcomes for each intervention not reported	Ethyl-EPA dominant Results robust to various parameters tested in sensitivity analysis	Perspective: NHS and PSS Currency: UK£ Cost year: 2008/9 Time horizon: 1 year Discounting: NA Applicability: Directly applicable Quality: Very serious limitations Efficacy data for ethyl-EPA were based on a 12-week RCT of adults with bipolar depression, NOT adults in a stable state; cost and effectiveness data from the RCT were extrapolated to stable adults with bipolar disorder experiencing acute episodes, over 1 year; efficacy of ethyl-EPA in reducing depressive symptoms over 12 weeks was assumed to correspond to efficacy in preventing acute manic and depressive episodes over 1 year

1.7 PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS FOR ADULTS WITH BIPOLAR DISORDER

References to included studies:

1. Lam DH, McCrone P, Wright K, Kerr N. Cost-effectiveness of relapse-prevention cognitive therapy for bipolar disorder: 30-Month study. British Journal of Psychiatry. 2005;186:500-06.
2. Scott J, Colom F, Popova E, Benabarre A, Cruz N, Valenti M, et al. Long-term mental health resource utilization and cost of care following group psychoeducation or unstructured group support for bipolar disorders: a cost-benefit analysis. Journal of Clinical Psychiatry. 2009;70:378-86

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Lam and colleagues (2005) UK Cost-effectiveness analysis	Intervention: Cognitive behavioural therapy (CBT) added to standard care (14 sessions on average for 6 months and two booster sessions for the following 6 months) Comparator: Standard care (mood stabilisers at a recommended level and regular psychiatric outpatient follow-up)	Population: Adult outpatients with bipolar I disorder aged 18–70 years, without a bipolar episode at enrolment, who experienced frequent relapses despite the prescription of commonly used mood stabilisers Study design: RCT (N = 101) (LAM2003) Source of effectiveness data: RCT (N = 101) Source of resource use	Costs: *Direct health and social services:* • Hospital care: inpatient (psychiatric and general), outpatient, day hospital, accident and emergency • Staff: psychiatrists, GPs, psychologists, social workers, counsellors, other therapists • Community mental healthcare, day centres • Residential care, support groups • Medication Mean cost per person: ***12 months:*** *CBT:* £4,383 (SD £5,264) *Standard care:* £5,356 (SD £6,599) ***30 months:*** *CBT:* £10,352 (SD £13,464) *Standard care:* £11,724 (SD £12,061) (differences not statistically significant) Primary outcome: Mean number of days in / free from bipolar episodes	CBT added to standard care dominated standard care alone Probabilistic analysis: Probability of CBT being cost-effective 0.85 at 12 months and 0.80 at 30 months, at a zero willingness to pay per additional day free from bipolar episodes Probability of CBT being cost-effective 0.90 at 12 months and 0.85 at 30 months, at a £10 willingness to pay per additional day free from bipolar episodes	Perspective: NHS and social care Currency: UK£ Cost year: 1999/2000 Time horizon: 12 and 30 months Discounting: Not undertaken Applicability: Directly applicable Quality: Minor limitations

		<u>data:</u> RCT (N = 91 for 12 months and N = 83 Ffor 30 months), based on self report and hospital records <u>Source of unit cost data:</u> National sources	per person <u>Mean number of days in bipolar episodes per person:</u> *12 months:* CBT: 26.6 (SD 46.0) Standard care 88.4 (SD 108.9) *30 months:* CBT: 95.3 (SD 152.1) Standard care: 201.0 (SD 95.3) (differences statistically significant)		

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Scott and colleagues (2009) Spain Cost consequence analysis	Intervention: Group psychoeducation (up to 21 sessions over 6 months) Comparator: Unstructured group support	Population: Adults with bipolar disorder type I or II aged 18–65 years, with at least 6 months of euthymia prior to entering the study Study design: RCT (N = 120) (COLOM2003A) Source of effectiveness data: RCT Source of resource use data: RCT based on self report and hospital records Source of unit cost data: \hospital and other published sources	Costs: *Direct healthcare:* Inpatient, outpatient, emergency visits, medication, laboratory testing, group and individual psychological therapy Mean cost per person: *Group psychoeducation:* €17,582 (SD €16,395) *Unstructured group support:* €20,909 (SD €17,392) (p > 0.05) Primary outcomes: • Number of people experiencing at least one relapse • Mean number of relapses per person • Mean number of days in episode per person Number of people experiencing a relapse: *Group psychoeducation:* 51 (85%) *Unstructured group support:* 57 (95%) (p > 0.05) Mean number of relapses per person: *Group psychoeducation:* 3.86 (SD 4.18) *Unstructured group support:* 8.37 (SD 6.02) (p < 0.05) Mean number of days in acute episode per person: *Group psychoeducation:* 154.73 *Unstructured group support:* 586.45 (p = 0.01)	Group psychoeducation dominant (significantly more effective at no extra cost)	Perspective: Healthcare system Currency: Euros (€) Cost year: Not reported, likely 2006 Time horizon: 5.5 years (6 months of intervention plus 5 years post-intervention) Discounting: Not undertaken Applicability: Partially applicable Quality: Minor limitations

1.8 PHARMACOLOGICAL INTERVENTIONS FOR MANIA, HYPOMANIA AND MIXED EPISODES IN CHILDREN AND YOUNG PEOPLE WITH BIPOLAR DISORDER

Reference to included study:

Uttley L, Kearns B, Ren S, Stevenson M. Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar I disorder in children and adolescents: a NICE single technology appraisal. PharmacoEconomics. 2013;31:981-90.

Study ID **Country** **Study type**	**Intervention details**	**Study population** **Study design** **Data sources**	**Costs: description and values** **Outcomes: description and values**	**Results: Cost-effectiveness**	**Comments**
Uttley and colleagues (2013) UK Cost-utility analysis	Interventions: ***Four drug sequences:*** *Strategy 1:* Risperidone, quetiapine, olanzapine, lithium *Strategy 2:* Risperidone, aripiprazole, quetiapine, lithium *Strategy 3:* Aripiprazole, risperidone, quetiapine, lithium *Strategy 4:* Risperidone, quetiapine, aripiprazole, lithium	Population: Young people aged 15 years with bipolar I disorder experiencing an acute manic or mixed episode Study design: Decision analytic modelling Source of effectiveness data: Network meta-analysis of published and unpublished RCTs (four studies) Source of resource use data: Expert opinion Source of unit cost data: National sources	Costs: *Direct medical:* inpatient and out-of-hospital care, medication, treatment of side effects Mean cost per person: *Strategy 1:* £75,066 *Strategy 2:* £74,133 *Strategy 3:* £74,379 *Strategy 4:* £74,888 Primary outcome: QALY Mean QALYs per person: *Strategy 1:* 2.51637 *Strategy 2:* 2.52466 *Strategy 3:* 2.52348 *Strategy 4:* 2.52297	Strategy 2 dominates all other options Results very sensitive to consideration of personalised medicine, reflected in small changes (1-2%) in costs and QALYs (Strategy 2 becomes dominated by all other strategies)	Perspective: NHS and PSS Currency: UK£ Cost year: 2011 Time horizon: 3 years Discounting: Not reported but likely 3.5% Applicability: Directly applicable Quality: Potentially serious limitations; efficacy data on aripiprazole taken from RCT with participants potentially different from typical UK paediatric population with bipolar I disorder (US population of low mean age; high prevalence of comorbid attention deficit hyperactivity disorder; suicidal children and adolescents excluded; percentage of hospitalisation unknown)