

APPENDIX 33: HEALTH ECONOMICS – ECONOMIC EVIDENCE PROFILES

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Abbreviations

CBT	cognitive behavioural therapy
GDG	Guideline Development Group
HAM-D	Hamilton Rating Scale for Depression
HCHS	hospital and community health service
ICER	incremental cost-effectiveness ratio
MDQ	Mood Disorder Questionnaire
MRS	Mania Rating Scale
N/A	not applicable
NHS	National Health Service
NNT	number needed to treat
PPP	purchasing power parities
PSS	personal social services
QALY	quality-adjusted life year
RCT	randomised controlled trial
SF(-6D, -36)	Short Form Questionnaire (-6 Dimensions, -36 items)
WTP	willingness to pay
XR	extended release
YMRS	Young Mania Rating Scale

1.1 CASE IDENTIFICATION AND ASSESSMENT OF ADULTS WITH BIPOLAR DISORDER

1.1.1 Clinical/economic question: Mood Disorder Questionnaire (MDQ) versus no screening for identification of adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Menzin and colleagues (2009) US	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 5 years • Population: adults presenting for the first time with symptoms of major depressive disorder in primary care • Measure of outcome: number of correctly diagnosed people • Model-based 	£1,491	38 per 1000 people screened	MDQ dominant	<p>Probability of MDQ being cost-saving: 76%</p> <p>Results robust under various alternative scenarios considering different prevalence of bipolar disorder, sensitivity/specificity, time horizon, treatment costs, and so on</p>

1. Costs converted and uplifted to 2014 UK pounds, using purchasing power parities (PPP) exchange rates (<http://www.oecd.org/std/ppp>) and the UK hospital and community health service (HCHS) inflation index.
2. Measure of outcome people correctly diagnosed, efficacy data based on literature review and further assumptions, resource use based on published literature.
3. US study, third party payer perspective, no quality-adjusted life years (QALYs) estimated but intervention dominant according to the outcome measure used.

1.1.2 Pharmacological interventions for mania, hypomania and mixed episodes in adults with bipolar disorder

Clinical / economic question: olanzapine versus valproate semisodium for adults with mania

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Revicki and colleagues (2003) US	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 12 weeks • Alongside randomised controlled trial (RCT) • Olanzapine now available in generic form • Outcomes: clinical improvement based on Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia-Change Version and the Hamilton Rating 	£1,935	Similar effects between drugs	N/A	Differences in costs and outcomes not statistically significant

			Scale For Depression; health-related quality of life based on Quality of Life Enjoyment and Satisfaction Questionnaire and restricted activity days				
Zhu and colleagues (2005) US	Potentially serious limitations ⁴	Partially applicable ⁵	<ul style="list-style-type: none"> • Time horizon: 47 weeks • Alongside RCT • Olanzapine now available in generic form • Outcomes: clinical improvement based on YMRS and rate of symptom remission (YMRS ≤ 12) at 3 weeks (acute phase); median time to remission of manic symptoms 	-£833	Better effects for olanzapine		Difference in costs statistically non-significant; differences in outcomes statistically significant
Bridle and colleagues (2004) UK	Potentially serious limitations ⁶	Partially applicable ⁷	<ul style="list-style-type: none"> • Time horizon: 3 weeks • Model-based analysis • Drugs included: olanzapine, haloperidol, lithium, quetiapine, valproate • Olanzapine now available in generic form • Outcome: number of responders 	£32	90 per 1,000 people	≈£351/additional responder	Comparison not relevant as valproate dominated by haloperidol; probability of cost effectiveness at willingness to pay (WTP) £20,000 per additional responder: olanzapine 0.44; valproate 0.01
Guideline economic analysis UK	Potentially serious limitations ⁸	Partially applicable ⁹	<ul style="list-style-type: none"> • Time horizon: 3 weeks • Model-based analysis • Drugs included: aripiprazole, asenapine, carbamazepine, olanzapine, risperidone, lithium, haloperidol, quetiapine, valproate • Outcomes: YMRS change scores, number of responders, QALYs 	-£19	0.0008 QALYs Better effect for olanzapine in other outcomes	Olanzapine dominant	Not examined

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (<http://www.oecd.org/std/ppp>) and the UK HCHS inflation index.
2. Resource use estimates based on RCT and further assumptions, health-related quality of life and resource use data collected via telephone interviews, funded by industry.
3. US study, cost consequence analysis, no QALYs measured.
4. Resource use estimated only for people who entered maintenance phase, funded by industry.
5. US study, cost consequence analysis, no QALYs measured.
6. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on assumptions and information from manufacturers.
7. UK study, National Health Service (NHS) and personal social services (PSS) perspective, but lack of QALYs makes judgements on relative cost effectiveness difficult.
8. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on Guideline Development Group (GDG) expert opinion.
9. UK analysis, NHS and PSS perspective, QALYs estimated based on vignette-based descriptions, valued by US outpatients with bipolar disorder.

Clinical / economic question: quetiapine versus usual care for adults with mania

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Caro and colleagues (2006) US	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 100 days • Model-based analysis • Quetiapine now available in generic form • Outcomes: % of people responding at 21 days and remitting at 84 days 	-£1,157	Better effects for quetiapine	Quetiapine dominant	Results sensitive to drug prices, discharge criteria and side-effect management costs

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (<http://www.oecd.org/std/ppp>) and the UK HCCHS inflation index.
2. Clinical and resource use data based on a literature review and administrative databases, funded by industry.
3. US study, cost consequence analysis, no QALYs measured, usual care may not reflect routine clinical care in the UK.

Clinical / economic question: various pharmacological interventions for adults with mania

Study Country	Limitations	Applicability	Other comments	Incremental cost versus valproate ¹	Incremental effect versus valproate	ICER (£/effect)	Uncertainty
Bridle and colleagues (2004) UK	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 3 weeks • Model-based analysis • Olanzapine and quetiapine now available in generic form • Outcome: number of responders 	Olanzapine: £32 Haloperidol: -£132 Lithium: £33 Quetiapine: £37	Extra responders per 1000 people: Olanzapine: 90 Haloperidol: 70 Lithium: 50 Quetiapine: 20	Lithium, valproate and quetiapine dominated by haloperidol Olanzapine versus haloperidol: £10,560 per extra responder	Probability of cost effectiveness at WTP £20,000 per extra responder: Olanzapine: 0.44 Haloperidol: 0.37 Lithium: 0.16 Quetiapine: 0.02 Valproate: 0.01 Results robust under alternative scenarios
Guideline economic analysis UK	Potentially serious limitations ⁴	Partially applicable ⁵	<ul style="list-style-type: none"> • Time horizon: 3 weeks • Model-based analysis • Outcomes: YMRS change scores, number of responders, QALYs 	Carbamazepine: -£14 Haloperidol: -£16 Olanzapine: -£19 Risperidone: -£20 Quetiapine: -£17 Aripiprazole: £52 Lithium: -£12 Asenapine: £51	QALYs: Carbamazepine: 0.0022 Haloperidol: 0.0012 Olanzapine: 0.0008 Risperidone: 0.0006 Quetiapine: 0 Aripiprazole: 0 Lithium: -0.0009 Asenapine: -0.0016	(using QALYs) Carbamazepine versus risperidone £3,842/QALY – all other drugs dominated by absolute or extended dominance Carbamazepine not cost effective using YMRS change score	Not examined

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on assumptions and information from manufacturers.
3. UK study, NHS and PSS perspective, lack of QALYs makes judgements on relative cost effectiveness difficult.
4. Short time horizon, side effects not considered, all people assumed to be hospitalised over the time horizon of the analysis, resource use estimates based on GDG expert opinion.
5. UK study, NHS and PSS perspective, QALY estimates based on vignette-based descriptions valued by US outpatients with bipolar disorder.

1.1.3 Pharmacological interventions for acute depression in adults with bipolar disorder

Clinical / economic question: various drugs for adults with acute depression

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect (QALY)	ICER (£/QALY)	Uncertainty
Guideline economic analysis UK	Minor limitations ²	Directly applicable ³	<ul style="list-style-type: none"> • Time horizon: 18 weeks • Model-based analysis • Outcome: QALYs 	Versus placebo: Valproate: -£87 Fluoxetine and olanzapine: -£143 Quetiapine: -£95 Olanzapine: -£58 Lithium: £123 Lamotrigine: -£38 Paroxetine: -£30 Imipramine: £14 Moclobemide: £117	Versus placebo: Valproate: 0.031 Fluoxetine and olanzapine: 0.027 Quetiapine: 0.023 Olanzapine: 0.020 Lithium: 0.019 Lamotrigine: 0.018 Paroxetine: 0.017 Imipramine: 0.015 Moclobemide: 0.010	Valproate versus Fluoxetine and olanzapine: £16,572 All other interventions dominated	Probability of valproate being cost-effective at £20,000/QALY: 0.47 After excluding valproate: probability of fluoxetine and olanzapine being cost-effective at £20,000/QALY: 0.73 Results robust under alternative scenarios

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy data based on systematic review and network meta-analysis, side effects indirectly considered through discontinuation, relatively short time horizon, resource use estimates based on national sources, other published data and GDG expert opinion.
3. UK study, NHS and PSS perspective, QALYs estimated based on the European Quality of Life-5 Dimensions (all states except mania) and vignette-based descriptions, valued by US outpatients with bipolar disorder (mania).

1.1.4 Services for adults with bipolar disorder

Clinical / economic question: mood disorder clinic versus standard care for adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Kessing and colleagues (2013) Denmark	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 2 years • Alongside RCT • Measure of outcome: rate of first readmission to hospital 	-£2,990	-18.6%	Mood disorder clinic dominant	<p>Mood disorder clinic showed significantly better outcome</p> <p>Cost results sensitive to intervention costs and length of hospital re-admission</p>

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (<http://www.oecd.org/std/ppp>) and the UK HCHS inflation index.
2. Measure of outcome rate of first readmission to the hospital, resource use estimates based on RCT, published literature and further assumptions, statistical analysis done only for clinical outcomes; sensitivity analysis done only regarding cost results.
3. Danish study, no QALYs estimated but intervention dominant according to the outcome measure used.

1.1.5 Pharmacological interventions for the long-term management of adults with bipolar disorder

Clinical / economic question: lithium versus no pharmacological treatment for the long-term management of adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Guideline economic analysis UK	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 1 year • Model-based analysis • Cost analysis 	<p>Intervention: £734</p> <p>Savings per relapse averted: £6,714</p> <p>Number needed to treat (NNT) for lithium to become cost-neutral: 9</p>	NA	NA	NNT for lithium to become cost-neutral became 15 after considering a higher preventative effect of lithium for mania

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Effects not considered due to heterogeneity across studies, side effects considered in a narrative analysis, resource use estimates based on GDG expert opinion.
3. UK cost analysis, NHS and PSS perspective, threshold analysis undertaken to reveal the NNT required for lithium to be cost-neutral.

Clinical / economic question: valproate semisodium versus lithium for the long-term management of adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Revicki and colleagues (2005) US	Potentially serious limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 1 year • Alongside pragmatic trial • Outcomes: Number of months without acute symptoms; mental and physical component summary scores of Short Form Questionnaire-36 items (SF-36), Mental Health Index-17 item, disability days; adverse events and continuation rates 	-£1,935	Similar effects between drugs	N/A	Differences in costs and outcomes not statistically significant

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (<http://www.oecd.org/std/ppp>) and the UK HCHS inflation index.
2. Pragmatic trial, resource use data based on trial and further assumptions, health-related quality of life and resource use data collected via telephone interviews, funded by industry.
3. US study, cost consequence analysis, no QALYs measured.

Clinical / economic question: olanzapine versus lithium for the long-term management of adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
McKendrick and colleagues (2007) UK	Potentially serious limitations ²	Directly applicable ³	<ul style="list-style-type: none"> • Time horizon: 1 year • Model-based study • Olanzapine now available in generic form • Outcome: Number of acute episodes averted 	-£1,109	0.23	Olanzapine dominant	Results most sensitive to risk, length and cost of hospitalisation for mania, and time horizon; results ranging from olanzapine being dominant to ICER of olanzapine versus lithium £365 /acute episode avoided

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy data based on an RCT, resource use data based on UK chart review and other published sources, costs of side effects not considered, funded by industry.
3. UK study, NHS and PSS perspective, QALYs not estimated but intervention was dominant so lack of QALYs did not affect conclusions.

Clinical / economic question: quetiapine (extended release [XR]) adjunctive to mood stabiliser versus mood stabiliser alone for the long-term management of adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Fajutrao and colleagues (2009) UK	Potentially serious limitations ²	Directly applicable ³	<ul style="list-style-type: none"> • Time horizon: 2 years • Model-based analysis • Quetiapine now available as generic • Outcome: QALY (+ other outcomes) • Comparator: mood stabiliser alone 	-£601	0.07	Quetiapine + mood stabiliser dominant	Results most sensitive to risk and length of hospitalisation, cost of hospital stay, and quetiapine acquisition cost
Woodward and colleagues (2009) US	Potentially serious limitations ⁴	Partially applicable ⁵	<ul style="list-style-type: none"> • Time horizon: 2 years • Model-based analysis • Quetiapine now available as generic • Outcome: QALY (+ other outcomes) • Comparator: mood stabiliser alone 	-£5	0.05	Quetiapine + mood stabiliser dominant	Results most sensitive to cost of quetiapine, risk, length and cost of hospitalisation especially for mania
Woodward and colleagues (2010) US	Potentially serious limitations ⁶	Partially applicable ⁷	<ul style="list-style-type: none"> • Time horizon: 2 years • Model-based analysis • Quetiapine XR • Comparator: mood stabiliser alone • Outcome: QALY (+ other outcomes) 	£857	0.05	£16,647/QALY	Results most sensitive to efficacy, utility for euthymia, cost of quetiapine XR, risk, length and cost of hospitalisation for mania

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (<http://www.oecd.org/std/ppp>) and the UK HCHS inflation index.
2. Efficacy data pooled from two RCTs, resource-use estimates based on expert opinion based on published guidelines, costs of side effects not included, results of sensitivity analysis insufficiently reported, funded by industry.
3. UK study, NHS and PSS perspective, QALYs estimated based on SF-36 unpublished data and using the Short Form Questionnaire-6 Dimensions (SF-6D) logarithm.
4. Efficacy data pooled from 2 RCTs, resource use estimates based on published data and further assumptions, costs of side effects not included, results of sensitivity analysis insufficiently reported, funded by industry.
5. US study, QALYs estimated based on SF-36 unpublished data and using the SF-6D logarithm.
6. Efficacy data for quetiapine pooled from 2 RCTs for quetiapine and NOT quetiapine XR, other efficacy data from published literature identified via a non-systematic review, other comparisons available but evidence synthesis inappropriate due to different study designs, resource use estimates based on published data and further assumptions, costs of side effects not included, funded by industry.
7. US study, QALYs estimated based on SF-36 unpublished data and using the SF-6D logarithm.

Psychological and psychosocial interventions for adults with bipolar disorder

Clinical / economic question: cognitive behavioural therapy (CBT) plus standard care versus standard care alone for adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Lam and colleagues (2005) UK	Minor limitations ²	Directly applicable ³	<ul style="list-style-type: none"> • Time horizon: 30 months • Alongside RCT • Outcome: number of days free from episode 	-£2,156	106	CBT plus standard care dominant	Probability of CBT being cost-effective 0.80 at WTP zero; 0.85 at WTP £10 per additional day free from episode

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy and resource use data based on RCT, resource use data taken from hospital records and self-reports, sufficient time horizon, appropriate statistical and sensitivity analysis
3. UK study, NHS and PSS perspective, no QALYs estimated but intervention dominant according to the outcome measure used

Clinical / economic question: Group psychoeducation versus unstructured group support for adults with bipolar disorder

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect	ICER (£/effect)	Uncertainty
Scott and colleagues (2009) Spain	Minor limitations ²	Partially applicable ³	<ul style="list-style-type: none"> • Time horizon: 5.5 years • Alongside RCT • Outcome: number of relapses per person and number of days free from episode per person 	-£3,087	Number of relapses: -2.16 Number of days in episode: -432	Group psychoeducation dominant	Significant difference in outcomes Non-significant difference in costs

1. Costs converted and uplifted to 2014 UK pounds, using PPP exchange rates (<http://www.oecd.org/std/ppp>) and the UK HCHS inflation index.
2. Efficacy and resource use data based on RCT, resource use data taken from hospital records and self-reports, sufficient time horizon, appropriate statistical analysis.
3. Spanish study, no QALYs estimated but intervention dominant according to the outcome measure used.

1.1.6 Pharmacological interventions for mania, hypomania and mixed episodes in children and young people with bipolar disorder

Clinical / economic question: aripiprazole included in pharmacological strategies for adolescents with mania

Study Country	Limitations	Applicability	Other comments	Incremental cost ¹	Incremental effect (QALY)	ICER (£/QALY)	Uncertainty
Uttley and colleagues (2013) UK	Potentially serious limitations ²	Directly applicable ³	<ul style="list-style-type: none"> • Time horizon: 3 years • Model-based analysis • Outcome: QALYs • Four strategies: <ul style="list-style-type: none"> • <i>Strategy 1 (S1):</i> Risperidone-quetiapine-olanzapine-lithium • <i>Strategy 2 (S2):</i> Risperidone-aripiprazole-quetiapine-lithium • <i>Strategy 3 (S3):</i> Aripiprazole-risperidone-quetiapine-lithium • <i>Strategy 4 (S4):</i> Risperidone-quetiapine-aripiprazole-lithium 	Versus S1: S2: -£933 S3: -£687 S4: -£178	Versus S1: S2: 0.0083 S3: 0.0071 S4: 0.0066	S2 dominant	Results very sensitive to consideration of personalised medicine, reflected in small changes (1-2%) in costs and QALYs (S2 becomes dominated by all other strategies)

1. Costs uplifted to 2014 UK pounds using the HCHS inflation index.
2. Efficacy data taken from network meta-analysis of published and unpublished data, resource use estimates based mainly on expert opinion, funded by industry but reviewed by independent panel, high uncertainty of the results.
3. UK study, NHS and PSS perspective, QALYs estimated based mostly on European Quality of Life-5 Dimensions (outpatient depression) and vignette-based descriptions.