Study ID Country Type of evaluation QHES score	Population Setting	Treatment options	Study design Type of model (if applicable) Time horizon Discounting Main events /states (model- based studies) d cycling in adults with bipolar of	Primary measure(s) of outcome Source of • efficacy data • utility data (if applicable)	Perspective Cost categories Source of • resource use • unit costs Funding
Bridle et	Adults with BD		Decision modelling	Probability of response (≥ 50%	UK NHS
al., 2004	in an acute	<ul> <li>Que</li> <li>Olz</li> </ul>		reduction in YMRS)	
al., 2004 [19] UK	manic episode Hospital	• Val • Li	Decision-tree	SR & NMA (7 studies)     NA	Medication, laboratory testing, inpatient care (same across all arms)
UK	setting	• Hal	NA	• NA	<ul> <li>Expert opinion, information from</li> </ul>
CEA					manufacturers and further assumptions
75			Response		National sources
					HTA Programme on behalf of NICE
Caresano et al., 2014	Adults with BD I in an acute	<ul><li>Ase</li><li>Olz</li></ul>	Decision modelling	QALY (clinical outcome measured as response, defined	Italian NHS
[20]	mixed episode	• 012	Decision-tree followed by Markov model	as ≥50% change on YMRS and MADRS)	Medication, laboratory testing, inpatient care, GP and specialist visits, day hospital,
Italy	Hospital and				treatment of side effects
CUA	outpatient setting		9 weeks acute phase + 5 years maintenance phase	<ul> <li>Post-hoc analysis of 2 RCTs &amp; further assumptions,</li> </ul>	<ul> <li>Published literature and expert opinion</li> </ul>
	0		3.5% per year	published meta-analyses	National sources
87			Response, acute, sub-acute & euthymic phase, treatment discontinuation, relapse to manic, mixed or depressive episode, side effects (EPS, weight gain), death	Published [39;40;43] and unpublished utility data; further modifications	Lundbeck Italy SpA

## Table 1. Overview of methods of published economic evaluations of pharmacological interventions for bipolar disorder

Study ID	Population	Treatment options	Study design	Primary measure(s) of outcome	Perspective
Country	Setting		Type of model (if applicable)		Cost categories
	-		<u> </u>	Source of	
Type of			Time horizon	efficacy data	Source of
evaluation			Discounting	<ul> <li>utility data (if applicable)</li> </ul>	resource use
QHES			Main events /states (model-		• unit costs
score			based studies)		Funding
Klok et al.,	Adults with BD	Que	Decision modelling	Probability of major side effects	Healthcare provider
2007	in an acute	• Li		(EPS & weight gain); length of	
[21]	manic episode	• Val	DES	hospital stay; probability of	Medication, laboratory testing, inpatient and
<b></b> .		<ul> <li>Que+Li</li> </ul>		response	outpatient care, treatment of side effects (EPS,
The	Hospital and	<ul> <li>Olz+Li</li> </ul>	100 days		constipation, nausea, vomiting, diarrhoea),
Netherland	outpatient	<ul> <li>Ris+Li</li> </ul>	NA	Comparison of 4 RCTs of Que alone or in combination and	suicide
S	setting	Plc	Compliance, response,	other RCTs: efficacy (change	<ul> <li>Unclear; some data based on RCTs</li> </ul>
CEA			remission, hospital discharge,	on YMRS) assumed to be the	<ul> <li>National sources and published literature</li> </ul>
0 = / 1			side effects, death	same across all interventions	
38				• NA	Astra Zeneca
Namjoshi	Adults with BD	<ul> <li>Olz 5–20 mg/day</li> </ul>	Double-blind RCT (N=139)	Clinical improvement based on	3rd party payer
et al., 2002	I, experiencing	<ul> <li>Plc / no treatment</li> </ul>	followed by a 49-week open	YMRS; HRQoL based on SF-36.	
[22]	an acute		label extension		Medication, day hospital, inpatient care,
	manic or		N10	RCT (available data on	outpatient contacts with health professionals
US	mixed episode		NA	n=139) followed by a 49-week open label extension	(psychiatrists, psychologists, other physicians, social workers), case management, home
CCA	Hospital		3 weeks	(available resource use data	care, emergency room visits
	setting		NA	on n=76)	
59	followed by			• NA	• Before-after study (n=76) by comparing cost
	outpatient care		NA		data from the open label extension with 12- month pre-randomisation data
					National and local sources
					Eli Lilly & Company

Study ID	Population	Treatment options	Study design	Primary measure(s) of outcome	Perspective					
Country	Setting		Type of model (if applicable)	oucome	Cost categories					
-	-			Source of	-					
Type of			Time horizon	<ul> <li>efficacy data</li> </ul>	Source of					
evaluation			Discounting	<ul> <li>utility data (if applicable)</li> </ul>	resource use					
0					unit costs					
QHES			Main events /states (model-							
score			based studies)		Funding					
Revicki et	Adults aged	<ul> <li>Val 20 mg /kg/day</li> </ul>	Double-blind, multi-centre RCT	Clinical improvement based on	Likely 3rd party payer (NR)					
al., 2003	18-65 years,	<ul> <li>Olz 10–20 mg/day</li> </ul>	(21 US sites, N=120)	MRS from the SADS Change						
[23]	with BD I,		NA	Version and the HAM-D; HRQoL	Medication, inpatient care, physicians' fee,					
US	experiencing an acute		NA	based on Q-LES-Q and restricted activity days.	emergency room, psychiatric, physician, psychologist or other mental health provider					
03	manic episode		12 weeks	restricted activity days.	visits, home visits					
CCA	manic episode		NA	<ul> <li>RCT (available data on n=52)</li> </ul>						
OOA	Hospital			<ul> <li>NA</li> </ul>	<ul> <li>RCT (available data on n=52) and further</li> </ul>					
49	setting		NA		assumptions					
	followed by				National sources					
	outpatient care									
					Abbott Laboratories					
Sawyer et	Adults with BD	Ase	Decision modelling	QALY (clinical outcome	UK NHS & PSS					
al., 2014	I in an acute	• Olz	_	measured as response, defined						
[24]	mixed episode		Decision-tree followed by	as ≥50% change on YMRS and	Medication, laboratory testing, inpatient and					
			Markov model	MADRS)	outpatient care, crisis resolution team,					
UK	Hospital and				treatment of side effects					
	outpatient		9 weeks acute phase + 5	Post-hoc analysis of 2 RCTs						
CUA	setting		years of maintenance phase	• Published [39;40;43] and	Published literature and expert opinion					
87			3.5% per year	unpublished utility data &	<ul> <li>National sources</li> </ul>					
07			Response, acute, sub-acute	further modifications	Lundbeck SAS					
			and euthymic phase, treatment		Lunubeck SAS					
			discontinuation, relapse to							
			manic, mixed or depressive							
			episode, side effects (EPS,							
			weight gain), death							
Managemer	t of manic, hypo	manic and/or mixed en	sodes in children and young pe	onle with hinolar disorder						
manayenner	n or marrie, nypo	manne anu/or mixeu ep	soues in children and young pe	Management of manic, hypomanic and/or mixed episodes in children and young people with bipolar disorder						

Study ID Country Type of evaluation	Population Setting	Treatment options	Study design Type of model (if applicable) Time horizon Discounting	Primary measure(s) of outcome Source of • efficacy data • utility data (if applicable)	Perspective Cost categories Source of • resource use
QHES score			Main events /states (model- based studies)		• unit costs Funding
Uttley et al., 2013 [25] (refers to NICE TA 292) UK CUA 92	Young people aged 15 years with BD I experiencing an acute manic or mixed episode Inpatient and outpatient setting	<ul> <li>Drug sequences:</li> <li>Strategy 1: Ris, Que, Olz, Li</li> <li>Strategy 2: Ris, Ari, Que, Li</li> <li>Strategy 3: Ari, Ris, Que, Li</li> <li>Strategy 4: Ris, Que, Ari, Li</li> </ul>	Decision modelling Markov model 3 years 3.5% per year Response, euthymia, therapy resistance, side effects, death	QALY NMA of published and unpublished RCTs (4 studies) Published utility studies [39;40;42-45] identified in a SR	<ul> <li>UK NHS &amp; PSS</li> <li>Medication, inpatient and outpatient care, treatment of side effects implicitly included</li> <li>Expert opinion <ul> <li>National sources</li> </ul> </li> <li>Otsuka Pharmaceuticals submission to NICE; reviewed &amp; supplemented with extra analyses by independent Evidence Review Group</li> </ul>
		pisodes in adults with			
Ekman et al., 2012 [18] UK CUA 73	Adults aged 40 years with BD I or II in an acute depressive episode Outpatient setting – hospitalisation possible	<ul> <li>Que</li> <li>Que+ MS (Li or Val)</li> <li>Olz</li> <li>Olz+Li, Olz replaced by Ven in acute depression [Olz+Li1]</li> <li>Olz+Li, Olz replaced by Par in acute depression [Olz+Li2]</li> <li>Ari replaced by Olz+Ven in acute depression</li> <li>Ris in mania, Ven+Li in depression, Olz in maintenance [Mixed]</li> </ul>	Decision modelling DES 5 years 3.5% per year Remission (stable state), relapse to manic or depressive episode, treatment discontinuation, side effects (EPS, weight gain), death	<ul> <li>QALY</li> <li>Indirect comparisons between drugs, using Plc or Li as common comparator, based on RCTs and published meta-analyses</li> <li>Published utility studies [39;40;46] and further assumptions</li> </ul>	<ul> <li>UK NHS (societal in sensitivity analysis)</li> <li>Medication, laboratory testing, inpatient &amp; outpatient care, crisis teams, staff costs (senior house officer, GP, community psychiatric nurse, practice nurse, dietician), treatment of side effects</li> <li>Clinical guidelines mainly based on expert opinion</li> <li>National sources</li> <li>AstraZeneca Pharmaceuticals LP</li> </ul>

Study ID	Population	Treatment options	Study design	Primary measure(s) of outcome	Perspective
Country	Setting		Type of model (if applicable)	Source of	Cost categories
Type of			Time horizon	efficacy data	Source of
evaluation			Discounting	<ul> <li>utility data (if applicable)</li> </ul>	resource use
			3		• unit costs
QHES			Main events /states (model-		
score			based studies)		Funding
Rajagopala	Adults with BD	● Lur	Decision modelling	Percentage of patients achieving	3 <sup>rd</sup> party payer
n et al.,	I in an acute	<ul> <li>Que XR</li> </ul>		remission (MADRAS total score	
2015	depressive		Decision-tree	≤12 by weeks 6–8)	Medication, inpatient and outpatient care,
[26]	episode				emergency department visits
				<ul> <li>Adjusted indirect comparison</li> </ul>	
USA	Outpatient		3 months	of pivotal RCTs using Plc as	<ul> <li>Published expert panel data &amp; a</li> </ul>
	setting -		NA	common comparator	retrospective database study
CEA	hospitalisation				National sources
	possible		Remission		
75					Sunovion Pharmaceuticals Inc.
Maintenance	e treatment of ad	ults with bipolar disord	er		
Calvert et	Adults with BD	• Lam	Decision modelling	Number of acute episodes	3 <sup>rd</sup> party payer
al.,	I stabilised	• Li		avoided; number of euthymic	
2006	after resolution	• Olz	Markov model	days achieved; QALY	Medication, laboratory testing, physician's
[27]	of a mixed or	<ul> <li>Plc/no treatment</li> </ul>			time, hospitalisation
	manic episode			<ul> <li>Indirect comparisons using</li> </ul>	
USA			18 months	double-blind placebo-	<ul> <li>Published data, clinical guidelines based on</li> </ul>
	Outpatient		NA	controlled RCTs	expert opinion and a physician survey
CEA &	setting –			<ul> <li>Pivotal RCTs [unpublished</li> </ul>	<ul> <li>National sources</li> </ul>
CUA	hospitalisation		Euthymia, acute mania or	data on SF-36] & further	
	possible		depression, treatment	modifications	GlaxoSmithKline (GSK)
53			discontinuation		
Ekman et	Adults aged 40	See Ekman et al.	See Ekman et al. 2012, under	See Ekman et al. 2012, under	See Ekman et al. 2012, under 'Management of
al., 2012	years with BD	2012, under	'Management of depressive	<i>Management of depressive</i>	depressive episodes'
[18]	l or II in	Management of	episodes'	episodes'	
[10]	remission	depressive episodes'			
UK	10111001011				
U.V.	Outpatient				
CUA	setting -				
	hospitalisation				
i	nosonausanon				

Study ID	Population	Treatment options	Study design	Primary measure(s) of outcome	Perspective
Country	Setting		Type of model (if applicable)		Cost categories
				Source of	
Type of			Time horizon	efficacy data	Source of
evaluation			Discounting	<ul> <li>utility data (if applicable)</li> </ul>	resource use
					unit costs
QHES			Main events /states (model-		
score			based studies)		Funding
Fajutrao et	Adults with BD	<ul> <li>Que + MS (Li or</li> </ul>	Decision modelling	Number of acute episodes	UK NHS
al., 2009	I who remitted	Val)		avoided; % of people	
[28]	from an acute	MS (Li or Val) alone	Markov model	hospitalised due to acute	Medication, laboratory testing, staff time
	mood episode	[MS]	0	episode; QALY	(psychiatrist, senior house officer, GP,
UK	following Que+MS		2 years		community psychiatric nurse, laboratory
CEA &	treatment		3.5% per year	<ul> <li>Pooled data from 2 double-</li> </ul>	nurse), inpatient care, crisis resolution and home care
	liealment		Euthymia, acute mania or	<ul> <li>Pooled data from 2 double- blind placebo-controlled RCTs</li> </ul>	nome care
COA	Outpatient		depression, treatment	<ul> <li>Pivotal RCTs [unpublished</li> </ul>	<ul> <li>Clinical guidelines mainly based on expert</li> </ul>
72	setting –		discontinuation	data on SF-36] & further	opinion
12	hospitalisation		diocontinuation	modifications	National sources
	possible			modifications	• National Sources
	P 000.010				AstraZeneca Pharmaceuticals LP
McKendric	Adults with BD	• Olz	Decision modelling	Number of acute episodes	UK NHS
k et al.,	I newly	• Li		avoided	
2007	stabilised after		Markov model		Medication, laboratory testing, day hospital,
[29]	combination			<ul> <li>Double-blind RCT</li> </ul>	inpatient and outpatient care (GP, psychiatrist,
	treatment with		1 year	• NA	specialist non-psychiatric, case manager,
UK	Olz + Li for		NA		group therapy), home visits (nurse, social
054	acute mania				worker, physical therapist, GP), emergency
CEA	Outpatient		Euthymia, acute mania or		room visits
<u> </u>	Outpatient		depression, treatment		
69	setting –		discontinuation		UK chart review, other published sources     and expert opinion
	hospitalisation possible				and expert opinion
	hossinie				National sources
					Eli Lilly and Company Ltd
	l				

Study ID	Population	Treatment options	Study design	Primary measure(s) of outcome	Perspective
Country	Setting		Type of model (if applicable)	Source of	Cost categories
Type of			Time horizon	efficacy data	Source of
evaluation			Discounting	• utility data (if applicable)	resource use
0.1150					unit costs
QHES score			Main events /states (model- based studies)		Funding
Revicki et	Adults with BD	<ul> <li>Val 15-20 mg</li> </ul>	Pragmatic multi-centre, open-	Number of months without	Likely 3 <sup>rd</sup> party payer (NR)
al, 2005	I, following	/kg/day	label RCT, maintenance phase	depressive or manic symptoms;	
[30]	discharge after	• Li 900-1200 mg/day	(33 US sites, N=201)	functioning and HRQoL	Medication, outpatient psychiatric, physician,
USA	hospitalisation for an acute		NA	measured using the MCS and PCS scores of the SF-36, the	psychologist and other mental health provider visits, inpatient care, emergency room visits,
004	manic or			MHI-17 and a questionnaire on	home care
CCA	mixed episode		12 months following hospital	disability days; adverse events;	
			discharge	continuation rates	<ul> <li>Pragmatic RCT (n=172) and further</li> </ul>
68	Outpatient		NA		assumptions
	setting –		N14	Pragmatic trial (n=172)	<ul> <li>National sources</li> </ul>
	hospitalisation possible		NA	• NA	Abbott Laboratories
Soares-	Adults with	Car	Decision modelling	QALY	UK NHS
Weiser et	stabilised BD I.	• Imi	Decision modelling		
al., 2007	whose most	• Lam	Markov model	• SR & NMA	Medication, laboratory testing, inpatient care,
[31]	recent episode	• Li		<ul> <li>Published utility studies</li> </ul>	staff time (psychiatric consultant, senior house
	was either	• Li+lmi	Lifetime	[39;40]	officer, GP, community psychiatric nurse,
UK	depressive or	• Olz	3.5% per year		practice nurse), crisis resolution & home
CUA	manic	• Val	Euthymia, acute mania or		treatment teams
	Outpatient		depression, treatment		National guidelines based on expert opinion,
74	setting –		sequencing following		published data & further assumptions
	hospitalisation possible		treatment failure, death		National sources
					HTA Programme

Study ID	Population	Treatment options	Study design	Primary measure(s) of	Perspective
Country	Sotting		Type of model (if applicable)	outcome	Cast astagarias
Country	Setting		i ype of model (if applicable)	Source of	Cost categories
Type of			Time horizon	efficacy data	Source of
evaluation			Discounting	<ul> <li>utility data (if applicable)</li> </ul>	resource use
			5		• unit costs
QHES			Main events /states (model-		
score			based studies)		Funding
Woodward	Adults with BD	<ul> <li>Que+ MS (Li or</li> </ul>	Decision modelling	Number of acute episodes	3 <sup>rd</sup> party payer
et al., 2009	I who remitted	Val)		avoided; % of people	
[32]	from an acute	<ul> <li>MS (Li or Val) alone</li> </ul>	Markov model	hospitalised due to acute	Medication, laboratory testing, physician's
	mood episode		2 1/2017	episodes; QALY	time, hospitalisation
USA	following Que+MS		2 years 3% per year	<ul> <li>Pooled data from 2 double-</li> </ul>	<ul> <li>Published data including physician survey</li> </ul>
CEA &	treatment			<ul> <li>Pooled data from 2 double- blind placebo-controlled RCTs</li> </ul>	data, and clinical guidelines
CUA	louinon		Euthymia, acute mania or	<ul> <li>Pivotal RCTs [unpublished</li> </ul>	National sources
	Outpatient		depression, treatment	data on SF-36] & further	
77	setting –		discontinuation, death	modifications	AstraZeneca Pharmaceuticals LP
	hospitalisation				
	possible				
Woodward	Adults with BD	Que XR+MS (Li or	Decision modelling	Number of acute episodes avoided	3 <sup>rd</sup> party payer & societal
et al., 2010 [33]	I who remitted from an acute	Val)	Markov model	% of people hospitalised due to	Medication, laboratory testing, physician's
[55]	mood episode	<ul> <li>MS (Li or Val) alone</li> <li>Li</li> </ul>		acute episodes	time, hospitalisation; productivity losses
USA		• Lam	2 years	QALY	
	Outpatient	• Olz	3% per year		<ul> <li>Published data including physician survey</li> </ul>
CEA &	setting –	• Ari		<ul> <li>Pooled data from 2 double-</li> </ul>	data, and clinical guidelines
CUA	hospitalisation	<ul> <li>Pllc/no treatment</li> </ul>	Euthymia, acute mania or	blind placebo-controlled RCTs	National sources
05	possible		depression, treatment	evaluating Que (not Que XR)	
65			discontinuation, death	and other indirect	AstraZeneca Pharmaceuticals LP
				comparisons using RCTs identified via a non-systematic	
				review	
				<ul> <li>Pivotal RCTs [unpublished</li> </ul>	
				data on SF-36] & further	
				modifications	
Managemen	t of patients in a	ny phase of bipolar disc	order		

Study ID	Population	Treatment options	Study design	Primary measure(s) of outcome	Perspective
Country	Setting		Type of model (if applicable)	Source of	Cost categories
Type of evaluation			Time horizon Discounting	<ul><li>efficacy data</li><li>utility data (if applicable)</li></ul>	Source of • resource use • unit costs
QHES score			Main events /states (model- based studies)		Funding
Chisholm et al., 2005 [34] Global (14 WHO sub- regions) CUA 59	Patients with BD, in any phase of the disorder Hospital and community setting	<ul> <li>Li</li> <li>Li+PC</li> <li>Val</li> <li>Val+PC</li> <li>No treatment</li> <li>Each provided in either hospital-based or community-based setting</li> <li>[10-year treatment implementation]</li> </ul>	Decision modelling Epidemiological mathematical model – possibly individual- based Markov although not explicitly stated Lifetime 3% per year Acute mania or depression, relatively euthymic health states during which persons are non-symptomatic or symptomatic below the threshold of an acute episode, remission, death	<ul> <li>DALYs averted</li> <li>Published literature (reviews, meta-analyses, RCTs)</li> <li>Based on published evidence (WHO Global Burden of Disease study)</li> </ul>	<ul> <li>Healthcare provider</li> <li>Medication, laboratory testing, psychosocial support, primary, inpatient and outpatient care, residential care, central administration (planning, monitoring, implementation), training (adaptation of guidelines, printing of materials)</li> <li>Published empirical or modelling studies and a multinational Delphi consensus panel</li> <li>WHO sub-regional unit costs</li> <li>Funded by WHO</li> </ul>
Chisholm et al., 2012 [35] 2 WHO sub- regions: sub- Saharan Africa & South East Asia CUA 57	Patients with BD, in any phase of the disorder Hospital and community setting	<ul> <li>Li</li> <li>Li+PC</li> <li>Val</li> <li>Val+PC</li> <li>No treatment</li> <li>Each provided in either hospital-based or community-based setting</li> <li>[10-year treatment implementation]</li> </ul>	Decision modelling Epidemiological mathematical model; possibly individual- based Markov model although not explicitly stated Lifetime 3% per year Acute depression or mania, relatively euthymic health states (non-symptomatic or symptomatic below threshold for acute episode), remission, death	<ul> <li>DALYs averted</li> <li>Published literature (reviews, meta-analyses, RCTs)</li> <li>Published evidence (WHO Global Burden of Disease study)</li> </ul>	<ul> <li>Healthcare provider</li> <li>Medication, laboratory testing, psychosocial support, primary, inpatient and outpatient care, residential care, central administration (planning, monitoring, implementation), training (adaptation of guidelines, printing of materials)</li> <li>Published empirical or modelling studies and a multinational Delphi consensus panel</li> <li>WHO sub-regional unit costs</li> <li>Funded by WHO</li> </ul>

## Table abbreviations:

BD: Bipolar Disorder; CCA: Cost Consequence Analysis; CEA: Cost Effectiveness Analysis; CUA: Cost-Utility Analysis; DALY: Disability Adjusted Life Year; DES: Discrete Event Simulation; EPS: Extra-Pyramidal Symptoms; GP: General Practitioner; HAM-D: Hamilton Rating Scale for Depression; HRQoL: Health-Related Quality of Life; HTA: Health Technology Assessment; ICER: Incremental Cost Effectiveness Ratio; MADRS: Montgomery–Åsberg Depression Rating Scale; MCS: Mental Component Summary; MHI: Mental Health Index; MRS: Mania Rating Scale; NA: Non-Applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; NR: Not Reported; PCS: Physical Component Summary; PSS: Personal Social Services; QALY: Quality-Adjusted Life Year; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; RCT: Randomised Controlled Trial; SADS: Schedule for Affective Disorders and Schizophrenia; SF-36: short form 36 items; SR: systematic review; WHO: World Health Organization; YMRS: Young Mania Rating Scale

## Abbreviations of drug names used in the table:

Ari: Aripiprazole; Ase: Asenapine; Car: Carbamazepine; Hal: Haloperidol; Imi: Imipramine; Lam: Lamotrigine; Li: Lithium; Lur: Lurasidone; MS: mood stabiliser; Olz: Olanzapine; Par: Paroxetine; PC: Psychosocial Care; Plc: Placebo; Que: Quetiapine; Que XR: Quetiapine extended release; Ris: Risperidone; Val: Valproic acid or sodium valproate; Ven: Venlafaxine