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

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)**	**Primary measure(s) of outcome** **Source of** • **efficacy data** • **utility data (if applicable)**	**Perspective** **Cost categories** **Source of** • **resource use** • **unit costs** **Funding**
Management of manic / mixed episodes and/or rapid cycling in adults with bipolar disorder					
Bridle et al., 2004 [19] UK CEA 75	Adults with BD in an acute manic episode Hospital setting	• Que • Olz • Val • Li • Hal	Decision modelling Decision-tree 3 weeks NA Response	Probability of response (≥ 50% reduction in YMRS) • SR & NMA (7 studies) • NA	UK NHS Medication, laboratory testing, inpatient care (same across all arms) • Expert opinion, information from manufacturers and further assumptions • National sources HTA Programme on behalf of NICE
Caresano et al., 2014 [20] Italy CUA 87	Adults with BD I in an acute mixed episode Hospital and outpatient setting	• Ase • Olz	Decision modelling Decision-tree followed by Markov model 9 weeks acute phase + 5 years maintenance phase 3.5% per year Response, acute, sub-acute & euthymic phase, treatment discontinuation, relapse to manic, mixed or depressive episode, side effects (EPS, weight gain), death	QALY (clinical outcome measured as response, defined as ≥50% change on YMRS and MADRS) • Post-hoc analysis of 2 RCTs & further assumptions, published meta-analyses • Published [39;40;43] and unpublished utility data; further modifications	Italian NHS Medication, laboratory testing, inpatient care, GP and specialist visits, day hospital, treatment of side effects • Published literature and expert opinion • National sources Lundbeck Italy SpA

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Klok et al., 2007 [21] The Netherlands CEA 38	Adults with BD in an acute manic episode Hospital and outpatient setting	• Que • Li • Val • Que+Li • Olz+Li • Ris+Li • Plc	Decision modelling DES 100 days NA Compliance, response, remission, hospital discharge, side effects, death	Probability of major side effects (EPS & weight gain); length of hospital stay; probability of response • Comparison of 4 RCTs of Que alone or in combination and other RCTs: efficacy (change on YMRS) assumed to be the same across all interventions • NA	Healthcare provider Medication, laboratory testing, inpatient and outpatient care, treatment of side effects (EPS, constipation, nausea, vomiting, diarrhoea), suicide • Unclear; some data based on RCTs • National sources and published literature Astra Zeneca
Namjoshi et al., 2002 [22] US CCA 59	Adults with BD I, experiencing an acute manic or mixed episode Hospital setting followed by outpatient care	• Olz 5–20 mg/day • Plc / no treatment	Double-blind RCT (N=139) followed by a 49-week open label extension NA 3 weeks NA NA	Clinical improvement based on YMRS; HRQoL based on SF-36. • RCT (available data on n=139) followed by a 49-week open label extension (available resource use data on n=76) • NA	3rd party payer Medication, day hospital, inpatient care, outpatient contacts with health professionals (psychiatrists, psychologists, other physicians, social workers), case management, home care, emergency room visits • Before-after study (n=76) by comparing cost data from the open label extension with 12-month pre-randomisation data • National and local sources Eli Lilly & Company

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Revicki et al., 2003 [23] US CCA 49	Adults aged 18-65 years, with BD I, experiencing an acute manic episode Hospital setting followed by outpatient care	• Val 20 mg /kg/day • Olz 10–20 mg/day	Double-blind, multi-centre RCT (21 US sites, N=120) NA 12 weeks NA NA	Clinical improvement based on MRS from the SADS Change Version and the HAM-D; HRQoL based on Q-LES-Q and restricted activity days. • RCT (available data on n=52) • NA	Likely 3rd party payer (NR) Medication, inpatient care, physicians' fee, emergency room, psychiatric, physician, psychologist or other mental health provider visits, home visits • RCT (available data on n=52) and further assumptions • National sources Abbott Laboratories
Sawyer et al., 2014 [24] UK CUA 87	Adults with BD I in an acute mixed episode Hospital and outpatient setting	• Ase • Olz	Decision modelling Decision-tree followed by Markov model 9 weeks acute phase + 5 years of maintenance phase 3.5% per year Response, acute, sub-acute and euthymic phase, treatment discontinuation, relapse to manic, mixed or depressive episode, side effects (EPS, weight gain), death	QALY (clinical outcome measured as response, defined as ≥50% change on YMRS and MADRS) • Post-hoc analysis of 2 RCTs • Published [39;40;43] and unpublished utility data & further modifications	UK NHS & PSS Medication, laboratory testing, inpatient and outpatient care, crisis resolution team, treatment of side effects • Published literature and expert opinion • National sources Lundbeck SAS
Management of manic, hypomanic and/or mixed episodes in children and young people with bipolar disorder					

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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	Drug sequences: • Strategy 1: Ris, Que, Olz, Li • Strategy 2: Ris, Ari, Que, Li • Strategy 3: Ari, Ris, Que, Li • Strategy 4: Ris, Que, Ari, Li	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	UK NHS & PSS Medication, inpatient and outpatient care, treatment of side effects implicitly included • Expert opinion • National sources Otsuka Pharmaceuticals submission to NICE; reviewed & supplemented with extra analyses by independent Evidence Review Group
Management of depressive episodes in adults with bipolar disorder					
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	• Que • Que+ MS (Li or Val) • Olz • Olz+Li, Olz replaced by Ven in acute depression [Olz+Li1] • Olz+Li, Olz replaced by Par in acute depression [Olz+Li2] • Ari replaced by Olz+Ven in acute depression • Ris in mania, Ven+Li in depression, Olz in maintenance [Mixed]	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	QALY • Indirect comparisons between drugs, using Plc or Li as common comparator, based on RCTs and published meta-analyses • Published utility studies [39;40;46] and further assumptions	UK NHS (societal in sensitivity analysis) Medication, laboratory testing, inpatient & outpatient care, crisis teams, staff costs (senior house officer, GP, community psychiatric nurse, practice nurse, dietician), treatment of side effects • Clinical guidelines mainly based on expert opinion • National sources AstraZeneca Pharmaceuticals LP

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Rajagopalan et al., 2015 [26] USA CEA 75	Adults with BD I in an acute depressive episode Outpatient setting – hospitalisation possible	• Lur • Que XR	Decision modelling Decision-tree 3 months NA Remission	Percentage of patients achieving remission (MADRAS total score ≤12 by weeks 6–8) • Adjusted indirect comparison of pivotal RCTs using Plc as common comparator	3rd party payer Medication, inpatient and outpatient care, emergency department visits • Published expert panel data & a retrospective database study • National sources Sunovion Pharmaceuticals Inc.
Maintenance treatment of adults with bipolar disorder					
Calvert et al., 2006 [27] USA CEA & CUA 53	Adults with BD I stabilised after resolution of a mixed or manic episode Outpatient setting – hospitalisation possible	• Lam • Li • Olz • Plc/no treatment	Decision modelling Markov model 18 months NA Euthymia, acute mania or depression, treatment discontinuation	Number of acute episodes avoided; number of euthymic days achieved; QALY • Indirect comparisons using double-blind placebo-controlled RCTs • Pivotal RCTs [unpublished data on SF-36] & further modifications	3rd party payer Medication, laboratory testing, physician's time, hospitalisation • Published data, clinical guidelines based on expert opinion and a physician survey • National sources GlaxoSmithKline (GSK)
Ekman et al., 2012 [18] UK CUA 67	Adults aged 40 years with BD I or II in remission Outpatient setting – hospitalisation possible	*See Ekman et al. 2012, under 'Management of depressive episodes'*	*See Ekman et al. 2012, under 'Management of depressive episodes'*	*See Ekman et al. 2012, under 'Management of depressive episodes'*	*See Ekman et al. 2012, under 'Management of depressive episodes'*

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Fajutrao et al., 2009 [28] UK CEA & CUA 72	Adults with BD I who remitted from an acute mood episode following Que+MS treatment Outpatient setting – hospitalisation possible	• Que + MS (Li or Val) • MS (Li or Val) alone [MS]	Decision modelling Markov model 2 years 3.5% per year Euthymia, acute mania or depression, treatment discontinuation	Number of acute episodes avoided; % of people hospitalised due to acute episode; QALY • Pooled data from 2 double-blind placebo-controlled RCTs • Pivotal RCTs [unpublished data on SF-36] & further modifications	UK NHS Medication, laboratory testing, staff time (psychiatrist, senior house officer, GP, community psychiatric nurse, laboratory nurse), inpatient care, crisis resolution and home care • Clinical guidelines mainly based on expert opinion • National sources AstraZeneca Pharmaceuticals LP
McKendrick et al., 2007 [29] UK CEA 69	Adults with BD I newly stabilised after combination treatment with Olz + Li for acute mania Outpatient setting – hospitalisation possible	• Olz • Li	Decision modelling Markov model 1 year NA Euthymia, acute mania or depression, treatment discontinuation	Number of acute episodes avoided • Double-blind RCT • NA	UK NHS Medication, laboratory testing, day hospital, inpatient and outpatient care (GP, psychiatrist, specialist non-psychiatric, case manager, group therapy), home visits (nurse, social worker, physical therapist, GP), emergency room visits • UK chart review, other published sources and expert opinion • National sources Eli Lilly and Company Ltd

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

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Woodward et al., 2009 [32] USA CEA & CUA 77	Adults with BD I who remitted from an acute mood episode following Que+MS treatment Outpatient setting – hospitalisation possible	• Que+ MS (Li or Val) • MS (Li or Val) alone	Decision modelling Markov model 2 years 3% per year Euthymia, acute mania or depression, treatment discontinuation, death	Number of acute episodes avoided; % of people hospitalised due to acute episodes; QALY • Pooled data from 2 double-blind placebo-controlled RCTs • Pivotal RCTs [unpublished data on SF-36] & further modifications	3rd party payer Medication, laboratory testing, physician's time, hospitalisation • Published data including physician survey data, and clinical guidelines • National sources AstraZeneca Pharmaceuticals LP
Woodward et al., 2010 [33] USA CEA & CUA 65	Adults with BD I who remitted from an acute mood episode Outpatient setting – hospitalisation possible	• Que XR+MS (Li or Val) • MS (Li or Val) alone • Li • Lam • Olz • Ari • Pllc/no treatment	Decision modelling Markov model 2 years 3% per year Euthymia, acute mania or depression, treatment discontinuation, death	Number of acute episodes avoided % of people hospitalised due to acute episodes QALY • Pooled data from 2 double-blind placebo-controlled RCTs evaluating Que (not Que XR) and other indirect comparisons using RCTs identified via a non-systematic review • Pivotal RCTs [unpublished data on SF-36] & further modifications	3rd party payer & societal Medication, laboratory testing, physician's time, hospitalisation; productivity losses • Published data including physician survey data, and clinical guidelines • National sources AstraZeneca Pharmaceuticals LP
Management of patients in any phase of bipolar disorder					

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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	• Li • Li+PC • Val • Val+PC • No treatment Each provided in either hospital-based or community-based setting [10-year treatment implementation]	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	DALYs averted • Published literature (reviews, meta-analyses, RCTs) • Based on published evidence (WHO Global Burden of Disease study)	Healthcare provider Medication, laboratory testing, psychosocial support, primary, inpatient and outpatient care, residential care, central administration (planning, monitoring, implementation), training (adaptation of guidelines, printing of materials) • Published empirical or modelling studies and a multinational Delphi consensus panel • WHO sub-regional unit costs Funded by WHO
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	• Li • Li+PC • Val • Val+PC • No treatment Each provided in either hospital-based or community-based setting [10-year treatment implementation]	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	DALYs averted • Published literature (reviews, meta-analyses, RCTs) • Published evidence (WHO Global Burden of Disease study)	Healthcare provider Medication, laboratory testing, psychosocial support, primary, inpatient and outpatient care, residential care, central administration (planning, monitoring, implementation), training (adaptation of guidelines, printing of materials) • Published empirical or modelling studies and a multinational Delphi consensus panel • WHO sub-regional unit costs Funded by WHO

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