Table 2. Overview of results of published economic evaluations of pharmacological interventions for bipolar disorder

Results listed by form of economic evaluation (CUA, CEA or CCA); within CEAs, results listed by outcome measure used

Study ID Country, currency and cost year	Base-case results in original currency (2016 US$)	Results of sensitivity analysis
Cost-utility analyses		
Management of manic / mixed episodes and/or rapid cycling in adults with BD		
Caresano et al., 2014 [20] Italy, Euro(€), 2014	Ase dominates Olz	PSA: Probability of Ase being cost-effective 0.63 and 0.72 at WTP of zero/QALY and €30,000/QALY, respectively Results robust to different assumptions in resource use; conclusions robust to changes in transition probabilities between non-response, stable health state and sub-acute health state.
Sawyer et al., 2014 [24] UK, GBP£, 2013	Ase vs Olz: £1302 ($1946) per QALY	PSA mean results: Ase dominant Probability of Ase being cost-effective 0.51, 0.61 and 0.65 at WTP of zero/QALY, £20,000/QALY and £30,000/QALY, respectively. Results sensitive to changes in short and longer-term efficacy; conclusions robust to changes in time horizon, unit costs and utility values
Management of manic, hypomanic and/or mixed episodes in children & young people with BD		
Uttley et al., 2013 [25] UK, GBP£, 2011	Sequencing strategy 2 (Ris, Ari, Que, Li) dominates all other sequencing strategies (i.e. strategy 1: Ris, Que, Olz, Li; strategy 3: Ari, Ris, Que, Li; strategy 4: Ris, Que, Ari, Li)	PSA conducted 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)
Management of depressive episodes in adults with bipolar disorder		
Ekman et al., 2012 [18] UK, GBP£, 2011	Que+MS dominates all other strategies (i.e. Que, Olz, Olz+Li with Olz replaced by Ven or Par in acute depression, Ari replaced by Olz+Ven in acute depression, Ris in mania, Ven+Li in depression, Olz in maintenance [Mixed]) Que dominates all strategies except Olz and Mixed Que vs Olz: £8591 ($13,033) per QALY Que vs Mixed: £18,570 ($30,164) per QALY	PSA: Compared with Olz, probability of Que being cost-effective at WTP zero/QALY and £30,000/QALY: 0.21; 0.90 Results (Que vs Olz) robust to changes in inpatient or outpatient costs, starting age of the cohort, disutilities for discontinuation and side effects; sensitive to inclusion of indirect costs, use of a 6% discount rate, changes in time horizon, treatment discontinuation and dosages
Maintenance treatment of adults with BD		
Calvert et al., 2006 [27] US, US$, 2004	All drugs dominate no treatment Lam dominates Olz Lam vs Li: $26,000 ($33,151) per QALY :	Results robust to changes in length of acute episodes and length of hospitalisation. Results sensitive to changes in transition probabilities and costs of maintenance treatments.

Study ID Country, currency and cost year	Base-case results in original currency (2016 US$)	Results of sensitivity analysis
Soares-Weiser et al., 2007 UK, GBP£, 2005 [31]	Most recent episode depressive: Car, Imi, Lam and Olz dominated Li vs Val £10,409 ($20,178) per QALY Li+Imi vs Li £21,370 ($41,426) per QALY Most recent episode manic: Car, Imi, Lam, Li+Imi and Val dominated Li vs Olz £11,359 ($22,020) per QALY	Most recent episode depressive: PSA: Probability of cost effectiveness at WTP £20,000/QALY: Car 0.00; Imi 0.00; Lam 0.05; Li 0.36; Li+Imi 0.47; Olz 0.00; Val 0.12 Most recent episode manic: PSA: Probability of cost effectiveness at WTP £20,000/QALY: Car 0.00; Imi 0.00; Lam 0.00; Li 0.77; Li+Imi 0.09; Olz 0.11; Val 0.02 Results robust to alternative approaches for handling missing data; variation in RCTs included in the analysis; and alternative discount rates. Results sensitive to the assumption that Li reduces mortality.
Fajutrao et al., 2009 [28] UK, GBP£, 2007	Que+MS dominates MS alone	PSA: probability of Que+MS being cost-effective at zero WTP /QALY: 0.82 Results most sensitive to risk and length of hospitalisation, cost of hospital stay, and Que acquisition cost
Woodward et al., 2009 [32] US, US$, 2007	Que+MS dominates MS alone	PSA: Probability of Que+MS being cost-effective at WTP of $50,000/QALY: 1.00 Results most sensitive to Que acquisition cost, risk and length of hospitalisation for acute episodes (especially manic), cost of inpatient treatment for a manic episode
Ekman et al., 2012 [18] UK, GBP£, 2011	Que+MS dominates all other strategies (i.e. Que, Olz, Olz+Li with Olz replaced by Ven or Par in acute depression, Ari replaced by Olz+Ven in acute depression, Ris in mania, Ven+Li in depression, Olz in maintenance [Mixed]) Que dominates all strategies except Olz and Mixed Que vs Olz: £27,437 ($44,568) per QALY Que vs Mixed: £41,691 ($67,722) per QALY	PSA: Compared with Olz, probability of Que being cost-effective at WTP zero/QALY and £30,000/QALY: 0.29; 0.92, respectively Results of deterministic sensitivity analysis not presented for this population
Woodward et al., 2010 [33] US, US$, 2009	3rd party payer perspective: Que XR+MS dominates Lam, Olz, Ari and no treatment. Que XR+MS vs MS: $22,959 ($25,775) per QALY Que XR+MS vs Li: $100,235 ($112,530) per QALY Societal perspective: Que XR + MS dominates MS, Lam, Olz, Ari and no treatment Que XR+MS vs Li: $81,712 ($91,735) per QALY	3rd party payer perspective: PSA: Probability of cost effectiveness at WTP $100,000/QALY: Que XR+MS: 50%; Li: 50% Results most sensitive to efficacy, utility for the euthymia state, Que XR acquisition cost, risk and length of hospitalisation for manic episodes, and cost of inpatient treatment for a manic episode
Management of patients in any phase of BD		
Chisholm et al., 2005 [34] World regions, I$, likely 2003	All hospital-based options and all options with Val dominated ICER vs no treatment ranged from I$2165 ($2844) per DALY averted (Li+PC, community-based service model in African sub-region that includes Nigeria, Senegal, etc.) to I$37,244 ($48,929) per DALY) averted (Val, hospital-based model in Western Pacific sub-region that includes Australia, Japan, etc.)	Results robust to changes in suicide risk, use of alternative disability weights, small changes to relative effects of Li vs Val; results modestly sensitive to consideration of age-weights, changes in adherence, discount rate, resource use and costs.

Study ID Country, currency and cost year	Base-case results in original currency (2016 US$)	Results of sensitivity analysis
Chisholm et al., 2012 [35] World regions, International I$, 2005	All hospital-based options and all options with Val dominated Li in community setting vs no treatment: I$1800 ($2228) per DALY averted in sub-Saharan Africa; I$2001 ($2477) per DALY averted in South-East Asia Li+PC vs Li, both in community setting: I$9,916 ($12,273) per DALY averted in sub-Saharan Africa; I$13,444 ($16,640) per DALY averted in South-East Asia	Results robust to PSA that took account of a 15-25% variation in data inputs
Cost Effectiveness analyses		
Outcome: number of responders or remitters		
Management of manic / mixed episodes and/or rapid cycling in adults with BD		
Bridle et al., 2004 [19] UK GBP£, 2002	Hal dominates Li, Val and Que Olz vs Hal: £7179 ($15,313) per additional responder	PSA: Probability of being best at WTP £20,000/responder: Olz 0.44; Hal 0.37; Li 0.16; Que 0.02; Val 0.01 Results robust to the following scenarios: • hospitalisation of non-responders beyond 3 weeks • 2nd and 3rd line treatment for non-responders • reductions in laboratory testing costs • modified ITT approach inclusion of treatment costs for EPS caused by Hal
Klok et al., 2007 [21] The Netherlands, Euro(€), 2003	Olz+Li, Li, Que, Val and Plc dominated Que+Li vs Ris+Li: €12,667 ($19,052) per additional responder	Results robust to changes in inpatient care costs and discharge criteria; results sensitive to baseline and changes in YMRS scores and compliance
Management of depressive episodes in adults with bipolar disorder		
Rajagopalan et al., 2015 [26] US, US$, likely 2013	Lur vs Que XR: $3474 ($3592) per additional remission	PSA: Probability of Lur being cost-effective at WTP $10,000/remission: 0.86 Results most sensitive to remission rates and drug acquisition costs
Outcome: number of acute episodes avoided		
Maintenance treatment of adults with BD		
Calvert et al., 2006 [27] US, US$, 2004	All drugs dominate no treatment Lam dominates Olz Lam vs Li: $2400 ($3060) per acute episode avoided	Results robust to changes in length of acute episodes and length of hospitalisation. Results sensitive to changes in transition probabilities and costs of maintenance treatments.
McKendrick et al., 2007 [29] UK, GBP£, 2003	Olz dominates Li	Results most sensitive to risk and length of hospitalisation for mania, cost of hospitalisation and time horizon Sensitivity analysis: results ranging from Olz being dominant to Olz vs Li £367 per acute episode avoided ($552 in 2016 US$ prices)

Study ID Country, currency and cost year	Base-case results in original currency (2016 US$)	Results of sensitivity analysis
Fajutrao et al., 2009 [28] UK, GBP£, 2007	Que+MS dominates MS alone	PSA: probability of Que+MS being cost-effective at zero WTP /acute episode avoided: 0.85 Results most sensitive to risk and length of hospitalisation, cost of hospital stay, and Que acquisition cost
Woodward et al., 2009 [32] US, US$, 2007	Que+MS dominates MS alone	Results most sensitive to Que acquisition cost, risk and length of hospitalisation for acute episodes (especially manic), cost of inpatient treatment for a manic episode
Woodward et al., 2010 [33] US, US$, 2009	3rd party payer perspective: Que XR+MS dominates Lam, Olz, Ari and no treatment. Que XR+MS vs MS: $1045 ($1174) per acute episode avoided Que XR+MS vs Li: $5515 ($6191) per acute episode avoided Societal perspective: Que XR + MS dominates MS, Lam, Olz, Ari and no treatment Que XR+MS vs Li: $4496 ($5047) per acute episode avoided	Results most sensitive to efficacy, utility for the euthymia state, Que XR acquisition cost, risk and length of hospitalisation for manic episodes, and cost of inpatient treatment for a manic episode
Outcome: number of euthymic days gained		
Maintenance treatment of adults with BD		
Calvert et al., 2006 [27] US, US$, 2004	All drugs dominate no treatment Lam dominates Olz Lam vs Li: $30 ($38) per extra euthymic day	Results robust to changes in length of acute episodes and length of hospitalisation. Results sensitive to changes in transition probabilities and costs of maintenance treatments.
Outcome: number of inpatient days avoided or % of people hospitalised due to an acute episode		
Management of manic / mixed episodes and/or rapid cycling in adults with BD		
Klok et al., 2007 [21] The Netherlands, Euro(€), 2003	Ris+Li dominates all other options (Que, Li, Val, Que+Li, Olz+Li, Plc) in terms of number of inpatient days avoided	Results robust to changes in inpatient care costs and discharge criteria; results sensitive to baseline and changes in YMRS scores and compliance
Maintenance treatment of adults with bipolar disorder		
Fajutrao et al., 2009 [28] UK, GBP£, 2007	Que+MS dominates MS alone in terms of % of people hospitalised due to an acute episode	PSA: probability of Que+MS being cost-effective at zero WTP /hospitalisation avoided: 0.85 Results most sensitive to risk and length of hospitalisation, cost of hospital stay, and Que acquisition cost
Woodward et al., 2009 [32] US, US$, 2007	Que+MS dominates MS alone in terms of % of people hospitalised due to an acute episode	Results most sensitive to Que acquisition cost, risk and length of hospitalisation for acute episodes (especially manic), cost of inpatient treatment for a manic episode

Study ID Country, currency and cost year	Base-case results in original currency (2016 US$)	Results of sensitivity analysis
Woodward et al., 2010 [33] US, US$, 2009	<u>3rd party payer perspective:</u> Que XR+MS dominates Lam, Olz, Ari and no treatment. Que XR+MS vs MS: $3464 ($3889) per hospitalisation avoided Que XR+MS vs Li: $21,112 ($23,702) per hospitalisation avoided <u>Societal perspective:</u> Que XR + MS dominates MS, Lam, Olz, Ari and no treatment Que XR+MS vs Li: $17,211 ($19,322) per hospitalisation avoided	Results most sensitive to efficacy, utility for the euthymia state, Que XR acquisition cost, risk and length of hospitalisation for manic episodes, and cost of inpatient treatment for a manic episode
Outcome: number of major side effects avoided		
Management of manic / mixed episodes and/or rapid cycling in adults with BD		
Klok et al., 2007 [21] The Netherlands, Euro(€), 2003	Que, Li, Que+Li, Olz+Li dominated Val vs Ris+Li: €399 ($599) per major side effect avoided Plc vs Val: €317,667 ($477,784) per major side effect avoided	Results robust to changes in inpatient care costs and discharge criteria; results sensitive to baseline and changes in YMRS scores and compliance
Cost consequence analyses		
Management of manic / mixed episodes and/or rapid cycling in adults with BD		
Namjoshi et al., 2002 [22] US, US$, 1995	Total monthly medical costs per person for Olz: Open label phase: mean $649 ($1026), SD $399 ($631); Pre-randomisation: mean $1533 ($2423), SD $2262 ($3575); p<0.01 Changes in YMRS scores at 3 weeks: Olz: -10.3 (baseline 28.6), Plc: -4.9 (baseline 27.6); p=0.02 Changes in SF-36 dimension scores at 3 weeks: Significantly better change score for Olz in physical functioning (p=0.02); no statistically significant differences in other dimensions Open label extension: Change in YMRS score for Olz: 7.5 (baseline 19.3); p<0.01 Significant improvements in SF-36 dimensions of bodily pain, vitality, general health, role-emotional and social functioning	NA

Study ID Country, currency and cost year	Base-case results in original currency (2016 US$)	Results of sensitivity analysis
Revicki et al., 2003 [23] US, US$, 1992	Total medical costs per person: Val mean $13,703 ($23,524), SD $8,708 ($14,949); Olz mean $15,180 ($ 26,060), SD $16,780 ($28,806); p=0.88 Changes in MRS scores: Val: -14.9 (baseline 30.8); Olz -16.6 (baseline 32.3); p=0.368 Changes in Q-LES-Q scores (subjective feelings): Val -4.4, Olz -4.7; p=0.95 No statistically significant differences in any other outcomes	NA
Maintenance treatment of adults with bipolar disorder		
Revicki et al, 2005 [30] US, US$, 1997	Total medical costs per person: Val mean $28,911 ($43,385), SE $3599 ($5401); Li mean $30,666 ($46,019), SE $7364 ($11,051); p = 0.693 Mean number of months without DSM-IV mania or depression (SD): Val 5.3 (4.6); Li 5.4 (4.4), p = 0.814 Non-significant differences in any other outcomes between groups	NA

Cost effectiveness figures converted and uplifted to 2016 US dollars using purchasing power parity (PPP) exchange rates (http://www.oecd.org/std/ppp) and the US Consumer Price Index (http://www.usinflationcalculator.com/)

Table abbreviations:
BD: bipolar disorder; DALY: Disability Adjusted Life Year; ICER: Incremental Cost Effectiveness Ratio; NA: non-applicable; PSA: probabilistic sensitivity analysis; SD: Standard Deviation; SE: Standard Error

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