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