APPENDIX 19: INTERVENTIONS FOR THE LONG-TERM MANAGEMENT OF BIPOLAR DISORDER – STUDY CHARACTERISTICS

Pharmacological interventions

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
Lithium											
Lithium at different doses											
GELENBERG1989	USA	39	50%	100%	None	47	47	Lithium	1400mg	7	52
						47	47	Lithium	900mg	7	52
JENSEN1995	DNK	59	58%	86%	Additional antipsychotics or antidepressants. Hypnotics allowed.	25	25	Lithium	800mg	7	65
						25	25	Lithium	1200mg	3.5	48
Lithium compared with placebo											
DUNNER1976	USA	51	58%	0%	Amitriptyline or imipramine for depression and chlorpromazine for mania	16	16	Lithium	0.8-1.2mEq/L	7	69
						24	24	Placebo	N/A	7	69
STALLONE1973	USA	51	52%	100%	Amitriptyline or imipramine for depression and chlorpromazine for mania	25	25	Lithium	900mg	7	121
						27	27	Placebo	N/A	7	121
PRIEN1973	USA	44	35%	NR	None	101	NR	Lithium	1000mg	7	104
						104	NR	Placebo	N/A	7	104
Lithium compared with carbamazepine											
COXHEAD1992	GBR	48	71%	NR	Temazepam only	16	NR	Lithium	400mg	14	52

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
						15	NR	Carbamazepine	200mg	14	52
HARTONG2003	NED	42	54%	76%	Benzodiazepines only	72	50	Lithium	800mg	7	104
						72	44	Carbamazepine	400mg	7	104
KLEINDIENST2000	DEU	40	56%	100%	Psychotropic comedication avoided but allowed.	58	NR	Lithium	26.8mmol	7	130
						56	NR	Carbamazepine	635mg	7	130
WOLF1997	HUN	44	64%	NR	Short-time hypnotics	84	84	Lithium	NR	7	52
						84	84	Carbamazepine	NR	7	52
Lithium, carbamazepine, combined lithium and carbamazepine											
DENICOFF1997	USA	41	52%	64%	None allowed	50	29	Lithium	0.5-1.2 mmol/L	7	52
						46	22	Carbamazepine	4-12mg/L	7	52
						31	22	Lithium and carbamazepine	0.5-1.2 mmol/L/4-12mg/L	7	52
Lithium, valproate, combined lithium and valproate											
GEDDES2010	GBR, FRA, USA, ITA	43	49%	100%	Non-investigational co-therapies allowed	110	87	Lithium	0.4–1.0 mmol/L	7	104
						110	89	Valproate	1000mg	7	104
						110	87	Lithium & valpraote	0.4–1.0 mmol/L /1000mg	7	104

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
Lithium, valproate and placebo											
BOWDEN2000	NR	39	76%	100%	Lorazepam allowed. Haloperidol permitted during the second consecutive week of lorazepam use (first month only)	187	187	Lithium	0.8-1.2 mmol/L	7	52
						91	89	Valproate	71-125 ug/mL	7	52
						94	93	Placebo	N/A	7	52
Lithium compared with valproate											
CALABRESE2005c	USA	37	52%	40%	Lorazepam or alprazolam	32	NR	Lithium	1400mg	7	80
						28	NR	Valproate	1600mg	7	80
Lithium compared with lamotrigine											
LICHT2010	DNK, SWE	38	49%	100%	Antipsychotics and antidepressants allowed (≤ 6 months), benzodiazepines only (>6 months)	78	NR	Lithium	0.69 mmol /L	7	104
						77	NR	Lamotrigine	379mg	7	104
Lamotrigine, lithium and placebo											
BOWDEN2003	USA; AUS; AUT; BEL; CAN; GRE; NZL; NOR; POL; UKR	41	53%	100%	Chloral hydrate, lorazepam, temazepam or oxazepam	59	58	Lamotrigine	200mg	7	76
						46	44	Lithium	0.8-1.1mEq/L	7	76
						70	69	Placebo	N/A	7	76
CALABRESE2003	Multiple (not specified)	42	39%	100%	Chloral hydrate, lorazepam, temazepam,	121	NR	Lamotrigine	200mg	7	72
						121	NR	Lithium	900mg	7	72

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
					oxazepam or midazolam.	121	NR	Placebo	N/A	7	72
Lithium, imipramine and placebo											
PRIEN1973B	USA	43	23%	NR	None	18	18	Lithium	1250mg	7	104
						13	13	Imipramine	125mg	7	104
						13	13	Placebo	N/A	7	104
Lithium, imipramine and lithium and imipramine combined											
PRIEN1984	NR	38	58%	NR	None	42	NR	Lithium	0.6-0.9 mEq/L	7	104
						36	NR	Imipramine	150mg	7	104
						36	NR	Lithium and Imipramine	0.6-0.9 mEq/L/150mg	7	104
Olanzapine compared with lithium											
TOHEN2005	Multiple (not specified)	42	53%	100%	Haloperidol, zuclopenthixol, benzidiazepine and anticholinergics	217	101	Olanzapine	11.9mg	7	52
						214	70	Lithium	1102.7mg	7	52
Quetiapine, lithium and placebo											
WEISLER2011	Multiple (not specified)	40	53%	100%	None	404	404	Quetiapine	546mg	7	104
						364	364	Lithium	900mg	7	104
						404	404	Placebo	N/A	7	104
Antipsychotics											
Aripiprazole compared with placebo											
CARLSON2012	USA	39	65%	100%	Lorazepam,	178	NR	Aripiprazole	17.4mg	7	52

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
					oxazepam, diazepam, chlorazepate and anticholinergics allowed	173	NR	Placebo	N/A	7	52
Aripiprazole compared with placebo (all on lithium or valproate)											
MARCUS2011	USA, BRA, BGR, HVR, CZE, FRA, IND, RUS, ZAF	39	55%	100%	All on lithium or valproate. Benzodiazepines, propranolol and anticholinergics allowed.	168	162	Aripiprazole	15mg	7	52
						169	164	Placebo	N/A	7	52
TOHEN2004	USA, CAN	41	52%	100%	All on lithium or valproate. Lorazepam and benzatropine mesylate allowed	51	51	Olanzapine	8.6mg	14	78
						48	48	Placebo	N/A	14	78
Paliperidone, olanzapine and placebo											
BERWAERTS2012	Multiple (not specified)	40	55%	100%	Lorazepam, clonazepam, or diazepam, nonbenzodiazepine hypnotics and anticholinergics	152	146	Paliperidone XR	6mg	7	129
						83	82	Olanzapine	10mg	7	129
						148	144	Placebo	N/A	7	129
Quetiapine compared with placebo											
YOUNG2012	Multiple (not	40	60%	60%	Zolpidem tartrate or chloral hydrate	141	NR	Quetiapine	300mg	7	52

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
	specified)				and anticholinergics allowed	149	NR	Quetiapine	600mg	7	52
						296	NR	Placebo	N/A	7	52
Quetiapine compared with placebo (all on lithium or valproate)											
SUPPES2009	USA, CAN	40	53%		All on lithium or valproate. Non-psychoactive medications, lorazepam, zolpidem tartrate, zopiclone, chloral hydrate and anticholinergics allowed	310	173	Quetiapine	519mg	7	104
						313	229	Placebo	N/A	7	104
VIETA2008b	USA, AUS, BEL, BGR, CZE, FRA, DEU, HUN, ITA, NOR, POL, RUS, ZAF, ESP, SVK, TUR, GBR	42	55%	100%	All on lithium or valproate. Zolpidem, zaleplon, zopiclone, chloral hydrate, lorazepam and anticholinergics allowed.	336	336	Quetiapine	497mg	7	104
						367	367	Placebo	N/A	7	104
Quetiapine compared with valproate											
LANGOSCH2008	DEU	42	60%	50%	No psychoactive medication allowed	24	21	Quetiapine	500mg	7	52
						20	16	Valproate	1300mg	7	52

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
Risperidone long-acting injectable compared with placebo											
QUIROZ2010	AUT, IND, MYS, POL, RUS, SVK, ESP, TWN, UKR, USA	39	49%	100%	Nonbenzodiazepine hypnotics, benzodiazepines, propranolol, and anticholinergic medications allowed	154	135	Risperidone (injection)	25mg	0.5	104
						149	133	Placebo (injection)	N/A	0.5	104
Risperidone long-acting injectable, olanzapine and placebo											
VIETA2012	Multiple (unspecified)	36	52%	100%	Non-benzodiazepine hypnotics, lorazepam, clonazepam, diazepam and anticholinergic medications allowed	137	135	Risperidone (injection)	25mg	0.5	78
						138	137	Olanzapine	10mg	7	78
						140	138	Placebo (injection)	N/A	0.5	78
Risperidone long-acting injectable compared with treatment as usual											
MACFADDEN2009	USA, IND	39	28%	100%	Antidepressants, mood stabilisers or anxiolytics	65	65	Risperidone (injection) + TAU	12.5mg	0.5	52
						59	59	Placebo (injection) + TAU	N/A	0.5	52
BOBO2011b	USA	40	67%	73%	Oral antipsychotics, mood stabilizers, antidepressants,	25	20	Risperidone (injection) + TAU	27mg	0.5	52

Study	Country	Age	% Female	% BPI	Concomitant medication	N Rand	N Post	Group	Dose	Freq	Dur
					benzodiazepines and anticholinergics.	25	25	TAU	N/A	0.5	52
Anticonvulsants											
Gabapentin compared with placebo											
VIETA2006	ESP	49	72%	76%	Lithium, valproate, carbamazepine or combination	12	12	Gabapentin	300mg	7	52
						13	13	Placebo	N/A	7	52
Oxcarbazepine compared with placebo											
VIETA2008	ESP	44	65%	76%	All on lithium, lorazepam allowed	26	26	Oxcarbazepine	1200mg	7	52
						29	29	Placebo	N/A	7	52
Antidepressants											
Imipramine compared with placebo (all on lithium)											
QUITKIN1981	USA	37	52%	100%	Lithium only	37	37	Imipramine	125mg	7	82
						38	38	Placebo	N/A	7	82
Antidepressants compared with placebo											
GHAEMI2010	USA	37	50%	50%	Lithium, lamotrigine and/or divalproex.	32	32	Antidepressants¥	Variable	7	52
						38	38	Placebo	N/A	7	52

¥The most frequently employed antidepressant class was serotonin reuptake inhibitors (52%). Common specific agents were bupoprion and paroxetine (22% each) and citalopram and venlafaxine (19% each). No tricyclic antidepressants were used.