

Additional file 3: Individual adverse events

Study	Drug comparison	Method of collection	Category reported	Somnolence	Weight gain	Increased appetite	Headache	Dry mouth	Nervousness	Asthenia	Anxiety	Depression	Insomnia	Diarrhoea	Nausea	Vomiting
Mania/mixed: less than 6 weeks																
Segal et al. 1998	risperidone v lithium v haloperidol	Documented	not reported													
Tohen et al. 1999	olanzapine v placebo	no information	in ≥10% of group or stat sig between-group diff	(1) 23/70 (2) 12/69	(1) 8/70 (1) 1/69		(1) 12/70 (2) 11/69	(1) 18/70 (2) 6/69	(1) 6/70 (2) 9/69	(1) 13/70 (2) 16/69	(1) 10/70 (2) 7/69	(1) 9/70 (2) 8/69				
Berk et al. 1999	olanzapine v lithium	Noted	not reported													
Tohen et al. 2000	olanzapine v placebo	Assessed	in ≥10% of group or stat sig between-group diff	(1) 21/55 (2) 5/60	sig larger mean weight gain for olanzapine		(1) 10/55 (2) 13/60	(1) 9/55 (2) 3/55	(1) 5/55 (2) 12/60	(1) 6/55 (2) 3/60	(1) 2/55 (2) 9/60					
Tohen et al. 2002	olanzapine v divalproex	Monitored	in ≥10% of group or stat sig between-group diff	(1) 49/125 (2) 26/126	(1) 15/125 (2) 10/126	(1) 15/125 (2) 3/126	(1) 28/125 (2) 29/126	(1) 42/125 (2) 8/126	(1) 13/125 (2) 21/126	(1) 20/125 (2) 17/126		sleep disorder (1) 7/125 (2) 1/126	(1) 8/125 (2) 17/126	(1) 13/125 (2) 36/126	(1) 10/125 (2) 18/126	
Hirschfeld et al. 2004	risperidone v placebo	General and directed questioning	in ≥10% of group	(1) 38/134 (2) 9/125			(1) 19/134 (2) 19/125								(1) 15/134 (2) 3/125	
Yatham et al. 2003	risperidone+MS v placebo+MS	no information	most frequent		sig larger mean weight gain for risperidone		(1) 9% (2) 9%					given antidepressant (1) 1/75 (2) 2/75	(1) 4% (2) 8%		(1) 5% (2) 3%	
Sachs et al. 2002	risperidone+MS v haloperidol+MS v placebo+MS	Obtained	in ≥10% of group	(1) 13/52 (2) 16/53 (3) 6/51	sig larger mean weight gain for risperidone		(1) 11/52 (2) 8/53 (3) 12/51									
Sachs et al. 2004	quetiapine+MS v placebo+MS	Examination and questioning every study day	in ≥10% of group	(1) 36/90 (2) 10/100			(1) 24/90 (2) 21/100	(1) 17/90 (2) 4/100		(1) 10/90 (2) 3/100						
Yatham et al. 2004	quetiapine+MS v placebo+MS	Examination, patient reports, medical records	in ≥5% of group (1) and x2 incidence in group (2)	(1) 66/196 (2) 19/203	(1) 12/196 (2) 5/203			(1) 38/196 (2) 6/203		(1) 19/196 (2) 8/203						
Keck et al. 2003	ziprasidone v placebo	Observed or reported	in ≥10% of group	(1) 52/140 (2) 9/70	no sig diff		(1) 30/140 (2) 13/70					(1) 11/140 (2) 7/70		(1) 16/140 (2) 7/70		
Keck et al. 2003b	aripiprazole v placebo	Obtained	in ≥10% of group	(1) 26/127 (2) 6/127			(1) 46/127 (2) 40/127				(1) 23/127 (2) 13/127	(1) 19/127 (2) 11/127	(1) 15/127 (2) 11/127	(1) 29/127 (2) 13/127	(1) 20/127 (2) 6/127	
Potkin et al. 2005	ziprasidone v placebo	Observed or volunteered	T-R in ≥5% of group	(1) 31/139 (2) 4/66			(1) 17/139 (2) 5/66			(1) 7/139 (2) 1/66				(1) 9/139 (2) 1/66		

Khanna et al. 2005	risperidone v placebo	no information	in ≥10% of group			no sig diff												(1) 9/146 (2) 14/144
Smulevich et al. 2005	risperidone v haloperidol v placebo	Monitored and assessed	in ≥10% of active treatment groups	(1) 7/154 (2) 5/144 (3) 2/140														
Sachs et al. 2006	aripiprazole v placebo	Obtained and measured	in ≥10% of group	(1) 27/136 (2) 14/133			(1) 34/136 (2) 33/133				(1) 14/136 (2) 11/133			(1) 9/136 (2) 13/133	(1) 29/136 (2) 21/133	(1) 15/136 (2) 10/133		
Mania/mixed: 6-12 weeks																		
Tohen et al. 2002b	olanzapine+MS v placebo+MS	no information	in ≥10% of group or stat sig between-group diff	(1) 118/229 (2) 31/115	(1) 60/229 (2) 8/115		(1) 54/229 (2) 9/115	(1) 36/229 (2) 21/115	(1) 73/229 (2) 9/115	(1) 24/229 (2) 17/115	(1) 42/229 (2) 15/115		(1) 41/229 (2) 20/115					(1) 27/229 (2) 17/115
Zajack et al. 2002	olanzapine v divalproex	spontaneous reports and monitoring	stat sig diff between groups	(1) 27/57 (2) 18/63	(1) 14/57 (2) 6/63													
Tohen et al. 2003	olanzapine v haloperidol	non-directed, open-ended questioning, spontaneous report, clinical observation	in ≥10% of group	(1) 35/234 (2) 19/219	(1) 32/234 (2) 9/219													
Bowden et al. 2005	quetiapine v placebo v lithium	questioning and examination	in ≥5% of group	(1) 21/107 (2) 3/97 (3) 9/98	(1) 16/107 (2) 1/97 (3) 6/98		(1) 8/107 (2) 4/97 (3) 12/98	(1) 26/107 (2) 2/97 (3) 6/98			(1) 7/107 (2) 1/97 (3) 4/98		(1) 6/107 (2) 1/97 (3) 1/98	(1) 10/107 (2) 20/97 (3) 16/98	(1) 5/107 (2) 4/97 (3) 5/98	(1) 1/107 (2) 2/97 (3) 6/98	(1) 1/107 (2) 2/97 (3) 6/98	
McIntyre et al. 2005	quetiapine v placebo v haloperidol	open-ended questioning, spontaneous report, clinical observation	in ≥5% of active treatment groups	(1) 13/102 (2) 5/101 (3) 9/99			(1) 5/102 (2) 4/101 (3) 8/99	(1) 7/102 (2) 4/101 (3) 4/99					(1) 2/102 (2) 4/101 (3) 1/99	(1) 20/102 (2) 20/101 (3) 14/99				

Vieta et al. 2005	aripiprazole v haloperidol	reports gathered, measured	in ≥10% of group		small mean changes, not sig diff	(1) 19/174 (2) 20/172						(1) 24/175 (2) 12/172		
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Mania/mixed: more than 12 weeks

Tohen et al. 2003b	olanzapine v divalproex	Assessed	in ≥10% of group or stat sig between- group diff	(1) 58/125 (2) 31/126	(1) 31/125 (2) 15/126	(1) 17/125 (2) 7/126	(1) 33/125 (2) 34/126	(1) 43/125 (2) 9/126	(1) 15/125 (2) 28/126	(1) 29/125 (1) (2) 23/126 16/125 (2) 22/126	(1) 43/125 (3) 38/126	(1) 10/125 (2) 20/126	(1) 13/125 (1) (2) 24/126 20/125 (2) 40/126	(1) 17/125 (2) 23/126
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Tohen et al. 2004	olanzapine+MS v placebo+MS	no information	in ≥10% of group	(1) 10/51 (2) 4/48	(1) 10/51 (2) 3/48					(1) 5/51 (2) 6/48	(1) 7/51 (2) 7/48	(1) 19/51 (2) 14/48	(1) 2/51 (2) 13/48	(1) 5/51 (2) 8/48
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Tohen et al. 2005	olanzapine v lithium	Reported	in ≥5% of either group [hypersomnia]	(1) 14/217 (1) 6/217 (2) 0/214	(1) 10/214			(1) 9/217 (2) 11/214		(1) 12/217 (2) 10/214	(1) 45/217 (2) 25/214	(1) 17/217 (2) 48/214		(1) 1/217 (2) 8/214
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Tohen et al. 2006	olanzapine v placebo	Spontaneous report	in ≥10% of group(most in open label phase)	(1) 6/225 (2) 2/136	(1) 18/225 (2) 2/136	(1) 4/225 (2) 0/136		(1) 4/225 (2) 1/136					(1) 5/225 (2) 19/136	
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Keck et al. 2006	aripiprazole v placebo	Asked about adverse events and observed	≥5% in either group	(1) 4/77 (2) 6/83				(1) 6/77 (2) 13/83	(1) 8/77 (2) 5/83	(1) 6/77 (2) 7/83	(1) 13/77 (2) 12/83	(1) 9/77 (2) 12/83	(1) 12/77 (2) 16/83	(1) 7/77 (2) 4/83
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Depression: 8-12 weeks

Tohen et al. 2003d	olanzapine v olanzapine+fluoxetine v placebo	Recorded, assessed	in ≥10% of group	(1) 104/351 (2) 18/82 (3) 47/355				(1) 50/351 (2) 11/82 (3) 19/355	(1) 46/351 (2) 12/82 (3) 70/355	(1) 41/351 (2) 12/82 (3) 70/355	(1) 39/351 (2) 8/82 (3) 30/355	(1) 36/351 (2) 11/82 (3) 12/355	(1) 31/351 (2) 8/82 (3) 57/355	(1) 24/351 (1) (2) 16/82 16/351 (3) 25/355 (2) 10/82 (3) 33/355
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Shelton et al. 2004	risperidone v parox v risperidone+paroxetine	not specified	all {not all shown here}	(1) 5/10 (2) 2/10 (3) 2/10	(1) 1/10 (2) 1/10 (3) 4/10	(1) 2/10 (2) 2/10 (3) 2/10	(1) 1/10 (2) 1/10 (3) 0/10	(1) 1/10 (2) 3/10 (3) 1/10		(1) 1/10 (2) 0/10 (3) 0/10		(1) 0/10 (2) 2/10 (3) 1/10	(1) 2/10 (3) 3/10 (3) 1/10	(1) 0/10 (2) 2/10 (3) 0/10
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Calabrese et al. 2005	quetiapine600 v quetiapine300 v placebo	Assessed	in ≥10% of group	(1) 44/180 (2) 49/179 (3) 15/180			(1) 18/180 (2) 22/179 (3) 36/180	(1) 73/180 (2) 79/179 (3) 14/180		(1) 6/180 (2) 14/179 (3) 23/180
Brown et al. 2006	olanzapine+fluoxetine v lamotrigine	nonprobing inquiry	In >5% of either group	(1) 38/205 (2) 17/204	(1) 29/205 (2) 4/204	(1) 36/205 (2) 17/204	(1) 24/205 (2) 19/204	(1) 32/205 (2) 12/204	(1) 9/205 (2) 18/204	(1) 16/205 (2) 16/204
Thase et al. 2006	quetiapine600 v quetiapine300 v placebo	Evaluated	in ≥10% of any group	(1) 50/168 (2) 51/171 (3) 8/167			(1) 14/168 (2) 15/171 (3) 28/167	(1) 79/168 (2) 73/171 (3) 30/167		(1) 18/168 (2) 13/171 (3) 22/167

EP = extrapyramidal;

Dyspepsia	Constipation	Dizziness	Agitation	Fatigue	Pain	Hostility	Personality disorder	Pharyngitis	Tongue oedema	Postural hypotension	Accidental injury	Prolactin	Glucose	Lipids	Extrapyramidal symptom related
	(1) 8/70 (2) 2/69	(1) 16/70 (2) 4/69	(1) 13/70 (2) 16/69		(1) 8/70 (2) 3/69	(1) 6/70 (2) 8/69	(1) 5/70 (2) 8/69								
(2) 7/55 (2) 3/60	(1) 6/55 (2) 5/60	(1) 7/55 (2) 4/60	(1) 5/55 (2) 15/60			(1) 1/55 (2) 6/60	(1) 1/55 (2) 7/60								
(1) 18/125 (2) 14/126	(1) 18/125 (2) 15/126	(1) 20/125 (2) 15/126	(1) 14/125 (2) 14/126		(1) 17/125 (2) 18/126				(1) 6/125 (2) 0/126						Tremor (1) 12/125 (2) 4/126 Neck rigidity (1) 9/125 (2) 2/126 Speech disorder (1) 10/125 (2) 1/126
(1) 15/134 (2) 8/125		(1) 15.134 (2) 11/125										sig inc in mean for risperidone group	no sig diff		Hyperkinesia (1) 21/134 (2) 6/125 EP rel (1) 16/75 (2) 6/75
(1) 9/52 (2) 9/53 (3) 9/51	(1) 2/52 (2) 6/53 (3) 2/51	(1) 7/52 (2) 4/53 (3) 1/51													EP disorder (1) 7/52 (2) 15/53 (3) 2/51 Tremor (1) 2/52 (2) 6/53 (3) 2/51
		(1) 9/90 (2) 6/100							(1) 10/90 (2) 3/100				no sig diff		
								(1) 11/196 (2) 5/203	(1) 13/196 (2) 3/203						E-P rel (1) 42/196 (2) 39/203 [Akathisia (1) 7/196 (2) 10/203]
(1) 14/140 (2) 7/70		(1) 38/140 (2) 7/70													Akathisia (1) 15/140 (2) 4/70 Hypertonia (1) 16/140 (2) 2/70
(1) 28/127 (2) 13/127	(1) 17/127 (2) 7/127	Lightheadedness (1) 18/127 (2) 10/127 (1) 14/139 (2) 1/66	(1) 25/127 (2) 24/127		abbdominal (1) 2/139 (2) 5/66						(1) 15/127 (2) 3/127	above ULN: (1) 14/127 (2) 22/127 both gps dec	no sig diff	cholesterol - no sig diff	Akathisia (1) 14/127 (2) 3/127 Tremor (1) 8/127 (2) 4/127
													elevated triglycerides (1) 8/139 (2) 7/66		EP syndrome (1) 15/139 (2) 1/66 Akathisia (1) 13/139 (2) 3/66 Tremor (1) 11/139 (2) 1/66

(1) 21/136 (2) 9/133	(1) 16/136 (2) 7/133	(1) 20/136 (2) 19/133	extremity (1) 14/136 (2) 7/133	inc in risperidone group			EP disorder (1) 51/146 (2) 9/145 Tremor (1) 15/146 (2) 1/145 Dystonia (1) 7/146 (2) 0/145 Hyperkinesia (1) 1/146 (2) 0/145
				inc in both active groups, more in risperidone			EP disorder (1) 26/154 (2) 58/144 (3) 12/140 Hyperkinesia (1) 14/154 (2) 22/144 (3) 4/140 Tremor (1) 10/154 (2) 16/144 (3) 8/140 Hypertonia (1) 6/154 (2) 13/144 (3) 0/140
				dec in both groups, stat greater with aripiprazole ≥ULN (1) 5/136 (2) 15/133	no clinically sig diff	no clinically sig diff	Akathisia (1) 24/136 (2) 6/133
	(1) 31/229 (2) 8/115			>ULN (1) 43/229 (2) 5/115	no sig diff		Tremor (1) 53/229 (2) 15/115 Speech disorder (1) 15/229 (2) 1/115
			Oedema (1) 8/57 (2) 0/63		no sig diff overall, but one olanzapine patient died from diabetic ketoacidosis	cholesterol- sig increase in mean total and LDL for olanzapine group	Speech disorder (1) 4/57 (2) 0/63
				<200 to ≥200 mg/dl (1) 3/209 (2) 4/194		cholesterol <200 to ≥240 mg/dl (1) 9/134 (2) 8/133	Akathisia (1) 15/234 (2) 65/219 Tremor (1) 13/234 (2) 34/219 Hypertonia (1) 12/234 (2) 39/219 EP syndrome (1) 5/234 (2) 52/219 Dystonia (1) 3/234 (2) 15/219 Dyskinesia (1) 1/234 (2) 7/219 Hypokinesia [sic] (1) 1/234 (2) 8/219 Tardive dyskinesia (1) 0/234 (2) 5/219
	(1) 13/107 (2) 2/97 (3) 7/98			Mean levels high at baseline Shift to >ULN: (1) 6/53 (2) 6/47 (3) 7/55	no clinically important differences		Tremor (1) 6/107 (2) 4/97 (3) 18/98 Akathisia (1) 1/107 (2) 6/97 (2) 3/98
		(1) 8/102 (2) 9/101 (3) 8/99		(1) 6/102 (2) 1/101 (3) 2/99	Mean levels high at baseline, dec in all groups, but more in quetiapine group		EPS-rel (1) 13/102 (2) 16/101 (3) 59/99 Tremor (1) 8/102 (2) 6/101 (3) 30/99 Akathisia (1) 6/102 (2) 6/101 (3) 33/99 EP syndrome (1) 6/102 (2) 6/101 (3) 35/99

>ULN
 (1) 25/175
 (2) 97/169
 Mean dec in (1)
 and inc in (2)

cholesterol -no
 clin meaningful
 diff

EP rel (1) 42/175 (2) 108/172
 EP syndrome (1) 16/175 (2) 61/172
 Tremor (1) 12/175 (2) 17/169
 Akathisia (1) 20/175 (2) 40/169

(1) 21/125 (2) 19/126	(1) 19/125 (2) 19/126	(1) 23/125 (2) 21/126	(1) 20/125 (2) 17/126	(1) 23/125 (2) 27/126	(1)13/125 (2) 14/126	abnormally high glucose (1) 0/113 (2) 0/114	abnormally high cholesterol (1) 1/118 (2) 0/115	Akathisia (1) 12/125 (2) 2/126 Tremor (1) 15/125 (2) 14/126	
			(1) 14/225 (2) 2/136			prolactin measured but not reported	No case of clin relevant inc (<11.1 to ≥11.1 mmol/l)	cholesterol - no case of clin relevant inc (<5.17 mmol/l to ≥ 6.20 mmol/l)	Tremor (1) 7/51 (2) 4/48
							<200 to ≥200 mg/dl (1) 8/206 (2) 2/198	cholesterol <200 to ≥240 mg/dl (1) 4/54 (2) 1/55	not reported
						(1) 12/104 (2) 2/64	<200 to ≥200 mg/dl (1) 3/206 (2) 2/122	cholesterol <200 to ≥240 mg/dl (1) 2/64 (2) 0/45	not reported
		(1) 6/77 (2) 9/83		(1) 7/77 (2) 6/83		(1) mean dec (2) mean dec diff just sig	no sig diff betseen groups	no sig diff between groups	Akathisia (1) 5/77 (2) 1/83 Tremor (1) 7/77 (2) 1/83 Hypertonia (1) 3/77 (2) 1/83

≥30 mm Hg
dec in syst BP
(1) 5/346
(2) 6/82
(3) 5/352

no data

Mean changes
sig greater in
both olanzapine
groups (4 to 6
mg/dl)
<200 to ≥200
mg/dl:
(1) 4/289
(2) 1/65
(3) 1/298

Cholesterol -
mean baseline
levels high, with
inc in both
olanzapine
groups (6 to 10
mg/dl)

(1) 1/10 (2) 0/10 (3) 0/10	(1) 0/10 (2) 1/10 (3) 1/10	(1) 0/10 (2) 0/10 (3) 1/10	(1) 2/10 (2) 2/10 (3) 1/10
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no data no data no data

(1) 20/180
(2) 21/179
(3) 8/180

(1) 41/180
(2) 30/179
(3) 15/180

(1) 28/205
(2) 16/204

(1)
17/205
(2) 11/204

(1) 17/168
(2) 14/171
(3) 5/167

(1) 27/168
(2) 24/171
(3) 9/167

(1)
19/168
(2)
16/171
(3)
13/167

no clinically relevant differences between groups in mean changes from baseline inc in mean from baseline with (1) but not (2)

no clinically relevant differences between groups in mean changes from baseline no sig diff in mean change from baseline

no clinically relevant differences between groups in mean changes from baseline Sig diff in mean change from baseline for cholesterol and triglycerides in favour of lamotrigine

EP-related (1) 16/180 (2) 12/179 (3) 4/180

Tremor (1) 22/205 (2) 3/204

No significant differences between groups in mean changes from baseline

EP symptoms (1) 17/168 (2) 21/171 (3) 11/167