

Additional file 1: Trials of atypical antipsychotics in depression - design, details, and outcomes

Reference [number]	Patients	Treatment	Mean daily dose Other medication	Duration (weeks)	QS	Response	Remission	CGI	Emergence of mania	Discontinuations				Adverse event reporting			Scale-defined adverse events	
										All cause	Lack of efficacy	Adverse event	T-E mania	Patients experiencing any adverse event	Severe	Serious	Treatment related	EP symptoms
Tohen et al. 2003 [18]	Bipolar I depression, (MADRS >19) Age:42 ±12 years M:47% Psychotic: 12.5% Rapid cycling: 37%	(1) olanzapine 5-20 mg/day, n=351 (2) olanzapine-fluoxetine 6/25, 6/50 or 12/50 mg/day, n=82 (3) placebo, n=355	(1) 9.7 mg (2) 7.4 mg/39.4 mg Benzodiazepines (36-44%) Anticholinergics to treat EP sympt (3-8%)	8	R2, D1, W1	≥50% improvement in MADRS, min 4 wks (1) 137/351 (2) 46/82 (3) 108/355 Median time to response (days): (1) 57 (2) 42 (3) 59	MADRS ≤12, min 4 wks (1) 115/351 (2) 40/82 (3) 87/355 Median time to remission(days): (1) 57 (2) 42 (3) 59	no categorical data Mean improvements sig greater for (2) than (1) than (3)	YMRS <15 at baseline and ≥15 any time thereafter (1) 19/335 (2) 5/78 (3) 23/345	(1) 191/351 (2) 31/82 (3) 232/355	(1) 73/351 (2) 8/82 (3) 121/355	(1) 34/351 (2) 2/82 (3) 19/355	(1) 15/351 (2) 4/82 (3) 24/355	no data	no data	no data	SAS and AIMS No sig diff	
Shelton, Stahl. 2004 [19]	Bipolar I and II disorder, depressive episode (HAM-D>17), receiving mood stabiliser Age:36 ±10 years M:50% Psychotic: 0%	(1) risperidone 1-4 mg/day + placebo plus mood stabiliser, n=10 (2) paroxetine 20-40 mg/day + placebo plus mood stabiliser, n=10 (3) risperidone +paroxetine plus mood stabiliser, n=10	(1) 2.15 mg (2) 35 mg (3) 1.16 mg/22 mg Lorazepam in first 4 weeks	12	R1, D2, W1	≥50% improvement on HAM-D and 1 or 2 on CGI-S (LOCF) (1) 3/10 (2) 2/10 (3) 3/10	HAM-D ≤7 and no longer MDD on DSM-IV (LOCF) (1) 3/10 (2) 2/10 (3) 3/10	no categorical data none (one pt in (2) experienced v mild hypomania)	(1) 5/10 (2) 2/10 (3) 4/10	(1) 3/10 (2) 0/10 (3) 1/10	(1) 1/10 (2) 1/10 (3) 3/10	none	no data	no data	no data	SAS, BARS No sig diff		
Calabrese et al. 2005 [20]	Bipolar I and II disorder, major depressive episode (HAM-D≥20, YMRS≤12) Age:37 ±11 years M:42% Excl: history non-response to >2 classes antidepressants for current episode	(1) quetiapine 600 mg/day, n=170 (2) quetiapine 300 mg/day, n=172 (3) placebo, n=169 [ITT cohort]	N/A Lorazepam and zolpidem during first 3 weeks - generally <10%	8	R2, D2, W1	≥50% improvement in MADRS (1) 99/170 (2) 99/172 (3) 61/169 Median time to response(days): (1) 22 (2) 22 (3) 36	MADRS ≤12 in MADRS (1) 90/170 (2) 91/172 (3) 48/169 Median time to remission (days): (1) 27 (2) 29 (3) 65	normal/not at all ill/borderline ill (1) 72/170 (2) 66/172 (3) 40/169	YMRS ≥16 on 2 consec visits or at end point or AE of mania (using safety population) (1) 7/179 (2) 7/180 (3) 7/180	(1) 82/180 (2) 60/181 (3) 74/181	(1) 1/180 (2) 4/181 (3) 24/181	(1) 47/180 (2) 29/181 (3) 15/181	no data	no data	no data	(1) 9/180 (2) 6/181 (3) 16/181 (none T-R)	SAS, BARS: 9% to 15% with an inc from baseline, with no sig diff between groups	
Brown et al. 2006 [21]	Bipolar I disorder, depressive episode, (MADRS >19) Age:37 ±11 years M:40% Psychotic: 6% Rapid cycling: 34% Excl: YMRS≥15, history non-response to study drugs	(1) olanzapine-fluoxetine 6/25, 12/25, 6/50 or 12/50 mg/day, n=205 (2) Lamotrigine 150-200 mg/day, n=205	(1) 10.7/38.3 mg (2) 106.4 mg Benzodiazepines (22%) Anticholinergics (1%)	7	R1, D1, W1	≥50% improvement in MADRS (1) 141/205 (2) 122/205 Median time to response(days): (1) 17 (2) 23	MADRS ≤12, at last observation (1) 116/205 (2) 101/205 Median time to remission(days): (1) 32 (2) 41	CGI-S ≤3 (1) 147/205 (2) 132/205 Mean improvement sig greater for (1) than (2)	YMRS>15 at any time (1) 8/205 (2) 11/205	(1) 68/205 (2) 71/205	(1) 2/205 (2) 4/205	(1) 17/205 (2) 15/205	no data	no data	incomplete data Suicide attempts: (1) 1/205 (2) 2/205 All suicidal and self harm events: (1) 1/205 (2) 7/205	no data	AIMS: no sig diff between groups in severity of tardive dyskinesia (1) 48/205 (2) 0/205	
Thase et al. 2006 [22]	Bipolar I and II disorder, major depressive episode (HAM-D≥20, YMRS≤12) Age:37 ±11 years M:43% Excl: history non-response to >2 classes antidepressants for current episode. Current episode <4 weeks or >12 months	(1) quetiapine 600 mg/day, n=151 (2) quetiapine 300 mg/day, n=155 (3) placebo, n=161 [ITT cohort]	N/A Lorazepam and zolpidem during first 3 weeks - generally low, <4%	8	R1, D2, W1	≥50% improvement in MADRS (1) 88/151 (2) 93/155 (3) 71/161 Sig diff between (1) or (2) and (3) by week 2	MADRS ≤12 (1) 79/151 (2) 80/155 (3) 48/161 Sig diff between (2) and (3) by week 2, and for (1) and (3) by week 3	normal/not at all ill/borderline ill (1) 49/151 (2) 64/155 (3) 39/161 Much improved/very much improved (1) 91/151 (2) 95/155 (3) 62/161	YMRS ≥16 on 2 consec visits or at end point or AE of mania (using safety population) (1) 6/168 (2) 3/171 (3) 11/167	(1) 79/169 (2) 71/172 (3) 58/168	(1) 5/169 (2) 3/172 (3) 13/168	(1) 19/169 (2) 14/172 (3) 2/168	no data	no data	no data	(1) 7/169 (2) 3/172 (3) 1/168 (none T-R)	SAS, BARS No sig change from baseline in any group (1) 11/168 (2) 5/171 (3) 4/167	

QS = quality score; R = randomised; D = double blind; W = withdrawals or drop outs; CGI = clinical global impression; TE = treatment emergent; EP = extrapyramidal; AIMS = abnormal involuntary movement scale; SAS = Simpson-Angus rating scale; BARS = Barnes akathisia rating scale