Additional file 2: Trials of atypical antipsychotics in mania/mixed states - design, details, and outcomes

Reference [number]	Patients	Treatment	Median/modal dose	Concommitant medication	Duration (weeks)	QS	Response	Remission	CGI	Depression score	Symptomatic depression or affective episode
Less than 6 weeks											
Segal et al. 1998 [23]	**Bipolar disorder, manic Age: 34 years M: 22%**	**(1) risperidone 6 mg/day, n=15 (2) haloperidol 10 mg/day, n=15 (3) lithium to give 0.6-1.2mmol/L, n=15**	**no data**	**Benzodiazepines Anticholinergics for EP symptoms**	**4**	**R1, D1, W0**	**mean data only**	**no data**	**mean changes small and did not differ between groups**	**no data**	**no data**
Tohen et al. 1999 [24]	Bipolar disorder, manic or mixed Age:40±11 years M: 52% manic:83% mixed:17%	(1) olanzapine 5-20 mg/day, n=70 (2) placebo, n=69	15 mg/day	Benzodiazepines (86%) Anticholinergics for EP symptoms (9.4%) No sig differences	3	R1, D1, W1	≥50% dec in YMRS at endpoint (1) 34/70 (2) 16/69	no data	mean changes in CGI-BP scales given, no categorical data Overall: no sig diff between olanzapine and placeo	no data	no data
Berk et al. 1999 [25]	Bipolar disorder, manic Age: 31 years M: 57%	(1) olanzapine 10 mg/day, n=15 (2) lithium 800 mg/day	no data	Benzodiazepines Anticholinergics for EP symptoms	4	R1 D1 R1	mean data only	no data	mean changes in CGI-BP scales given, no categorical data Overall: olanzapine sig better than lithium	no data	no data
Tohen et al. 2000 [26]	Bipolar disorder, manic or mixed Age:39 years M: 50% manic:58% mixed:42%	(1) olanzapine 5-20 mg/day, n=55 (2) placebo, n=60	20 mg/day	Benzodiazepines (70%) Anticholinergics for EP symptoms (negligible) No sig differences	4	R1, D1, W1	≥50% dec in YMRS at endpoint (1) 35/55 (2) 25/60	Euthymic: YMRS ≤12 (1) 33/55 (2) 20/60	mean changes in CGI-BP scales given, no categorical data Overall: olanzapine better than placeo	Mean values improved in both groups. Greater improvement seen for olanzapine in subset with HAMD-21 ≥20 at baseline	≥3 point worsening in HAMD-21 (1) 6/55 (2) 10/60
Tohen et al. 2002 See Tohen 2003b for 47 week study [27]	Bipolar disorder, manic or mixed Age:40±12 years M: 42% manic:57% mixed:43% Excl: history of intolerance to olanzapine or divalproex	(1) olanzapine 5-20 mg/day, n=125 (2) divalproex 500-2500 mg/day, n=126	[mean modal] (1) 17 mg/day (2) 1401 mg/day	Benzodiazepines (65%) Anticholinergics for EP symptoms (13%, 10%) No sig differences	3	R1, D2, W1	≥50% dec in YMRS at endpoint (1) 68/125 (2) 52/126 Time to respsponse sig shorter in olanzapine group Greater mean change for nonpsychotic vs psychotic patients	YMRS≤12 (1) 59/125 (2) 42/126 Time to remission sig shorter in olanzapine group	no data	Mean values improved in both groups. Greater improvements seen in subset with HAMD-21 ≥20 at baseline	no data
Hirschfeld et al. 2004 [28]	Bipolar I disorder, manic Age:39±12 years M: 57% Excl: history of poor response to monotherapy with antimanic or antipsychotic drug	(1) risperidone 1-6 mg/day, n=134 (2) placebo, n=125	[mean modal] 4 mg/day More placeo pts took max dose, and dose escalation faster	Benzodiazepines (81%, 82%) Anticholinergics for EP symptoms (22%, 11%)	3	R2, D1, W1	≥50% dec in YMRS at any time (1) 55/127 (2) 29/119 Greater mean change for nonpsychotic vs psychotic patients	YMRS≤12 (1) 48/127 (2) 24/119	not ill/mildy ill at endpoint: (1) 68/127 (2) 31/119	Mean values improved in both groups	no data
Yatham et al. 2003 [29]	Bipolar disorder, manic or mixed Age:40(19-65) years M: 42% manic:92% mixed:8%	(1) risperidone 1-6 mg/day plus mood stabiliser, n=75 (2) placebo plus mood stabiliser, n=75 [ITT]	4 mg/day	Benzodiazepines (72%, 63%) Anticholinergics for EP symptoms (16%, 8%)	3	R2, D1, W1	≥50% dec in YMRS (1) 40/75 (2) 30/75	no data	much/v much improved at endpoint: (1) 40/75 (2) 31/75	Mean values decreased in both groups	depressive symptoms - given antidepressants (1) 1/75 (2) 2/75

Sachs et al. 2002 [30]	Bipolar disorder, manic or mixed Age:43(18-66) years M: 51% manic:79% mixed:21% Excl: sensitivity to any trial drug, lab value outside normal range	(1) risperidone 1-6 mg/day plus mood stabiliser, n=52 (2) haloperidol 2-12 mg/day plus mood stabiliser, n=53 (3) placebo plus mood stabiliser, n=51 [ITT]	[mean modal] (1) 4 mg/day (2) 6 mg/day	Benzodiazepines (67%, 64%, 59%) Anticholinergics for EP symptoms (17%, 20%, 8%) sig diff tween (2) and (3) for antichol	3	R1, D1, W1	mean data anly	no data	much/v much improved at endpoint: (1) 27/51 (2) 25/50 (3) 14/47	no data	no data
Sachs et al. 2004 [31]	Bipolar disorder, manic Age:41 years M: 56% Excl: intolerance or lack of response to quetiapine or clozapine, rapid cycling	(1) quetiapine 200-800 mg/day plus mood stabiliser, n=90 (2) placebo plus mood stabiliser, n=100 [ITT]	[mean last week dose] 504 mg/day No difference in use of mood stabilisers	Benzodiazepine and other sleep medication use limited and not sig diff in serum levels bet groups No anticholinergics	3	R1, D2, W1	≥50% dec in YMRS at endpoint (1) 44/81 (2) 29/89	YMRS≤12 (1) 37/81 (2) 23/89	much/v much improved (1) 41/81 (2) 28/89	Total scores decreased in both groups	MADRS ≥18 with inc ≥4 from baseline on two consec assess or at endpoint (1) 14/90 (2) 12/100
Yatham et al. 2004 [32]	Bipolar I disorder, manic Age:40(18-70) years M: 53% Excl: intolerance or lack of response to quetiapine, lithium, divalproex or clozapine	(1) quetiapine 200-800 mg/day plus mood stabiliser, n=185 (2) placebo plus mood stabiliser, n=185 [ITT]	[mean last week dose in responders] (1) 492 mg/day No difference in serum levels of mood stabilisers	Benzodiazepines, no anticholinergics	3	R1, D1, W1	≥50% dec in YMRS at endpoint (1) 103/185 (2) 77/185	YMRS≤12 (1) 90/185 (2) 61/185	much/v much improved (1) 108/185 (2) 80/185	Mean baseline values low, similar reduction for both groups	MADRS ≥18 with inc ≥4 from baseline on two consec assess or at endpoint (1) 19/185 (2) 18/185
Keck et al. 2003 [33]	Bipolar I disorder, manic or mixed Age:38(19-64) years M: 54% manic:65% mixed:35% Excl: history of hypersensitivity to antipsychotic drugs, previous treatment with ziprasidone	(1) ziprasidone 40-80 mg/day, n=131 (2) placebo, n=66 [ITT]	[mean last week dose 130 mg/day	Benzodiazepines, no sig diff bet groups Anticholinergics for EP symptoms	3	R2, D2, W1	≥50% dec in YMRS at endpoint (1) 66/131 (2) 23/66	no data	mean changes in CGI-BP scales given, no categorical data Overall: ziprasidone better than placeo	Sig greater red in mean score for ziprasidone than placebo	no data
Keck et al. 2003b [34]	Bipolar I disorder, manic or mixed Age:40±12 years M: 44% manic: 67% mixed: 33% Excl: non response to clozapine, anticipated requirement for prohibited drugs	(1) aripiprazole 30 mg/day, n=127 (2) placebo, n=127 [ITT]	[mean dose at endpoint] 28 mg/day	Benzodiazepines (86%, 85%) Anticholinergics for EP symptoms	3	R1, D1, W1	≥50% dec in YMRS (1) 51/127 (2) 24/127	no data	mean changes in CGI-BP scales given, no categorical data Overall: aripiprazole better than placeo	no data	no data
Potkin et al. 2005 [35]	Bipolar I disorder, manic or mixed Age: 39±12 years M: 51% manic: 60% mixed: 40%	(1) ziprasidone 80-160 mg/day, n=139 (2) placebo, n=66 [ITT]	[mean] (1) 112 mg/day (2) "slightly higher"	Benzodiazepines (73%, 62%) Anticholinergics for EP symptoms (25%, 6%)	3	R2, D2, W1	≥50% dec in MRS (SADS-CB) (1) 64/139 (2) 19/66	no data	mean changes in CGI-BP scales given, no categorical data Overall: ziprasidone better than placeo	Mean improvement greater for ziprasidone throughout study, but not sig	no data

Khanna et al. 2005 [36]	Bipolar I disorder, manic or mixed Age: 35 years M: 62% manic: 96% mixed: 4% Excl: rapid cycling, antidepressant-induced mania	(1) risperidone 1-6 mg/day, n=146 (2) placebo, n=144	no data	Benzodiazepines (99%) Antiparkinsonian med for EP symptoms (36%, 6%)	3	R1, D1, W1	≥50% dec in YMRS at endpoint (1) 107/146 (2) 52/144 No sig diff between psychotic/non-psychotic and manic/mixed subgroups	no data	not ill/mildy ill at endpoint: (1) 104/146 (2) 356/144	Mean baseline scores low, but improvement sig better in risperidone group than placebo	no data
Smulevich et al. 2005 [37]	Bipolar I disorder, manic or mixed Age: 40 years M: 52% manic/mixed: not given Excl: history poor response to antipsychotic monotherapy, rapid cycling	(1) risperidone 1-6 mg/day, n=154 (2) haloperidol 2-12 mg/day, n=144 (3) placebo, n=140	(1) 4 mg/day (2) 8 mg/day	Benzodiazepines (50%) Antiparkinsonian med for EPS	3	R1, D1, W1	≥50% dec in YMRS at 21 days (1) 74/154 (2) 68/144 (3) 46/140 No sig diff in change for nonpsychotic vs psychotic patients taking risperidone	no data	mean changes in CGI-BP scales given, no categorical data Overall: risperidone and haloperidol better than placeo, no sig diff between risperidone and haloperidol	Mean improvement in all groups: sig more in active groups than placebo	no data
Sachs et al. 2006 [38]	Bipolar I disorder, manic or mixed relapse, requiring hospitalisation, with YMRS≥20 at randomisation Age: 39 years M: 49% manic: 58% mixed: 42% rapid cyclinng: 18% Excl: history of no response to clozapine, previousaripiprazole trial	(1) aripiprazole 15-30 mg/day, n=136 (2) placebo, n=133	(1) 27.7 mg/day	Lorazepam	3	R1, D1, W1	≥50% dec in YMRS at 21 days (1) 72/136 (2) 42/132 Sig diff between groups by 7 days, and inc to 21 days Subgroups with rapid cycling and mixed episodes showed sig benefits for aripiprazole over placebo	no data	mean changes in CGI-BP scales sig greater for aripiprazole by day 7, no categorical data	Baseline scores low, non-sig improvement	no data
Six to 12 weeks												
Tohen et al. 2002b [39]	Bipolar disorder, manic or mixed, with inadequate response to monotherapy Age:41±11 years M: 48% manic: 52% mixed: 48%	(1) olanzapine 5-20 mg/day plus mood stabiliser, n=229 (2) placebo plus mood stabiliser, n=115	10 mg/day	Benzodiazepines (29%, 34%) Antiparkinsonian med for EPS	6	R1, D1, W1	≥50% dec in YMRS (1) 149/220 (2) 51/114 Median time to response (days) (1) 18 (2) 28 Cotherapy better than mono for non-psychotic patients	YMRS≤12 (1) 173/220 (2) 75/114 Median time to remission (days) (1) 14 (2) 22	mean changes in CGI-BP scales given, no categorical data	sig improvement in mean HAMD-21 for olanzapine group For subset with mixed episode and HAMD-21 ≥20 at baseline (n=21), sig greater reduction in group with olanzapine	As AE (1) 41/225 (2) 20/115
Zajecka et al. 2002 Efficacy to 3 weeks, Safety to 12 weeks in responders [40]	Bipolar I disorder, manic or mixed Age:38±12 years M: 54% manic:52% mixed:48% Excl: previous non-responders to olanzapine or divalproex	(1) olanzapine 5-20 mg/day, n=57 (2) divalproex 20 mg/kg/day-20 mg/kg/day+1000mg, n=63 First 3 weeks as inpatient	[mean maximum] (1) 15 (5-25) mg/day (2) 2115 (750-3250) mg/day	No sig diff between groups for rescue meds	12	R1, D2, W1	Change in MRS from baseline, at 3 weeks: both groups had decrease of about 50% with no sig diff between groups. Improvements maintained to 12 weeks, with no diff between groups	no data	Mean improvement in both groups: no sig diff, maintained to 12 weeks	Mean improvement in both groups: no sig diff, maintained to 12 weeks	incomplete data, but one case of serious depression in each group

Tohen et al. 2003 [41]	Bipolar I disorder, manic or mixed Age:40±13(18-86) years M: 40% manic:94% mixed:6%	(1) olanzapine 5-20 mg/day, n=234 (2) haloperidol 3-15 mg/day, n=219	[median at week 6] (1) 15 mg/day (2) 5 mg/day [median at week 12] (1) 10 mg/day (2) 3 mg/day	Benzodiazepines (60%, 65%) Anticholinergics for EP symptoms (18%, 60%)	12	R2, D1, W1	≥50% dec in YMRS at 6 weeks (1) 169/234 (2) 162/219 at 12 weeks (1) 154/160 (2) 130/138	YMRS≤12 and HAM-D ≤8 at 6weeks (1) 112/234 (2) 101/219 Median time to remission (days) (1) 34 (2) 29 Olanzapine sig better than haloperidol for non-psychotic patients	no data	Mean baseline values low. Small mean changes not likely to be clinically relevant For subgroups with mixed episode or HAMD-21 ≥20 at baseline, greater changes seen	affective episode (YMRS ≥15 and HAM-D ≥15 foll remission) (1) 16/122 (2) 15/101 Switch to depression (HAM-D ≥15 foll ≤8 at entry (1) 12/128 (2) 22/131
Bowden et al. 2005 [42]	Bipolar I disorder, manic Age:39(18-73) years M: 57% Excl: intolerance to quetiapine or lithium, or lack of response to clozapine, quetiapine or lithium. Clinically sig abbnormalities in ECG or labvalues	(1) quetiapine 100-800 mg/day, n=107 (2) placebo, n=95 (3) lithium to give 0.6-1.4 mEq/L, n=98	(1) [mean last week dose in responders] 3 weeks: 586 mg/day 12 weeks: 618 mg/day (2) [median serum conc] 3 weeks: 0.8 mEq/L 12 weeks: 0.8 mEq/L	Benzodiazepines (36%, 31%, 46%) Anticholinergics for EP symptoms (11%, 12%, 8%)	12	R1, D2, W1	≥50% dec in YMRS at 21 days (1) 57/107 (2) 26/95 (3) 52/98 at 84 days (1) 77/107 (2) 39/95 (3) 74/98	YMRS≤12 at 21 days (1) 50/107 (2) 21/95 (3) 48/98 at 84 days (1) 74/107 (2) 32/95 (3) 71/98	much/v much improved at 21 days (1) 68/107 (2) 29/95 (3) 63/98 at 84 days (1) 77/107 (2) 35/95 (3) 71/98	Mean baseline values low. At 3 weeks quetiapine sig better than placebo, at 84 days, both quetiapine and lithium better than placebo	MADRS ≥18 with inc ≥4 from baseline on two consec assess or at endpoint (1) 6/107 (2) 8/97 (3) 3/99 As AE: (1) 6/107 (2) 1/97 (3) 1/98
McIntyre et al. 2005 [43]	Bipolar I disorder, manic Age:43(18-79) years M: 37% Excl: rapid cycling, mixed episode, intolerance or lack of response to quetiapine or clozapine	(1) quetiapine 100-800 mg/day, n=102 (2) placebo, n=101 (3) haloperidol 2-8 mg/day, n=99	no data	Benzodiazepines (48%, 54%, 46%) Anticholinergics for EP symptoms (10%, 53%, 12%)	12	R1, D2, W1	≥50% dec in YMRS at 21 days (1) 43/101 (2) 35/100 (3) 55/98 at 84 days (1) 62/101 (2) 39/100 (3) 69/98 Greater mean change for nonpsychotic vs psychotic patients	YMRS≤12 at 21 days (1) 28/101 (2) 24/100 (3) 36/98 at 84 days (1) 62/101 (2) 38/100 (3) 62/98	much/v much improved at 21 days (1) 44/101 (2) 35/100 (3) 52/98 at 84 days (1) 51/101 (2) 30/100 (3) 59/98	Mean baseline values low. At 3 weeks quetiapine and haloperidol sig better than placebo, at 84 days, only quetiapine better than placebo	MADRS ≥18 with inc ≥4 from baseline on two consec assess or at endpoint (1) 3/102 (2) 9/101 (3) 8/99 As AE: (1) 2/102 (2) 4/101 (3) 1/99
Vieta et al. 2005 [44]	Bipolar I disorder, manic or mixed Age:42 (0.6) years M: 38% manic:89% mixed:11% Excl: rapid cycling, considered unresponsive to antipsychotics	(1) aripiprazole 15-30 mg/day, n=174 (2) haloperidol 10-15 mg/day, n=170 [ITT]	no data	Benzodiazepines No anticholinergics for sympt or prophylact treatment of EP sympt	12	R1, D1, W1	≥50% dec in YMRS at 3 weeks (1) 88/174 (2) 72/170 at 12 weeks (1) 86/174 (2) 48/170 ≥50% dec in MADRS at 3 weeks (1) 80/174 (2) 63/170 at 12 weeks (1) 80/174 (2) 56/170	YMRS<12 at 3 weeks (1) 61/174 (2) 53/170 at 12 weeks (1) 87/174 (2) 46/170	mean changes in CGI-BP scales given, no categorical data	≥50% dec in MADRS at 3 weeks (1) 89/174 (2) 63/170 at 12 weeks (1) 89/174 (2) 56/170 Sig diff in mean scores up to week 6, then ns diff	CGI-BP depression scale dec ≥2 points (1) 19/173 (2) 29/164 AsAE: (1) 20/175 (2) 24/169

Longer than 12 weeks

Tohen et al. 2003b See Tohen 2002, for analysis to 3 weeks [45]	Bipolar disorder, manic or mixed Age:40±12 years M: 42% manic:57% mixed:43% Excl: history of intolerance to olanzapine or divalproex	(1) olanzapine 5-20 mg/day, n=125 (2) divalproex 500-2500 mg/day, n=126	(1) 16 mg/day (2) 2585 mg/day	Benzodiazepine use limited Anticholinergics to treat EP symptoms	47	R1, D2, W1	Mean YMRS scores sig better for olanzapine than divalproex from wk 2 to 15, then no sig diff wk 30 to 47 Mean HAM-D scores non sig better for olanzapine than divalproex	YMRS≤12 (1) 71/125 (2) 57/126 Median time to remission (days) (1) 14 (2) 62 YMRS≤12 and MADRS≤8 at endpoint (1) 39/125 (2) 39/126	no sig diff between groups	no data	symp relapse into affective episode (YMRS≥15 or HAM-D ≥15 foll remission) (1) 14/33 (2) 13/23 As AE: (1) 43/125 (2) 38/126
Tohen et al. 2004 See Tohen 2002b for parent study [46]	Bipolar I disorder with remission of manic episode after treatment with olanzapine plus lithium or valproate Age: 41 (19-69) years M:48% manic:50% mixed:50% Excl: history of intolerance to olanzapine	additional (1) olanzapine 5-20 mg/day plus lithium or valproate, n=51 (2) placebo plus lithium or valproate, n=48	9 mg/day lithium or valproate doses very similar between groups	Benzodiazepine use limited (29%, 20%) Anticholinergics to treat EP symptoms (15%, 10%)	78	R2, D2, W1	n/a	n/a	no data	no data	Sympt relapse into affective episode (YMRS +/or HAM-D≥15) without symptoms initially (1) 11/30 (2) 21/38 Median time to relapse (days) (1) 163 (2) 42 Depression alone: (1) 7/30 (163 days) (2) 15/38 (55 days) Mania alone: (1) 6/30 (172 days) (2) 11/38 (59 days)
Tohen et al. 2005 [47]	Bipolar disorder with remission of manic/mixed episode after open-label treatment with olanzapine plus lithium for 6 weeks Age: 42 (13) years M:47% manic:93% psychotic:26% Excl: history of intolerance or lack of response to lithium or olanzapine	(1) olanzpine 5-20 mg/day, n=217 (2) lithium to give 0.6-1.4 mEq/L, n=214 Patients started on open-label doses of drugs, then 4 week d-b taper to monotherapy	(1) 12 mg/day (2) 1103 mg/day	Benzodiazepine use limited (36%, 52%) Anticholinergics to treat EP symptoms (7%, 8%)	52	R2, D2, W1	n/a	n/a	no data	no data	Sympt recurrence of any mood episode (YMRS +/or HAM-D≥15) (1) 65/217 (2) 83/214 Mania: (1) 30/217 (2) 50/214 Depression: (1) 34/217 (2) 23/214 Time to recurrence not sig diff between groups

Tohen et al. 2006 [48]	Bipolar I disorder with remission of manic/mixed episode after open-label treatment with olanzapine for 6-12 weeks Age: 40 (12) years M:39% manic:67% mixed:33% psychotic:18% Excl: intolerance to minimum dose of olanzapine in open-lael phase	(1) olanzapine 5-20 mg/day, n=225 (2) placebo, n=136	12.5 mg/day	Benzodiazepine use limited (27%, 36%) Anticholinergics to treat EP symptoms (4%, 4%)	48	R1, D1, W1	n/a	n/a	n/a	no data	Sympt recurrence of any mood episode (YMRS +/or HAM-D≥15) (1) 105/225 (2) 109/136 Mania: (1) 27/225 (2) 44/136 Depression: (1) 68/225 (2) 53/136 Mixed: (1) 10/225 (2) 12/136 Time to any relapse: (1) 174 days (2) 22 days Olanzapine better for pts with/w'out rapid cycling and with/w'out psychotic features, and manic/mixed index episode
Keck et al. 2006 [49]	Bipolar I disorder with recent stabilisation of manic/mixed episode after treatment aripiprazole (YMRS<10, MADRS≤13 for ≥6 weeks) Age: 40±1 years M:33% manic:70% mixed:30% Excl: history of cognitive disorder, schizophrenia/ schizoaffective disorder,psychoactive or substance use disorder, unresponsive to clozapine, intolerence to aripiprazole	(1) aripiprazole 15-30 mg/day, n=78 (2) placebo, n=83	mean 25mg/day	Lorazepam (39%, 46%) Anticholinergics for EPS (39%, 31%) Analgesic/antipyretic (34%, 36%)	26	R1, D1, W1	n/a	n/a	n/a	no data	Relapse (withdrawal due to LoE) (1) 19/77 (2) 36/83 Manic relapse: (1) 6/77 (2) 19/83 Depressive relapse: (1) 9/77 (2) 11/83 Mixed/unknown: (1) 4/77 (2) 6/83 Time to relapse sig longer for (1) than (2)

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

Discontinuations				Adverse events				Scale-defined adverse events	
All cause	**LoE**	**AE**	**T-E depression**	**All cause**	**Severe**	**Serious**	**T-R**	**EPS**	**Weight gain ≥7%**
no data	**no data**	**no data**	**no data**	**no data**	**no data**	**no data**	**no data**	**SAS** **Mean score in lithium group lower than in risperidone or halooperidol groups**	**no data**
(1) 27/70 (2) 45/69	(1) 20/70 (2) 33/69	(1) 0/70 (2) 2/69	no data	no data	no data	no data	no data	SAS, BARS, AIMS Infrequent No sig diff	no data
(1) 1/15 (2) 3/15	no data	(1) 1/15 (2) 1/15	no data	no data	no data	no data	no data	SAS , BARS No sig diff in SAS between groups Akathisia (1) 0/15 (2) 0/15	no data
(1) 21/55 (2) 35/60	(1) 15/55 (2) 23/60	(1) 2/55 (2) 1/60	no data	no data	no data	no data	no data	SAS, BARS Infrequent No sig diff	no data
(1) 39/125 (2) 45/126	(1) 11/125 (2) 12/126	(1) 12/125 (2) 9/126	no data	no data	no data	no data	no data	SAS, BARS, AIMS No sig diff	no data
(1) 59/134 (2) 73/125	(1) 19/134 (2) 45/125	(1) 10/134 (2) 7/125	no data	no data	no data	no data	no data	EPRS Small but sig inc Risp vs Placebo overall but not indiv subscales	no data
(1) 12/75 (2) 14/75 Disc early and entered open (1) 15/75 (2) 25/75	(1) 2/75 (2) 1/75	(1) 1/75 (2) 3/75	no data	(1) 43/75 (2) 38/75	no data	no data	no data	EPRS No sig diff in means	no data

(1) 18/52 (2) 28/53 (3) 25/51	(1) 3/52 (2) 3/53 (3) 5/51	(1) 2/52 (2) 1/53 (3) 2/51	no data	(1) 42/52 (2) 49/53 (3) 43/51	no data	no data	no data	EPRS Significantly greater increase with haloperidol than placebo.	no data
(1) 34/90 (2) 51/100	(1) 7/90 (2) 14/100	(1) 5/90 (2) 6/100	no data	no data	no data	no data	no data	SAS, BARS Low levels No sig diff	(1) 4/90 (2) 1/100
(1) 52/197 (2) 71/205	(1) 22/197 (2) 30/205	(1) 6/197 (2) 8/205	no data	no data	no data	no data	no data	SAS, BARS Small changes No sig diff	no data
(1) 65/140 (2) 39/70	(1) 27/140 (2) 25/70	(1) 9/140 (2) 3/70	no data	(1) 126/140 (2) 54/70	no data	no T-R	(1) 99/140 (2) 38/70	SAS, BARS, AIMS Infreq No sig diff	no data
(1) 76/130 (2) 104/132 Entered open-label treatment (1) 17/130 (2) 37/132	(1) 13/130 (2) 16/132 but see open label treatment	(1) 14/130 (2) 13/132	no data	no data	no data	(1) 4/130 (2) 4/132	no data	SAS, BARS small but sig inc in (1) AIMS no sig diff	(1) 2/127 (2) 0/127
(1) 55/140 (2) 30/66	(1) 18/140 (2) 19/66	(1) 9/140 (2) 1/66 T-R (1) 8/139 (2) 1/66	no data	(1) 109/139 (2) 44/66	(1) 4/139 (2) 1/66	no data	(1) 90/139 (2) 27/66	SAS, BARS, AIMS No sig diff	(1) 6/125 (2) 2/59

(1) 16/146 (2) 42/144	(1) 7/146 (2) 21/144	(1) 5/146 (2) 3/144	no data	no data	most mild to moderate	similar in both groups	no data	ESRS Small, insig changes	no data
(1) 17/154 (2) 14/144 (3) 21/140	(1) 5/154 (2) 2/144 (3) 9/140	(1) 6/154 (2) 4/144 (3) 7/140	no data	no data	most mild to moderate	no data	no data	ESRS Sig diff from placebo for haloperidol, not risperidone	no data
(1) 61/136 (2) 63/133	(1) 12/136 (2) 28/133	(1) 12/136 (2) 10/133	no data	no data	Somnolence and gi events with aripiprazole generally mild to moderate and transient	(1) 12/136 (2) 10/133	no data	SAS, AIMS Changes small and not sig diff between groups BARS Changes small, with sig diff at endpoint, but no sig diff between number of patients with score ≥2 (clinical sig)	(1) 1/136 (2) 5/133

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(1) 69/229 (2) 33/115	(1) 7/229 (2) 14/115	(1) 25/229 (2) 2/115	(1) 0/229 (2) 2/115	no data	no data	no data	no data	SAS, BARS, AIMS No sig diff	no data
(1) 38/57 (2) 45/63	(1)11/57 (2) 14/63	(1) 5/57 (2) 7/63	no data	sig less with olanzapine than divalproex	no data	(1) 2/57 (2) 5/63 T-R (1) 1/57 (2) 1/63	no data	SAS, BARS No sig diff	no data

(1) 94/234 (2) 103/219	(1) 35/234 (2) 33/219	(1) 19/234 (2) 25/219	no data	no data	no data	no data	no data	SAS, AIMS, BARS EPS sig worse with haloperidol Parkinsonism (1) 24/187 (2) 92/169 Akathisia (1) 20/203 (2) 78/193 Dyskinesia (1) 7/223 (2) 19/208	(1) 91/229 (2) 34/211
(1) 35/107 (2) 62/97 (3) 31/98	(1) 16/107 (2) 38/97 (3) 12/98	(1) 7/107 (2) 4/97 (3) 6/98	no data	no data	most mild to moderate	no data	no data	SAS, BARS EPS rel events (1) 14/107 (2) 9/97 (3) no data Overall no sig diff between quetiapine and placebo. More tremor in lithium group	no data
(1) 47/102 (2) 59/101 (3) 45/99	(1) 27/102 (2) 43/101 (3) 25/99	(1) 5/102 (2) 6/101 (3) 10/99	(1) 1/102 (2) 3/101 (3) 0/99	no data	no data	no data	no data	SAS, BARS No sig diff bet (1) and (2), but (3) sig worse	(1) 13/102 (2) 4/101 (3) 5/99
at 3 weeks (1) 41/175 (2) 77/172 at 12 weeks (1) 86/175 (2) 122/172 Time to disc greater for aripiprazole than haloperidol	(1) 30/175 (2) 10/172	(1) 32/175 (2) 84/172 T-R (1) 0/175 (2) 1/172	no data	no data	no data	(1) 6/175 (2) 12/172	no data	SAS, BARS, AIMS show minimal change for aripiprazole, sig worsening for haloperidol	no data

(1) 106/125 (2) 106/127	(1) 24/125 (2) 28/126	(1) 31/125 (2) 25/126	no data	no data	no data	no data	no data	SAS, BARS, AIMS No sig diff	(1) 29/123 (2) 22/123
(1) 35/51 (2) 43/48	(1) 13/51 (2) 17/48	(1) 5/51 (2) 8/48	no data	no data	no data	no data	no data	SAS, BARS No sig diff (Akathisia) (1) 4/51 (2) 3/48 (Parkinsonism) (1) 3/51 (2) 4/48 (Dyskinesia) (1) 0/51 (2) 2/48	(1) 14/51 (2) 3/48
(1) 116/217 (2) 144/214	(1) 31/217 (2) 34/214	(1) 41/217 (2) 55/214	no data	no data	no data	no data	no data	SAS, BARS, AIMS Changes small and not sig diff between groups (Akathisia) (1) 0/189 (2) 4/197 (Parkinsonism) (1) 6/177 (2) 5/176 (Dyskinesia) (1) 3/206 (2) 2/209	(1) 64/217 (2) 21/214

(1) 72/225 (2) 18/136 19/225 olanzapine pts lost to foll up, vs 5/136 placebo	(1) 4/225 (2) 2/136	(1) 17/225 (2) 0/136	no data	no data	no data	(1) 7/225 (2) 13/136 most due to worsening of illness	no data	SAS, BARS, AIMS Few events, not sig diff between groups (Akathisia) (1) 9/194 (2) 1/119 (Parkinsonism) (1) 5/206 (2) 0/118 (Dyskinesia) (1) 0/216 (2) 1/113	(1) 36/225 (2) 3/136
(1) 39/78 (2) 55/83	(1) 19/78 (2) 36/83	(1) 5/78 (2) 1/83	(1) <3% (2) 6/83	(1) 57/77 (2) 58/83	no data	(1) 6/77 (2) 11/83	no data	SAS, AIMS, BARS changes minimal SAS≥15 (moderate severity): (1) 7/76 (2) 6/81 BARS≥3 (moderate to severe): (1) 4/76 (2) 2/81 EPS more frequent with aripiprazole than placebo (Akathisia) (1) 5/77 (2) 1/83 (Tremor) (1) 7/77 (2) 1/83 (Hypertonia) (1) 3/77 (2) 1/83	(1) 7/56 (2) 0/60