**Appendix Table E-2. Data abstraction of randomized controlled trials of pharmacological interventions**

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Amr, 2013 | Amman, Jordan;  10/2009 to  9/2011 | Age: 18-60;  Met DSM diagnosis of schizophrenia; First episode of schizophrenia; Exclusion: current or past use of antipsychotics; concurrent DSM Axis 1 diagnosis; DSM-VI Axis II diagnosis of borderline personality disorder, antisocial personality, substance dependence or abuse, clinically significant or unstable medical illness. | Initial doses:  haloperidol=5 mg/day  quetiapine=200 mg/day; Co-admin of psychotropic medications not allowed, except lorazepam and zopiclone and biperiden.  Dose at 12 weeks: haloperidol=14.2 mg; quetiapine=705.8 mg | 12 weeks | Age: haloperidol=30.7; quetiapine=31.3.  Sex (M/F): H: 21/12; Q: 25/15; Duration of illness (mos; SD): haloperidol=4.8 (1.6); quetiapine=5.0 (2.1);  Marital status (unmarried/married): haloperidol=19/14; quetiapine=23.17;  Employment (unemployed/ employed): haloperidol= 22/11; quetiapine=28/12;  Education (above/below secondary): haloperidol=23/10; quetiapine=31/9;  Income (satisfactory/ unsatisfactory): haloperidol=7/26; quetiapine=8/32;  Type of schizophrenia (paranoid/not paranoid): haloperidol=24/9; quetiapine=32/8. |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Amr, 2013 | NR | 156 | **PANSS Positive:**  haloperidol (n=33); quetiapine (n=40); t-test; p-value:  Baseline: haloperidol=23.8 (SD=5.12); quetiapine=26.0 (SD=4.41);  t=1.90; p=0.06  6 weeks: haloperidol=18.2 (5.90); quetiapine=21.3 (2.51); t=2.86;  p=0.006;  12 weeks: haloperidol=18.9 (7.84); quetiapine=15.3 (2.18); t=2.55;  p=0.013  **PANSS Negative:**  Baseline: haloperidol=22.2 (8.51); quetiapine 21.3 (6.38); t=0.48;  p=0.63  6 weeks: haloperidol=20.4 (8.28); quetiapine=18.9 (6.21); t=0.86;  p=0.39  12 weeks: haloperidol=15.5 (7.39); quetiapine=11.6 (4.76); t=2.58;  p=0.012  **PANSS General Psychopathology:**  Baseline: haloperidol=39.0 (11.01); quetiapine=43.4 (8.36); t=1.939;  p=0.056  6 weeks: haloperidol=35.1 (11.3); quetiapine=37.3 (11.01); t=0.79;  p=0.43  12 weeks: haloperidol=23.8 (6.24); quetiapine=27.7 (6.33); t=2.58;  p=0.012  **PANNS Depression/Anxiety:**  Baseline: haloperidol=10.18 (2.11); quetiapine-9.88 (1.92); t=0.6;  p=0.55  6 weeks: haloperidol=9.88 (1.95); quetiapine=9.29 (1.64); t=1.53;  p=0.183  12 weeks: haloperidol=9.56 (1.87); quetiapine=4.74 (1.50); t=11.92;  p<0.0001  **PANSS Total:**  Baseline: haloperidol=82.3 (21.88); quetiapine=90.8 (11.32); t=1.939;  p=0.056  6 weeks: haloperidol=73.8 (19.50); quetiapine=77.6 (8.90); t=1.02;  p=0.31  12 weeks: haloperidol=58.3 (16.59); quetiapine=54.8 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Amr, 2013 | Haloperidol= out of 78; quetiapine= out of 78;  Akathisia: haloperidol=53/78 (78%): quetiapine=0; p<.00001; Cold: haloperidol=23 (29.5%); quetiapine=18 (23%); p=0.363  Headache: haloperidol=9 (11.5%); quetiapine=28 (35.9%); p<0.0001; Fatigue: haloperidol=66 (84.6%); quetiapine=52 (66.6%); p=0.009; Parkinsonism: haloperidol=52 (66.6%); quetiapine=0; p<0001; Insomnia: haloperidol=37 (47.4%); quetiapine=41 (52.5%); p=0.521; Dizziness: haloperidol=28 (35.9%); quetiapine=22.28.2%); p=0.303.  **SAS: H (n-33); Q (n-40); t-test; p-value**  6 weeks: haloperidol=5.94 (1.83); quetiapine=0.18 (0.38); t=18.020; p<0.0001;  12 weeks haloperidol=8.62 (2.08); quetiapine=0.26 (0.45); t=22.949; p<0.0001 | Not stated | Poor |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Citrome, 2016 | US | Adult patients (18 to 65 years) with DSM-  IV-TR diagnosis of schizophrenia confirmed by the MINI International Neuropsychiatric Interview. | Brexpiprazole 3 mg/day  (N=64)  vs.  Aripiprazole 15 mg/day  (N=33) | 6 weeks | Age, year: 42.2  Gender, % Female: 29.2% Ethnicity, %:  White: 23.1%  African-American: 73.9% Asian: 0.8%  Other: 2.3% |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Citrome, 2016 | PANSS total score baseline, mean: 93.7  Duration of current episode: 3.1 weeks | 97 | Brexpiprazole vs. Aripiprazole  Change in baseline PANSS total score, LS mean at 6 w:  -22.9; P<0.0001 vs. -19.4; P<0.0001  Response rate at 6 w, % (n/N)\*: 60.9% (39/64), (95% CI 47.9 to 72.9)  vs. 48.5% (16/33), (95% CI 30.8 to 66.5) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Citrome, 2016 | Brexpiprazole vs. Aripiprazole  Overall AEs, % (n/N): 57.8% (37/64) vs. 63.6% (21/33) Withdrawal due to AEs, % (n/N): 4.7% (3/64) vs. 3.0% (1/33) All-cause mortality: 0 vs. 0  Clinically relevant weight gain ( ≥7% increase from baseline) at 6 weeks, % (n/N): 35% (14/40)  vs. 19% (4/21)  Extrapyramidal AEs, % (n/N): 14.1% (9/64) vs. 30.3% (10/33).  Simpson Angus, Abnormal Involuntary Movement, and BARS global clinical assessment scales used but no differences were found between them. | Funding: Otsuka Pharmaceutical  Commercialization and Development Inc.; H. Lundbeck A/S  \*Reduction of 30% or more from baseline in PANSS total score, or CGI-I score of 1 or 2. | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Crespo-Facorro, 2011  Crespo-Facorro, 2012  Spain | Spain | Age 15-60 years, experiencing first psychotic episode, <6 weeks lifetime antipsychotic treatment, meet DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder. Excluded DSM-IV criteria for drug dependence or mental retardation, history of neurological disease or head injury. | Haloperidol: n, 56; mean  dose, 2.9 (1.4) mg/day Olanzapine: n, 55; mean dose, 10.1 (3.9) mg/day Risperidone: n, 63; mean dose, 3.4 (1.8) mg/day | 156 weeks | Age, mean: 27.4  Gender: 38% female  Ethnicity: NR |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Crespo-Facorro, 2011  Crespo-Facorro, 2012  Spain | Age, psychosis onset: 26 years  Duration of illness: 25 months  Duration of psychosis: 11 months  Diagnosis: Schizophrenia, 60.8%; Schizophreniform,  24.1%; Schizoaffective, 2.4%, Brief psychotic disorder,  5.4%; Unspecified psychotic disorder, 7.2% | 174 | Haloperidol vs. Olanzapine vs. Risperidone:  Relapse Rate: 11.1% vs. 18.5% vs. 13.8%; p=0.541  Time to relapse, mean (95% CI): 10.9 (10.89-11.72) vs. 10.78 (9.99-11.56) vs. 10.98 (10.25-11.71); p=0.857  Relapse, adherent vs. nonadherent: 11.2% vs. 26.9%, p=0.040  Remission at 1 year: 25% vs. 32.7% vs. 34.9%; x 2=1.471, p=0.479  Remission at 1 year, patients continuing on drug: 25% vs. 43.2% vs. 41.5%, p=0.308  Remission, adherent vs. nonadherent: 36.9% vs. 27.6%, p=0.347  Treatment discontinuation at 1 year: (Haloperidol %, Olanzapine %, Risperidone %, p) Discontinuation for any cause: 57% (32/56) vs. 33% (18/55) vs. 35% (22/63) Discontinuation due to adverse events: 25% (14/56) vs. 6% (3/55) vs. 11% (7/63) Treatment discontinuation at 3 years:  Discontinuation for any cause: 80% (45/56) vs. 51% (28/55) vs. 67% (42/63) Discontinuation for adverse events: 32% (18/56) vs. 13% (7/55) vs. 25% (16/63) Adherence and global functioning at 3 year followup:  Adherence NSD between treatment (83.3% haloperidol, 68.2% olanzapine, 78.9% risperidone, p=0.605)  Global functional outcome NSD between treatment (81.8% haloperidol-treated, 63% olanzapine-treated, 71.4% risperidone-treated with good functionality at 3 year followup, p=0.505)  Clinical efficacy:  No advantages to any of the 3 treatments in reduction of symptomology at 3 years  Safety:  NSD in increment of extrapyramidal signs @ 3 yrs between treatments (p=0.132) NSD in treatment-emergent parkinsonism between treatment arms (p=0.114)  Greater increase in akathisia severity w/ haloperidol treatment @ 3 yr assessment (p=0.013) Sig. increase in akathisia severity in risperidone-treated patients compared to olanzapine-treated patients (p=0.042)  Sig. higher number in haloperidol-treated group experienced treatment-emergent akathisia compared to risperidone-treated and olanzapine-treated patients (p=0.013) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Crespo-Facorro, 2011  Crespo-Facorro, 2012  Spain | Haloperidol % vs. Olanzapine % vs. Risperidone %, P  Concentration difficult: 9.1 vs. 7.7 vs. 0.0, 0.419  Asthenia: 9.1 vs. 23.1 vs. 0.0, 0.057  Daytime drowsiness: 0.0 vs. 34.6 vs. 10.0, 0.022  Increased sleep hours: 9.1 vs. 11.5 vs. 5.0, 0.739  Akathisia: 27.3 vs. 0.0 vs. 5.0, 0.011  Sialorrhea: 0.0 vs. 0.0 vs. 15.0, 0.053  Dry mouth: 0.0 vs. 7.7 vs. 10.0, 0.571  Weight gain: 9.1 vs. 26.9 s. 20.0, 0.473  Amenorrhea (only females, n=23): 0.0 vs. 0.0 vs. 40.0, 0.043  Sexual dysfunctions (only males, n=34): 14.3 vs. 5.9 vs. 40.0, 0.078 | NR | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Detke, 2014 | Multisite, USA  and France | Outpatients (18 to 65 years) who met the criteria for schizophrenia based on DSM-IV or the DSM-IV Text Revision. Required to be ‘‘at risk for relapse’’ (at least 2 episodes of clinical worsening of schizophrenia symptoms in the previous  24 months) | Olanzapine long-acting  injection 405 mg/4 weeks  (n=264)  vs.  Oral olanzapine 10 mg/day  (n=260) | 2 years | Age, mean years: 40.9  Gender, % female: 32.8  Ethnicity, %: White: 62.0  African: 16.8  Hispanic: 8.0  East Asian: 8.8  West Asian: 3.6  Native American: 0.8 |
| Di Fiorino 2014 | Italy | Adults (aged 18 to 65 years) with a documented DSM-IV diagnosis of diagnosis of schizophrenia or schizoaffective disorder. | Quetiapine extended-  release 400 to 800 mg/day  (n=109)  vs.  Risperidone 4 to 6 mg/day  (n=107) | 12 weeks | Age, years: 42.3  Gender, % female: 43.3  Ethnicity, %: White: 100 |
| Durgam, 2014 | International | Adults ages 18 to 60 years with schizophrenia (first episode excluded). | Cariprazine 1.5 mg/day  (n=145) vs.  Cariprazine 3.0 mg/day  (n=146) vs.  Cariprazine 4.5 mg/day  (n=147) vs.  Risperidone 4.0 mg/day  (n=140)  (Placebo arm also included.) | 6 weeks | Age, mean years: 36.5  Gender, % female: 31.0  Ethnicity, %: White: 50.0  African American: 24.0% Asian: 25.0  Other: 0.7  (Placebo arm excluded.) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Detke, 2014 | Age of onset of schizophrenia, mean y (SD): 26.2 (8.9)  Previous episodes in last 24 months, mean (SD): 2.7 (1.6) Length of current episode, mean days (SD): 175.0 (148.0) Poor medication adherence, n (%): 24.0 (4.6) | 524 | Olanzapine long-acting injection vs. oral olanzapine  All-cause discontinuation rate, %: 53.8 vs. 51.2; p=0.600  Time to all-cause discontinuation, median days: 645 vs. 678; p=0.612  Rate of relapse, %: 20.1 vs. 18.5, p=0.659  Time to relapse/rescue, median days: 539 vs. 281; p<0.001  Baseline-to-endpoint least-squares mean change on PANSS total score, (SE):  -0.82 (1.2) vs. -1.14 (1.2); p=0.834 |
| Di Fiorino 2014 | PANSS severity of illness score: 101.4  Schizoaffective, %: 47.7 | 216 | Quetiapine extended-release 400 to 800 mg/day vs. risperidone 4 to 6  mg/day  PANSS total score, LSM (SD): -30.0 (22.9) vs. -21.1 (23.8) Treatment difference: -8.9, P=0.0002 |
| Durgam, 2014 | Duration of illness: 11.5 years  Duration of current illness/psychosis: less than 2 weeks to be eligible  Hospitalization data (current): NR Severity of illness: 97.3 (PANSS) Schizoaffective: 0% (excluded) Substance use: 0% (excluded)  Antipsychotic drug naïve: first episode of psychosis excluded | 578  (active treatment arms) | Cariprazine 1.5 mg/day vs. cariprazine 3.0 mg/day vs. cariprazine 4.5  mg/day vs. risperidone 4.0 mg/day  PANSS responders (≥30% improvement from baseline): % (n/N)  31.4 (44/140) vs. 35.7 (50/140) vs. 35.9 (52/145) vs. 43.5 (60/138) (No p-values comparing active treatments reported.) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Detke, 2014 | Olanzapine long-acting injection vs. Oral olanzapine  Any adverse event, n/N (%): 182/264 (68.9) vs. 176/260 (67.7) Discontinuations due to adverse events, n/N (%): 26/264 (9.8) vs. 25/260 (9.6) Death, n/N (%): 0/264 vs. 2/260 (0.8)  Weight increased, n/N (%): 44/264 (16.7) vs. 43/260 (16.5) Weight decreased, n/N (%): 15/264 (5.7) vs. 14/260 (5.4)  Extrapyramidal symptoms/akathisia, n/N (%): 7/264 (2.7) vs. 10/260 (3.8) | Eli Lilly and Co. | Poor |
| Di Fiorino 2014 | Quetiapine extended-release 400 to 800 mg/day vs. risperidone 4 to 6 mg/day  Overall AE, n/N (%): 40/107 (37.4) vs. 36/103 (35.0) Withdrawals due to AE, n/N (%): 10/107 (9.4) vs. 7/103 (6.8) | AstraZeneca Italy  \*Included disorientation, psychotic disorder, delusion, and extrapyramidal syndrome vs. fainting, acute psychosis, acute respiratory failure, social stay hospitalization, and cardiocirculatory arrest | Fair |
| Durgam, 2014 | Cariprazine 1.5 mg/day vs. cariprazine 3.0 mg/day vs. cariprazine 4.5 mg/day vs. risperidone  4.0 mg/day  Treatment-emergent adverse events: % (n/N)  68.3 (99/145) vs. 71.2 (104/146) vs.73.5 (108/147) vs. 67.9 (95/140)  WAE: % (n/N)  9.7 (14/145) vs. 5.5 (8/146) vs. 8.2 (12/147) vs. 9.3 (13/140)  Extrapyramidal disorder (treatment-emergent):  9.0 (13/145) vs. 8.9 (13/146) vs. 11.6 (17/142) vs. 12.9 (18/140) | Forest Research Institute and  Gedeon Richter Plc. | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Fleischhacker, 2014  ASPIRE EU, NCT00706654 | International | Adults ages 18 to 60 years, DSM-IV-TR schizophrenia for ≥3 years and a history of symptom exacerbation when not receiving antipsychotic treatment. | Aripiprazole once-monthly  400 mg (n = 265)  vs.  Oral aripiprazole 10 to 30 mg/day (n = 266)  vs.  Aripiprazole once-monthly  50 mg (n = 131) | 38 weeks | Age, mean years: 41.0  Gender, % female: 38.7  Ethnicity, %: White: 58.5  Black or African American: 23.1  Asian: 10.4  Other: 8.0 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Fleischhacker, 2014  ASPIRE EU, NCT00706654 | PANSS total score, mean: 56.9  CGI-Severity score, mean: 3.07  CGI-Improvement score, mean: 3.2 | 662 | Aripiprazole once-monthly 400 mg vs. oral aripiprazole (10 to 30  mg/day) vs. aripiprazole once-monthly 50 mg  Estimated relapse rate, %: 7.12 vs. 7.76 vs. 21.80  Treatment difference: -0.6 (95% CI -5.26 to 3.99) Discontinued, n (%): 69 (26) vs. 83 (33.1) vs. 70 (53.4)  Observed impending relapse (ITT sample): 22/265 (8.30) vs. 21/266 (7.89) vs. 29/131 (22.14); HR (vs. aripiprazole once-monthly 50 mg)  3.158 (95% CI 1.81 to 5.50) vs. 3.131 (95% CI 1.78 to 5.49) Responders (ITT sample), %: 237/264 (89.8) vs. 235/263 (89.4) vs.  97/129 (75.2)  Remitters (ITT sample), %: 105/215 (48.8) vs. 107/201 (53.2) vs. 43/72 (59.7)  PANSS Total Score (efficacy sample, LOCF):  Change from baseline at w 38, least square mean (SE): -1.66 (0.72)  vs. 0.58 (0.71) vs. 3.08 (1.01)  CGI Severity (efficacy sample, LOCF):  Change from baseline at w 38, least square mean (SE): -0.13 (0.05)  vs. 0.05 (0.05) vs. 0.23 (0.07)  CGI Improvement (efficacy sample, LOCF):  At week 38, mean (SD): 3.27 (1.16) vs. 3.66 (1.16) vs. 4.02 (1.32) Safety sample, observed cases:  SAS total score, change from baseline at week 38, LS mean (SE): -0.16 (0.09) vs. -0.22 (0.09) vs. -0.21 (0.16)  AIMS movement rating score, change from baseline at week 38, LS  mean (SE): -0.00 (0.07) vs. -0.11 (0.07) vs. -0.01 (0.12)  BARS global score, change from baseline at week 38, LS mean (SE):  0.06 (0.03) vs. -0.05 (0.03) vs. -0.06 (0.06) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Fleischhacker, 2014  ASPIRE EU, NCT00706654 | Aripiprazole once-monthly 400 mg vs. oral aripiprazole (10 to 30 mg/day) vs. aripiprazole once-  monthly 50 mg  Discontinued due to AE, n (%): 8 (3.0) vs. 7 (2.6) vs. 7 (5.3) Weight increased, n (%): 24 (9.1) vs. 35 (13.2) vs. 7 (5.3) Suicidality, safety sample, observed cases:  CGI-SS, change from baseline at week 38, LS mean (SE): -0.01 (0.10) vs. 0.00 (0.00) vs. -0.02 (0.13)  C-SSRS, change from baseline at week 38, LS mean (SE): -0.1 (1.0) vs. 0.1 (1.3) vs. 0.0 (0.0) | Otsuka Pharmaceutical  Commercialization, Inc. | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Green, 2015 | CMHCs and VA  clinics (four total) | Age 18-65, with EtOH Use Disorder plus  schizophrenia (48.4%) or schizoaffective disorder | LAI risperidone 25-50 mg  every 2 weeks (49) vs. oral risperidone (up to  6mg/day) (46) | 6 months | Age, mean years: 41.7  Gender, % female: 23.2  Ethnicity, %: White: 51.6  Black: 44.2 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Green, 2015 | Education 11.0 years  Ever employed 97% Single 51%  Lifetime Hospitalizations 7.5  Cannabis use 1.1 days/week  Other drugs 0.3 days/week | 95 | ITT analyses: no significant difference in drinking  Explanatory analyses using weeks 5-23:  Trend significance change in days heavy drinking (5 or more/day) oral  (0.68 days/week) vs. LAI (-0.11 days/week) t63.5= -1.96, p=0.054  Good adherence (exposed to meds 75% of study days): oral 61% vs. LAI 88%, chi2=9.08, p=0.003 (oral vs. LAI: 28/46 [61%] vs. 43/49 [88%], RR 3.20 [95% CI 1.39 to 7.34])  No between-group differences in total PANSS, GAF, or CGI |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Green, 2015 | No differences in side effects between oral and LAI | Janssen | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Ishigooka, 2015 | Asia | Asian adults (18 years and older) diagnosed with schizophrenia according to DSM-IV-TR criteria. | Aripiprazole 300 to 400 mg  once-monthly injection  (n=228)\*  vs.  Aripiprazole 6 to 24 mg/day orally (n=227) | 52 weeks (double-  blind phase) | Age, years: 39.2  Gender, % female: 39.2  Ethnicity, % Asian: 100 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Ishigooka, 2015 | Duration of illness (time since first episode), months  (mean): 151.6  PANSS severity of illness: 53.9 | 455 | Aripiprazole 300 to 400 mg monthly vs. aripiprazole 6 to 24 mg/day  Nonexacerbation of psychotic symptoms/nonrelapse rate at week 26 (Kaplan-Meier)\*\*: 95.0 vs. 94.7  Difference 0.3 (95% Cl -3.9 to 4.5)  Time to exacerbation of psychotic symptoms/relapse (Kaplan-Meier): HR 0.94 (95% Cl 0.46 to 1.92)  Proportion of patients achieving remission\*\*  exacerbation of psychotic symptoms/relapse, % (n/N): 6.6% (15/228)  vs. 6.6% (15/227)  Stabilization of psychotic symptoms/relapse, % (n/N): 92.5% (211/228)  vs. 92.5% (210/227)  Remission, % (n/N): 69.4% (129/228) vs. 71.1% (123/227)  Quality of life, mean change from baseline in MOS 36-item SF-36 at week 52  Mental component: 0.82 vs. 0.38  Difference 0.44 (95% Cl -1.24 to 2.12) ANCOVA Physical component: 0.23 vs. -0.27  Difference 0.50 (95% Cl -1.11 to 2.11) ANCOVA  All-cause discontinuation: 25.9% vs. 33.5%  Time to all-cause discontinuation: HR 0.74 (95% Cl 0.52 to 1.03) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Ishigooka, 2015 | Aripiprazole 300 to 400 mg monthly vs. aripiprazole 6 to 24 mg/day  Overall AE: % (n/N): 77.2% (176/228) vs. 79.3% (180/227) Withdrawal due to AE: % (n/N): 7.5% (17/228) vs. 11.5% (25/227) Extrapyramidal AE: % (n/N): 16.2% (40/228) vs. 14.1% (32/227) Tardive dyskinesia: % (n/N): 0 vs. 0.4% (1/227)  Akathisia: % (n/N): 6.6% (12/228) vs. 6.2% (14/227) | Otsuka Pharmaceutical Co., Ltd.  \*Injection arm patients received 6 or 12 mg/day of oral aripiprazole for 2 weeks after start of randomized period  \*\*Exacerbation/relapse based on CCG-I and PANSS scores, hospitalization, violent behavior resulting in injury | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Koshikawa, 2016  Companion: Takekita, 2016 | Japan | ≥20 years old, DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder (nonacute phase of the disease), PANSS total score ≤120, received risperidone long- acting for ≥2 months. | Risperidone long-acting  injection, adjustable dose (upper limit of 50 mg) every 2 weeks (N=16)  vs.  Paliperidone palmitate adjustable dose (upper limit of 150 mg) every 4 weeks (N=14) | 28 weeks | Age, year: 45.0  Gender, % female: 38.0  Ethnicity: Japanese (% NR) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Koshikawa, 2016  Companion: Takekita, 2016 | Duration of illness, year\*: 13.8  PANSS total score, mean: 80.6  Schizoaffective disorder, %: 5.0 | 30 | Risperidone long-acting injection vs. paliperidone palmitate  Koshikawa, 2016:  Social Functioning Scale total score, mean change from baseline (SD): -  1.64 (17.56) vs. 14.60 (18.75), p=0.038  No difference in PANSS total score between treatment groups at 6 months  Takekita, 2016:  PANSS total score, mean change from baseline to 6 months (SD): -  5.09 (8.18) vs. -1.70 (5.08), p=0.349 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Koshikawa, 2016  Companion: Takekita, 2016 | Risperidone long-acting injection vs. paliperidone palmitate  Koshikawa, 2016: Overall AEs, n: 0 vs. 2  Takekita, 2016:  DIEPSS\*\* total score, mean change from baseline (SD): -0.09 (0.30) vs. 0.30 (1.06), p=0.220 | Funding: NR  \*Duration of illness calculated based on average age at onset and average age at study enrollment.  \*\*Drug-induced extrapyramidal symptoms scale. | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Li, 2014 | China | Adults (18 to 65 years) with a DSM-IV diagnosis of schizophrenia. | Aripiprazole 10 to 30  mg/day orally (n=139)  vs.  Risperidone 2 to 6 mg/day orally (n=140) | 6 weeks | Age, year: 32.4  Gender, % female: 67.0  Ethnicity, %:  Han Chinese 100 |
| Lieberman, 2005  (CATIE Study) Rosenheck, 2014  Fervaha, 2014  Caroff, 2011  Arnold, 2013 | 57 sites  United States | Patients age 18-65, DSM-IV criteria for schizophrenia, be appropriate candidates for oral therapy (patient’s assessment in conjunction with clinician), have adequate decisional capacity to decide to participate. | Olanzapine 7.5 mg  Quetiapine 200 mg Risperidone 1.5 mg Perphenazine 8 mg Ziprasidone 40 mg  The dose of medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment | 78 weeks | Mean age: 40.6 years  26% female  Ethnicity: white 60%; black 35%; Hispanic 12%; 5% other |
| Liu, 2014 | China | Female patients (age 18 to 44 years) with first-episode schizophrenia diagnosis based on Chinese Classification of Mental Disorders-3rd edition. | Risperidone 3.4 mg/day  (mean) orally (n=40)  vs.  Quetiapine 420 mg/day  (mean) (n=40) | 52 weeks | Age, years: 29.0  Gender, % Female: 100  Ethnicity, %  Asian: 100 (Chinese) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Li, 2014 | Duration of illness: 7.3 years  PANSS severity of illness: 87.1  Schizoaffective, %: 0  Substance use, %: 0 | 279 | Aripiprazole 10 to 30 mg/day vs. risperidone 2 to 6 mg/day  PANSS responders (≥30% decrease in total score from baseline), n/N (%): 99/139 (71.0) vs. 107/140 (76.0); p=0.323 |
| Lieberman, 2005  (CATIE Study) Rosenheck, 2014  Fervaha, 2014  Caroff, 2011  Arnold, 2013 | Depression 28%  Alcohol dependence or alcohol abuse 25% Drug dependence or drug abuse 29% Obsessive-compulsive disorder 5%  Other anxiety disorder 14% | NR/NR/1493 | **Rosenheck 2014**  Olanzapine vs. quetiapine vs. risperidone  PANSS, difference in total score from perphenazine at 18 months: 1.79 (95% CI −0.04 to 3.54) vs. −0.30 (95% CI −2.08 to 1.49) vs. −1.92 (95% CI −3.70 to −0.14)  **Fervaha 2014**  Olanzapine vs. quetiapine vs. risperidone  Life satisfaction score, difference in total score from perphenazine at 12 months: 0.15 (SD 1.62) vs. 0.26 (SD 1.30) vs. 0.32 (SD 1.55); p=0.93  **Caroff 2011: Tardive dyskinesia vs. no tardive dyskinesia** No difference in time to discontinuation (p=0.743), rates of discontinuation (74% vs. 74%), or change in PANSS total score (p=0.366)  **Arnold 2013: Ethnicity subgroups**  No differences between whites, blacks, and Hispanics in all-cause discontinuations, discontinuation due to adverse events, change in total PANSS scores, or quality of life. |
| Liu, 2014 | Duration of illness, mean months: 4.5  PANSS severity of illness: 80.4 | 80 | Risperidone 3.4 mg/day vs. quetiapine 420 mg/day  PANSS total score, change at 12 weeks: -37.2 vs. -40.9 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Li, 2014 | Aripiprazole 10 to 30 mg/day vs. risperidone 2 to 6 mg/day  Overall AE, n/N (%): 105/139 (76.0) vs. 116/140 (83.0) Withdrawal due to AE, n/N (%): 0 vs. 1/140 (<1.0)  Clinically relevant weight increase ( ≥7% in body weight), n/N (%): 4/139 (3.0) vs.17/140 (12.0) Extrapyramidal symptoms, n/N (%): 35/139 (25.0) vs. 34/140 (24.0)  Akathisia, n/N (%): 32/139 (23.0) vs. 31/140 (22.0) Cardiovascular system, n/N (%): 11/139 (8.0) vs. 9/140 (6.0) | Jiangsu Nhwa Pharmaceutical  Co., Ltd and the National Key Project (2012ZX09303-003), and the Shanghai municipal incubation grant for talented researcher of health care (XBR2011049) | Fair |
| Lieberman, 2005  (CATIE Study) Rosenheck, 2014  Fervaha, 2014  Caroff, 2011  Arnold, 2013 | NR | NR | Good |
| Liu, 2014 | Risperidone 3.4 mg/day vs. quetiapine 420 mg/day  Dropout rate of 20% over 1-year treatment period. | Huzhou Ministry of  Technology | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Maat, 2014 | The Netherlands | Patients ages 16 to 50 years with clinical diagnosis of schizophrenia (DSM- IV-TR criteria) and an adequate understanding of Dutch. | Aripiprazole 7.5 or 15 mg  (n=20)  vs.  Risperidone 1 or 2 mg  (n=28)  Dosage could be  increased to maximum of 6 mg risperidone or 30 mg of aripiprazole. | 8 weeks | Age, mean years: 26.2  Gender, % female: 20.4  Ethnicity, %: Caucasian: 66.2  Moroccan: 8.4  Surinamese: 8.3  Turkish: 6.2  Other: 10.9 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Maat, 2014 | Baseline drug abuse, %:  Nicotine: 69.8  Alcohol: 64.1  Cannabis: 49.8  Cocaine: 9.2 | 80 randomized  (48 completed study) | Aripiprazole vs. risperidone  Mean change in PANSS total score (SD): -17.24 (15.89) vs. -12.85 (17.58)  Quality of life, mean (SD): 4.88 (9.41) vs. 6.47 (12.73); p=0.37  Mean change in SFS\* (SD): 4.94 (17.55) vs. -3.25 (17.14); p=0.35 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Maat, 2014 | Aripiprazole vs. risperidone  Discontinuations due to lack of tolerability, n/N (%): 6/38 (15.8) vs. 6/42 (14.3) | Bristol-Myers Squibb | Poor |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| McEvoy, 2014  (ACCLAIMS) | 22 US clinical  research sites: March 2011 to July 2013 | Inclusion: Adults with schizophrenia or  schizoaffective disorder who were clinically assessed to be at risk of relapse or likely to benefit from a long- acting injectable antipsychotic. | Haloperidol decanoate 25-  200 mg (n-145); Paliperidone palmitate 39-  234 mg (n-145); | Monthly for as long  as 24 months | Paliperidone versus haloperidol:  Age, mean (SD): 43 (12.6); 45 (12.3);  % Men: 106 (73.1%); 110 (75.9); Race, White: 56 (38.6%); 54 (37.2%);  Race, Black: 83 (57.2%); 83 (57.2%);  Race, Other: 6 (4.1%); 8 (5.5%); Spanish, Hispanic, or Latino: 6 (4.1%); 8 (5.5%); |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| McEvoy, 2014  (ACCLAIMS) | Paliperidone versus haloperidol:  Age at first treatment, mean (SD): 23 (9.3); 24 (10.9); Age at first antipsychotic med, mean (SD):  26 (9.0); 27 (10.1) | 311 | Adjusted HR for rate of efficacy failure:  Paliperidone compared to haloperidol: HR=0.98 (95% CI: 0.64 to 1.47); Paliperidone: 49 (33.8%) experienced efficacy failure;  Haloperidol: 47 (32.4%) experienced efficacy failure. |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| McEvoy, 2014  (ACCLAIMS) | Weight change at 6 months, as least squares mean weight change:  Paliperidone: +2.17 kg (95% CI 1.25 to 3.09); Haloperidol : -0.96 kg (95% CI -1.88 to -0.04). Weight change at 24 months:  Paliperidone: 6.04 kg (95% CI 2.88 to 9.20); Haloperidol : -3.88 (95% CI -7.92 to -0.73); p<0.001; AIMS Global Severity Score (incidence of AIMS >2), n(%):  Paliperidone: 28 (21.4%); Haloperidol: 30 (23.85); p=0.57; BAS Global Score (incidence of BAS ≥3), n (%); Paliperidone: 4 (2.8%); Haloperidol: 15 (10.6%); p=0.006; SAS Mean Score (Incidence of SAS ≥1), n (%); Paliperidone: 109 (79%); Haloperidol: 101 (74.8%); Maximum levels of serum prolactin (men):  Paliperidone: 34.56 mcg/L (95% CI 29.75 to 39.37); Haloperidol : 15.41 mcg/L (95% CI 10.73 to 20.08); p<0.001; Maximum levels of serum prolactin (women):  Paliperidone: 75.19 (95% CI 63.03 to 87.36); Haloperidol: 26.84 (95% CI 13.29 to 40.40); p<0.001. Global rating scale of akathisia  Paliperidone: 0.73 (95% CI 0.59 to 0.87); Haloperidol: 0.45 (95% CI 0.31 to 0.59); p=0.006.  No significant difference in mean change in glycated hemoglobin, glucose, total cholesterol, LDL, triglycerides or lowest recorded HDL.  No significant differences in mean change in AIMS global score or tardive dyskinesia.  AEs (ITT, n=147 per arm);  Any serious AE: Paliperidone=53 (36.1%); Haloperidol=45 (30.6%);  Suicidal or homicidal ideation: Paliperidone=23 (15.6%); Haloperidol=21 (14.3%); Any moderate or severe AE: Paliperidone=100 (68.0%); Haloperidol=88 (59.9%) | NIMH | Good |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Naber, 2013  RECOVER NCT00600756 | International | Adults 18 to 65 year, a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, and a certain level of reduced subjective well-being. | Quetiapine XR (400 to 800  mg) (n=395)  vs.  Risperidone (2 to 6 mg) (n=403) once daily | 52 weeks | Age, mean year: 39.65  Gender, % female: 41.8  Ethnicity, %: NR |
| Naber, 2015  QUALIFY  Companion: Potkin, 2015 | International | Adults (18 to 60 y) with DSM-IV-  TR–defined schizophrenia. | Aripiprazole 300 to 400 mg  monthly injection (n=148)  vs.  Paliperidone 50 to 150 mg (EU/Canada) or Paliperidone palmitate 78 to 234 mg (US) monthly injection (n=147) | 28 weeks | Age, years: 41.9  Gender, % female: 40.2  Ethnicity, %: White: 69.7  Black/African American: 27.0  Asian: 1.5  Other: 1.1  Unknown: 0.7 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Naber, 2013  RECOVER NCT00600756 | Concurrent substance abuse:  Alcohol use, %: 12.1  Cannabis use, %: 1.9  DSM-IV schizophrenia subtype diagnosis, %: Schizoaffective disorder of bipolar type: 8.3  Schizoaffective disorder of depressive type: 7.8  Median duration of present episode, m: 2.5  Mean years since first known schizophrenia diagnosis:  11.35  Hospitalizations due to  schizophrenia in the previous 6 months, % patients: 16.1  SWN-K total score, mean: 64.35 | 798 | Quetiapine XR (400 to 800 mg) vs. Risperidone (2 to 6 mg)  Discontinued at month 12, n (%): 183 (46.3) vs. 176 (43.7) CGI–SCH overall severity:  Month 12 mean, change from baseline to m 12, mean (SD): 2.3 vs.  2.5; -1.5 (1.07) vs. -1.3 (1.15)  CGI change score improved n (%): 176/379 (83.4) vs. 178/392 (78.4) Treatment effect for improved: 1.46 (95% CI 0.87 to 2.43)  CDSS Total score:  Month 12 mean, change from baseline to m 12, mean (SD): 1.7 vs.  2.6; -5.3 (5.10) vs. -3.8 (4.6)  Treatment difference: -1.0 (95% CI -1.6 to -0.4) |
| Naber, 2015  QUALIFY  Companion: Potkin, 2015 | CGI-S severity of illness score: 4.0 | 295 | Aripiprazole 300 to 400 mg monthly vs. paliperidone 50-150 mg/  paliperidone palmitate 78 to 234 mg monthly  Naber, 2015:  Heinrichs-Carpenter QLS, LSM change from baseline at week 28: 7.47 (n=136) vs. 2.80 (n=132)  LSM difference 4.67 (95% Cl 0.32 to 9.02)  Potkin, 2015:  QLS total score, difference in change from baseline to 28 weeks: 4.67 (95% CI 0.32 to 9.02)  QLS total score, LS mean changes (SE): 7.47 (1.53) vs. 2.80 (1.62) CGI-S LS mean (SE) change from baseline to 28 weeks: -0.75 (0.07) vs. –0.46 (0.07)  LS mean difference: –0.28 (95% CI –0.48 to –0.09)  Patient-rated TooL scale, LSM treatment difference: –0.70 (95% CI:  –1.51 to 0.12)  Clinician-rated WoRQ total scores, LSM treatment difference: –1.16 (95% CI: –1.96 to –0.37)  'No' to 'Yes' in readiness to work at 28 weeks, %: 26.4 vs. 12.2 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Naber, 2013  RECOVER NCT00600756 | Quetiapine XR (400 to 800 mg) vs. Risperidone (2 to 6 mg)  Discontinued due to AE at month 12, n (%): 53 (13.4) vs. 44 (10.9)  n/N (%); number of events  TEAE: 238/391 (60.9); 791 vs. 258/402 (64.2); 834  TEAE leading to discontinuation: 57/391 (14.6); 72 vs. 48/402 (11.9); 80  Serious TEAE: 45/391 (11.5); 49 vs. 26/402 (6.5); 31  Serious TEAE leading to death: 0 (0) vs. 1/402 (0.2); 1  Weight increased: 18/391 (4.6); 18 vs. 25/402 (6.2); 25 | AstraZeneca. | Fair |
| Naber, 2015  QUALIFY  Companion: Potkin, 2015 | Aripiprazole 300 to 400 mg monthly vs. paliperidone 50-150 mg/ paliperidone palmitate 78 to  234 mg monthly  Naber, 2015:  Overall AE: % (n/N): 62/119 (52.1%) vs. 72/109 (66.1%)\*  Overall withdrawal due to AE: % (n/N): 11.1% (16/148) vs. 19.7% (27/147) AE related extrapyramidal symptoms: % (n/N)  Akathisia: 2.5% (2/119) vs. 1.8% (2/109)\* Dystonia: 0.8% (1/119) vs. 0%\* Extrapyramidal disorder: 0% vs. 0% \* Muscle rigidity: 0.8% (1/119) vs. 0  Muscle spasms: 0 vs. 0.9% (1/109) Tremor: 1.7% (2/119) vs.1.8% (2/109)  Potkin, 2015:  Discontinuation due to AE, n/N (%): 16/144 (11.1) vs. 27/137 (19.7) Weight increased, n/N (%): 0 (0.0) vs. 2/137 (1.5)  ASEX total score mean (SD) change from baseline to 28 weeks: -1.9 (6.3) vs. -0.8 (6.1) Decrease in sexual dysfunction at 28 weeks, %: 30 vs. 4 | H. Lundbeck A/S and Otsuka  Pharmaceutical Development & Commercialization, Inc  \*Treatment continuation period (main period of interest with respect to safety evaluation (n=119 vs. n=109) | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Nemeth, 2017 | 66 study centers  in 11 European countries (Bulgaria, Croatia, Czech Republic,  France, Hungary, Poland,  Romania, Serbia, Spain, Russia, and Ukraine) | Adults aged 18–65 years who had a  diagnosis of schizophrenia (DSM-IV-TR) criteria, with onset occurring at least 2 years before screening. Patients had to be in a stable condition for at least 6 months before screening (i.e., no psychiatric hospital admissions, acute exacerbations, or imprisonments) and meet the following clinical criteria: predominant negative symptoms for at least 6 months (based on medical records/investigator judgment), Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS- FSNS) of 24 or more, and score of 4 or more on at least two of three core negative PANSS items (blunted affect, passive or apathetic social withdrawal, lack of spontaneity, and flow of conversation) at screening and during a lead-in period. Additionally, patients were required to have a PANSS-FSNS score that diverged less than 25% from the screening score during a lead-in period. | Cariprazine 4.5 mg (target  dose) daily (n=230) Risperidone 4 mg (target dose) daily (n=231) | 26 weeks | Cariprazine vs. risperidone:  Age, mean years: 40.2 vs. 40.7  Gender, % female: 46 vs. 39  Ethnicity, %: White: 96 vs. 94  (Ethnicity not recorded: 4 vs. 6) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Nemeth, 2017 | Cariprazine vs. risperidone:  Time from schizophrenia diagnosis to informed consent, years: 11.98 vs. 12.96  Number of acute exacerbations  <5: 64% (148/230) vs. 55% (126/230)  5-10: 27% (61/230) vs. 34% (79/230)  11-15: 5% (11/230) vs. 9% (20/230)  >15: 4% (10/230) vs. 2% (5/230) | 461 randomized  460 included in safety population  456 in modified  ITT | Cariprazine vs. risperidone:  CGI-S score: -0.95 vs. -0.74, LSMD -0.21 (95% CI -0.36 to -0.06), p=0.0052  PANSS total score: -16.90 vs. -14.80, LSMD -2.10 (95% CI -4.34 to  0.13), p=0.065  PANSS negative subscale score: -8.63 vs. -7.16, LSMD -1.48 (95% CI -  2.38 to -0.57), p=0.0015  CGI-I score: 2.53 vs. 2.89, LSMD -0.37 (95% CI -0.55 to -0.19), p<0.0001  SAS items 1-8: 0.01 vs. 0.05, LSMD 0.05 (95% CI -0.21 to 0.12), p=0.58  Achieved response to treatment (decrease > 20% in PANSS-FSNS):  69% (157/227) vs. 58% (133/229), OR 2.08, p=0.0022, NNT 9 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Nemeth, 2017 | Cariprazine vs. risperidone:  Discontinuations due to adverse events: 10% (22/230) vs. 11% (25/230) Any serious adverse events: 3% (7/230) vs. 3% (7/230)  Any adverse events: 53% (123/230) vs. 57% (131/230) | Gedeon Richter Plc (Budapest,  Hungary) | Good |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Parabiaghi, 2016  Companion to  Parabiaghi, 2011 | Italy | >18 years old, DSM-IV diagnosis of schizophrenia based on the Mini- International Neuropsychiatric Interview. | Aripiprazole 19.7 mg/day\*  (N=100)  vs.  Olanzapine 13.7 mg/day\* (N=103)  Haloperidol 4.0 mg/day  (N=97) | 52 weeks | Age, years: 42.7  Gender, % female: 42.0  Ethnicity: Italian (% NR) |
| Park, 2013 | South Korea | Age 18-65 years; diagnosed by a psychiatrist with a brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder (DSM-IV criteria); no other active illness. | Ziprasidone 40 mg initial  dose (range 20-160 mg; mean 109 mg) (n=10) vs.  Olanzapine 10 mg initial dose (range 5-20 mg; mean 11.6 mg) (n=10) | 12 weeks | Age, mean years: 33.0  Gender, % female: 50.0  Ethnicity: NR |
| Robinson, 2015  See also: Zhang, 2015 | US and Canada | Adults and adolescent (15 to 40 years) with DSM-IV-defined diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder not otherwise specified. | Aripiprazole 5 to 30  mg/day orally (n=106)  vs.  Risperidone 1 to 6 mg/day orally (n=103) | 12 weeks | Age, years: 22.1  Gender, % female: 29  Ethnicity, %: Caucasian: 24.0  African-American: 37.0  Hispanic: 10.0  Other/mixed: 9.0 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Parabiaghi, 2016  Companion to  Parabiaghi, 2011 | Duration of illness, year from first psychiatric contact (%):  0-2 years: 12.0  3+ years: 72.0  Hospitalization, % in-patient: 20.0  Current substance abuse or dependence, %: 5.0  Antipsychotic drug-naïve, %: 6.0 | 300 | NR |
| Park, 2013 | PANSS total score at baseline: 74.8 | 20 | NR |
| Robinson, 2015  See also: Zhang, 2015 | Duration of current illness/psychosis, weeks: 125.5\*  BPRS-A severity of illness: 45.1  Schizoaffective, %: 3  Substance use, %: 0  Antipsychotic drug naïve: lifetime antipsychotic drug medication treatment 2 weeks or less | 209 | Aripiprazole 5-30 mg/day vs. risperidone 1-6 mg/day  Cumulative response rate at week 12\*\*: 62.8% (95% Cl 50.8 to 74.8)  vs. 56.8% (95% Cl 43.9 to 69.9)  Mean time to response, w: 8.0 (95% Cl 7.9 to 8.1) vs. 8.2 (95% Cl 7.3 to  9.2)  Discontinuation of controlled treatment before 12 weeks (n, due to  safety concerns): 0 vs. 3 (1 metabolic syndrome, 1 tardive dyskinesia, 1 hematologic abnormalities )  **Zhang, 2015**  C/C homozygotes vs. T carriers  BPRS Positive Symptoms Scores at week 12 (Least Square Estimate, mean±SE, unadjusted; sample size): 6.51±0.52 38 vs. 7.64±0.57 33 p=0.143 |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Parabiaghi, 2016  Companion to  Parabiaghi, 2011 | Aripiprazole vs. olanzapine vs. haloperidol  Metabolic syndrome at 1 year in ITT population, n/N (%): 37/100 (37.0) vs. 48/103 (46.6) vs.  41/97 (42.3); aripiprazole vs. olanzapine: OR 1.50 (95% CI 0.8 to 2.6); aripiprazole vs. haloperidol: OR 0.88 (95% CI 0.62 to 1.24); olanzapine vs. haloperidol: OR 1.10 (95% CI 0.81 to  1.51)  Withdrawals due to AEs, n (%): 6 (12.6) vs. 6 (18.8) vs. 8 (22.2); aripiprazole vs. olanzapine: OR 0.98 (95% CI 0.3 to 3.19); aripiprazole vs. haloperidol: OR ); olanzapine vs. haloperidol: OR 1.10 (95% CI 0.81 to 1.51) | Funding: IRCCS-Istituto di  Ricerche Farmacologiche ‘Mario  Negri’ and Bristol-Myers Squibb  \*Mean dose of treatment. | Fair |
| Park, 2013 | Ziprasidone vs. olanzapine  Body weight, median change in kg (IQR): 3.43 (0.61, 9.20) vs. 10.35 (9.27, 14.65); p=0.016 | Pfizer Pharmaceuticals Korea | Poor |
| Robinson, 2015  See also: Zhang, 2015 | Aripiprazole 5-30 mg/day vs. risperidone 1-6 mg/day  Sexual dysfunction, % (n/N): 7.8% (8/102) vs. 12.5% (12/96) | National Institutes of  Health and NARSAD Young  Investigator Grant to  J.A.G. from the Brain & Behavior  Research Foundation  \*Report states: "duration of psychotic symptoms before study week (weeks)"  \*\*Response criteria based on  BPRS-A and CGI scores | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| San, 2012  RCT Spain | Spain | 18 years old, presence of psychotic symptoms at admission (4 or more on PANSS items 1, 3, 5 or 6 and 3), naïve to psychotropic drugs. Excluded:  presence of major medical or neurological disease or mental retardation, suspicion of substance use directly contributing to the symptoms | Haloperidol 1.5–8.5  olanzapine 7.5–40 risperidone1.5–7.0 quetiapine100–1500  and ziprasidone 40–240 mg/day | 52 weeks | Mean age 25.6  74.6% male  Ethnicity NR |
| Sanz-Fuentenebro,  2013 | Spain | Diagnosis of schizophrenia or  schizophreniform disorder (DSM-IV  criteria); age <35 years in males and  <40 years in females. | Clozapine 12.5-900 mg  (n=15)  vs.  Risperidone 2-10 mg  (n=15) | 1 year | Age, mean years: 24.5  Gender, % female: 30.0  Ethnicity, %: Caucasian: 77.0 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| San, 2012  RCT Spain | BMI 22.7  82.5% single  46.5% elementary school education  44.7% diagnosed with schizophrenia Duration of untreated psychosis: 52.5 weeks baseline PANSS: 91.0 | 114 | Proportion discontinuing treatment by 12 months:  85.7% (18/21) vs. 40% (10/25) vs. 56.5% (13/23) vs. 64% (16/20) vs.  80% (16/25)  Mean time to all-cause discontinuation:  haloperidol 125 days; olanzapine 260 days; quetiapine 187 days;  risperidone 206 days; ziprasidone 142 days (p=0.005) |
| Sanz-Fuentenebro,  2013 | Active substance abuse:  Alcohol, %: 10  Cannabis, %: 3.3  Cocaine, %: 6.7  DUP\*, months: 9.9 | 30 | Clozapine vs. Risperidone  Total rate of protocol discontinuation was 53.3%  Maintenance of initial treatment, weeks (SD): 41.1 (15.9) vs. 23.3 (20.1); p=0.015  LOCF\*\* change from baseline in PANSS total score, mean (SD): -35.5 (26.6) vs.  -17.1 (27.7)  12-month change from baseline in PANSS total score, mean (SD): -  48.0 (24.7) vs. NR |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| San, 2012  RCT Spain | Discontinuations due to adverse events:  11.1% haloperidol; 20% olanzapine, 7.7% quetiapine; 6.2% risperidone; 25% ziprasidone  Time to discontinuation due to adverse events: NR  UKU scores were higher in haloperidol group compared to second-generation drugs, and no differences were found between the other drugs.  Weight gain ranged from 3 kg with ziprasidone to 9 kg with olanzapine but no statistically significant differences were found. | La Marato´ TV3 Foundation and  Eli Lilly | Good |
| Sanz-Fuentenebro,  2013 | NR | Spanish Ministry of Health,  Ayudas  para el fomento de la traslación de la aplicación terapéutica de medicamentos  huérfanos y terapias avanzadas (grant number: TRA-035); and the Instituto de Salud  Carlos III (grant number: PI-  060219). | Poor |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Savitz, 2016 | International | Adult patients age 18 to 70 years with a  DSM-IV diagnosis of schizophrenia. | Paliperidone palmitate 3-  month injection (N=504)  vs.  Paliperidone palmitate 1- month injection (N=512) | 48 weeks | Age, years: 38.7  Gender, % Female: 47%  Ethnicity, %: White: 58%  African American: 6% American Indian: 35% Other: 1% |
| Shoja Shafti, 2015 | Iran | Female inpatients diagnosed as having schizophrenia, according to the DSM-V. | Aripiprazole 5 to 25  mg/day orally (n=25)  vs.  Quetiapine 25 to 600 mg/day (n=25) | 12 weeks | Age, years: 36.8  Gender, % female: 100  Ethnicity: NR |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Savitz, 2016 | Prior hospitalizations, %:  None: 41.0  Once: 37.0  Twice: 16.0  Three times: 3.0  Four or more: 2.0  PANSS Total Score at baseline: 85.0 (ITT); 57.8 (double blind)  Previous antipsychotic use, %: 76.0 (new-generation antipsychotics) | 1,016 | Paliperidone palmitate 3-month injection vs. paliperidone palmitate 1-  month injection  Relapse-free patients, % (n/N)\*: 8.0% (37/504) vs. 9.0% (45/512) Clinical response (≥20% reduction in PANSS total score), % (n/N):  50.1% (241/481) vs. 47.3% (237/501)  ≥30%: 36.4% (175/481) vs. 36.1% (181/501)  ≥40%: 26.4% (127/481) vs. 27.1% (136/501)  Symptomatic remission (meeting Andreasen remission criteria 6 months before end of study), %: 58.0% vs. 59.0%  Psychiatric hospitalizations, % (n/N): 3.0% (16/504) vs. 4.0% (22/512) |
| Shoja Shafti, 2015 | Duration of illness, y: 6.4  Hospitalization, %: 100  CGI-S severity of illness: 3.74  Schizoaffective, %: 0 | 50 | NR |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Savitz, 2016 | Paliperidone palmitate 3-month injection vs. paliperidone palmitate 1-month injection  Overall AEs, % (n/N): 68.0% (342/504) vs. 66.0% (340/512) Withdrawals due to AEs, % (n/N): 3.0% (15/504) vs. 3.0% (13/512) All-cause mortality, n: 1 vs. 3  Diabetes mellitus/hyperglycemia, % (n/N): 2.6% (13/504) vs. 4.9% (25/512) Extrapyramidal AEs, % (n/N): 8.0% (42/504) vs. 7.0% (38/512)  Weight change of ≥7%, % (n/N): 27.0% (136/504) vs. 30.0% (150/512) Tardive dyskinesia, n: 1 vs. 1 | Funding: Otsuka, Janssen,  Cilag, and Lundbeck  \*Relapse as ≥1 of following:  1)hospitalization for schizophrenia symptoms; 2) 25% increase in PANSS total score for patients scoring >40 or a 10-point  increase for patients scoring ≤40;  3) increase PANSS items; 4) clinically significant self-injury or violent behavior resulting in suicide, injury, or damage; 5) suicidal/homicidal ideation | Good |
| Shoja Shafti, 2015 | Aripiprazole 5 to 25 mg/day vs. quetiapine 25 to 600 mg  Withdrawal due to AE, n/N (%): 0 vs. 0 | Research received no specific  grant from any funding agency in the public, commercial, or not-for- profit sectors | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Subotnik, 2015 | United States | Adults (18 to 45 years) with DSM-IV diagnosis of schizophrenia, schizoaffective disorder, mainly depressed type, or schizophreniform disorder, with an onset of psychosis within the last 2 years. | Risperidone modal dosage  25 mg biweekly (12.5 to  37.5 mg) long acting injectable (n=43)  vs.  Risperidone modal dosage  2 mg daily (1.0 to 7.5mg)  oral (n=43)  Both arms subsequently randomized in cognitive remediation or healthy- behaviors training. | 52 weeks | Age, years: 21.5  Gender, % female: 22.0  Ethnicity, %: White: 49.0  Asian: 11.0  Native American: 5.0  African American: 28.0  Pacific Islander: 1.0  Mixed: 6.0 |
| Tybura, 2013 | Poland | Caucasian patients of Polish descent with paranoid schizophrenia (confirmed with Polish CIDI\* and ICD-10 criteria). | Olanzapine 10-20 mg  (n=19)  vs.  Ziprasidone 120-160 mg  (n=20)  vs.  Perazine 300-600 mg  (n=19) | 3 months | Age, mean years (SD): 36.2 (12.0)  Gender, % female:  51.7  Ethnicity, %: Caucasian: 100.0 |
| Tybura, 2014 | Poland | Caucasian patients of Polish descent suffering from paranoid schizophrenia. Diagnosis based on Polish version of the CIDI and the ICD-10 criteria. | Ziprasidone 120-160  mg/day orally (n=59)  vs.  Olanzapine 10-20 mg/day orally (n=72)  vs.  Perazine 300-600 mg/day orally (n=60) | 12 weeks | Age, years: 35.8  Gender, % female: 55.1  Ethnicity, %:  Caucasian: 100 (Polish descent) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Subotnik, 2015 | Duration of illness, months: 7.4  (time since psychosis onset) Severity of illness (BPRS):  Thought disturbance factor at randomization: 2.1  Withdrawal-retardation factor at randomization: 1.9  Schizophrenia, %: 55.0  Schizophreniform disorder, %: 33.0  Schizoaffective, %: 12.0  Substance use, %: 0 | 86 | Risperidone 25 mg biweekly long acting vs. risperidone 2 mg daily  Psychotic exacerbation/relapse, n/N (%)\*: 2/40 (5.0) vs. 14/43 (33.0); P<0.001  Hospitalizations due to mental illness, n/N (%): 2/40 (5.0) vs. 8/43 (18.6); P=0.05  Early discontinuation due to inadequate treatment response, n/N (%):  1/40 (2.5) vs. 7/42 (17.0), P=0.01  Risk of exacerbation and/or relapse over time was significantly lower for long-acting injectable risperidone than for oral risperidone: p<0.004  Mean time to relapse, days: 298.5 vs. 218.6  Medication adherence was better for long-acting risperidone vs. oral risperidone: p<0.001  Medication adherence was associated with prevention of exacerbation and/or relapse (p=0.003) and control of breakthrough psychotic symptoms (p=0.04). |
| Tybura, 2013 | Mean age (SD) at first psychotic episode, years: 26.9 (6.9) | 58 | Olanzapine vs. ziprasidone vs. perazine  PANSS total score (SD) after 3 months: -64.8 (18.9) vs. -75.2 (27.1) vs. -  68.0 (28.3) |
| Tybura, 2014 | Duration of illness: 9.9 years\*  PANSS severity of illness: 99.8  Schizoaffective, %: 0  Antipsychotic drug naïve, %: 0 | 191 | Ziprasidone 120-160 mg/day vs. olanzapine 10-20 mg/day vs. perazine  300-600 mg/day  All-cause discontinuation at week 12, n/N (%)\*\*: 41/60 (68.0) vs. 52/72 (76.0) vs. 40/59 (68.0) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Subotnik, 2015 | Risperidone 25 mg biweekly long acting vs. risperidone 2 mg daily  WAE, n/N (%): 4/40 (10.0) vs. 9/43 (21.0) | NIH and Janssen Scientific  Affairs, LLC  \*Based on BPRS scale | Fair |
| Tybura, 2013 | NR | Grant of Ministry of Since and  High Education (grant no. N N402  456738) and by a Pfizer Independent Research Grant (grant no. 2005-0039). | Poor |
| Tybura, 2014 | NR | Pfizer Independent Research  Grant  \*Based mean age upon entering trial and mean age of first psychotic episode  \*\*Based on retention rate | Fair |

| **Author, Year** | **Setting**  **Country** | **Inclusion Criteria** | **Interventions and Ns per**  **Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Wani, 2015 | India | Adult patients with schizophrenia who  had achieved clinical stability with olanzapine and who were assessed as having metabolic syndrome using modified NCEP ATP-III criteria. Schizophrenia diagnoses were made using the DSM IV. | Olanzapine 10-20 mg/day  orally (n=31)  vs.  Aripiprazole 5-20 mg/day orally (n=31)\* | 24 weeks | Age (years): 29.8  Gender, % female: 37.1  Ethnicity: Asian (Indian) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Wani, 2015 | Duration of illness: 4.75 years  PANSS severity of illness: 68.9  Antipsychotic drug naïve, %: 0 | 62 | Olanzapine 10-20 mg/day vs. aripiprazole 5 to 20mg/day  All-cause hospitalization, n/N %: 2/26 (7.7) vs. 2/21 (9.5) |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Wani, 2015 | Olanzapine 10-20 mg/day vs. aripiprazole 5 to 20mg/day  Patients meeting modified NCEP ATP-III criteria for the presence of metabolic syndrome, n/N (%)\*\*: 26/26 (100) vs. 15/31 (42.8); P<0.001 | Funding NR  \*With accompanying reduction of continuing olanzapine (reduction from 25% to 100% after 3 weeks  \*\*Based on modified NCEP ATP- III criteria for the Asian population (waist circumference, triglycerides, HDL, Systolic BP, fasting glucose) | Fair |

**Please see Appendix B. Included Studies for full study references**

AE=adverse event, AIMS=Abnormal Involuntary Movement Scale, ANOVA=analysis of variance, AP=antipsychotic, BARS=Brief Adherence Rating Scale, BAS=behavioral activation system, BHL=behavioral health lab, BP=blood pressure, BPRS=Brief Psychiatric Rating Scale, BMI=body mass index, BMS=Bristol-Myers Squibb, CATIE=Clinical Antipsychotic Trials of Intervention Effectiveness, CCMD-3=3rd edition of the Chinese Classification of Mental Disorders, CDSS=Calgary Depression Scale for Schizophrenia, CGI-I=Clinical Global Impressions-Improvement scale, CGI-S=Clinical Global Impressions-Severity scale, CHAT=clozapine haloperidol aripiprazole trial, CI=confidence interval, CIDI=Composite International Diagnostic Interview, CMHCs=Certified Mental Health Clinics, C-SSRS=Columbia Suicide Severity Rating Scale, DC=discontinuation, DIEPSS=drug-induced extrapyramidal symptoms scale, d/o=diagnosis, DUP=duration of untreated psychosis, ECG=electrocardiogram, EPS=extrapyramidal symptoms, ETOH=alcohol/ethanol, EU=European Union, F=female, FGA=first-generation antipsychotic, GAF=global assessment functioning, HDL=high-density lipoprotein, HR=hazard ratio, ICD-10=10th revision of the International Statistical Classification of Diseases and Related Health Problems, IQR=interquartile range, ITT=intention-to-treat, J&J=Johnson and Johnson, kg=kilogram, LAI=long acting injectable, LDL=low-density lipoprotein, LOCF=last observation carried forward, LOS=living on site, LUNSERS=Liverpool University Neuroleptic Side Effect Rating Scale, LS=life skills, LSM=life skills mean, M=male, MINI=International Neuropsychiatric Interview, mos=months, NARSAD=National Association for Research on Schizophrenia and Depression, NCEP ATP-III=National Cholesterol Education Program Adult Treatment Panel III, NSD=no significant difference, PANSS=positive and negative syndrome scale, PSP=Personal and Social Performance scale, QLS=Quality of Life Scale, RCT=randomized controlled trial, RR=relative risk, SANS=scale for assessment of negative symptoms, SAPS=scale for the assessment of positive symptoms, SAS=social adjustment scale, SD=standard deviation, SDS=Sheehan Disability Scale, SE=side effects, SES=socioeconomic status, SFS=social functioning scale, SGA=second-generation antipsychotic, TD=tardive dyskinesia, TEAE=treatment emergent adverse event, UKU=UKU Side Effect Rating Scale, VA=Veteran’s Affairs, WAE=withdrawals due to adverse events, w=weeks, WHO=World Health Organization, XR=extended release, y=years, YMRS=Young Mania Rating Scale