**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 to9/2011 | 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/dayquetiapine=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=0.066 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=0.636 weeks: haloperidol=20.4 (8.28); quetiapine=18.9 (6.21); t=0.86;p=0.3912 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=0.0566 weeks: haloperidol=35.1 (11.3); quetiapine=37.3 (11.01); t=0.79;p=0.4312 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=0.556 weeks: haloperidol=9.88 (1.95); quetiapine=9.29 (1.64); t=1.53;p=0.18312 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=0.0566 weeks: haloperidol=73.8 (19.50); quetiapine=77.6 (8.90); t=1.02;p=0.3112 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=0.363Headache: 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: 42.2Gender, % 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: 93.7Duration of current episode: 3.1 weeks | 97 | Brexpiprazole vs. AripiprazoleChange in baseline PANSS total score, LS mean at 6 w:-22.9; P<0.0001 vs. -19.4; P<0.0001Response 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. AripiprazoleOverall 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. 0Clinically 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 PharmaceuticalCommercialization 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, 2011Crespo-Facorro, 2012Spain | 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; meandose, 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: 27.4Gender: 38% femaleEthnicity: NR |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Crespo-Facorro, 2011Crespo-Facorro, 2012Spain | Age, psychosis onset: 26 yearsDuration of illness: 25 monthsDuration of psychosis: 11 monthsDiagnosis: 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=0.541Time 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=0.857Relapse, adherent vs. nonadherent: 11.2% vs. 26.9%, p=0.040Remission at 1 year: 25% vs. 32.7% vs. 34.9%; x 2=1.471, p=0.479Remission at 1 year, patients continuing on drug: 25% vs. 43.2% vs. 41.5%, p=0.308Remission, adherent vs. nonadherent: 36.9% vs. 27.6%, p=0.347Treatment 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 yearsSafety: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, 2011Crespo-Facorro, 2012Spain | Haloperidol % vs. Olanzapine % vs. Risperidone %, PConcentration difficult: 9.1 vs. 7.7 vs. 0.0, 0.419Asthenia: 9.1 vs. 23.1 vs. 0.0, 0.057Daytime drowsiness: 0.0 vs. 34.6 vs. 10.0, 0.022Increased sleep hours: 9.1 vs. 11.5 vs. 5.0, 0.739Akathisia: 27.3 vs. 0.0 vs. 5.0, 0.011Sialorrhea: 0.0 vs. 0.0 vs. 15.0, 0.053Dry mouth: 0.0 vs. 7.7 vs. 10.0, 0.571Weight gain: 9.1 vs. 26.9 s. 20.0, 0.473Amenorrhea (only females, n=23): 0.0 vs. 0.0 vs. 40.0, 0.043Sexual 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, USAand 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 previous24 months) | Olanzapine long-actinginjection 405 mg/4 weeks(n=264)vs.Oral olanzapine 10 mg/day(n=260) | 2 years | Age, mean years: 40.9Gender, % female: 32.8Ethnicity, %: White: 62.0African: 16.8Hispanic: 8.0East Asian: 8.8West Asian: 3.6Native 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: 42.3Gender, % female: 43.3Ethnicity, %: 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: 36.5Gender, % female: 31.0Ethnicity, %: White: 50.0African American: 24.0% Asian: 25.0Other: 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 olanzapineAll-cause discontinuation rate, %: 53.8 vs. 51.2; p=0.600Time to all-cause discontinuation, median days: 645 vs. 678; p=0.612Rate of relapse, %: 20.1 vs. 18.5, p=0.659Time to relapse/rescue, median days: 539 vs. 281; p<0.001Baseline-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: 101.4Schizoaffective, %: 47.7 | 216 | Quetiapine extended-release 400 to 800 mg/day vs. risperidone 4 to 6mg/dayPANSS 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 yearsDuration of current illness/psychosis: less than 2 weeks to be eligibleHospitalization 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 4.5mg/day vs. risperidone 4.0 mg/dayPANSS 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 olanzapineAny 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/dayOverall 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. risperidone4.0 mg/dayTreatment-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 andGedeon Richter Plc. | Fair |

| **Author, Year** | **Setting****Country** | **Inclusion Criteria** | **Interventions and Ns per****Group** | **Duration (intervention and longest followup)** | **Age Gender Race/Ethnicity** |
| --- | --- | --- | --- | --- | --- |
| Fleischhacker, 2014ASPIRE 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-monthly400 mg (n = 265)vs.Oral aripiprazole 10 to 30 mg/day (n = 266)vs.Aripiprazole once-monthly50 mg (n = 131) | 38 weeks | Age, mean years: 41.0Gender, % female: 38.7Ethnicity, %: White: 58.5Black or African American: 23.1Asian: 10.4Other: 8.0 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Fleischhacker, 2014ASPIRE EU, NCT00706654 | PANSS total score, mean: 56.9CGI-Severity score, mean: 3.07CGI-Improvement score, mean: 3.2 | 662 | Aripiprazole once-monthly 400 mg vs. oral aripiprazole (10 to 30mg/day) vs. aripiprazole once-monthly 50 mgEstimated relapse rate, %: 7.12 vs. 7.76 vs. 21.80Treatment 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, LSmean (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, 2014ASPIRE EU, NCT00706654 | Aripiprazole once-monthly 400 mg vs. oral aripiprazole (10 to 30 mg/day) vs. aripiprazole once-monthly 50 mgDiscontinued 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 PharmaceuticalCommercialization, 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 VAclinics (four total) | Age 18-65, with EtOH Use Disorder plusschizophrenia (48.4%) or schizoaffective disorder | LAI risperidone 25-50 mgevery 2 weeks (49) vs. oral risperidone (up to6mg/day) (46) | 6 months | Age, mean years: 41.7Gender, % female: 23.2Ethnicity, %: White: 51.6Black: 44.2 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Green, 2015 | Education 11.0 yearsEver employed 97% Single 51%Lifetime Hospitalizations 7.5Cannabis use 1.1 days/weekOther drugs 0.3 days/week | 95 | ITT analyses: no significant difference in drinkingExplanatory 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=0.054Good 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 mgonce-monthly injection(n=228)\*vs.Aripiprazole 6 to 24 mg/day orally (n=227) | 52 weeks (double-blind phase) | Age, years: 39.2Gender, % female: 39.2Ethnicity, % Asian: 100 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Ishigooka, 2015 | Duration of illness (time since first episode), months(mean): 151.6PANSS severity of illness: 53.9 | 455 | Aripiprazole 300 to 400 mg monthly vs. aripiprazole 6 to 24 mg/dayNonexacerbation of psychotic symptoms/nonrelapse rate at week 26 (Kaplan-Meier)\*\*: 95.0 vs. 94.7Difference 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 52Mental component: 0.82 vs. 0.38Difference 0.44 (95% Cl -1.24 to 2.12) ANCOVA Physical component: 0.23 vs. -0.27Difference 0.50 (95% Cl -1.11 to 2.11) ANCOVAAll-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/dayOverall 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, 2016Companion: 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-actinginjection, 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: 45.0Gender, % female: 38.0Ethnicity: Japanese (% NR) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Koshikawa, 2016Companion: Takekita, 2016 | Duration of illness, year\*: 13.8PANSS total score, mean: 80.6Schizoaffective disorder, %: 5.0 | 30 | Risperidone long-acting injection vs. paliperidone palmitateKoshikawa, 2016:Social Functioning Scale total score, mean change from baseline (SD): -1.64 (17.56) vs. 14.60 (18.75), p=0.038No difference in PANSS total score between treatment groups at 6 monthsTakekita, 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, 2016Companion: Takekita, 2016 | Risperidone long-acting injection vs. paliperidone palmitateKoshikawa, 2016: Overall AEs, n: 0 vs. 2Takekita, 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 30mg/day orally (n=139)vs.Risperidone 2 to 6 mg/day orally (n=140) | 6 weeks | Age, year: 32.4Gender, % female: 67.0Ethnicity, %:Han Chinese 100 |
| Lieberman, 2005(CATIE Study) Rosenheck, 2014Fervaha, 2014Caroff, 2011Arnold, 2013 | 57 sitesUnited 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 mgQuetiapine 200 mg Risperidone 1.5 mg Perphenazine 8 mg Ziprasidone 40 mgThe 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 years26% femaleEthnicity: 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: 29.0Gender, % Female: 100Ethnicity, %Asian: 100 (Chinese) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Li, 2014 | Duration of illness: 7.3 yearsPANSS severity of illness: 87.1Schizoaffective, %: 0Substance use, %: 0 | 279 | Aripiprazole 10 to 30 mg/day vs. risperidone 2 to 6 mg/dayPANSS 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, 2014Fervaha, 2014Caroff, 2011Arnold, 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. risperidonePANSS, 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. risperidoneLife 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: 4.5PANSS severity of illness: 80.4 | 80 | Risperidone 3.4 mg/day vs. quetiapine 420 mg/dayPANSS 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/dayOverall 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 PharmaceuticalCo., 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, 2014Fervaha, 2014Caroff, 2011Arnold, 2013 | NR | NR | Good |
| Liu, 2014 | Risperidone 3.4 mg/day vs. quetiapine 420 mg/dayDropout rate of 20% over 1-year treatment period. | Huzhou Ministry ofTechnology | 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: 26.2Gender, % female: 20.4Ethnicity, %: Caucasian: 66.2Moroccan: 8.4Surinamese: 8.3Turkish: 6.2Other: 10.9 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Maat, 2014 | Baseline drug abuse, %:Nicotine: 69.8Alcohol: 64.1Cannabis: 49.8Cocaine: 9.2 | 80 randomized(48 completed study) | Aripiprazole vs. risperidoneMean 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=0.37Mean 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. risperidoneDiscontinuations 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 clinicalresearch sites: March 2011 to July 2013 | Inclusion: Adults with schizophrenia orschizoaffective 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 longas 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 akathisiaPaliperidone: 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, 2013RECOVER 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 800mg) (n=395)vs.Risperidone (2 to 6 mg) (n=403) once daily | 52 weeks | Age, mean year: 39.65Gender, % female: 41.8Ethnicity, %: NR |
| Naber, 2015QUALIFYCompanion: Potkin, 2015 | International | Adults (18 to 60 y) with DSM-IV-TR–defined schizophrenia. | Aripiprazole 300 to 400 mgmonthly 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: 41.9Gender, % female: 40.2Ethnicity, %: White: 69.7Black/African American: 27.0Asian: 1.5Other: 1.1Unknown: 0.7 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Naber, 2013RECOVER NCT00600756 | Concurrent substance abuse:Alcohol use, %: 12.1Cannabis use, %: 1.9DSM-IV schizophrenia subtype diagnosis, %: Schizoaffective disorder of bipolar type: 8.3Schizoaffective disorder of depressive type: 7.8Median duration of present episode, m: 2.5Mean years since first known schizophrenia diagnosis:11.35Hospitalizations due toschizophrenia in the previous 6 months, % patients: 16.1SWN-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, 2015QUALIFYCompanion: 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 monthlyNaber, 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, 2013RECOVER 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 eventsTEAE: 238/391 (60.9); 791 vs. 258/402 (64.2); 834TEAE leading to discontinuation: 57/391 (14.6); 72 vs. 48/402 (11.9); 80Serious TEAE: 45/391 (11.5); 49 vs. 26/402 (6.5); 31Serious TEAE leading to death: 0 (0) vs. 1/402 (0.2); 1Weight increased: 18/391 (4.6); 18 vs. 25/402 (6.2); 25 | AstraZeneca. | Fair |
| Naber, 2015QUALIFYCompanion: Potkin, 2015 | Aripiprazole 300 to 400 mg monthly vs. paliperidone 50-150 mg/ paliperidone palmitate 78 to234 mg monthlyNaber, 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. 0Muscle 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 OtsukaPharmaceutical 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 centersin 11 European countries (Bulgaria, Croatia, Czech Republic,France, Hungary, Poland,Romania, Serbia, Spain, Russia, and Ukraine) | Adults aged 18–65 years who had adiagnosis 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 (targetdose) daily (n=230) Risperidone 4 mg (target dose) daily (n=231) | 26 weeks | Cariprazine vs. risperidone:Age, mean years: 40.2 vs. 40.7Gender, % female: 46 vs. 39Ethnicity, %: 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. 12.96Number 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 randomized460 included in safety population456 in modifiedITT | Cariprazine vs. risperidone:CGI-S score: -0.95 vs. -0.74, LSMD -0.21 (95% CI -0.36 to -0.06), p=0.0052PANSS total score: -16.90 vs. -14.80, LSMD -2.10 (95% CI -4.34 to0.13), p=0.065PANSS negative subscale score: -8.63 vs. -7.16, LSMD -1.48 (95% CI -2.38 to -0.57), p=0.0015CGI-I score: 2.53 vs. 2.89, LSMD -0.37 (95% CI -0.55 to -0.19), p<0.0001SAS items 1-8: 0.01 vs. 0.05, LSMD 0.05 (95% CI -0.21 to 0.12), p=0.58Achieved 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** |
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| 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, 2016Companion toParabiaghi, 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: 42.7Gender, % female: 42.0Ethnicity: 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 initialdose (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: 33.0Gender, % female: 50.0Ethnicity: NR |
| Robinson, 2015See 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 30mg/day orally (n=106)vs.Risperidone 1 to 6 mg/day orally (n=103) | 12 weeks | Age, years: 22.1Gender, % female: 29Ethnicity, %: Caucasian: 24.0African-American: 37.0Hispanic: 10.0Other/mixed: 9.0 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Parabiaghi, 2016Companion toParabiaghi, 2011 | Duration of illness, year from first psychiatric contact (%):0-2 years: 12.03+ years: 72.0Hospitalization, % in-patient: 20.0Current substance abuse or dependence, %: 5.0Antipsychotic drug-naïve, %: 6.0 | 300 | NR |
| Park, 2013 | PANSS total score at baseline: 74.8 | 20 | NR |
| Robinson, 2015See also: Zhang, 2015 | Duration of current illness/psychosis, weeks: 125.5\*BPRS-A severity of illness: 45.1Schizoaffective, %: 3Substance use, %: 0Antipsychotic drug naïve: lifetime antipsychotic drug medication treatment 2 weeks or less | 209 | Aripiprazole 5-30 mg/day vs. risperidone 1-6 mg/dayCumulative 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 to9.2)Discontinuation of controlled treatment before 12 weeks (n, due tosafety concerns): 0 vs. 3 (1 metabolic syndrome, 1 tardive dyskinesia, 1 hematologic abnormalities )**Zhang, 2015**C/C homozygotes vs. T carriersBPRS 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, 2016Companion toParabiaghi, 2011 | Aripiprazole vs. olanzapine vs. haloperidolMetabolic 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 to1.51)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 diRicerche Farmacologiche ‘MarioNegri’ and Bristol-Myers Squibb\*Mean dose of treatment. | Fair |
| Park, 2013 | Ziprasidone vs. olanzapineBody 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, 2015See also: Zhang, 2015 | Aripiprazole 5-30 mg/day vs. risperidone 1-6 mg/daySexual dysfunction, % (n/N): 7.8% (8/102) vs. 12.5% (12/96) | National Institutes ofHealth and NARSAD YoungInvestigator Grant toJ.A.G. from the Brain & BehaviorResearch Foundation\*Report states: "duration of psychotic symptoms before study week (weeks)"\*\*Response criteria based onBPRS-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, 2012RCT 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 1.5–8.5olanzapine 7.5–40 risperidone1.5–7.0 quetiapine100–1500and ziprasidone 40–240 mg/day | 52 weeks | Mean age 25.674.6% maleEthnicity NR |
| Sanz-Fuentenebro,2013 | Spain | Diagnosis of schizophrenia orschizophreniform disorder (DSM-IVcriteria); 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: 24.5Gender, % female: 30.0Ethnicity, %: Caucasian: 77.0 |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| San, 2012RCT Spain | BMI 22.782.5% single46.5% elementary school education44.7% 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, %: 10Cannabis, %: 3.3Cocaine, %: 6.7DUP\*, months: 9.9 | 30 | Clozapine vs. RisperidoneTotal rate of protocol discontinuation was 53.3%Maintenance of initial treatment, weeks (SD): 41.1 (15.9) vs. 23.3 (20.1); p=0.015LOCF\*\* 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, 2012RCT Spain | Discontinuations due to adverse events:11.1% haloperidol; 20% olanzapine, 7.7% quetiapine; 6.2% risperidone; 25% ziprasidoneTime to discontinuation due to adverse events: NRUKU 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 andEli Lilly | Good |
| Sanz-Fuentenebro,2013 | NR | Spanish Ministry of Health,Ayudaspara el fomento de la traslación de la aplicación terapéutica de medicamentoshuérfanos y terapias avanzadas (grant number: TRA-035); and the Instituto de SaludCarlos 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 aDSM-IV diagnosis of schizophrenia. | Paliperidone palmitate 3-month injection (N=504)vs.Paliperidone palmitate 1- month injection (N=512) | 48 weeks | Age, years: 38.7Gender, % 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 25mg/day orally (n=25)vs.Quetiapine 25 to 600 mg/day (n=25) | 12 weeks | Age, years: 36.8Gender, % female: 100Ethnicity: NR |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Savitz, 2016 | Prior hospitalizations, %:None: 41.0Once: 37.0Twice: 16.0Three times: 3.0Four or more: 2.0PANSS 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 injectionRelapse-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: 6.4Hospitalization, %: 100CGI-S severity of illness: 3.74Schizoaffective, %: 0 | 50 | NR |

| **Author, Year** | **Harms Outcomes** | **Funding** | **Quality Rating** |
| --- | --- | --- | --- |
| Savitz, 2016 | Paliperidone palmitate 3-month injection vs. paliperidone palmitate 1-month injectionOverall 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. 3Diabetes 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-pointincrease 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 mgWithdrawal due to AE, n/N (%): 0 vs. 0 | Research received no specificgrant 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 dosage25 mg biweekly (12.5 to37.5 mg) long acting injectable (n=43)vs.Risperidone modal dosage2 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: 21.5Gender, % female: 22.0Ethnicity, %: White: 49.0Asian: 11.0Native American: 5.0African American: 28.0Pacific Islander: 1.0Mixed: 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:51.7Ethnicity, %: 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 120-160mg/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: 35.8Gender, % female: 55.1Ethnicity, %: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: 2.1Withdrawal-retardation factor at randomization: 1.9Schizophrenia, %: 55.0Schizophreniform disorder, %: 33.0Schizoaffective, %: 12.0Substance use, %: 0 | 86 | Risperidone 25 mg biweekly long acting vs. risperidone 2 mg dailyPsychotic exacerbation/relapse, n/N (%)\*: 2/40 (5.0) vs. 14/43 (33.0); P<0.001Hospitalizations due to mental illness, n/N (%): 2/40 (5.0) vs. 8/43 (18.6); P=0.05Early discontinuation due to inadequate treatment response, n/N (%):1/40 (2.5) vs. 7/42 (17.0), P=0.01Risk of exacerbation and/or relapse over time was significantly lower for long-acting injectable risperidone than for oral risperidone: p<0.004Mean time to relapse, days: 298.5 vs. 218.6Medication adherence was better for long-acting risperidone vs. oral risperidone: p<0.001Medication 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. perazinePANSS 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: 99.8Schizoaffective, %: 0Antipsychotic drug naïve, %: 0 | 191 | Ziprasidone 120-160 mg/day vs. olanzapine 10-20 mg/day vs. perazine300-600 mg/dayAll-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 dailyWAE, n/N (%): 4/40 (10.0) vs. 9/43 (21.0) | NIH and Janssen ScientificAffairs, LLC\*Based on BPRS scale | Fair |
| Tybura, 2013 | NR | Grant of Ministry of Since andHigh Education (grant no. N N402456738) and by a Pfizer Independent Research Grant (grant no. 2005-0039). | Poor |
| Tybura, 2014 | NR | Pfizer Independent ResearchGrant\*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 whohad 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/dayorally (n=31)vs.Aripiprazole 5-20 mg/day orally (n=31)\* | 24 weeks | Age (years): 29.8Gender, % female: 37.1Ethnicity: Asian (Indian) |

| **Author, Year** | **Other Population Characteristics** | **Total N** | **Benefits Outcomes** |
| --- | --- | --- | --- |
| Wani, 2015 | Duration of illness: 4.75 yearsPANSS severity of illness: 68.9Antipsychotic drug naïve, %: 0 | 62 | Olanzapine 10-20 mg/day vs. aripiprazole 5 to 20mg/dayAll-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/dayPatients 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