Therapeutic Class Overview
Extended-Release Injectable Atypical (Second-Generation) Antipsychotics

Therapeutic Class Overview/Summary:
This review will focus on the extended-release (ER) injectable atypical antipsychotics and will not cover oral or immediate-release injectable formulations. Collectively, all of the ER injectable atypical antipsychotic agents are Food and Drug Administration (FDA)-approved for the maintenance treatment of schizophrenia in adult patients.[1-6] Additionally, risperidone microspheres (Risperdal Consta®) is approved for the treatment of bipolar I disorder and paliperidone palmitate (Invega Sustenna®) is approved for the treatment of schizoaffective disorder.[4,6] Other ER injectable atypical antipsychotic products include aripiprazole (Abilify Maintena®), aripiprazole lauroxil (Aristada®), olanzapine pamoate (Zyprexa Relprevv®), and paliperidone palmitate (Invega Trinza®). Partial or total nonadherence with oral antipsychotics in the treatment of schizophrenia has been associated with significant increases in the risk of relapse and rehospitalization.[7] Long-acting injectable (LAI) antipsychotics were developed to ensure drug delivery through decreased dosing frequency, improved bioavailability, and more stable concentrations of drug. These attributes, coupled with the regular monitoring that is attendant to injectable treatment regimens, presumably can enhance medication adherence in patients with schizophrenia, thereby reducing the risk of relapse and improving the long-term prognosis of the illness.

Antipsychotic medications have been used for over fifty years to treat schizophrenia and a variety of other psychiatric disorders.[8] Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D2 in the mesolimbic and/or mesocortical regions of the brain. Antipsychotic medications exert their effect in part by blocking D2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with the disorder.[9] As a class, atypical antipsychotics, or second-generation antipsychotics are more selective in targeting the mesolimbic D_2 pathway compared with older first-generation antipsychotics. They also block or partially block serotonin $(5\text{-HT})_{2A}$ and 5-HT_{1A} receptors and have a greater affinity for 5-HT_2 receptors than D_2 receptors.[9,10] The neuropharmacology of aripiprazole differs from other atypical antipsychotics, as it is a partial D_2 and 5-HT_{1A} agonist and a 5-HT_{2A} and 5-HT_{2C} antagonist. It is referred to as a D_2-serotonin system stabilizer since the partial agonist activity allows for blockade of an overstimulated receptor and stimulation of a receptor when activity is needed.[16] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[9,10]

The ER injectable atypical antipsychotics are all administered via intramuscular administration. The location where the injection can be made varies by drug and also sometimes varies by strength. The acceptable locations may include the gluteus or deltoid muscles.[1-6] During maintenance therapy, aripiprazole, aripiprazole lauroxil, and paliperidone palmitate are dosed once a month. Additionally, aripiprazole lauroxil may be given once every six weeks in some cases. Risperidone microsphere is dosed every two weeks, olanzapine pamoate is dosed every two or four weeks, and paliperidone palmitate is dosed once every three months. Prior to initiating therapy with paliperidone palmitate (Invega Trinza®), the patient should be stabilized on once-monthly paliperidone palmitate (Invega Sustenna®) for at least four months.[1-6]

Table 1. Current Medications Available in the Therapeutic Class[1-6]

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
Aripiprazole (Abilify Maintena®)	Schizophrenia	ER Suspension for Injection (pre-filled dual chamber syringe): 300 mg 400 mg ER Suspension for Injection (single-use vial): 300 mg 400 mg Administer only via the deltoid or gluteal muscle. Must be administered by a health care professional.	-
Aripiprazole Lauroxil (Aristada®)	Schizophrenia	ER Suspension for Injection (pre-filled syringe): 441 mg/1.6 mL 662 mg/2.4 mL 882 mg/3.2 mL Administer via the deltoid (441 mg only) or gluteal muscles (all doses). Must be administered by a health care professional.	-
Olanzapine pamoate (Zyprexa Relprevv®)	Schizophrenia	ER Suspension for Injection (single-use vial): 210 mg 300 mg 405 mg Administer via the gluteal muscles. Must be administered by a health care professional.	-
Paliperidone palmitate (Invega Sustenna®, Invega Trinza®)	Schizoaffective disorder* (Invega Sustenna), Schizophrenia	ER Suspension for Injection (pre-filled syringe [Invega Sustenna®]): 39 mg/0.25 mL 78 mg/0.5 mL 117 mg/0.75 mL 156 mg/1 mL 234 mg/1.5 mL Administer via the deltoid or gluteal muscles. Must be administered by a health care professional. ER Suspension for Injection (pre-filled syringe [Invega Trinza®]): 273 mg/ 0.875 mL	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
		410 mg/1.315 mL 546 mg/1.75 mL 819 mg/2.625 mL	
Risperidone microsphere (Risperdal Consta®)	Bipolar I Disorder†, Schizophrenia	ER Suspension for Injection (single-use vials): 12.5 mg 25 mg 37.5 mg 50 mg	-

*Monotherapy and as an adjunct to mood stabilizers or antidepressants
†Monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment

Evidence-based Medicine

- Numerus Clinical trials evaluating the safety and efficacy of the ER injectable atypical antipsychotics have been conducted.[11-49]
  - Safety and efficacy of these agents has been established in numerous clinical trials, mostly comparing each ER injectable to placebo.[1-6,11-49]
- Risperidone microsphere was compared to paliperidone palmitate (Invega Sustenna®) in two open-label studies. Results suggest there is a slight benefit in favor of paliperidone palmitate (Invega Sustenna®); however, the difference was not statistically significant in either trial.[41,42]
- In another study, after 12 months of treatment with risperidone microsphere or a typical antipsychotic, the time to all-cause treatment discontinuation was significantly shorter for individuals assigned to switch to risperidone than for individuals assigned to stay on a first generation injectable antipsychotic (P=0.01).[43]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The National Institute for Health and Clinical Excellence 2014 practice guideline for psychosis and schizophrenia in adults identifies candidates for injectable antipsychotic formulations as patients who prefer an injectable formulation after an acute episode or if the clinical treatment priority is to avoid non-adherence.[50]
  - Similarly, the American Psychiatric Association 2004 practice guidelines for schizophrenia state long-acting injectable antipsychotics may include patients have compliance issues.[51]
  - Clinical guidelines do not note a preference among the ER injectable antipsychotic agents.
- Other Key Facts:
  - There are no generic products currently available.
  - Dosing and injection site vary by drug and/or strength
    - The acceptable locations may include the gluteus or deltoid muscles.[1-6]
    - During maintenance therapy, aripiprazole, aripiprazole lauroxil, and paliperidone palmitate are dosed once a month. Additionally, aripiprazole lauroxil may be given once every six weeks in some cases. Risperidone microsphere is dosed every two weeks, olanzapine pamoate is dosed every two or four weeks, and paliperidone palmitate is dosed once every three months.
  - Prior to initiating therapy with paliperidone palmitate (Invega Trinza®), the patient should be stabilized on once-monthly paliperidone palmitate (Invega Sustenna®) for at least four months.[1-6]

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Overview/Summary

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Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Aripiprazole (Abilify Maintena®)	Atypical antipsychotic	-
Aripiprazole Lauroxil (Aristada®)	Atypical antipsychotic	
Olanzapine pamoate (Zyprexa Relprevv®)	Atypical antipsychotic	-
Paliperidone palmitate (Invega Sustenna®, Invega Trinza®)	Atypical antipsychotic	-
Risperidone microsphere (Risperdal Consta®)	Atypical antipsychotic	-

Indications

Table 2. Food and Drug Administration Approved Indications[1-6]

Generic Name	Schizoaffective disorder*	Schizophrenia	Bipolar I Disorder†
Aripiprazole		a	
Aripiprazole Lauroxil		a	
Olanzapine pamoate		a	
Paliperidone palmitate	a (Invega Sustenna®)	a	
Risperidone microsphere		a	a

*Monotherapy and as an adjunct to mood stabilizers or antidepressants
†Monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment

Pharmacokinetics

Table 3. Pharmacokinetics[1-6,52]

Generic Name	Protein Binding (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (days)
Aripiprazole	>99	<1	Dehydro-aripiprazole	29.9 to 46.5‡
Aripiprazole Lauroxil	>99	<1%	Aripiprazole, dehydro-aripiprazole	29.2 to 34.9
Olanzapine pamoate	93	7	Not reported	30
Paliperidone palmitate	74	59	Not reported	25 to 49 (Sustenna®)§ 84 to 95* (Trinza®) 118 to 139† (Trinza®)
Risperidone microsphere	90	70	9-hydroxyrisperidone	3 to 6

*Administered via the deltoid muscle.
†Administered via the gluteal muscle.
‡For the 300 and 400 mg doses respectively
§ Half-life depended on dose; range of 39 mg to 234 mg ranged from 25 to 49 days

Clinical Trials

The extended-release (ER) injectable atypical antipsychotics have all shown to be safe and effective for the maintenance treatment of schizophrenia and other FDA-approved diagnoses in numerous clinical trials.[1,6,11-49]

The efficacy of aripiprazole ER injection for treatment of schizophrenia was established in a 12-week, randomized, double-blind, placebo-controlled trial in acutely relapsed adults, and one longer-term, double-blind, placebo-controlled, randomized-withdrawal (maintenance) trial in adults.[1] The 12-week trial in acutely relapsed adults (N=168) evaluated the effect of treatment on Positive and Negative Syndrome Scale (PANSS) total score. After 10 weeks of treatment aripiprazole ER injection significantly improved PANSS total score compared to placebo (mean difference -15.1; 95% confidence interval [CI], -19.4 to -

10.8; P<0.0001).[1] The maintenance treatment of schizophrenia with aripiprazole ER injection significantly delayed time to exacerbation of psychotic symptoms or impending relapse when compared with placebo (HR, 0.199; 95% CI, 0.125 to 0.31, P<0.01)[1,11]

The efficacy of aripiprazole lauroxil in the treatment of patients with schizophrenia was established, in part, on the basis of efficacy data from trials with the oral formulation of aripiprazole. In addition, the efficacy of aripiprazole lauroxil was established in a 12-week, randomized, double-blind, placebo controlled, fixed-dose study in adult patients with schizophrenia. After 12 weeks of therapy, the least squares mean (standard error) change from baseline at week 12 in PANSS total score for the aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups was -20.9 (1.39), -21.8 (1.35), and -9.8 (1.39), respectively. Aripiprazole lauroxil 441 mg and 882 mg injections significantly improved PANSS total scores compared with placebo (placebo-subtracted difference, -10.9 [95% CI, -14.5 to -7.3; P<0.001] and -11.9 [95% CI, -15.4 to -8.3; P<0.001] for 441 mg and 882 mg, respectively).[2,12]

The short-term effectiveness of olanzapine pamoate was established in an 8-week, placebo-controlled trial in adult patients (N=404) who were experiencing psychotic symptoms and had a diagnosis of schizophrenia.[3] The primary endpoint, PANSS total score, was significantly improved with olanzapine pamoate compared to placebo (210 mg/2 weeks, -22.5, P<0.001; 300 mg/2 weeks, -26.3, P<0.001; 405 mg/4 weeks, -22.6, P<0.001). There was no difference in PANSS total score between active treatments.[13] A longer-term trial established the safety and efficacy in the maintenance treatment of schizophrenia in adults (N=1065). Patients must have remained stable for four to eight weeks on open-label treatment with oral olanzapine and were then randomized to continue their current oral olanzapine dose (10, 15, or 20 mg/day); or to olanzapine pamoate 150 mg every two weeks (405 mg every four weeks, 300 mg every two weeks, or 45 mg every four weeks). In all olanzapine pamoate groups, time to exacerbation was increase (P< 0.01). There was no difference between different olanzapine pamoate dosages.[15]

The safety and efficacy of paliperidone palmitate (Invega Sustenna®) for the treatment of schizophrenia and schizoaffective disorder have been evaluated in a number of clinical trials.[4,17-24,47] FDA-approval of paliperidone palmitate (Invega Sustenna®) for the treatment of schizophrenia as monotherapy in adults was granted based on four short-term, fixed-dose trials and one maintenance trial and one long-term flexible-dose trial for the maintenance treatment of schizoaffective disorder.[4,17,18,20,47] In each of the short-term schizophrenia trials, paliperidone palmitate (Invega Sustenna®) significantly improved PANSS total score compared with placebo except for 78 mg/4 weeks in Study 2 (P<0.05 for all study doses).[4,18,19] In the maintenance treatment of schizophrenia, patients randomized to continue on paliperidone palmitate during the double-blind phase experienced a significant delay in time-to-relapse compared with placebo-assigned patients (P<0.0001).[4,21] Paliperidone palmitate (Invega Sustenna®) was shown to be effective in a long term trial in patients with schizoaffective disorder. Paliperidone palmitate (Invega Sustenna®) was associated with significant delay in time to relapse compared with placebo (P<0.001) and correspondingly, a significantly lower percentage of subjects treated with paliperidone (Invega Sustenna®) experienced a relapse event (P<0.001).[47]

The efficacy of paliperidone palmitate (Invega Trinza®) was evaluated in a double-blind, placebo-controlled, randomized-withdrawal trial designed to evaluate time to relapse involving adults with schizophrenia.[5,25] The study included four phases: screening and oral tolerability testing phase, open-label transition phase, open-label maintenance phase, and a double-blind phase. Patients stable on other long-acting injectable antipsychotics were eligible. A pre-planned interim analysis showed a statistically significantly longer time to first relapse with paliperidone palmitate (Invega Trinza®) compared to placebo (hazard ratio [HR],3.45; 95% [CI, 1.73 to 6.88; P<0.001). Median time to relapse was 274 days with placebo and could not be estimated for Invega paliperidone palmitate (Trinza®) as the study was terminated early. Twenty-three percent of patients in the placebo group and 7.4% of patients in the Invega paliperidone palmitate (Trinza®) group experienced a relapse event.[25]

Risperidone microsphere has been evaluated in a number of clinical trials for the treatment of schizophrenia. Safety and efficacy is supported by many open label trials which tested different doses

and frequencies of administration compared to each other, placebo, or to various oral atypical antipsychotics.[26-40] Data from the trials comparing risperidone microsphere to oral atypical antipsychotics have demonstrated mixed results, but it is at least as effective as oral atypical antipsychotics, and potentially more effective.[36-40]

Risperidone microsphere was compared to paliperidone palmitate (Invega Sustenna®) in two open-label studies. Results suggest there is a slight benefit in favor of paliperidone palmitate (Invega Sustenna®); however, the difference was not statistically significant in either trial.[41,42] In another study, after 12 months of treatment with risperidone microsphere or a typical antipsychotic, the time to all-cause treatment discontinuation was significantly shorter for individuals assigned to switch to risperidone than for individuals assigned to stay on a first generation injectable antipsychotic (P=0.01).[43]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Schizophrenia				
Kane et al[10] Aripiprazole 400 mg IM depot every four weeks vs placebo Subjects initially received oral aripiprazole (10 to 30 mg once daily). Subjects meeting stability criteria for 4 weeks entered IM depot stabilization phase where aripiprazole 400 mg IM was given every 4 weeks (single decrease to 300 mg permitted) with co-administration of oral aripiprazole for the first 2 weeks. Subjects meeting stability criteria of this phase for 12 weeks were randomly assigned to aripiprazole IM depot or placebo for a 52 week maintenance phase.	DB, MC, PC, PG, RCT Patients (18 to 60 years of age) with schizophrenia according to DSM-IV-TR criteria for at least three years and history of symptom exacerbation or relapse when not receiving antipsychotic treatment	N=403 4 to 6 weeks oral conversion phase; 4 to 12 weeks oral stabilization phase; 12 to 36 weeks IM depot stabilization phase; up to 52 weeks maintenance treatment phase	Primary: Time to exacerbation of psychotic symptoms/ impending relapse any time during maintenance treatment phase Secondary: Proportion of patients meeting impending relapse criteria in maintenance treatment phase, mean change from DB baseline to end point in PANSS total score and mean change from baseline to end point in CGI-S score; safety assessed by AE reporting, clinical laboratory tests, urinalysis, 12-lead ECG, vital signs, injection	Primary: Time to impending relapse was significantly delayed (HR, 0.199; 95% CI, 0.125 to 0.31, P<0.01) with aripiprazole-IM-depot compared with placebo. Secondary: Relapse rates were significantly lower with aripiprazole-IM-depot than placebo at the final analysis time point (80 events; 10.0% [n=27/269] vs 39.6% [n=53/134]; HR, 5.03; 95% CI, 3.15 to 8.02). There were significant mean PANSS total scores increases from DB baseline for placebo (11.6) vs aripiprazole-IM-depot (1.4; P<0.001) The mean change in CGI-S (LOCF) score during DB treatment was statistically significant in favor of aripiprazole at week 52 (0.1 vs 0.7; P <0.0001) and at every assessment from week 4 onward. The most common TEAEs (occurring in ≥5% of aripiprazole-IM-depot patients and greater than placebo) were insomnia, headache, and tremor. The only serious AEs reported by >1% of patients in either group were psychotic disorder (1.5% in aripiprazole-IM-depot vs 3.0% placebo patients) and schizophrenia (0.7% in aripiprazole-IM-depot vs 1.5% placebo patients). Injections of aripiprazole-IM-depot were generally well tolerated. The incidence of potentially clinically relevant prolactin elevation (>upper limit of normal) during DB treatment was lower with aripiprazole-IM-depot than placebo (1.9 vs 7.1%). The incidence of potentially clinically relevant changed in vital signs, orthostatic hypotension, and ECG parameters were similar between treatment groups during DB treatment, as was the mean change in QTc intervals. During DB treatment, 14.9% of aripiprazole-IM-depot and 9.7% of placebo patients experienced treatment-emergent EPS AEs, dystonic, parkinsonism and residual. During DB treatment, mean change in body weight from DB baseline to last visit was -0.2 kg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			site evaluation, and physical exam	(n=267) for aripiprazole-IM-depot and -0.4 kg (n=134) for placebo (P=0.812, LOCF analysis).
Meltzer et al[12] Aripiprazole lauroxil 441 mg IM monthly vs aripiprazole lauroxil 882 mg IM monthly vs placebo	DB, MC, PC, PG, RCT Patients 18 to 70 years of age with schizophrenia according to DSM-IV-TR criteria, outpatient status for at least 3 months in the past year, BMI 18.5 to 40.0 kg/m^2, resides in a stable living situation, and is willing and able to be confined to an inpatient study unit for two weeks or longer	N=623 12 weeks	Primary: Change from baseline to end point in PANSS total score Secondary: CGI-I scores at 12 weeks	Primary: Least squares mean (standard error) for the change from baseline at week 12 in PANSS total score for the aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups was -20.9 (1.39), -21.8 (1.35), and -9.8 (1.39), respectively. Both active treatments significantly improved PANSS total score at week 12 when compared to placebo (P<0.001 for both). Secondary: The proportion of patients who were very much or much improved on the Clinical Global Impression - Improvement (CGI-I) scale at week 12 were significantly higher in the active treatment arms when compared to placebo (P<0.001 for both). The number of patients who reported “much improved” or “very much improved” was 95/196 (48%) for aripiprazole lauroxil 441 mg, 106/204 (52%) for aripiprazole lauroxil 882 mg, and 48/196 (24%) for the placebo group.
Lauriello et al[13] Olanzapine pamoate monohydrate (OPM) 210 mg every two weeks vs Olanzapine pamoate	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with schizophrenia according to DSM-IV or DSM-IV-TR criteria	N=404 (randomized to DB treatment) 8 weeks	Primary: Change from baseline to end point based on the LOCF approach in the PANSS total score after eight weeks of	Primary: At endpoint (LOCF), improvement in total PANSS total scores for each of the active treatment groups was significantly greater than that for placebo (210 mg/2 weeks, -22.5 [SD 21.8], P<0.001; 300 mg/2 weeks, -26.3 [SD 24.9], P<0.001; 405 mg/4 weeks, -22.6 [SD 22.1], P<0.001). No statistically significant differences were observed among the 3 OPM treatment groups at end point.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
monohydrate 300 mg every two weeks vs Olanzapine pamoate monohydrate 405 mg every two weeks vs Placebo Response was defined as a ≥40% improvement in PANSS total score	and had a PANSS derived BPRS total score ≥30 at baseline For patients treated previously with a depot antipsychotic, the last injection must have been received at least two weeks or one injection interval, whichever was longer, before DB treatment Patients who were randomly assigned to 405 mg/4 weeks OPM received a placebo injection at the 2-week interval between their active study drug injections, and patients randomly assigned to placebo received placebo		treatment Secondary: Change from baseline to end point based on the LOCF approach in the PANSS positive, negative, and general psycho-pathology subscales, PANSS-derived BPRS, and CGI-CGI-S after eight weeks of treatment; safety assessments (AEs, EPS, rating scales [AIMS, BARS, and SAS], clinical laboratory tests [including lipid panels, blood glucose levels])	Secondary: All three OPM treatment groups showed significantly greater baseline-to-end point decreases in PANSS positive, negative, and general psychopathology symptom subscales (all P<0.001), PANSS-derived BPRS total (all P<0.001), and CGI-S (all P<0.05) scores relative to placebo. The incidence of response was significantly higher for all 3 OPM dosages (210 mg/2 weeks, 47.2% [P<0.001]; 300 mg/2 weeks, 48.0% [P<0.001]; and 405 mg/4 weeks, 40.0% [P=0.003]) relative to placebo (20.4%). Nineteen patients (4.7%) experienced serious adverse events (210 mg/2 weeks, N=6; 300 mg/2 weeks, N=5; 405 mg/4 weeks, N=3; placebo, N=5); no deaths were reported. Mean baseline-to-end point changes in fasting glucose did not differ significantly among all groups. Mean baseline-to-end point changes in fasting total cholesterol differed significantly among all groups (210 mg/2 weeks, 8.2 mg/dL, P=0.004; 300 mg/2 weeks, 5.5 mg/dL, P=0.015; 405 mg/4 weeks, 10.4 mg/dL, P<0.001 vs. placebo, -7.0 mg/dL). Mean baseline-to-end point changes in fasting triglycerides differed significantly among some groups (210 mg/2 weeks, 26.3 mg/dL, P=0.016; 405 mg/4 weeks, 30.3 mg/dL, P<0.016 vs. placebo, -9.4 mg/dL). Mean baseline-to-end point (LOCF) weight gain was significantly greater for the OPM groups relative to placebo (all P≤0.001). The incidence of weight gain ≥7% of baseline was significantly higher in the OPM groups (210 mg/2 weeks, 23.6%, P=0.046; 300 mg/2 weeks, 35.4%, P<0.001; 405 mg/4 weeks, 27.0%, P=0.012) relative to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	injections every two weeks			(12.4%). None of the baseline-to-end point changes in the scales used to measure treatment-emergent extrapyramidal symptoms were either clinically or statistically significant.
Ascher-Svanum et al[14] Olanzapine pamoate monohydrate (OPM) 210 mg every two weeks vs olanzapine pamoate monohydrate 300 mg every two weeks vs olanzapine pamoate monohydrate 405 mg every four weeks vs placebo No oral antipsychotic supplementation was allowed throughout the trial.	PH of study by Lauriello et al Patients 18 to 75 years of age with acute schizophrenia, according to DSM-IV or DSM-IV-TR criteria, with a PANSS-derived BPRS total score ≥30 at baseline	N=233 8 weeks	Primary: Early responder (>30% improvement in PANSS total score at week-four), later responder (>40% improvement in PANSS total score at week-eight), discontinuation rate, SF-36, QLS Secondary: Not reported	Primary: At week four, 59% of patients met the study criteria for early response, while, 41% were classified as early non-responders. Of the patients who were early non-responders at four weeks, 80% were classified as later non-responders at week-eight, compared to 22% of patients previously categorized as early responders. Early responders exhibited significantly greater improvement in PANSS total score from baseline at every time point, compared to early non-responders (P<0.001). By week eight, early responders were associated with twice the reduction in PANSS scores compared to early non-responders. For all PANSS subscales, early responders exhibited significantly greater improvement from baseline compared to early non-responders (P<0.001). Response at week four predicted response at week eight, with a sensitivity of 84.9% and specificity of 72%. Rates of study discontinuation for any reason were higher for early non-responders compared to early responders (25 vs 17.5%; P=0.007). Patients' sense of health status also improved significantly more in patients who were early responders verse early non-responders, as evidenced by the following SF-36 subscale scores: mental component summary (P=0.01), mental health (P=0.004), and social functioning (P=0.002). Early responders had significantly greater improvement than early non-responders in the total QLS score as well as all of its subscales (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Kane et al[15] Olanzapine pamoate monohydrate 405 mg every four weeks vs olanzapine pamoate monohydrate 300 mg every two weeks vs olanzapine pamoate monohydrate 150 mg every two weeks vs olanzapine pamoate monohydrate 45 mg every four weeks vs olanzapine (oral) 10, 15, or 20 mg/day (assigned fixed dose was identical to that which achieved stabilization in a four to eight week open-label	AC, DB, MC, PG, RCT Patients 18 to 75 years of age with a DSM-IV or DSM-IV-TR diagnosis of schizophrenia previously stabilized over four to eight weeks on 10, 15, or 20 mg/day oral olanzapine with a BPRS positive symptom subscale score ≤4 (range: 1 to 7) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content) For patients treated	N=1065 (randomized to DB treatment) 24 weeks	Primary: Time to exacerbation of symptoms (defined in terms of either increases in BPRS positive symptoms [conceptual disorganization, hallucinations, suspiciousness, unusual thought content] or hospitalization) Secondary: Not reported Safety assessments (AEs; weight gain ≥7% of baseline; changes in plasma cholesterol, plasma triglycerides, plasma glucose, plasma prolactin;	Primary: Percentages of cohorts free of exacerbation at 24 weeks: OPM 45 mg every four weeks “very low dose/reference” (69%); OPM 150 mg every two weeks “low dose” (84%); OPM 405 mg every four weeks “medium dose” (90%); OPM 300 mg every two weeks “high dose” (95%); olanzapine oral 10, 15, or 20 mg/day (93%) Time to exacerbation was longer for all 3three standard OPM groups relative to OPM 45 mg every four weeks group (all log-rank test P<0.01), with no statistically significant differences among the therapeutically dosed groups except for a shorter time to exacerbation for the “low dose” injection group relative to the high dose (P=0.005) and the oral olanzapine (P=0.004) groups. No significant differences of exacerbation rates were detected between the pooled two-week (high and low doses combined) and therapeutic four week (medium dose) regimens, between the pooled two-week regimen and the oral formulation, or between the therapeutic four-week regimen and the oral formulation; all comparisons met criteria for noninferiority. All three standard OPM doses demonstrated significantly greater decreases in time to exacerbation compared to the very low reference dose. Secondary: Not reported The most common treatment-emergent adverse events were insomnia, weight gain, anxiety, and somnolence. Incidence of weight gain ≥7% from the time of randomization in either

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
period prior to randomization) No oral antipsychotic supplementation was allowed throughout the trial.	previously with a depot antipsychotic, the last injection must have been received at least two weeks or one injection interval (four weeks for injectable risperidone), whichever was longer, before DB treatment		EPS)	the combined two-week group (19%; P=0.42) or the medium 4-week dose group (15%; P=0.05) did not differ significantly from the oral olanzapine group (21%). The incidence of such weight gain was higher in the high dose (21%; P=0.004) and low dose (16%; P=0.05) groups relative to the very low reference dose group (8%). The very low reference dose group showed a greater mean decrease in total (-0.37 mmol/l [SD=0.80]) and low-density lipoprotein cholesterol (-0.32 mmol/l [SD=0.68]) relative to the other groups (all P<0.05). The high dose group showed a mean increase in prolactin (3.57 µg/l [SD=33.77]), whereas the other groups showed a decrease (all P<0.05). No significant between group differences were observed for baseline-to-end point changes in fasting triglyceride levels, plasma glucose, EPS measurements.
Hill et al[16] Olanzapine pamoate monohydrate (OPM) 405 mg every four weeks (medium dose group) vs olanzapine pamoate monohydrate 300 mg every two weeks (high dose group) vs olanzapine pamoate monohydrate 150 mg	Post hoc of the study by Kane et al Patients 18 to 75 years of age with a DSM-IV or DSM-IV-TR diagnosis of schizophrenia, clinically stable (outpatient status for at least four weeks before study onset), with a BPRS positive symptom	N=599 24 weeks	Primary: PANSS total score, relapse rate, discontinuation rate, adverse events Secondary: Not reported	Primary: PANSS total scores were significantly improved from baseline with the high dose group compared to patients receiving low-dose OPM (ES, 0.356; P<0.01). Dose related effects were also seen in terms of relapse rate (low, 16%; medium, 10%; high, 5%). The high dose group was associated with a significantly smaller relapse rate compared to the low dose group (P=0.003; NNT, 9). The following were all-cause discontinuation rates among the three groups (low, 36%; medium, 30%; high, 24%). The high dose group was associated with a significantly lower discontinuation rate compared to the low dose group (P=0.037; NNT, 9). Like-wise the rate of discontinuation due to efficacy-related reasons was dose-related (low, 20%; medium, 14%; high, 6%; P<0.001). Time to all-cause discontinuation (P=0.035) and time to relapse (P=0.005) were also significantly related to dose.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every two weeks (low dose group)	subscale score ≤4 (range: 1 to 7) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content			Weight gain was significantly related to dose (low, 0.67 kg; medium, 0.89 kg; high, 1.70 kg). The high dose group was associated with significantly greater weight gain compared to the low dose group (P=0.024). The following adverse events were also significantly related to dose: prolactin level, triglycerides, and high-density lipoprotein cholesterol level. For all of the above, the high dose group experienced significantly greater changes from baseline compared to the low dose group (P<0.05). Secondary: Not reported
Pandina et al[17] Paliperidone palmitate 39 mg vs paliperidone palmitate 156 mg vs paliperidone palmitate 234 mg vs placebo	DB, PC, PG, RCT Patients (18 years of age and older and BMI >17 and <40 kg/m^2) with schizophrenia according to DSM-IV criteria for at least one year before screening and had a PANSS total score at screening of 70 to 120 (inclusive) and at DB baseline of 60 to 120 (inclusive)	N=652 (randomized to DB treatment) 13 weeks Subjects randomized to active treatment groups were given an initial loading dose of 234 mg paliperidone palmitate on day one; subjects randomized to placebo	Primary: Change from baseline to endpoint (day 92 or the last postbaseline assessment in the DB period) in PANSS total score Secondary: Score changes in PSP scale, CGI-S scale, PANSS factor scores, PANSS subscales, onset of effect Safety	Primary: Mean change from baseline in total PANSS total scores for each of the active treatment groups was significantly greater compared with placebo at endpoint; response was dose related. Estimated effect sizes (vs. placebo) were: 0.26 (39 mg), 0.47 (156 mg), and 0.55 (234 mg) [no P reported] Note: results were only graphically presented; no raw data reported. Secondary: PSP scores increased significantly compared with placebo from baseline to endpoint in the 156 mg and 234 mg treatment groups (156 mg: 6.1, P<0.05; 234 mg: 8.3, P≤0.001) CGI-S scores decreased significantly compared with placebo from baseline to endpoint in the 156 mg and 234 mg treatment groups (156 mg: -1.0, P<0.05; 234 mg: -1.0, P≤0.001) PANSS scores decreased significantly compared with placebo from baseline to endpoint in the following groups and subscales: Positive symptom subscale: 156 mg (-4.1, P≤0.001), 234 mg (-4.4, P≤0.001); Negative symptom subscale: 156 mg (-1.9, P<0.05), 234 mg (-2.5,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Enrolled patients were hospitalized from days one to eight.	received a placebo injection on day one (both injections administered in deltoid muscle)	assessments included AEs, EPS rating scales, clinical laboratory tests, investigators' evaluation of the injection site	P≤0.001); General psychopathology subscale: 39 mg (-4.6, P<0.05), 156 mg (-5.6, P≤0.001), 234 mg (-6.4, P≤0.001). Safety assessments The overall frequency of AEs occurring in patients in any group was comparable across all active treatment (60%-63%) and placebo (65%) groups. Among the most common treatment-emergent AEs that occurred >1% more frequently in all 3 active treatment groups combined than in the placebo group were: injection site pain (8% vs 4%), dizziness (2% vs 1%), sedation (2% vs 1%), pain in extremity (2% vs 0%), and myalgia (1% vs 0%). Akathisia was the most frequently reported EPS-related AE across all groups (PBO=5%, 39 mg=1%, 156 mg=5%, 234 mg=6%). Prolactin levels increased from baseline to endpoint in all 3 active treatment groups (specific data per group not reported); glucose, insulin, serum lipid, liver and renal function tests showed no clinically relevant changes. Injection site tolerability was good; induration, swelling, and redness occurred in ≤10% of patients across the 4 treatment groups and were generally considered mild.
Sliwa et al[18] Paliperidone palmitate 39 mg vs paliperidone palmitate 156 mg	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of schizophrenia according to DSM-IV-TR criteria for at	N= 216 7 days screening period for washout of disallowed psychotropic medications and a DB	Primary: PANSS total score from baseline to the end of the DB treatment period Secondary: Changes from baseline to end	Primary: Improvement in the PANSS total score from baseline to the end of the treatment period was observed with paliperidone palmitate 156 mg (P=0.0001) and 234 mg (P<0.0001) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.0567) treatment group. Secondary: Improvement in the negative symptoms factor from baseline to the end of the treatment period was observed with paliperidone palmitate 156

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paliperidone palmitate 234 mg vs placebo Paliperidone palmitate subjects received a 234 mg day one dose, followed by their assigned dose on day eight and every four weeks thereafter.	least one year before screening and had been treated with oral risperidone within 2 weeks of randomization regardless of duration and had a PANSS total score between 60 and 120 at baseline	treatment period of 13 weeks	point on PANSS factor scores, the CGI-S score, the PSP scale, response (>30% improvement in PANSS total score) and safety evaluations (including AEs, body weight, and laboratory values)	mg (P=0.0036) and 234 mg (P=0.0042) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P= 0.1078) treatment group. Improvement in the positive symptoms factor from baseline to the end of the treatment period was observed with paliperidone palmitate 156 mg (P=0.0086) and 234 mg (P=0.0027) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.2483) treatment group. Improvement in the disorganized thoughts factor from baseline to the end of the treatment period was observed with paliperidone palmitate 156 mg (P<0.0001) and 234 mg (P=0.0007) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.497) treatment group. Improvement in the uncontrolled hostility/excitement factor from baseline to the end of the treatment period was observed with paliperidone palmitate 156 mg (P=0.0001) and 234 mg (P=0.0001) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.2284) treatment group. Improvement in anxiety/depression factor from baseline to the end of the treatment period was observed with paliperidone palmitate 156 mg (P=0.0091) and 234 mg (P=0.0058) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.1071) treatment group. Improvement in the CGI-S score from baseline to the end of the treatment period was observed with paliperidone palmitate 156 mg (P=0.0068) and 234 mg (P=0.0003) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.3728) treatment group. Improvement in the PSP score from baseline to the end of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment period was observed with paliperidone palmitate 156 mg (P=0.0061) and 234 mg (P=0.0009) compared with placebo. No statistically significant improvement was seen in the paliperidone palmitate 39 mg (P=0.2962) treatment group. Compared with placebo, insomnia, anxiety, headache, changes in body weight and increased prolactin levels were more frequent in the paliperidone palmitate treatment groups.
Nasrallah et al[19] Paliperidone palmitate 39mg vs paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo	DB, MC, PC, PG, RCT Patients (18 years of age and older and BMI >15.0 kg/m^2) with schizophrenia according to DSM-IV-TR criteria for at least one year before screening and had a PANSS total score at screening and baseline of 70 to 120 inclusive Fixed doses or placebo were administered by IM injection on days 1, 8, 36, and 64 of the DB	N=518 (randomized to DB treatment) 13 weeks	Primary: Change from baseline to end point based on the LOCF approach (day 92 or the last postbaseline assessment in the DB period) in the PANSS total score Secondary: PSP)scale, CGI-S scales Safety assessments included AEs, EPS rating scales (AIMS, BARS, and SAS), clinical laboratory tests (including plasma prolactin	Primary: At endpoint (LOCF), improvement in total PANSS total scores for each of the active treatment groups was significantly greater than that for placebo (39 mg, P=0.02; 78 mg, P=0.02; 156 mg, P<0.001). [Note: results were only graphically presented; no raw data reported.] Secondary: Each active treatment group showed significant improvement (P<0.01) compared with placebo for change from baseline to end point (LOCF) in CGI-S score. [Note: results were only graphically presented; no raw data reported.] No outcomes on the PSP scale were reported. Safety assessments The overall frequency of AEs occurring in at least 5% of patients in any group was comparable across all treatment groups and placebo with the following exceptions: weight increase (4% active drug overall vs. 0% placebo), and somnolence (4% active drug overall vs. 1% placebo). There were no clinically relevant differences between the active treatment groups and placebo in BARS, SAS, or AIMS scores. Parkinsonism was the most frequent category of EPS-related AEs and reported at a similar rate for overall paliperidone palmitate groups (6%) and placebo (5%). Increases in prolactin levels were observed with greater frequency in patients who received active drug, compared with placebo, and in a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	treatment period		levels), investigators' evaluation of the injection site, and patients' evaluations of pain at the injection site and pain of the injection.	dose-dependent manner (P not reported). Local injection-site tolerability was good as reported by investigators (no outcomes of patient-initiated evaluations were reported).
Kramer et al[20] Paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo	DB, PC, RCT Patients 18 to 65 years of age, with schizophrenia and PANSS scores between 60 and 120	N=197 9 weeks	Primary: Change in PANSS total score Secondary: PANSS Marder factors, 30% improvement in PANSS score, adverse events	Primary: Both paliperidone doses were associated with significant improvement in PANSS total scores compared to placebo (P≤0.001). Secondary: Both paliperidone doses were associated with significant improvement in all PANSS Marder factor subscale scores, except the uncontrolled hostility/excitement) compared to placebo (P<0.05). Only paliperidone 156 mg dose was associated with significant improvement from baseline in the hostility/excitement scores (P=0.006). At least 30% improvement from baseline in the PANSS total score was reached by 67% and 63% of patients receiving paliperidone 78 mg and 156 mg, respectively compared with 14% in the placebo group. Less than 30% improvement was experienced by 67%, 63%, and 86% of patients in the paliperidone 78 mg, 156 mg, and placebo groups (P<0.01). Fewer paliperidone-treated patients (2%) discontinued for treatment-emergent adverse events vs. placebo-treated (10%). Rates of treatment-emergent extrapyramidal syndrome-related adverse events were comparable between active treatment and placebo, with the exception of parkinsonism-related disorders (78 mg: 5%, 156 mg: 8%, placebo: 1%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hough et al[21] Paliperidone palmitate 39 mg vs paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo	DB, MC, PC, PG, RCT Patients (18 to 65 years of age and BMI >15.0 kg/m^2) with schizophrenia according to DSM-IV-TR criteria for at least one year before screening and had a Positive and Negative Syndrome Scale (PANSS) total score at screening and baseline of <120 The first two IM injections on days one and eight of the transition phase were 78 mg. Three adjustable doses of 39, 78, or 156 mg were administered every four weeks during the rest of the transition	N=410 (randomized to DB treatment) 9 weeks OL transition phase + 24 weeks OL maintenance phase + variable duration of DB recurrence prevention phase for patients who were clinically stable on a fixed dose for the last 12 weeks of the maintenance phase	Primary: Time between randomization to treatment in the DB recurrence prevention phase and the first documentation of a recurrence event during the DB phase (incl. hospitalization, deliberate self-injury or violent behavior, suicidal or homicidal ideation, and certain predefined PANSS scores) Secondary: None reported Safety assessments included AEs, laboratory tests (including prolactin), investigators' evaluation of the injection site,	Primary: An independent Data Monitoring Committee recommended that the study be terminated early because of the significant (P<0.0001) interim efficacy results for time-to-recurrence per interim ITT analysis. [Note: results were only graphically presented; no raw data reported.] The results of the time-to-recurrence analysis based on the data at the conclusion of the DB phase were reportedly consistent with the results based on the interim data [details not reported in poster]. Secondary: Not applicable Safety assessments The overall frequency of AEs occurring in ≥5% of patients in any group was comparable across all treatment groups and placebo with the exception of weight increase (7% active drug overall vs. 1% placebo). Local injection-site tolerability was good as reported by investigators. Patients' evaluations of injection site pain based on a visual analog scale showed a decrease in the intensity of pain at the injection site from DB baseline to endpoint for both active drug and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	phase and the first 12 weeks of the maintenance phase. The dose of paliperidone palmitate remained fixed for the last 12 weeks of the maintenance phase and the DB, PC recurrence prevention phase.		and patients' evaluations of pain at the injection site.	
Kozma et al[22] Paliperidone palmitate 50 mg IM depot vs placebo Subjects initially received paliperidone palmitate (50 mg once every four weeks); subjects who completed the PC RCT entered into the OL ES where all subjects received paliperidone palmitate with an initial dose of 50 mg	ES, MC, OL, PC, PG, RCT Patients (18 to 65 years) with a diagnosis of schizophrenia according to DSM-IV-TR criteria for at least 1 year before screening and a PANSS total score below 120 at screening and baseline	N=951 9 weeks OL injectable transition phase; 24 week maintenance phase; and optional 52 week OL extension phase	Primary: Change in the rate of hospitalizations Secondary: Change in the rate of emergency room visits	Primary: The change in hospitalizations per person for placebo-treated patients who were subsequently treated with paliperidone palmitate in the OL ES declined from 0.27 to 0.06, a 78% reduction (P=0.005). Statistically significant reduction in hospitalization was seen. The change in the rate of hospitalization per person for paliperidone palmitate treated patients was low between the DB and OL ES (P=0.76). There was no statistically significant change in hospitalization seen. Secondary: The event rate for emergency room visits was low for both treatment arms and did not reveal statistically significant results for either the placebo (P value not reported) or paliperidone palmitate (P=0.667) treated patients subsequently treated with paliperidone palmitate.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
with flexible-dosing from a second injection (25, 50, 75, or 100 mg eq.) once every 4 weeks for 12 dosing intervals.				
Gopal et al[23] Paliperidone palmitate 39 mg vs paliperidone palmitate 78 mg vs paliperidone palmitate 117 mg vs paliperidone palmitate 156 mg vs placebo Paliperidone palmitate subjects received a 50 mg day one dose, followed by their assigned dose every four weeks thereafter.	ES, MC, OL, PC, RCT Patients aged 18 to 65 with a BMI>15 kg/m^2, with a diagnosis of schizophrenia (by DSM-IV-TR criteria) and a PANSS score <120 were included in this study	N= 388 52 week OL ES following a 24 month DB RCT	Primary: The efficacy assessments included change in PANSS scores, CGI–S scores, and PSP Scale scores Secondary: TEAE were monitored to assess safety of paliperidone palmitate.	Primary: Patients who entered the OL ES had improvements in PANSS total scores, CGI-S scores, and social functioning (as assessed by PSP scores) from baseline to end point. Note: no raw data presented Secondary: TEAEs were reported in 56% (217) of the patients. The most frequent TEAEs were insomnia (7%), worsening of schizophrenia (6%), nasopharyngitis (6%), headache (6%), and weight increase (6%).
Bossie et al[24]	PH analysis of DB, PC, RCT[18]	N=652	Primary: PANSS total	Primary: Paliperidone palmitate 234 mg administered on Day 1 was associated

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Paliperidone palmitate 39 mg vs paliperidone palmitate 156 mg vs paliperidone palmitate 234 mg vs placebo All subjects received paliperidone palmitate 234 mg or placebo on Day 1, and then assigned doses on Day 8, 36 and 64.	Patients with schizophrenia and a PANSS total score of 70 to 120 (inclusive) at screening and 60 to 120 (inclusive) at DB baseline	13 weeks	scores Secondary: Tolerability assessment included TEAE reports and AE related study discontinuation	with a significantly greater improvement than placebo on mean PANSS total score at the Day 8 assessment (least square mean [SE] change from baseline -8.21 [0.87] vs -5.79 [1.20], P=0.037). All paliperidone palmitate groups continued to show greater PANSS total score improvement than placebo after the Day 8 injection and at subsequent Days 22 and 36 time points. After Day 8 injection of 156 mg, there was continued PANSS improvement at Day 22 (P≤0.007 vs placebo) and Day 36 (P<0.001). Results showed corresponding effect sizes for all dose arms suggesting a dose-related effect. Secondary: The overall rate of AE after paliperidone palmitate 234 mg Day 1 initiation was similar to that seen with placebo (38.0% vs 43.1%, respectively). The AE rate during the month following the Day 8 injection was 38.5% in the paliperidone palmitate 156 mg Day 8 group and 41.3% in the placebo group. Rates in the other paliperidone palmitate dose groups were 36.8% with 39 mg Day 8 and 41.3% with 234 mg Day 8. A total of 39 patients (29 paliperidone palmitate and 10 placebo patients) reported AE that were rated as serious during Days 8 to 36. During Days 1 to 7, the percentage of patients who discontinued study participation was 2.9% in those who received paliperidone palmitate and 4.4% in the placebo group. Discontinuation due to AE was 3.1% in the placebo group as well as the paliperidone palmitate 156 mg Day 8 treatment arm. No patients discontinued due to AE in the paliperidone palmitate 39 mg Day 8 arm and 5 discontinued in the 234 mg Day 8 arm.
Berwaerts et al[25] Paliperidone palmitate (Invega Trinza®) IM every three months, fixed dose (based on individualized maintenance phase dose)	DB, MC, PC, RCT Patients 18 to 70 years of age with a diagnosis of schizophrenia for	N=305 Variable Length (16 to 540 days)	Primary: Time from randomization to the first relapse event Secondary:	Primary: Time to relapse of schizophrenia in the per-protocol analysis (considered the primary analysis) was significantly different in favor of the paliperidone palmitate group when compared to placebo (HR,3.45; 95% CI, 1.73 to 6.88; P<0.001). The median time to relapse was not estimable for the group receiving paliperidone palmitate and was 274 days for the placebo group. Overall, 31 patients (23%) in the placebo

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vs placebo All patients were stabilized on once-monthly paliperidone palmitate (Invega Sustenna®) prior to randomization. Patients randomized to the placebo group discontinued once-monthly paliperidone palmitate.	at least one year before screening, PANSS total score <120 at screening and baseline, stabilized on a long-acting injectable antipsychotic, a stable place of residence for the previous three months before screening		Change from randomization baseline to end point in PANSS total, subscale, and 5-factor scores, CGIS score and PSP scores; safety assessments	group and 11 patients (7%) in the group receiving paliperidone palmitate experienced a relapse event. The independent data monitoring committee recommended early study termination for efficacy. The intention-to-treat analysis was consistent with the per-protocol analysis. Time to relapse of schizophrenia was significantly different in favor of the paliperidone palmitate group when compared to placebo (HR, 3.81; 95% CI, 2.08 to 6.99; P<0.001). As with the per-protocol analysis, median time to relapse was not estimable for the paliperidone palmitate group. For the placebo group, median time to relapse was 395 days. A total of 42 patients (29%) in the placebo group and 14 patients (9%) in the group receiving paliperidone palmitate experienced a relapse event. Secondary: The mean (standard deviation) PANSS total score at randomization baseline was 54.9 (9.95) in the paliperidone palmitate group and 54.2 (9.34) for the placebo group. The mean PANSS total score remained stable in the paliperidone palmitate group and increased in the placebo group. Mean (standard deviation) change in PANSS total score was −0.5 (8.36) in the paliperidone palmitate group compared with 6.7 (14.40) for the placebo group. Difference in mean change in PANSS total score was statistically significant in favor of paliperidone palmitate (P<0.001; least-squares means difference of −7.2; 95% CI, −9.87 to −4.60). There were also significant differences in mean change from randomization baseline to end point in favor of paliperidone palmitate in PANSS subscale and Marder factor scores (except negative subscale and negative symptoms factor; P≤0.005), CGIS score (P<0.001), and PSP scores (P<0.001). A total of 330 of 506 patients (65%) in the open-label phase and 183 of 305 patients (60%) in the randomized phase (62% of those receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				paliperidone palmitate three-month injection compared with 58% of those receiving placebo) had at least one treatment emergent adverse event. The most frequently reported treatment emergent adverse events (≥2%) in the group receiving paliperidone palmitate during the maintenance phase (part of the open-label phase) were anxiety (6%), insomnia (5%), weight increased (4%), and headache (3%). During the maintenance phase, the treatment emergent adverse events that led to study discontinuation in more than one patient included psychiatric disorders (1%) and schizophrenia (0.5%). The most commonly occurring EPS-related treatment-emergent adverse events (≥1%) were those grouped under hyperkinesia (2%) and parkinsonism (1%). One patient (0.3%) experienced a hyperglycemia-related treatment emergent adverse event of type 2 diabetes mellitus during the maintenance phase. During the randomization phase, the most common treatment emergent adverse events occurring in the paliperidone group were EPS-related adverse events, headache, nasopharyngitis and increased weight.
Lindenmayer et al[26] Long-acting injectable risperidone 25 mg biweekly vs long-acting injectable risperidone 50 mg biweekly	MC, OL Patients with symptomatically stable schizophrenia (DSM-IV-TR criteria) who had been taking haloperidol, quetiapine or olanzapine orally	N=141 12 weeks	Primary: Efficacy of long-acting injectable risperidone was evaluated using PANSS scores Secondary: Incidence of AE were monitored including body weight, ECG changes and EPS during 12-week treatment	Primary: Improvements in symptoms of schizophrenia were observed with use of long-acting injectable risperidone based on statistically significant reductions in total PANSS score over 12-week treatment (P<0.001). After 12 weeks of treatment 37% of patients were rated as clinically improved (>20% decrease in PANSS score). Secondary: Most frequently reported AEs were insomnia (16%), headache (15%), psychosis (11%) and agitation (11%). The mean increase in body weight of patients was 0.4 kg after 12-week treatment with long-acting injectable risperidone. No significant ECG changes were observed during treatment period. ESRS total scores were reduced during treatment with long-acting risperidone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Taylor et al[27] Long-acting injectable risperidone 25 mg biweekly All but one subject started at a dose of 25 mg long-acting injectable risperidone and that one subject started at a dose of 37.5 mg biweekly. Subjects' risperidone dose was increased from 25 mg to 37.5 mg as clinically appropriate.	OS Patients with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder	N=100 6 months	Primary: CGI score Secondary: All treatment discontinuations were investigated	Primary: Mean CGI scores fell from 4.7 to 3.6 over the study period (P<0.001). Overall, 61 patients (61%) showed an improvement in CGI scores between baseline and endpoint. Secondary: Fifty-one patients (51%) of the subjects discontinued long-acting injectable risperidone. The main reason for discontinuation was lack of effect (24 patients).
Rosa et al[28] Long-acting injectable risperidone Subjects were switched from oral olanzapine to long-acting injectable risperidone at a starting dose of 25 mg (higher doses for some subjects). Dosages were adjusted throughout treatment with available dosage options of 25, 37.5 or 50 mg every 2 weeks. Threee weeks after risperidone initiation, olanzapine was tapered off over one week or three	MC, OL Patients aged ≥18 years with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR confirmed by treating clinician and symptomatically non-acute on a stable dose of olanzapine	N=96 6 months	Primary: Change in PANSS, CGI-S and CGI-C from baseline to end point Secondary: Medical Outcome Survey Short Form, the GAF; safety and tolerability measured by occurrence of AE, body weight changes, and ESRS	Primary: Significant end point efficacy changes compared to baseline were observed for PANSS and CGI-S (P<0.0001). PANSS total score improvement was ≥20% for 65.6% of patients, ≥30% for 52.1% of patients, ≥40% for 41.7% of patients and ≥50% for 31.3%. CGI-C was improved in most patients, with half of all patients much improved, and an additional 29% minimally improved. CGI-S scores improved significantly compared to baseline as well (P<0.0001). Note: no raw data presented. Secondary: End point changes in the Medical Outcome Survey Short Form scores were not significant. A significant end point efficacy change for the entire sample was observed for GAF. TEAEs were generally mild (34.5%) or moderate (49.0%) in intensity. Mean (SD) change in body weight from baseline to end point was 1.5 (12.3) kg for the entire sample. Mean change in total ESRS score from baseline to end point was -0.6 for patients tapered over 1 week and -1.2 for patients tapered over 3 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks.				
Marinis et al[29] Long-acting injectable risperidone Patients were switched from conventional oral or depot antipsychotic therapy to long acting injectable risperidone for the six month duration of this study	MC, OL, sub-analysis	N=665 6 months	Primary: Efficacy assessments include PANSS total and subscale scores, GAF, quality of life, treatment satisfaction, hospitalization rates and TEAE Secondary: Not reported	Primary: Improvements were observed for PANSS total and subscale scores, GAF, quality of life, treatment satisfaction and hospitalization. TEAEs occurring in >5% of patients were: anxiety (11%), insomnia (9%), weight increase (6%) and disease exacerbation (5.3%). Secondary: Not reported
Macfadden et al[30] Long-acting injectable risperidone Starting dose recommended to physicians was 25 mg administered every two weeks and physicians permitted to provide higher dose if deemed necessary.	MC, OS, PRO Patients aged 18 years and older who required treatment initiation on long-acting injectable risperidone therapy and had a physician-based diagnosis of schizophrenia according to DSM-IV-TR	N=532 24 months	Primary: Demographic and clinical characteristics of patients including age, gender, ethnicity, and length of diagnosis; CGI-S change from baseline; functionality assessed by PSP scale, GAF and Strauss-Carpenter Levels of Functioning Secondary: Not reported	Primary: Mean (SD) age was 42.3 (12.8) years, and 66.4% of patients were male. Most patients were Caucasian (60.3%) or African American (23.7%). Mean length of diagnosis was 17.9 (12.3) years. All changes in CGI-S from baseline at each subsequent 3-month follow-up visit were statistically significant (P<0.0001). The CGI-S score ate baseline was 4.5 and decreased to 3.5 at 24 months. Improvements were noted for PSP, GAF, and total LOF. The mean PSP score, GAF score, and total LOF scale score at baseline was 48.3 and increased to 61.0, was 47.3 and increased to 60.5 and was 15.5 and increased to 19.9 at 24 months, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fleischhacker et al[31] Long-acting injectable risperidone 25 mg biweekly vs long-acting injectable risperidone 50 mg biweekly vs long-acting injectable risperidone 75 mg biweekly	MC, OL, RCT Patients over the age of 18 with a diagnosis of schizophrenia according to DSM-IV-TR criteria who had received an antipsychotic for at least 4 weeks prior to initial screening and was judged to be symptomatically stable by investigator	N=615 12 months	Primary: Efficacy was assessed every 3 months by PANSS and CGI-S Secondary: Severity of EPS was evaluated by ESRS monthly for the first 3 months and then every 3 months for the remainder of the study ECG changes and pain upon injection were measured through treatment period	Primary: Overall symptom severity (PANSS total scores) was reduced from baseline to end point in each treatment group. Clinical improvement (>20% reduction in PANSS total scores) was seen in 49% of patients, 55% of 25 mg treatment group, 56% of the 50 mg group and 40% of the 75 mg group. According to CGI-S the proportion of patients who were rated as not ill, very mildly ill or mildly ill were increased to 78% from 58% in the 25 mg treatment group, 65% from 40% in the 50 mg treatment group and 44% from 33% in the 75 mg treatment group. Secondary: EPS were reported as 25% of AE for all patients, including 21% (25/120) of 25 mg treatment group patients, 27% (61/228) of 50 mg treatment group patients and 25% (67/267) of 75 mg treatment group patients. Severity of EPS (ESRS total and factor scores) was low at baseline and decreased in each of the groups during the 12 months of treatment. No significant changes in ECGs were seen over the treatment period. Little pain at the injection site was reported by the patients and the pain ratings decreased during the trial.
Lasser et al[32] Long-acting injectable risperidone 25 mg biweekly vs long-acting injectable risperidone 50 mg biweekly	MC, OL, sub-analysis of larger RCT Patients 65 years or older with a diagnosis of schizophrenia or schizoaffective disorder	N=57 12 month	Primary: Efficacy was assessed every three months by PANSS and CGI-S Secondary: Incidence of AE was monitored during the 12	Primary: Mean PANSS total scores were reduced significantly at end point in all three groups. Clinical improvement (defined as >20% reduction in PANSS total scores) among these stable patients was achieved by 42% of the 25 mg group, 62% of the 50 mg group and 49% of the comorbid group of patients. PANSS data indicate that symptoms tended to be more severe in elderly patients than in younger patients (<65 years old). Symptom improvements seen in this 12 month trial with elderly patients were similar to the symptom improvements seen in younger patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs long-acting injectable risperidone 75 mg biweekly As there were only nine subjects in the 75 mg dose group their data is not presented separately but are included in the combined group.	according to DSM-IV criteria, with standard clinical laboratory tests within reference ranges, who had received a stable doses of an antipsychotic for at least four weeks preceding the initial screening for this trial		month treatment period. Severity of EPS was evaluated by ESRS monthly for the first three months and then every three months for the remainder of the study	Secondary: AE were reported by 20 patients (74%) of the 25 mg group, by 15 patients (71%) of the 50 mg group and by 7 patients (78%) of the 75 mg group. AE included insomnia, constipation, bronchitis, psychosis and rhinitis. Severity of movement disorders was significantly reduced during the treatment with long-acting risperidone injection. Significant improvements were noted on the subjective overall EPS based on ESRS, physician's assessment of parkinsonism and CGI severity of parkinsonism.
Lasser et al[33] Long-acting injectable risperidone 25 mg biweekly vs long-acting injectable risperidone 50 mg biweekly vs long-acting injectable risperidone 75 mg biweekly	MC, OL, RCT Patients over the age of 18 with a diagnosis of schizophrenia according to DSM-IV criteria who had received an antipsychotic for at least 4 weeks prior to initial screening and was judged to be symptomatically stable by investigator	N=578 50 weeks	Primary: Remission criteria patients were evaluated using PANSS, CGI-S and patient-rated health status (based on 36 Item Short-Form survey) Secondary: Improvements in patients not meeting remission criteria, positive-symptom remission after	Primary: Eighty-two patients (20.8%) met the primary outcome measure of symptom remission for at least three months during the study after the initiation of long-acting injectable risperidone treatment. In patients who met remission criteria for at least three months (n=82), a statistically significant decrease was observed in total PANSS scores (P≤0.0001). The percentage of patients rated 'not ill' to 'mild' (CGI-S score of 1, 2, or 3) increased from 39% at baseline to 88% at end point (P=0.0001). The 36 Item Short-Form survey showed significant improvement in subscales for the mental-health index, role/emotional, social functioning, vitality, and standardized mental component (P=0.0001). Secondary: Among the 312 patients (79.2%) who did not meet the criteria for symptoms remission for at least six months, significant improvements were still observed in total PANSS scores (baseline: 75.5; endpoint: 66.9; P≤0.0001). Additionally, CGI-S scores showed improvement, with 23% of patients classified as 'not ill', 'very mild' at baseline, versus 44% at endpoint (P≤0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			treatment with long acting injectable risperidone, maintenance of remission from baseline	Sicty-eight patients (25.3) patients achieved positive-symptom remission criteria for at least six months during treatment with long acting injectable risperidone. One hundred fifty-six patients (84.4%) of the 184 patients meeting the severity component of symptoms remission criteria at baseline maintained these low symptom criteria to endpoint. AE were reported by 505 patients (87.4%) through the 50 week study period. The most common adverse events among patients not meeting symptom remission criteria at baseline were anxiety (28.7%), insomnia (25.6%), psychosis (20.1%), depression (19.8%) and headache (14.7%). The most common adverse events among patients who met symptom remission criteria at baseline were anxiety (24.5%), insomnia (25.0%), psychosis (15.8%), depression (15.7%) and headache (14.7%).
Parellada et al[34] Long-acting injectable risperidone 25 mg biweekly vs long-acting injectable risperidone 37.5 mg biweekly vs long-acting injectable risperidone 50 mg biweekly	MC, OL, Post-hoc of a single arm, sub-group analysis Patients 18 to 45 years old, who had been diagnosed with schizophrenia or schizoaffective disorder per DSM-IV within the last three years, who had been symptomatically stable and	N=382 6 months Subjects were followed for 6 months with a 3 week run-in phase where patient continued on their previous oral medication	Primary: Efficacy of long-acting injectable risperidone was measured using PANSS score and CGI-S scale Secondary: Functioning was monitored based on the change in the GAF from baseline to end point, quality of life and patient satisfaction assessments	Primary: The total PANSS score and all its subscale scores improved significantly (P<0.0001), with 40% of patients showing a 20% improvement on total PANSS score. Statistically significant improvements (P<0.0001) in disease severity were reflected in the numbers of patients with improved CGI classifications during the study. Secondary: Functioning improved from baseline to end point, with a mean GAF score of 57.6 at baseline improving to 65.3 at end point (P<0.0001). The overall improvement in quality of life and patient satisfaction from baseline to end point was statistically significant (P<0.0001). AEs were reported by 263 (69%) patients, with TEAEs reported by 217 patients (57%). The most serious TEAEs reported include psychiatric disorders and general disorders of the body as a whole. Scores for EPS using ESRS improved significantly from baseline to end point and

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Subjects received biweekly IM risperidone injections at a starting dose of 25 mg, with an increase to 37.5 or 50 mg based on subject's response to therapy.	treated with the same dose of an antipsychotic therapy for at least 1 month before study entry		were carried out at baseline, three months and six months and satisfaction	at each assessment point during the study (P<0.0001). Mean body weight and mean BMI increased slightly by 1.8 kg and 0.6 kg/m2, respectively, from baseline to end point (P<0.0001).
Van Os et al[35] Long-acting injectable risperidone 25 mg biweekly vs long-acting injectable risperidone 50 mg biweekly vs long-acting injectable risperidone 75 mg biweekly	MC, OL Patients were aged 18 to 85 years, with a DSM-IV TR diagnosis of schizophrenia or schizoaffective disorder, judged by the investigator to be clinically stable and were using antipsychotic mono therapy at study entry	N=46 50 weeks During a 2 week run-in period all antipsychotics were switched to 2, 4 or 6 mg/day of oral risperidone to be used in addition to long-acting injectable risperidone over treatment period	Primary: Efficacy was assessed every 3 months by means of the PANSS scale and each month by the CGI scale Secondary: AE were recorded every two weeks over 50 week study period. EPS were evaluated monthly (month one to three) and quarterly (months 4 to 12) using ESRS	Primary: Significant improvement in the mean PANSS total score was achieved at all-time points during the study (P=0.0006). The proportion of patients with CGI-Severity ratings representing the least severe levels of illness (not ill, very mild or mild) increased from 27% at baseline to 52% at end point. Secondary: During the 50 week study period AE were reported in 54% of all patients. The most common AEs reported were anxiety (26%), insomnia (22%), hyperkinesia (17%), depression (15%) and psychosis (15%). Mean subjective ESRS patient ratings improved significantly from baseline to end point (P=0.0173).
Chue et al[36] Long-acting injectable risperidone vs	DB, MC, PG, RCT Inpatients or outpatients aged 18 to 65 years,	N=640 8 week OL run-in period during which patients were	Primary: Change from DB baseline to end point in the PANSS total score	Primary: The PANSS total scores improved significantly from DB treatment baseline to end point in both the oral and long-acting treatment groups (P<0.001 for each). The upper limit of the 95% CI of the difference in least squares mean changes from baseline was less than 6 points, demonstrating that long-acting risperidone was not inferior to oral

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oral risperidone Subjects were discontinued on antipsychotics other than risperidone and received 2, 4 or 6 mg/day of risperidone. Symptomatically stable subjects were randomly assigned to continue on same dose of oral risperidone or 25, 50 or 75 mg of long-acting injectable risperidone every two weeks.	diagnosis of schizophrenia according to DSM-IV criteria, total PANSS score ≥50, and no clinically relevant abnormal biochemistry, hematology or urinalysis laboratory values	stabilized on oral risperidone; then 12 weeks of oral or long-acting risperidone	Secondary: Changes in PANSS factor scores and CGI ratings from DB baseline to end point; safety assessment include AE, vital signs, clinical laboratory tests, movement disorder, and injection site evaluation	risperidone. Secondary: Scores on the PANSS positive and negative factors also improved significantly (P<0.001). Significant reductions were also seen in scores on the three other PANSS factors. The CGI scores improved in both treatment groups from DB baseline to end point. AE were reported in 189 patients (59.9%) in the oral risperidone group and 195 patients (61.1%) in the long-acting risperidone group. There were no significant changes in vital signs, or clinical laboratory tests other than prolactin from baseline to end point. Mean prolactin levels were 37.4±1.7 and 38.9±1.6 ng/mL at baseline in the long-acting and oral risperidone groups, respectively. At end point, the mean levels decreased to 32.6±1.6 ng/mL (range: 3.2 to 184 ng/mL) (P<0.001) in the long-acting group and were essentially unchanged at 38.0±1.8 ng/mL (range: 2.4 to 193 ng/mL) (P=0.012) in the oral group. The ESRS scores were low at baseline and no between group differences or changes from baseline were demonstrated in ESRS total scores. Pain at injection site was low (mean scores of 18 to 20 out of 100).
Gaebel et al[37] Long-acting injectable risperidone vs quetiapine Long-acting injectable risperidone was initiated at 25 mg every 2 weeks titrated to a maximum of 50 mg every 2 weeks. Quetiapine was initiated at 25 mg twice daily and	MC, OL, RCT Symptomatically stable adult patients aged ≥18 years with DSM-IV-TR criteria for schizophrenia or schizoaffective disorder that were candidates for switching therapy because of insufficient symptomatic	N=710 Up to 24 months	Primary: Time to relapse Secondary: Changes in total PANSS scores, safety assessed by TEAEs, laboratory tests, ESRS score, weight, and BMI	Primary: Patients treated with long-acting injectable risperidone had significantly longer relapse-free periods compared to quetiapine (P<0.0001). Relapse occurred in 54 of 327 patients (16.5%) with risperidone and 102 of 326 patients (31.3%) with quetiapine. Secondary: Total PANSS improved significantly compared with baseline for both groups at each post treatment assessment (P<0.001). Numerical improvements at end point reached statistical significance for risperidone (P<0.001), but not for quetiapine (P=0.10). The incidence of TEAEs was similar between both groups (P value not reported). Elevated prolactin plasma levels based on laboratory testing occurred in 43 patients with risperidone (13.1%) and 5 patients with quetiapine (1.5%). Decrease in ESRS compared with baseline were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated to target dosage of 300 to 400 mg daily in divided doses (maximum 750 mg daily).	control, side effects, or patient request			significant at each assessment for both the risperidone and quetiapine group (P<0.001). Weight gain was reported in 23 patients (7.0%) in the risperidone group and 21 patients (6.2%) in the quetiapine group. Mean BMI increase from baseline to end point were small and not significantly different between treatment groups (0.3±2.38 kg/m^2 with risperidone vs 0.3±2.59 kg/m^2 with quetiapine).
de Arce et al[38] Long-acting injectable risperidone vs oral aripiprazole	MC, OL, RCT Symptomatically stable adult patients aged ≥18 years with DSM-IV-TR criteria for schizophrenia or schizoaffective disorder and were currently treated with monotherapy with oral risperidone ≤6 mg daily, oral olanzapine ≤20 mg daily or an oral neuroleptic (≤10 mg haloperidol daily or its equivalent) that were candidates for switching therapy because of insufficient symptomatic	N=401 24 months	Primary: Time from randomization to relapse Secondary: Achievement and maintenance of remission and change in PANSS total and subscale scores, PANSS factors based on Marder, MADRS scores, and CGI-S and CGI-C scores	Primary: Relapse occurred in 54 out of 327 patients treated with long-acting injectable risperidone (16.5%; 95% CI, 12.7 to 21.0%) and 12 out of 44 patients with aripiprazole (27%; 95% CI, 15.0 to 42.8%). The Kaplan-Meier estimate of mean (SE) relapse-free period was 607.1 (11.4) days with long-acting injectable risperidone and 313.7 (20.4) days with aripiprazole. Secondary: Remission was achieved at some point during the study in 167 patients treated with long-acting injectable risperidone (51.5%; 95% CI, 45.5 to 56.6%) and 15 patients treated with aripiprazole (34.1%; 95% CI, 20.5 to 49.9%). Although numerical differences of end point changes in PANSS total and subscale scores, PANSS factor scores based on Marder, MADRS and CGI often seemed to favor long-acting injectable risperidone, there was no statistical evidence because CIs within the aripiprazole treatment arm were quite wide and overlapped with the CI for long-acting injectable risperidone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	control, side effects, or patient request			
Keks et al[39] Olanzapine oral tablet 5 mg once daily (titrated to optimal dose up to 20 mg daily) vs long-acting injectable risperidone (25 or 50 mg every 2 weeks)	MC, OL, RCT, Schizophrenic or schizoaffective adult patients with a PANSS score ≥50 at randomization, a BMI ≤40, hospitalized or required medical intervention for acute exacerbation of psychotic symptoms within two months of screening and who had at least one other exacerbation during the last two years prior to screening that required medical intervention and provided informed consent	N=618 12 months Part 1: 13 weeks Part 2: 40 weeks	Primary: Change in PANSS total score at 13 weeks to demonstrate non-inferiority Secondary: Change in PANSS total score at 12 months, changes in PANSS factor scores, changes in CGI-S scores and Wisconsin Quality of Life Index, clinical improvement (20% minimum reduction in PANSS), and time to significant deterioration in psychotic condition and adverse events	Primary: Changes in PANSS total scores at the end of 13 weeks were as follows: –16.9 (SD, 15.5) for risperidone and –17.8 (SD, 15.4) for the olanzapine group (95% CI, –2.7 to 3.0; P<0.0001). The upper limit of the PANSS 95% CI was 3.0, well below the non-inferiority margin of 8.0, demonstrating that risperidone was at least as effective as olanzapine. Secondary: Both treatment groups demonstrated significant improvements in PANSS total and factor scores at month 12 and at end-point (P<0.0001 for all measures). Patients in the risperidone group experienced a significantly greater improvement on one PANSS factor score (disorganized thoughts) compared to oral olanzapine (P<0.05); however, significantly greater improvement in anxiety/depression was seen in the olanzapine group (P<0.05). Both treatment groups demonstrated similar reductions in CGI-S scores (P value not reported). Both treatment groups demonstrated similar mean scores on the Wisconsin Quality of Life Index (P value not reported). Significantly more patients in the risperidone group achieved clinical improvement compared to the olanzapine group (91% vs 79%, respectively; P<0.001) at 12 months; however, at study endpoint, the treatment groups were not statistically different (79% vs 73%, respectively; P=0.057). Time to first deterioration was not significantly different (HR, 1.38; 95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				CI, 0.82 to 2.33). Reports of EPS were more frequent in the risperidone group (25.0%) compared to the olanzapine group (15.0%; P<0.05). Weight gain was significantly higher in the olanzapine group compared to the risperidone group (4.0 kg vs 1.7 kg; P<0.05).
Weiden et al[40] Long-acting injectable risperidone initiation vs oral antipsychotics treatment continuation	OL, PG, RCT Patients who experienced their first acute psychotic episode, met diagnostic criteria for schizophreniform disorder, schizophrenia, or schizoaffective disorder confirmed by DSM-IV TR criteria, and had limited lifetime prior exposure to antipsychotic medication	N=37 104 weeks	Primary: Symptom assessment with PANSS and CGIS Secondary: AE monitoring by AIMS, the BARS and the SAS for EPS related AE and the Clinical Antipsychotic Trials of Intervention Effectiveness AE scale for other common AE; adherence attitude	Primary: There were no statistically significant differences between groups for CGI-S or the 5 PANSS factors at any time point. Note: no raw data presented. Secondary: Depending on the cutoffs used, AIMS severity criteria were met at any time after baseline by 5.3% (n=1) of the risperidone group vs 6.7% (n=1) (cutoff of ≥3) or 13.3% (n=2) (cutoff of ≥2) of the oral antipsychotics group; BARS criteria were met by 5.3% (n=1) of the risperidone group vs 13.3% (n=2) (≥3) or 20.0% (n=3) (≥2) of the oral antipsychotic group; and SAS severity criteria were met by 5.3% (n=1) of the risperidone group and 6.7% (n=1) of the oral antipsychotic group. The most commonly reported AE for both groups were menstrual irregularity at any time after baseline, weight gain and sexual side effects. Overall, adherence attitudes did not differ by treatment group.
Li et al[41] Long-acting injectable paliperidone palmitate 150 mg on day-1, 100 mg on day-8, and 50 mg, 100 mg, or 150 mg once monthly	OL, PG Patients, 18 years of age and older, diagnosed with schizophrenia, with PANSS total	N=452 13 weeks	Primary: Change from baseline in PANSS total scores Secondary: CGI-S, Personal	Primary: There was no significant difference between treatment groups in the change from baseline in mean PANSS total scores (difference, -2.3; 95%CI, -5.20 to 0.63). Secondary: There was no significant difference between treatment groups in the change from baseline in mean CGI-S scores (difference, -0.1; 95%CI, -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs long-acting injectable risperidone 25 mg, 37.5 mg, or 50 mg biweekly	score between 60 and 120		and Social Performance Scale (PSP), PANSS subscales, PANSS Marder Factors	0.33 to 0.10). There was no significant difference between treatment groups in the change from baseline in mean PSP scores (difference, 0.5; 95%CI, -2.14 to 3.12). There were no significant differences between treatment groups in the change from baseline in PANSS negative symptoms (difference, -0.0; 95%CI, --0.95 to 0.93) and general psychopathology subscale scores (difference, -0.9; 95%CI, -2.30 to 0.55). In addition, there were no significant differences between the groups in the PANSS Marder factor negative symptom, disorganized thoughts, and uncontrolled excitement/hostility scores. Risperidone was associated with significantly greater reduction in PANSS positive symptoms (difference, -1.2; 95%CI, -2.14 to -0.21), PANSS Marder positive symptoms (difference, -1.4; 95%CI, -2.61 to -0.24), and PANSS Marder anxiety/depression (difference, -0.1; 95%CI, -0.54 to -0.34) subscale scores compared to paliperidone. The incidence of treatment-emergent adverse events was comparable in the paliperidone and risperidone treatment groups (73.4% vs. 74.9%). Discontinuation rate due to adverse events was 3.5% with paliperidone and 4% with risperidone injection. A greater percentage of patients required the use of antiparkinson medication in the risperidone group (46.2%) compared to patients in the paliperidone group (31.4%). The incidence of prolactin-related adverse events was similar with paliperidone and risperidone (8.3% vs. 9%, respectively). The two groups exhibited similar weight gain from baseline, 1.5 kg. There were no serious cardiac adverse events reported in the study.
Pandina et al[42]	DB, DD, MC,	N=1,220	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Paliperidone palmitate 150 mg on day-1, 100 mg on day-8, and 50 mg or 100 mg on day-36, and 25-150 mg injection on day-64 vs risperidone 25 mg on day-8 and -22, 25-37.5 mg on day-36 and -50, and 25-50 mg on day-64 and-78 long-acting injection	PG, RCT Patients, aged 18 years and older, diagnosed with Schizophrenia, with PANSS score between 60 and 120	13 weeks	Change from baseline in PANSS total score Secondary: CGI-S, PSP, PANSS subscale scores, Schedule for Deficit Syndrome (SDS), adverse events	The change in PANSS total scores favored paliperidone treatment over risperidone; however, the difference between the two groups was not statistically significant (difference, 1.2; 95%CI, -0.78 to 3.16). Secondary: There was no statistically significant difference between the two groups in the change in PSP scores from baseline (difference, 0.2; 95%CI, -1.22 to 1.69). There was no statistically significant difference between the two groups in the change in CGI-S scores from baseline (difference, 0.0; 95%CI, -0.07 to 0.17). There was no statistically significant difference between the two groups in the change in SDS scores from baseline (difference, 0.0; 95%CI, -0.35 to 0.95). There were no statistically significant differences between the two groups in the change in PANSS subscale scores from baseline (P value not reported). The frequency of discontinuation due to adverse events was low in both paliperidone and risperidone groups (3% vs. 1.6%). Treatment emergent adverse events reported at a greater frequency with paliperidone compared to risperidone included insomnia, injection site pain, and anxiety. Only constipation occurred at a greater frequency in the risperidone groups versus paliperidone. The incidence of extrapyramidal and cardiac adverse events was similar for both groups. There were no clinically relevant changes in ECG, fasting glucose or lipid levels.
Covell et al[43] Long-acting injectable risperidone	MC, NAT, RCT Patients 18 years or older with DSM-IV-TR	N=53 12 months Study patients	Primary: Time to all cause medication discontinuation	Primary: After 12 months of treatment the time to all-cause treatment discontinuation was significantly shorter for individuals assigned to switch to risperidone than for individuals assigned to stay on a first generation injectable antipsychotic (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs long-acting injectable haloperidol or long-acting injectable fluphenazine Subjects were randomly assigned to either stay on current injectable medication (haloperidol every four weeks or fluphenazine every two weeks) or switched to long-acting injectable risperidone every 2 weeks	Axis I disorder patient edition diagnosis of schizophrenia or schizoaffective disorder who were currently taking fluphenazine decanoate or haloperidol decanoate for whom a change in medication was a reasonable clinical option but not required and at least one clinical visit every three months for the past six months	continued with their assigned treatment for 6 months (unless clinically contraindicated) followed by a 6 month NAT extension	Secondary: Psychiatric symptoms (PANSS), hospitalization, and medication AE including EPS, tardive dyskinesia and BMI	Secondary: Treatment groups did not differ significantly on psychopathology over time as measured by PANSS. Treatment groups did not differ with respect to likelihood of being hospitalized for psychiatric reasons during the first 6 months of treatment (P=0.59) or during the NAT months (P=0.62) Treatment groups did not differ with respect to incidence of sexual side effects, new onset EPS within 6 months (P=0.61) or 12 months (P=0.93) or new onset tardive dyskinesia within 6 months (P=0.23) or 12 months (P=0.32). Those assigned to long-acting injectable risperidone treatment had statistically significant increase in their BMI compared to those assigned to stay. Individuals assigned to switch to risperidone gained a mean of 1.5 BMI (at 6 months) and 1 BMI (at 12 months) compared to those in first generation injectable treatment group (0.5 BMI at 6 months and -0.3 BMI at 12 months).
Fusar-Poli et al[44] Atypical long-acting injectable antipsychotics (paliperidone palmitate, risperidone, and olanzapine pamoate) vs placebo or oral antipsychotics	MA Adult patients with DSM-IV-TR or ICD schizophrenia	N=6,313 (13 trials) Study durations varied	Primary: PANSS total change from baseline to end point Secondary: Proportion of responders, proportion of patients leaving the study for any	Primary: Primary efficacy measures showed that second generation long acting antipsychotics were better than placebo injections (Hedge's g=0.336; 95% CI, 0.246 to 0.426; Z=7.325; P<0.001), but not significantly different from oral antipsychotics (Hedge's g=0.072; 95% CI, -0.072 to 0.217; Z=0.983; P=0.326). Secondary: Proportion of responders was higher in the long-acting injectable group when compared with placebo (RR, 1.841; P<0.001) with 24% of response in the placebo arm and 47% in the long-acting injectable arm. However, long-acting injectable group was not superior to oral group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			reason and the proportion of patients with inefficient response; safety outcome measures included proportion of deaths, any type of treatment-AE, insomnia, injection site pain, QT prolongation, EPS, proportion of patients using anti-EPS medications during the trial, anxiety and weight gain	(RR, 0.962; P=0.094). Long-acting injectable group showed superior efficacy in the number of patients leaving the study for any reasons as compared with both the placebo group (RR, 0.692; P<0.001) and oral group (RR, 0.833; P=0.017). Long-acting injectable group showed lower rates of inefficient response as compared with the placebo group (RR, 0.544; P<0.001) and no differences were observed as compared with oral group (RR, 1.176; P=0.547). No significant differences between the long-acting injectable group and placebo group or oral group were observed with respect to the number of deaths, overall number of treatment-AE, insomnia, or injection site pain. Most studies reported no significant QT prolongation in the long-acting injectable group as compared with the other two groups. There was a greater risk of developing EPS in the long-acting injectable group compared with placebo (RR, 2.037; P<0.001) and oral group (RR, 1.451; P=0.048). Consequently, patients receiving long-acting antipsychotics were more likely to use anti-EPS medications (long-acting vs placebo, RR, 1.514; P=0.005; long-acting vs oral RR, 1.540; P=0.007). The long-acting injectable group was effective in reducing anxiety levels when compared with placebo group, but not when compared with oral group. Finally, the long-acting injectable group doubled the risk of weight gain compared with the placebo group (RR, 2.750; P<0.001) but there was no difference as compared with the oral group.
Grimaldi-Bensouda et al[45] Long-acting injectable risperidone vs use of any other treatment (any first or second generation long-acting injectable or oral	Cohort Patients with DSM-IV-TR schizophrenia diagnosis, aged 15 to 65 years, ambulatory or hospitalized for less than 92 consecutive	N=1,859 12 months	Primary: Rate of hospitalization Secondary: Not reported	Primary: Long-acting injectable risperidone use compared to any other treatment was associated with a 34% reduced rate of hospitalization and 50% when use as monotherapy was considered. The adjusted Poisson regression analysis showed long-acting risperidone use to be associated with a lower rate of future hospitalization: 0.66 [95% CI, 0.46 to 0.96] compared to any other treatment and 0.53 [95% CI, 0.32 to 0.88] compared to use of other long-acting injectable antipsychotics. Secondary: Not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
antipsychotic)	days, and if at least one contact reported by their physician after identification			
Leucht et al[46] Long-acting injectable antipsychotics (fluphenazine decanoate, fluphenazine enanthate, haloperidol, risperidone, zuclopenthixol) vs oral antipsychotics (fluphenazine, olanzapine, pimozide, quetiapine, zuclopenthixol, other)	MA Patients with schizophrenia or related disorders (schizophrenia form, schizoaffective or delusional disorder, any diagnostic system, any age and gender, no language restrictions)	N=1,700 (10 trials) Study durations varied	Primary: Number of patients relapsed Secondary: Rehospitalization due to worsening psycho-pathology, non-adherence, and dropout due to inefficacy of treatment, AE, and any reason	Primary: Significantly fewer (21.6%) patients in the long-acting injectable group than in the oral group (33.3%) relapsed (RR, 0.70; CI, 0.57 to 0.87). Secondary: No significant difference in rehospitalization due to worsening psychopathology was seen between groups. Rehospitalization occurred in 13.7% of long-acting injectable group and 18.6% in oral group (RR, 0.78; CI, 0.57 to 1.05). No significant difference in non-adherence (RR, 0.76; CI, 0.37 to 1.56) or dropout rate (RR, 0.9; CI, 0.81 to 1.01) was seen between groups.
Schizoaffective Disorder				
Fu et al[47] Paliperidone palmitate 78 mg IM monthly vs paliperidone palmitate 117 mg IM monthly vs paliperidone palmitate 156 mg IM monthly	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a DSM-IV diagnosis of schizoaffective disorder, experiencing an acute exacerbation of psychotic symptoms,	N=667 15 months	Primary: Percentage of Participants Who Experienced Relapse Secondary: Change from baseline in PSP PANSS total score, HAM-D-21 total score, YMRS total score, CGI-S-	Primary: Paliperidone palmitate monthly injection was associated with significant delay in time to relapse compared with placebo (P<0.001). Correspondingly, a significantly lower percentage of subjects treated with paliperidone palmitate monthly injection experienced a relapse event (P<0.001). The rate of relapse was 33.5% (N=57) and 15.2% (N=25) in the placebo and paliperidone palmitate monthly injection groups, respectively. Relapse risk in the double-blind phase was 2.49-fold higher for placebo compared with paliperidone monthly (HR, 2.49; 95% CI, 1.55 to 3.99; P<0.001), corresponding to a 60% decrease in relapse risk with maintenance treatment. Relapse risk was significantly higher for placebo versus paliperidone palmitate monthly in both monotherapy (HR=3.38; P=0.002) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs paliperidone palmitate 234 mg IM monthly vs placebo	PANSS ≥4 in certain items (delusions, hallucinatory behavior, excitement, hostility, tension, uncooperativeness, and poor impulse control), HAM-D-21 score ≥16 and/or YMRS score ≥16, healthy based on physical exam, ECG, lab tests, medical history and vital signs		SCA overall score,	adjunctive therapy (HR, 2.03; P=0.021) subgroups. For the monotherapy subgroup, 32.9% (N=24) and 11.5% (N=9) of placebo and paliperidone monthly subjects, respectively, experienced a relapse. For the adjunctive therapy subgroup, relapse rates were 34.0% (N= 33) and 18.6% (N=16), respectively. Secondary: Mean change in PSP from baseline at month 15 significantly favored paliperidone monthly over placebo (P=0.014). The least squares mean difference between groups in change scores at month 15 was 3.3 (95% CI, 0.68 to 5.95). The proportion of placebo-treated subjects with good functioning (PSP total score > 70) was 50.6% at double-blind baseline and 41.1% at endpoint, whereas it was 57.9% at double-blind baseline and 59.0% at endpoint (between-group difference, P=0.002) for paliperidone monthly treated subjects with good functioning. The LS-mean between-group differences between treatment group significantly favored paliperidone monthly over placebo for changes in all of the following: HDRS-21 total score (2.5; 95% CI, -3.93 to -1.12; P<0.001), YMRS total score (-3.2; 95% CI, -4.53 to -1.83; P<0.001), PANSS (-6.9; 95% CI, -10.41 to -3.37; P<0.001), and CGI-S-SCA total scores (-0.5; 95% CI, -0.69 to -0.24; P<0.001). The proportions of subjects with CGI-S-SCA scores of “not ill” to “mildly ill” at double-blind baseline were 95.9% (88/170) and 97.6% (74/164) for the placebo and paliperidone monthly groups, respectively. These percentages decreased at double-blind endpoint to 64.9% (45/168) and 83.9% (46/161), respectively (between-group difference, P<0.001). The proportion of subjects who were satisfied with their antipsychotic medication per the MSQ scale favored paliperidone monthly treatment: for placebo (93.5% of subjects at double-blind baseline and 69.6% at endpoint) compared with paliperidone monthly (94.5% at double-blind

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				baseline and 85.7% at endpoint) (between-group difference, P<0.001)
Bipolar I Disorder				
Vieta et al[48] Long-acting injectable risperidone Oral risperidone was started at doses 3 to 6 mg/day during first week of hospitalization. The first injection of long-acting risperidone was administered during an acute episode after one week of hospitalization at calculated dose of 25 mg for each 3 mg of oral risperidone.	Cohort Acutely manic bipolar patients that met DSM-IV-TR criteria for mania, patients with prospectively documented medical and psychiatric hospital records for at least one year prior to inclusion	N=29 2 years	Primary: Number of hospitalizations due to relapse or recurrence during the follow-up period as compared to a similar period before study entry Secondary: Adherence; safety assessed by patient AE reporting and inpatient baseline laboratory tests	Primary: There was a significant decrease in the mean number of hospitalization per patient (Z=2.72, P<0.006) before (2.24 to 2.23 SD; range 1 to 12) and after (1.0 to 1.79 SD; range 0 to 6) long-acting risperidone treatment. Secondary: There was a significant reduction (P<0.0001) in the number of patients discontinuing all medication (oral and injections) before (n=25, 86%) and after (n=8, 27.5%) long-acting risperidone treatment. Tolerability issues were reported by nine patients; five reported EPS and needed antiparkinsonian medication, three had prolactin levels increased and one had sexual impotence.
Yatham et al[49] Continuation of usual oral atypical antipsychotic (olanzapine, quetiapine, or risperidone) vs switching to long-acting risperidone 25 mg injection every 2 weeks	MC, OL, PRO, RCT Stable adults aged 18 to 65 years of age diagnosed with Bipolar I or Bipolar II according to DSM-IV criteria and currently on one oral atypical	N=49 6 months	Primary: Safety measures (adverse events, lab tests, vital signs, weight and movement disorders scales such as the BARS, SAS, and AIMS) and efficacy measures (CGI-S, YMRS,	Primary: At least one treatment emergent adverse event was reported by 16 (70%) of patients in the injection group and 19 (73%) in the oral group (P value not reported). There were no clinical significant changes in laboratory tests in either group (P value not reported). There were no significant changes in weight or heart rate within each group; however, diastolic blood pressure was significantly different at the study endpoint in the risperidone injection group (–5.2±11.0; P=0.033). There were significant between group differences in reduction of diastolic blood pressure favoring the injection group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	antipsychotic agent in combination with a maximum of two of lithium, valproate or lamotrigine; and, if applicable, one antidepressant		MADRS, HAM-A, EuroQol EQ-5D, VAS and time to intervention) Secondary: Not reported	(P<0.05). There were no significant differences between groups for mean changes in AIMS (P=0.95), SAS (P=0.11) or BARS (P=0.52) scores. The differences in changes in CGI-S and YMRS scores between the two groups was not significant (P=0.67 and P=0.31, respectively). There were also no significant differences in changes in MADRS or HAM-A scores between the groups (P values not reported). There were no significant differences between the groups on changes in VAS, EuroQuol EQ-5D, or scores on the resource use questionnaire (P vales not reported). There were no significant differences between groups on the number of interventions or time to intervention (P value not reported). Secondary: Not reported

Drug regimen abbreviations: IM=intramuscular, IV=intravenous
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNT=number needed to treat, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, SE=standard error
Other abbreviations: AE=adverse event, AIMS=Abnormal Involuntary Movement Scale, BARS=Barnes Akathisia Rating Scale, BMI=body mass index, BPRS=Brief Psychiatric Rating Scale, CGI-C=Clinical Global Impression-Change, CGI-S=Clinical Global Impression-Severity, CGI-S-SCA=Clinical Global Impression-Severity-Schizoaffective Disorder, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders 4, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders 4-TR, EuroQol EQ-5D=quality of life in five dimensions and was developed by the EuroQol Research foundation, ECG=echocardiogram, EPS=extrapyramidal symptoms, ESRS=Extrapyramidal Symptom Rating Scale, GAF=Global Assessment of Functioning, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D-21=Hamilton Rating Scale for Depression-21, ICD=International Classification of Diseases, LOCF=last observation carried forward, MADRS=Montgomery Asberg Depression Rating Scale, OPM=olanzapine pamoate monohydrate, PANSS=Positive and Negative Syndrome Scale, PSP=Personal Social Performance scale, QLS=Quality of Life Scale, SAS=Simpson Angus Scale, SDS=Schedule for Deficit Syndrome, SF-36=Short-Form 36 item survey, TEAE=treatment-emergent adverse event, VAS=Visual Analogue Scale, YMRS Young Mania Rating Scale

Special Populations

Table 5. Special Populations[1-6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aripiprazole	Clinical studies did not include sufficient numbers of patients 65 years of age and older to determine safety and efficacy of this agent in this population. Safety and effectiveness in pediatric patients has not been established.	No dosage adjustment is required.	No dosage adjustment is required.	May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.	Yes; avoid breast feeding.
Aripiprazole Lauroxil	Safety and effectiveness of aripiprazole lauroxil in patients >65 years of age have not been evaluated.* Safety and effectiveness in pediatric patients has not been established.	No dosage adjustment is required.	No dosage adjustment is required.	May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.	Yes; avoid breast feeding.
Olanzapine pamoate	Clinical studies did not include sufficient numbers of patients 65 years of age and older to determine safety and efficacy of this agent in this population. Safety and effectiveness in pediatric patients has not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.	Yes; avoid breast feeding.
Paliperidone palmitate	Clinical studies did not include sufficient numbers of patients 65 years of age and older to determine safety and efficacy of this agent in this population (Invega Sustenna®). No evidence of overall differences in safety or	Dose adjustment required for mild renal dysfunction (CrCl 50 to 80). Use in moderate or severe renal dysfunction	Not studied in hepatic dysfunction.*	C May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	efficacy observed between elderly and younger adult patients (Invega Trinza®). Safety and effectiveness in pediatric patients has not been established.	(CrCl <50) is not recommended.			
Risperidone microsphere	Dose adjustment required for elderly patients. The recommended dose is 25 mg IM every two weeks. No differences in the tolerability were observed between healthy elderly and nonelderly patients. Safety and effectiveness in pediatric patients has not been established.	Patients with renal dysfunction should be titrated with oral risperidone prior to therapy. 25 mg every two weeks is recommended as an initial dose.	Patients with renal dysfunction should be titrated with oral risperidone prior to therapy. 25 mg every two weeks is recom-mended as an initial dose.	C May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.	Yes; avoid breast feeding.

CrCl=creatinine clearance
*No adequate or well-controlled trials.
† Include reference for guideline-based drug-of-choice for a given population

Adverse Drug Events

Table 6. Adverse Drug Events[1-6]

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Cardiovascular					
Angina	-	-	-	-	a
Atrioventricular block	-	-	-	>2	a
Bradycardia	-	-	-	a	a
Bundle branch block	-	-	-	>2	a
Electrocardiogram changes	-	-	-	>2	-
Hypertension	2	-	0 to 3	>2	>2
Hypotension	>1	-	-	>2	a
Myocardial infarction	0.1 to 1.0	-	-	-	-
Palpitation	0.1 to 1.0	-	-	a	a
Phlebitis	0.1 to 1.0	-	-	-	-
Pulmonary embolus	<0.1	-	-	-	-

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Q- and T-wave distortions	-	-	-	>2	-
QTc interval prolongation	0.1 to 1.0	-	0 to 2	>2	-
Sinus arrhythmia	-	-	-	>2	-
T-wave flattening	-	-	-	-	-
T-wave inversion	-	-	-	-	a
Tachycardia	>1	-	-	>2	-
Thrombophlebitis	<0.1	-	-	-	-
Twitch	0.1 to 1.0	-	-	-	-
Vasodilation	0.1 to 1.0	-	-	-	-
Central Nervous System					
Agitation	25	-	-	-	a
Akathisia	15 to 17	11	-	>2	>5
Akinesia	0.1 to 1.0	-	-	-	-
Amnesia	0.1 to 1.0	-	-	-	a
Anxiety	20	-	-	>2	a
Apathy	0.1 to 1.0	-	-	-	a
Asthenia	8	-	-	>2	a
Ataxia	0.1 to 1.0	-	-	-	a
Catatonic-like states	-	-	-	-	-
Cerebrovascular accident	-	-	-	-	-
Confusion	>1	-	-	a	a
Convulsions†	a	-	-	-	a
Delirium	0.1 to 1.0	-	-	-	a
Dementia	-	-	-	-	a
Depersonalization	-	-	-	-	a
Depression	>1	-	-	-	a
Dizziness	-	-	1 to 4	>2	>2
Dreams, abnormal/ bizarre/increased	≥1	-	0 to 2	-	>2
Drowsiness/sedation/ somnolence	7.5 to 15.3	-	8 to 13	>2	>5
Dysarthria	0.1 to 1.0	-	0 to 2	-	-
Dyskinesia	0.1 to 1.0	-	-	-	a
Dystonia	0.1 to 1.0	-	-	>2	a
Euphoria	<0.1	-	-	-	a
Extrapyramidal symptoms	6	-	-	>2	-
Fatigue	-	-	2 to 4	>2	>5
Gait abnormal	>1	-	-	a	a
Hallucinations	≥1	-	0 to 3	-	>2
Headache	31	3 to 5	13 to 18	>2	>2
Hostility	>1	-	-	-	-
Hyperactivity	0.1 to 1.0	-	-	-	-
Hyperkinesia	0.1 to 1.0	-	-	-	-
Hyperreflexia	0.1 to 1.0	-	-	-	-

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Hypertonia	-	-	-	>2	a
Hypesthesia	0.1 to 1.0	-	-	-	-
Hypoaesthesia	-	-	-	-	>2
Hypokinesia	0.1 to 1.0	-	-	-	a
Impaired concentration	-	-	-	-	a
Impaired thinking	-	-	0 to 3	-	-
Incoordination	<0.1	-	-	-	-
Insomnia	20	3 to 4	-	-	>2
Lethargy	-	-	-	-	-
Libido increased	0.1 to 1.0	-	-	-	-
Libido loss of/decreased	0.1 to 1.0	-	-	-	a
Light-headedness	11	-	-	-	-
Malaise	0.1-1.0	-	-	-	a
Manic reaction	-	-	-	-	a
Migraine	0.1 to 1.0	-	-	-	a
Nervousness	>1	-	-	-	a
Neuroleptic malignant syndrome	a	-	-	a	a
Neuropathy	0.1 to 1.0	-	-	-	-
Panic attack	-	-	-	-	-
Paranoid reaction	-	-	-	-	a
Paresthesia	0.1 to 1.0	-	-	-	a
Parkinsonism	-	-	-	>2	>5
Pseudo-parkinsonism	-	-	-	-	-
Psychosis	a	-	-	-	a
Restlessness	-	1 to 3	1 to 3	-	-
Seizure	a	-	-	a	a
Sleep disorder	-	-	0 to 2	-	-
Speech slurred	-	-	-	-	-
Suicide attempt/ thought	0.1 to 1.0	-	-	a	>2
Stupor	0.1 to 1.0	-	-	-	-
Syncope	-	-	-	a	>2
Tardive dyskinesia	0.1 to 1.0	-	-	a	a
Tardive dystonia	4-9	-	-	-	-
Tremor	-	-	0 to 3	>2	>2
Vertigo	0.1 to 1.0	-	-	-	a
Weakness	-	-	-	-	-
Dermatological					
Acne	0.1 to 1.0	-	0 to 2	-	>2
Alopecia	0.1 to 1.0	-	-	-	a
Angioedema	-	-	-	-	-
Dermatitis	<0.1†	-	-	-	a
Dry skin	-	-	-	-	>2
Ecchymosis	>1	-	-	-	-
Eczema	0.1 to 1.0	-	-	-	a
Erythema	-	-	-	-	a

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Increased sweating	-	-	-	-	a
Maculopapular skin reactions	<0.1	-	-	-	-
Pallor	0.1 to 1.0	-	-	-	-
Photosensitivity	0.1 to 1.0	-	-	-	a
Pruritus	0.1 to 1.0	-	-	-	a
Psoriasis	0.1 to 1.0	-	-	-	-
Rash	a	-	-	-	-
Rash, vesiculobullous	0.1 to 1.0	-	-	-	-
Seborrhea	0.1 to 1.0	-	-	-	a
Urticaria	<0.1	-	-	-	-
Gastrointestinal					
Abdominal discomfort/pain	a	-	3	>2	a
Abdominal distention/ enlargement	0.1 to 1.0	-	-	-	-
Anorexia	a	-	-	-	a
Appetite decreased	-	-	-	-	-
Appetite increased	0.1 to 1.0	-	1 to 6	-	a
Colitis	-	-	-	-	a
Constipation	13	-	-	-	>5
Diarrhea	a	-	2 to 7	-	>2
Diverticulitis	-	-	-	-	-
Dry mouth	a	-	2 to 6	>2	>5
Dyspepsia	15	-	-	>2	>5
Dysphagia	0.1 to 1.0	-	-	a	a
Eructation	0.1 to 1.0	-	-	-	-
Esophageal ulcer/ esophagitis	<0.1	-	-	-	-
Fecal impaction	0.1 to 1.0	-	-	-	-
Flatulence	0.1 to 1.0	-	1 to 2	-	a
Gastric ulcer	-	-	-	-	a
Gastritis	0.1 to 1.0	-	-	-	a
Gastroenteritis	0.1 to 1.0	-	-	-	-
Gastroesophageal reflux	0.1 to 1.0	-	-	-	a
Gingivitis	0.1 to 1.0	-	-	-	a
Glossitis	<0.1	-	-	-	-
Gum hemorrhage	<0.1	-	-	-	-
Hematemesis	<0.1	-	-	-	-
Hemorrhoids	0.1 to 1.0	-	-	-	a
Incontinence, fecal	0.1 to 1.0	-	-	-	a
Intestinal obstruction	0.1 to 1.0	-	-	-	-
Irritable bowel syndrome	-	-	-	-	a
Melena	<0.1	-	-	-	a
Mouth ulceration	0.1 to 1.0	-	-	-	-
Nausea	16	-	4 to 5	>2	a

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Paralytic ileus	-	-	-	-	-
Polydipsia	0.1 to 1.0	-	-	-	-
Rectal hemorrhage	0.1 to 1.0	-	-	-	a
Salivation	3	-	-	>2	>2
Stomatitis	0.1 to 1.0	-	-	-	a
Taste altered	0.1 to 1.0	-	-	-	-
Tongue discoloration	-	-	-	-	-
Tongue swollen	-	-	-	a	-
Tooth caries/ toothache	0.1 to 1.0	-	3 to 4	-	>2
Tooth infection	-	-	0 to 4	-	-
Vomiting	11	-	1 to 6	-	a
Weight gain	3 to 8	2	5 to 7	-	>5
Weight loss	>1	-	-	-	>2
Genitourinary					
Albuminuria	0.1 to 1.0	-	-	-	-
Amenorrhea	0.1 to 1.0	-	-	-	-
Breast enlargement	-	-	-	-	-
Breast pain	-	-	-	-	a
Dysmenorrhea	-	-	-	-	a
Dysuria	-	-	-	-	-
Ejaculation disorders	0.1 to 1.0	-	-	-	-
Galactorrhea	-	-	-	-	-
Glycosuria	<0.1	-	-	-	a
Gynecomastia	0.1 to 1.0	-	-	-	-
Hematuria	0.1 to 1.0	-	-	-	a
Impotence	0.1 to 1.0	-	-	-	a
Incontinence, urinary	>1	-	-	-	a
Mastalgia	0.1 to 1.0	-	-	-	-
Menorrhagia	<0.1	-	-	-	-
Metrorrhagia	-	-	-	-	-
Nocturia	<0.1	-	-	-	-
Polyuria	<0.1	-	-	-	-
Priapism	<0.1	-	-	a	a
Renal failure	-	-	-	-	-
Urinary frequency/ urgency increased	0.1 to 1.0	-	-	-	a
Urinary retention	0.1 to 1.0	-	-	-	a
Vaginal discharge	-	-	0 to 4	-	-
Vaginal hemorrhage	0.1 to 1.0	-	-	-	-
Vaginitis	-	-	-	-	a
Hematologic					
Agranulocytosis	-	-	-	-	-
Anemia	>1	-	-	-	a
Anemia, hypochromic	0.1 to 1.0	-	-	-	-
Edema	0.1 to 1.0	-	-	a	-
Edema, facial	0.1 to 1.0	-	-	-	-
Edema, peripheral	2	-	-	-	>2

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Eosinophilia	<0.1	-	-	-	-
Hemorrhage	0.1 to 1.0	-	-	-	-
Hypo-proteinemia	-	-	-	-	-
Leukocytosis	0.1 to 1.0	-	-	-	a
Leukopenia	0.1 to 1.0	-	-	-	a
Lymphadenopathy	0.1 to 1.0	-	-	-	a
Neutropenia	-	-	-	-	-
Pancytopenia	-	-	-	-	-
Thrombocythemia	<0.1	-	-	-	-
Thrombocytopenia	<0.1	-	-	a	a
Laboratory Test Abnormalities					
Alanine amino-transferase /aspartate amino-transferase elevation	0.1 to 1.0	-	a	-	a
Alkaline phosphatase increased	0.1 to 1.0	-	a	-	a
Cholecystitis	0.1 to 1.0	-	-	-	-
Cholelithiasis	0.1 to 1.0	-	-	-	-
Creatine phosphokinase elevated	>1	1 to 2	-	-	-
Creatinine increased	0.1 to 1.0	-	-	-	a
Hepatitis	<0.1	-	-	-	a
Hypercholesterolemia	0.1 to 1.0	-	a	-	a
Hyperglycemia	0.1 to 1.0	-	-	>2	a
Hyperkalemia	0.1 to 1.0	-	-	-	-
Hyperlipemia	0.1 to 1.0	-	-	-	a
Hyper-prolactinemia	-	-	-	a	a
Hyperthyroidism	<0.1	-	-	-	-
Hypertonia	a	-	-	-	-
Hyperuricemia	0.1 to1.0	-	-	-	a
Hypoglycemia	0.1 to 1.0	-	-	-	-
Hypokalemia	0.1 to 1.0	-	-	-	a
Hyponatremia	0.1 to 1.0	-	-	-	a
Hypothyroidism	0.1 to 1.0	-	-	-	-
Liver function impaired	-	-	1 to 4	-	a
Renal failure, acute	0.1 to 1.0	-	-	-	-
Musculoskeletal					
Arthralgia/joint pain	0.1 to 1.0	-	3	-	a
Arthritis	0.1 to 1.0	-	-	-	a
Bone pain	0.1 to 1.0	-	-	-	a
Bursitis	0.1 to 1.0	-	-	-	-
Leg cramps	-	-	-	-	a
Injection site pain	-	3 to 4	2 to 3	-	-
Injection site reactions	6.3	-	3.6	3 (Trinza®)	a
Muscle rigidity	-	-	-	-	a
Muscle spasms	-	-	1 to 3	-	-

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Muscle stiffness	-	-	1 to 4	-	-
Muscle weakness	0.1 to 1.0	-	-	-	a
Myalgia	4	-	-	-	>2
Myoclonus	0.1 to 1.0	-	-	-	-
Myopathy	0.1 to 1.0	-	-	-	-
Opisthotonos	-	-	-	-	-
Rhabdomyolysis	-	-	-	-	-
Rigidity	-	-	-	-	-
Tendinitis	-	-	-	-	a
Tetany	-	-	-	-	a
Torticollis	-	-	-	-	a
Respiratory					
Apnea	<0.1	-	-	-	a
Aspiration	-	-	-	-	-
Asthma	≥1	-	-	-	-
Cough, increased	3	-	3 to 9	>2	>2
Dyspnea	>1	-	-	a	-
Epistaxis	0.1 to 1.0	-	-	-	-
Hemoptysis	<0.1	-	-	-	a
Hyperventilation	-	-	-	-	-
Nasal congestion	-	-	1 to 7	-	-
Pharyngitis	4	-	-	-	-
Pharyngolaryngeal pain	-	-	2 to 3	-	-
Pneumonia	>1	-	-	-	a
Pulmonary edema/ embolus	-	-	-	a	a
Rhinitis	4	-	-	-	>2
Sinusitis	-	-	-	-	>2
Stridor	-	-	-	-	a
Upper respiratory tract infection	-	-	1 to 4	10 (Trinza®)	>2
Other					
Accidental injury	6	-	-	-	-
Allergic reaction	a	-	-	a	a
Anaphylactoid reactions	-	-	-	a	a
Back pain	a	-	3 to 5	>2	a
Blepharitis	0.1 to 1.0	-	-	-	-
Cataracts	0.1 to 1.0	-	-	-	-
Chest pain	>1	-	-	-	a
Chills	0.1 to 1.0	-	-	-	-
Choreoathetosis	-	-	-	-	-
Cogwheel rigidity	0.1 to 1.0	-	-	-	-
Conjunctivitis	>1	-	-	-	a
Death, sudden	-	-	-	-	-
Dehydration	≥1	-	-	-	a
Diabetes	a	-	-	a	a

Adverse Event	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Diaphoresis	>1	-	-	-	-
Diplopia	<0.1	-	-	-	-
Dry eyes	0.1 to 1.0	-	-	-	-
Ear disorder	-	-	-	-	>2
Ear pain	-	-	1 to 4	-	-
Edema, tongue	0.1 to 1.0	-	-	-	-
Eye hemorrhage	0.1 to 1.0	-	-	-	-
Eye pain	-	-	-	-	a
Fever	≥1	-	-	-	>2
Flu syndrome	>1	-	-	-	-
Glaucoma	-	-	-	-	-
Gout	<0.1	-	-	-	-
Hypertonia	a	-	-	-	-
Hypotonia	<0.1	-	-	-	-
Moniliasis	-	-	-	-	-
Mydriasis	-	-	-	-	-
Nasopharyngitis	-	-	1 to 6	-	-
Neck pain/rigidity	>1	-	-	-	-
Obesity	-	-	-	-	a
Oculogyric crisis	<0.1	-	-	-	-
Pain	≥1	-	0 to 3	>2	>2
Parotid swelling	-	-	-	-	-
Photophobia	<0.1	-	-	-	-
Pyrexia	-	-	0 to 2	-	-
Tinnitus	0.1 to 1.0	-	-	-	-
Viral infection	-	-	0 to 2	-	-
Vision abnormal	-	-	-	-	>2
Vision blurred	3	-	-	>2	-
Visual disturbances	-	-	-	-	-
Withdrawal syndrome	-	-	-	-	-

a Percent not specified.
- Event not reported or incidence <1%.
*Includes orthostatic.
†Includes petit and grand mal seizures.
‡Exfoliative dermatitis included.
§Contact dermatitis included.
‖Fungal dermatitis.
¶Gained at least 7% body weight.
#Narrow-angle glaucoma.

Contraindications

Table 7. Contraindications[1-6]

Contraindications	Aripiprazole	Aripiprazole Lauroxil	Olanzapine Pamoate	Paliperidone Palmitate	Risperidone Microsphere
Hypersensitivity to the drug or inactive component.	a	a	-	a	a

Black Box Warning for All Extended-Release Atypical Antipsychotics[1-6]

WARNING
Increased Mortality in Elderly Patients with Dementia-Related Psychosis · **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.** · **The product is not approved for use in patients with dementia-related psychosis**

Black Box Waring for Olanzapine Pamoate (Zyprexa Relprevv®)[3]

WARNING
Post-Injection Delirium/Sedation Syndrome · **Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of ZYPREXA RELPREVV.** · **ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services.** · **After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours.** · **Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment.**

Warnings/Precautions

Table 8. Warnings and Precaustions[1-6]

Warning(s)/Precaution(s)	Aripiprazole	Aripiprazole Lauroxil	Olanzapine pamoate	Paliperidone Palmitate	Risperidone Microsphere
Antiemetic effects have been observed which may mask signs of drug overdose or conditions such as intestinal obstruction, Reye's syndrome and brain tumor	-	-	-	-	a
Avoid administration into a blood vessel	-	-	-	a	-
Experience in patients with concomitant illness is limited	a	a	a	a	a
Worsening of depression and suicide risk may occur	a	a	a	a	a
Cognitive and motor impairment may occur	a	a	a	a	a
Disruption in the body's ability to reduce core body temperature has been associated with antipsychotic drugs	a	a	a	a	a
Dysphagia, esophageal dysmotility and aspiration	a	a	a	a	a
Hyperprolactinemia has been associated with antipsychotic drugs	-	-	a	a	a
Increased mortality and cerebrovascular adverse events including stroke have been observed in elderly patient with dementia-related psychosis	a	a	a	a	a
Leukopenia, neutropenia and agranulocytosis have been reported temporally related to antipsychotic drugs	a	a	a	a	a
Metabolic changes including hyperglycemia/	a	a	a	a	a

Warning(s)/Precaution(s)	Aripiprazole	Aripiprazole Lauroxil	Olanzapine pamoate	Paliperidone Palmitate	Risperidone Microsphere
diabetes mellitus, hyperlipidemia, and weight gain have been observed					
Neuroleptic malignant syndrome may occur with antipsychotic drugs	a	a	a	a	a
Orthostatic hypotension may occur	a	a	a	a	a
Osteodystrophy and tumors in animals	-	-	-	-	a
Post-injection delirium/sedation syndrome has been reported	-	-	a	-	-
Priapism has been reported	-	-	-	a	a
QT prolongation has been reported	-	-	-	a	-
Seizures and/or convulsions have been reported	a	a	a	a	a
Tardive dyskinesia may develop in patients treated with antipsychotic drugs	a	a	a	a	a
Thrombotic thrombocytopenic purpura has been reported	-	-	-	-	a

Table 9. Drug Interactions[1-6]

Drug(s)	Interacting Medication or Disease	Mechanism
Aripiprazole, olanzapine, paliperidone palmitate, or risperidone	Central Nervous System Depressants	Given the CNS depressant effects of these agents, use caution when these agents are taken in combination with other centrally-acting drugs or alcohol.
Aripiprazole, paliperidone palmitate, or risperidone	CYP3A4 Inducers (i.e., carbamazepine, rifampin, or St. John's wort)	Concomitant use of these agents with CYP3A4 inducers decreases the concentrations of aripiprazole, paliperidone palmitate or risperidone. As a result it may be necessary to increase the dose of these agents. On discontinuation of CYP 3A4 inducer, the dosage of aripiprazole, paliperidone palmitate or risperidone should be re-evaluated and, if necessary, decreased.
Aripiprazole, olanzapine, or risperidone	Anti-Hypertensive Agents	Due to its alpha adrenergic antagonism, these agents have the potential to enhance the effect of some anti-hypertensive agents.
Aripiprazole, olanzapine, or risperidone	Strong CYP2D6 Inhibitors (i.e. quinidine or fluoxetine)	Concomitant use of these agents with CYP2D6 inhibitors for more than 14 days increases the concentrations of aripiprazole, olanzapine or risperidone. For long term co-administration of these agents with CYP2D6 inhibitors, dose adjustment of aripiprazole, olanzapine or risperidone is recommended.
Olanzapine, paliperidone palmitate, or risperidone	Levodopa and Dopamine Agonists	These agents may antagonize the effects of levodopa and dopamine agonists.
Olanzapine,	Diazepam	The co-administration of diazepam with these agents may result

Drug(s)	Interacting Medication or Disease	Mechanism
paliperidone palmitate		in potentiated the orthostatic hypotension.
Aripiprazole	Strong CYP3A4 Inhibitors (i.e. ketoconazole)	Concomitant use of aripiprazole with CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole. For long term co-administration of aripiprazole and ketoconazole or other CYP3A4 inhibitors, dose adjustment of aripiprazole is recommended.
Olanzapine	Inducers of CYP1A2 (i.e., carbamazepine, omeprazole and rifampin)	Increased metabolism of olanzapine through CYP1A2 by concomitant administration of CYP1A2 inducers may result in decreased olanzapine concentrations, decreasing the therapeutic effects. Olanzapine dose should be adjusted as needed. On discontinuation of CYP1A2 inducer, the dosage of olanzapine should be re-evaluated and, if necessary, decreased.
Olanzapine	Inhibitors of CYP1A2 (i.e., fluvoxamine)	CYP1A2 inhibitors decrease the clearance of olanzapine. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with CYP1A2 inhibitors.
Risperidone	Clozapine	Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Dosage and Administration

Table 10. Dosing and Administration[1-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Aripiprazole	Schizophrenia: ER suspension: initial and maintenance, 400 mg IM monthly (no sooner than 26 days after the previous injection). Dose may be reduced to 300 mg IV monthly if adverse reactions occur with the 400 mg dose. Supplement with oral aripiprazole for 14 consecutive days after the first injection.	Safety and effectiveness in pediatric patients has not been established.	ER Suspension for Injection (pre-filled dual chamber syringe): 300 mg 400 mg ER Suspension for Injection (single-use vial): 300 mg 400 mg Administer only via the deltoid or gluteal muscle. Must be administered by a health care professional.
Aripiprazole Lauroxil	Schizophrenia: ER suspension: initial, 441 mg to 882 mg IM monthly based on tolerability with oral aripiprazole (10 mg/day oral equal to 441 mg/month; 15 mg/day oral equal to 662 mg/month; 20 mg/day or higher equal to 882 mg/month);	Safety and effectiveness in pediatric patients has not been established.	ER Suspension for Injection (pre-filled syringe): 441 mg/1.6 mL 662 mg/2.4 mL 882 mg/3.2 mL Administer via the deltoid

Generic Name	Adult Dose	Pediatric Dose	Availability
	maintenance, 441 mg to 882 mg IM monthly based on response (882 mg may be given once every six weeks) Supplement with oral aripiprazole for 21 consecutive days after the first injection.		(441 mg only) or gluteal muscles (all doses). Must be administered by a health care professional.
Olanzapine pamoate	Schizophrenia: ER suspension: initial, 210 mg to 300 mg every IM two weeks or 405 mg IM every four weeks based on tolerability with oral olanzapine for the first eight weeks; maintenance, after initial eight weeks, 150 mg to 210 mg IM every two weeks or 300 mg to 405 mg IM every four weeks based on inial dose 10 mg/day oral: 210 mg every two weeks (for the first eight weeks) followed by 150 mg every two weeks or 405 mg every four weeks (for the first eight weeks) followed by 300 mg every four weeks 15 mg/day oral: 300 mg every two weeks (for the first eight weeks) followed by 210 mg every two weeks or 300 mg every two weeks (for the eight weeks) followed by 405 mg every 4 weeks. 20 mg/day oral: 300 mg every two weeks (for the first eight weeks) followed by 200 mg every two weeks.	Safety and effectiveness in pediatric patients has not been established.	ER Suspension for Injection (single-use vial): 210 mg 300 mg 405 mg Administer via the gluteal muscles. Must be administered by a health care professional.
Paliperidone palmitate	Schizophrenia ER suspension (Invega Sustenna®): initial, 234 mg IM on day 1 followed by 156 mg IM on day 8; maintenance, 39 mg to 234 mg IM monthly; maximum, 234 mg/month ER suspension (Invega Trinza®): initial, 273 mg to 819 mg IM every three months based on dose of once-monthly paliperidone	Safety and effectiveness in pediatric patients has not been established.	ER Suspension for Injection (pre-filled syringe [Invega Sustenna®]): 39 mg/0.25 mL 78 mg/0.5 mL 117 mg/0.75 mL 156 mg/1 mL 234 mg/1.5 mL Administer via the deltoid or gluteal muscles. Must be administered by a

Generic Name	Adult Dose	Pediatric Dose	Availability
	palmitate over at least the last four months (78 mg/month equal to 273 mg every three months; 117 mg/month equal to 410 mg every three months; 156 mg/month equal to 546 mg every three months; 234 mg/month equal to 819 mg every three months). Schizoaffective Disorder: ER suspension (Invega Sustenna®): initial, 234 mg IM on day 1 followed by 156 mg IM on day 8; maintenance, 78 mg to 234 mg IM monthly; maximum, 234 mg/month		health care professional. ER Suspension for Injection (pre-filled syringe [Invega Trinza®]): 273 mg/ 0.875 mL 410 mg/1.315 mL 546 mg/1.75 mL 819 mg/2.625 mL
Risperidone microspehre	Bipolar I Disorder: ER suspension: initial, 25 mg IM every two weeks; maintenance, 25 mg every two weeks (some patients may benefit from higher doses); maximum, 50 mg every two weeks Schizophrenia: ER suspension: initial, 25 mg IM every two weeks; maintenance, 25 mg to 50 mg IM every two weeks; maximum, 50 mg IM every two weeks	Safety and effectiveness in pediatric patients has not been established.	ER Suspension for Injection (single-use vials): 12.5 mg 25 mg 37.5 mg 50 mg

ER=extended-release, IM=intramuscularly

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Health and Clinical Excellence: **Psychosis and Schizophrenia in Adults: Treatment and Management (2014)**[50]	· If a person is considered to be at increased risk of developing psychosis: o Offer individual cognitive behavioral therapy (CBT) with or without family intervention and o Offer interventions recommended in National Institute for Health and Clinical Excellence guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. · Do not offer antipsychotic medication: o To people considered to be at increased risk of developing psychosis or o With the aim of decreasing the risk of or preventing psychosis. First episode psychosis · Oral antipsychotic medication in conjunction with psychological interventions

Clinical Guideline	Recommendations
	· Psychological interventions are more effective when delivered in conjunction with antipsychotic medication. · The choice of antipsychotic medication should take into account: o Metabolic (weight gain and diabetes) o extrapyramidal (akathisia, dyskinesia and dystonia) o cardiovascular (QT prolongation) o hormonal (increased prolactin) o other (unpleasant subjective experience) · Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication) <u>Acute episode</u> · For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication in conjunction with psychological interventions · For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment o A single antipsychotic agent is first line. Regular use of combination therapy should not be initiated except when changing agents. · If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. · Clinical response and side effects should be routinely monitored. · Large loading doses should not be used with antipsychotics. · Combination antipsychotic therapy should not be prescribed except for a short duration while transitioning to a different antipsychotic agent. · Due to the high risk of relapse following an acute episode, it is recommended to continue antipsychotic medications for up to one to two years. <u>Recovery/relapse prevention</u> · The goal of pharmacologic treatment is to prevent relapse and maintain the patient's quality of life. · The same considerations for drug treatment should be given as in acute episodes: potential side effects, patient characteristics and preferences. · Depot preparations should be considered when adherence to oral medication is in question. <u>Inadequate response to treatment</u> · Factors for inadequate response should be evaluated including diagnosis, adherence to treatment, and comorbid conditions. · Consider clozapine for patients who have tried two antipsychotic agents (including one second generation antipsychotic) without significant improvement. · Adding a second antipsychotic to clozapine may be considered for patients who are unresponsive to clozapine alone at standard doses; however, the use of more than one antipsychotic is not recommended in other situations except during the conversion from one agent to another. <u>Treatment with long-acting injectable antipsychotic medication</u> · The main practical clinical advantage of using long-acting injectable

Clinical Guideline	Recommendations
	antipsychotic medications to emerge has been the avoidance of covert nonadherence (both intentional and unintentional) to antipsychotic drug treatment, where there is close supervision and documentation of clinic attendance · For those who continue with long-acting injections, there may be some adherence advantage over oral antipsychotics, indicated by a longer time to medication discontinuation and reduced risk of hospitalization.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Schizophrenia (2004)[51]***	Acute phase · Pharmacological treatment with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone should begin at once with the first episode. · Patients with persistent suicidal behavior or persistent hostility and aggressive behavior should be treated with clozapine. · Patients with tardive dyskinesia should be treated with clozapine or second generation antipsychotics. · Patients sensitive to extrapyramidal symptoms side effects should be treated with a second generation antipsychotics (except clozapine); if risperidone is used, high doses are not recommended. · Patients sensitive to prolactin elevations should be treated with a second generation antipsychotics (except clozapine and risperidone). · Patients sensitive to weight gain, hyperglycemia, or hyperlipidemia should be treated with either aripiprazole or ziprasidone. · Patients nonadherent to pharmacological treatment should be treated with long-acting injectable antipsychotic agents. · Agent should be chosen based on clinical circumstances and side effects. · For intolerable side effects, one of the following should be chosen: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. · For an inadequate response, a different agent should be chosen: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. · For an inadequate response to a second agent, a different agent should be chosen: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. · Clozapine should be used to treat persistent psychotic symptoms. Consider electroconvulsive therapy for persistent severe psychosis, catatonia, and/or suicidal behavior in patients who failed prior treatments (including clozapine). · Clozapine has the greatest efficacy on suicidal behavior and it should be considered in patients with suicidal ideation. · Electroconvulsive therapy is used when a patient has not responded to antipsychotic treatment. When electroconvulsive therapy is administered in conjunction with an antipsychotic agent (either a first or second generation antipsychotic) it provides the largest benefit; however electroconvulsive therapy should not be used prior to a trial of clozapine. Stabilization or maintenance phase · The goal of medication in the stable phase is to minimize the risk of relapse, severity of side effects and possible residual symptoms. · Continue with acute phase treatment. Electroconvulsive therapy should be considered for maintenance therapy for patients who have used electroconvulsive therapy in acute treatment with good response and who were not controlled with medication alone. · Maintenance electroconvulsive therapy may help patients who have

Clinical Guideline	Recommendations
	responded to acute electroconvulsive therapy and pharmacological prophylaxis is ineffective or intolerable. Evidence shows that antipsychotics should be used with electroconvulsive therapy maintenance. · For intolerable side effects, another agent should be chosen: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone.

* In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse (http://www.guideline.gov/), this guideline can no longer be assumed to be current.

Conclusions

Collectively, all of the extended-release (ER) injectable atypical antipsychotic agents are Food and Drug Administration (FDA)-approved for the maintenance treatment of schizophrenia in adult patients.[1-6] Additionally, risperidone microspheres (Risperdal Consta®) is approved for the treatment of bipolar I disorder and paliperidone palmitate (Invega Sustenna®) is approved for the treatment of schizoaffective disorder.[4,6] Safety and efficacy of these agents has been established in numerous clinical trials, mostly comparing each ER injectable to placebo.[1-6,11-49] The National Institute for Health and Clinical Excellence 2014 practice guideline for psychosis and schizophrenia in adults identifies candidates for injectable antipsychotic formulations as patients who prefer an injectable formulation after an acute episode or if the clinical treatment priority is to avoid non-adherence.[50] Similarly, the American Psychiatric Association 2004 practice guidelines for schizophrenia state candidates for long-acting injectable antipsychotics may include patients that may need options to improve treatment adherence.[51] Clinical guidelines do not note a preference among the ER injectable antipsychotic agents.

The major difference between agents for the management of schizophrenia is the administration. Each agent is given IM and is generally either the gluteus or deltoid muscles. However, the location may vary by drug and sometimes concentration.[1-6] Once monthly injections include: aripiprazole (Abilify Maintena®), aripiprazole lauroxil (Aristada®), olanzapine pamoate (Zyprexa Relprevv®) and paliperidone palmitate (Invega Sustenna®). Additionally, aripiprazole lauroxil may be given once every six weeks or olanzapine pamoate may be given every two weeks in some cases. Other agents include risperidone microsphere (Risperdal Consta®) which is dosed every two weeks and paliperidone palmitate (Invega Trinza®) which is dosed once every three months. Prior to initiating therapy with Invega Trinza®, the patient should be stabilized on once-monthly Invega Sustenna® for at least four months.[1-6] Of note, olanzapine pamoate is part of a restricted access program and has a black box warning for post-injection delirium. Due to the serious effect, must be administered in a registered healthcare facility with ready access to emergency response services and each patient must be observed at the healthcare facility for at least three hours.[3] There are currently no generic products available.

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