Chue, P., Llorca, P., Duchesne, I., et al (2005). Hospitalization rates in patients during long-term treatment with long-acting risperidone injection. *The Journal of Applied Research*, 5(2), 266-274.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: University of Alberta, Edmonton, Canada; Hospital Gabriel-Montpied, Clermont-Ferrand, France; CNS Health Economics, Janssen Pharmaceutica NV, Beerse, Belgium ***Design:*** A 1-year, international, open-label trial to assess hospitalization rates with long-acting risperidone injection ***Time frame:*** Exact months and year not specified ***Funding source and conflict of interest:*** Study was supported by Johnson & Johnson. Four of the authors have previously received financial support from Johnson & Johnson. Two authors are employees of Johnson & Johnson.	Pts (n=397) were ≥ 18 yrs of age with dx of schizophrenia or schizoaffective disorder according to DSM-IV criteria. Were required to be in good general health, with blood biochemistry, hematology and urinalysis tests within lab reference range. Pts could be inpts or outpts, but condition required to be "stable" as judged by investigator. Pts had to have been receiving a stable dose of their current antipsychotic medication for at least 4 wks before entering study. Excluded if dx of substance abuse/dependence w/in 3 mo of stating trial, or hx of tardive dyskinesia, neuroleptic malignant syndrome, drug allergy, or hypersensitivity. Pts w CNS disease, unstable/untreated somatic disease, pregnant or breast-feeding women also excluded. 249 males (63%) and 148 females participated. Mean age of 43.6 (SD = 15.2, range 18-84). 96 inpatients, 301 outpatients. 329 with schizophrenia dx and 68 with schizoaffective disorder dx. 86% on concomitant medications.	Before tx, pts entered 2-wk run-in where antipsychotics other than risperidone were discontinued. During run-in, all received oral risperidone, 1-6 mg/day at determined dose. Baseline levels taken at end of 2 wks. During 12-mo open-label phase, pts received long-acting risperidone injection, 25 mg, 50 mg, or 75 mg, ever 2 wks with initial dose depending on dose of oral risperidone at end of run-in period. (1-2 mg/day oral → 25 mg; 3-4 mg/day oral → 50mg; 5-6 mg/day oral → 75mg). Oral supplementation at same dose at end of run-in was mandatory for first 2-3 wks of tx with injection. Dose of injection could be increased at scheduled visits if pt experienced psychotic symptoms. Info on hospitalizations in previous 3 mo collected at baseline and every 3 mo after. Rate used as proxy measure of relapse.	Including those pts who were hospitalized at baseline, 144 pts (36%) required at least one hospitalization during 1-yr of tx with injection. The number of pts requiring hospitalization decreased continuously and significantly from 38% in the 3 mo before tx to 12% during the last 3 mo of tx ($P < 0.001$). Of baseline inpts, 71% were discharged during tx. Overall, the 1-year re-hospitalization rate was 17.6%, with a rate of 15.9% for baseline outpts. The rates of psychiatric hospitalizations were 15.4% and 14.3%, for all patients and outpts, respectively.	Need for hospitalization was significantly reduced in outpts and inpts with stable schizophrenia or schizoaffective disorder who received long-acting risperidone injection. Although 3 mo may be considered short period for assessment of pretrial hospitalization, fact that pts were classified as stable suggests that substantial changes in disease severity or artificially inflated hospitalization rates in pre-trial period are unlikely. Results show a continual decrease in hospitalization over time throughout study. Decrease in hospitalization rate did not seem to be related to pts dropping out of study. Dropout rate was low at 35% with respect to length of tx, and was similar in outpts and inpts. 1-yr rehospitalization rates seen with long-acting risperidone injection were lower than those reported for both conventional antipsychotics and oral atypical agents, regardless of the subgroup analyzed. As present study was open-label and uncontrolled, comparative controlled trials needed to define fully the benefits of long-acting risperidone injection on hospitalization rates, compared with other antipsychotic agents.

Comer, S.D., Sullivan, M.A., Yu, E., et al (2006). Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo-controlled trial. *Archives of General Psychiatry*, 63, 210-218.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: Division on Substance Abuse, NY State Psychiatric Institute, and Dept of Psychiatry, College of Physicians and Surgeons of Columbia University, NY; Dept of Psychiatry, University of PA, and Dept of Behavior Health, Philadelphia Veterans Affairs Medical Center, Philadelphia ***Design:*** Randomized, double-blind, placebo-controlled 8-weeks trial conducted at two medical centers to evaluate safety/efficacy of sustained-release depot formulation of naltrexone in treating opioid dependence. ***Time frame:*** Exact months and year not specified ***Funding source and conflict of interest:*** Supported by center grants from the National Institute on Drug Abuse (NIDA) and the VA/NIDA Interagency Agreement at Philadelphia VA Medical Center. Biopharmaceutical Research Consultants Inc received funding for data management and statistical support, and the University of Utah and Northwest Toxicologies Inc received funding for bioanalytical support.	Participants were 60 heroin-dependent adults, aged 18-59 years, and 77% male. 37% White, 35% Black. All were voluntarily seeking tx for their dependence. All were in good health based on medical hx, physical exam findings, vital sign measurements, and 12-lead EKG evidence, and lab results were within appropriate reference ranges. Participants were excluded from study if dependent on methadone or on drugs other than heroin, nicotine, or caffeine; pregnant or lactating; unwilling to use birth control; dx as having major DSM-IV Axis I psychiatric disorders; considered to have risk of suicide; had acute hepatitis; hx of allergy to study medication; regularly used psychoactive drugs; or had medical condition that might interfere with participation. Distributions of sex, age, and race not significantly different in the three groups (placebo, 192 mg depot naltrexone, 384 mg depot naltrexone).	Pts received initial inpt detoxification, followed by oral naltrexone for 3 consecutive days in order to determine tolerability. Participants stratified by sex and years of heroin use ($\geq$ 5 vs < 5) and randomized to receive placebo or 192 or 384 mg of depot naltrexone. Doses were administered at beginning of wks 1 and 5. All participants received twice-weekly relapse prevention therapy, provided observed urine samples, and completed other assessments at each visit. Main outcome measure was retention in tx and percentage of opioid-negative urine samples.	After administration of 192 mg of depot naltrexone, mean naltrexone plasma levels ranged from 0.4 to 1.9 ng/mL. After administration of 384 mg of depot naltrexone, mean naltrexone plasma levels ranged from 1.3 to 3.2 ng/mL. Across 8-wk study, plasma levels tended to be fairly constant. Retention in tx was dose related, with 39%, 60%, and 68% of patients in the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively, remaining in tx at the end of 2 months. Time to dropout had a significant main effect of dose, with mean time to dropout of 27, 36, and 48 days for the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively. Mean percentage of urine samples negative for opioids across study was lowest for placebo group (25.3%) and highest for the 384 mg of naltrexone group (61.9%). The main effect of group was significant. Adverse events were minimal and generally mild.	This formulation of naltrexone was well tolerated and produced a robust, dose-related increase in tx retention. These data provide new evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist txs for opioid dependence. Peak plasma levels measured after 1 wk of depot naltrexone were consistent with levels reported in previous studies. One concern with long-lasting antagonist is that pts will attempt to override blockade by using large amounts of heroin, thereby placing themselves at increased risk for overdose, especially during period when naltrexone blood levels are decreasing. Another concern is that use of non-opioid drugs may increase. This did not occur in present study. Potential adverse events that may be unique to sustained-release formulations of naltrexone include possibility that pts will attempt to remove medication and tissue reactions around site of drug administration. This did not occur in present study. Two patients dropped from the study because of injection site reactions; severity was considered to be moderate, and both reactions resolved spontaneously over time. One pt was diagnosed as having new-onset hepatitis C after administration, but clinically significant elevations in liver enzyme levels did not occur in present study otherwise.

Crivera, C., DeSouza, C., Kozma, C.M., et al (2011). Resource utilization in patients with schizophrenia who initiated risperidone long-acting therapy: Results from the Schizophrenia Outcomes Utilization Relapse and Clinical Evaluation (SOURCE). *BMC Psychiatry*, 11:168.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: Janssen Scientific Affairs, LLC, Raritan, New Jersey; Veterans Affairs Medical Center, Kansas City, Missouri; University of South Caroline, Columbia, SC ***Design:*** 24-month observational study to examine health care resource utilization in patients with schizophrenia initiated on risperidone long-acting therapy (RLAT) ***Time frame:*** September 2004 to January 2006 ***Funding source and conflict of interest:*** Study was supported by funding from Janssen Scientific Affairs, LLC, Titusville, New Jersey. Four authors are employees / consultants of Janssen Scientific Affairs and three are Johnson & Johnson stockholders. One author is employee of Johnson & Johnson Pharmaceutical Research and Development	Total of 532 pts enrolled in the study at 66 study sites. A total of 435 pts who had a baseline visit, >1 post-baseline visit, and valid hospitalization dates were studied for the primary medical resource utilization analysis. Pts eligible for enrollment were aged $\geq$ 18, were appropriate for initiation of RLAT, had physician-based dx of schizophrenia according to DSM-IV and had signed consent. Pts at imminent risk of injuring themselves or others or of causing significant damage to property, who were hypersensitive to RLAT or any of its components, or who had been tx with investigational agents within previous 30 days were not eligible for enrollment. Mean age of study population was 41.9 yrs, and 66.7% of pts were male. Mean duration of illness was 17.6 yrs. Twenty-two pts (5.1%) experienced an inpt hospitalization at baseline.	At baseline visit, prior hospitalization and ER visit dates were obtained for the previous 12 mo and subsequent hospitalization visit dates were obtained at 3-mo visits, if available. The health care resource utilization outcomes measures observed in this analysis were hospitalizations for any reason, psychiatric-related hospitalizations, and emergency room (ER) visits. Incidence density analysis was used to assess pre-event and post-event rates per person-year (PY). Study had a naturalistic design: after enrollment, specific txs or medical interventions were not mandated, so txs for schizophrenia could have been stopped, started, or changed throughout the study as deemed appropriate by treating physician.	Among the 435 pts who had a baseline visit, $\geq$ 1 post-baseline visits after RLAT initiation, and valid hospitalization dates, the number of hospitalizations and ER visits per PY declined significantly ($p < .0001$) after initiation with RLAT. 321 pts (73.8%) initiated on 25mg dose of RLAT, 62 (14.3%) on 37.5mg dose, and 51 (11.5%) on 50mg dose. In 38.9% of pts, the investigator reported they received other antipsychotics in addition to RLAT during study. A 41% decrease (difference of -0.29 hospitalizations per PY from baseline) in hospitalizations for any reason, a 56% decrease (difference of -0.35 hospitalizations per PY from baseline) in psychiatric-related hospitalizations, and a 40% decrease (-0.26 hospitalizations per PY from baseline) in ER visits were observed after the baseline period. The percentage of psychiatric-related hospitalizations decreased significantly after RLAT initiation, and pts had fewer inpt hospitalizations and ER visits (all $p < .0001$).	Results suggest that tx with RLAT may result in decreased hospitalizations for pts with schizophrenia. These results are in agreement with those of previous studies, which have shown that RLAT reduces hospitalization, ER visits, resource utilization, and inpatient bed days. As this was a nonrandomized, longitudinal, naturalistic, observational study, with no concurrent comparator group, there are several limitations that may influence generalizability of results. Pts were permitted to receive additional medications at discretion of clinicians. Therefore, the reductions in health care resource utilization observed cannot be attributed to any particular tx with certainty. However, although pts were permitted to receive additional medications, 76% who attended visit 9 were documented as having used RLAT, suggesting that RLAT might have contributed to the reduction in resource utilization. More than half the pts discontinued the study, suggesting potential selection bias for remaining pts to be responders to RLAT tx. Data on hospitalization were obtained through pt and clinician reports; therefore, these data rely on the accuracy in reporting hospitalizations.

Edwards, N.C., Rupnow, M.F., Pashos, C.L., et al (2005). Cost-effectiveness model of long-acting risperidone in schizophrenia in the US. *Pharmacoeconomics*, 23(3), 299-314. **(ABSTRACT REVIEW ONLY)**

Authors, Study Design	**Study Population**	**Treatment**	**Results**	**Conclusions/Limitations**
Locations: Health Services Consulting Corporation, Boxborough, MA ***Design:*** Decision-analysis model comparing four tx alternatives (risperidone LAI, oral risperidone, oral olanzapine, and haloperidol decanoate LAI) ***Time frame:*** N/A ***Funding source and conflict of interest:*** N/A	Outpatients with schizophrenia who had previously suffered a relapse requiring hospitalization in the US healthcare system.	Published medical literature, unpublished data from clinical trials and a consumer health database, and a clinical expert panel used to populate a decision-analysis model comparing four tx alternatives. Model captured rates of pt compliance; rates, frequency and duration of relapse; incidence of adverse events; and healthcare resource utilization and associated costs. Primary outcomes were: proportion of pts with relapse; frequency of relapse per pt; number of relapse days per pt; and total direct medical cost per patient per year. Costs are in year 2002 US dollars.	Based on model projections, proportions of pts experiencing relapse requiring hospitalization after 1 yr of tx were 66% for haloperidol decanoate LAI, 41% for oral risperidone and oral olanzapine, and 26% for risperidone LAI, while proportions of pts with a relapse not requiring hospitalization were 60%, 37%, 37%, and 24%, respectively. The mean number of days of relapse requiring hospitalization per pt per yr was 28 for haloperidol decanoate LAI, 18 for oral risperidone and oral olanzapine and 11 for risperidone LAI, while mean number of days of relapse not requiring hospitalization was 8, 5, 5, and 3, respectively. This would translate into direct medical cost savings with risperidone LAI compared with oral risperidone, oral olanzapine, and haloperidol decanoate Lai of $397, $1,742, and $8,328, respectively. These findings were supported by sensitivity analyses.	The use of risperidone LAI for tx of outpts with schizophrenia is predicted in this model to result in better clinical outcomes and lower total healthcare costs over 1 yr than its comparators. Risperidone LAI may therefore be a cost saving therapeutic option for outpts with schizophrenia in the US healthcare setting.

Edwards, N.C., Locklear, J.C., Rupnow, M.F. & Diamond, R.J. (2005). Cost-effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA *Pharmacoeconomics*, 23(Supp1), 75-89. **(ABSTRACT REVIEW ONLY)**

Authors, Study Design	**Study Population**	**Treatment**	**Results**	**Conclusions/Limitations**
Locations: Health Services Consulting Corporation, Boxborough, MA ***Design:*** Decision-analysis model comparing seven tx alternatives (long-acting risperidone, oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and haloperidol depot) ***Time frame:*** N/A ***Funding source and conflict of interest:*** N/A	Pts with schizophrenia from US healthcare system.	Published medical literature, unpublished data from clinical trials and a consumer health database, and a clinical expert panel were utilized to populate a decision analytical model comparing the seven treatment alternatives. The model captured rates of patient compliance, the rates, frequency and duration of relapse, incidence of adverse events, and healthcare resource utilization and associated costs. Primary outcomes were expressed in terms of percentage of patients relapsing per year, number of relapse days per year (number and duration of relapses per patient per year), and total direct 2003 medical cost per patient per year.	Pts experiencing relapse requiring hospitalization in 1 yr were 66% for haloperidol depot, 41% for oral risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and 26% for long-acting risperidone. Pts with exacerbation not requiring hospitalization were 60% for haloperidol depot, 37% for oral risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and 24% for long-acting risperidone. Mean days of relapse requiring hospitalization per pt per yr were 28 for haloperidol depot, 18 for oral risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and 11 for long-acting risperidone, Mean days of exacerbation not requiring hospitalization were 8 for haloperidol depot, 5 for oral risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and 3 for long-acting risperidone. Translates into direct medical cost savings with long-acting risperidone compared with oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and haloperidol depot of $161, $1425, $508, $259, $1068, and $8224, respectively.	The utilization of long-acting risperidone is predicted to result in better clinical outcomes and lower total healthcare costs than its comparators, oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and haloperidol depot. Long-acting risperidone may therefore be a cost saving therapeutic option for patients with schizophrenia.

Garbutt, J.C., Kranzler, H.R., O'Malley, S.S., et al (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA*, 293(13), 1617-1625.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: Dept of Psychiatry, UNC School of Medicine, Chapel Hill; Dept of Psychiatry, UConn School of Medicine, Farmington; Dept of Psychiatry, Yale University School of Medicine, New Haven, Conn; Dept of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston ***Design:*** 6-mo. randomized, double-blind, placebo-controlled trial at 24 US public hospitals, private and VA clinics, and tertiary care medical centers. ***Time frame:*** February 2002 – September 2003 ***Funding source and conflict of interest:*** Authors have served on advisory board and/or received research support from Bristol-Meyers Squibb, Alkermes, Oy Contral Pharma, Forest Laboratories, Wyeth-Ayerst, Pfizer, Ortho-McNeil, DuPont, Johnson & Johnson, etc. Manuscript prep supported by grant from NIMH. Study was funded, conducted, and designed by Alkermes with suggestions from investigators.	Of 899 individuals who were screened, 627 were determined eligible and were randomly assigned to receive tx (n=624 actually included). 423 (68%) males and 521 (83%) White. Mean age of 45 (range: 19-74). Mean heavy drinking days in 30 days before randomization was 20 days. 53 (8.8%) abstinent in 7 days before receiving first injection and 270 (43%) had tx goal of total abstinence. Participants were male or nonpregnant, nonlactating female outpts aged $\geq$ 18 yrs with current dx of alcohol dependence defined by DSM-IV. Pts also had minimum of 2 episodes of heavy drinking per week during 30 days before screening. Exclusion criteria included evidence of liver failure; alanine aminotransferase or aspartate aminotransferase levels greater than 3x upper limit of normal; clinically significant medical condition that would affect safety; major depression w suicidal ideation, psychosis or bipolar; benzodiazepines, opiates, or cocaine dependence; > 7 days of inpt tx for substance abuse in mo before screening.	A negative urine test result for opiates and methadone required on day of randomization. Pts randomized to 1 of 3 tx groups: long-acting injectable naltrexone 280 mg, long-acting injectable naltrexone 190 mg, or placebo (either 2- or 4-mL injections of microspheres w/out naltrexone). Over 24 wks, pts received at 4-wk intervals intramuscular gluteal injections of study medication on alternating sides. Were administered by individuals not involved in any of safety/efficacy assessments. All pts received standardized, supportive therapy (12 sessions) using the BRENDA model. Number of standard drinks consumer per day was recorded. Primary efficacy end point was event rate (frequency and pattern of heavy drinking days over 24 wks of tx).	In 401 pts (64%), all 6 injections were administered, and 463 (74%) received at least 4 injections. Time to discontinuation similar among groups. Median rate of therapy sessions completed was 92%, and 267 (43%) of pts attended all therapy sessions. Compared with placebo, 380 mg of long-acting naltrexone resulted in 25% decrease in event rate of heavy drinking days (P = .03) and 190 mg of naltrexone resulted in a 17% decrease (P = .07). Sex and pretreatment abstinence each showed significant interaction with the medication group on tx outcome, with mean and those with lead-in abstinence both exhibiting greater tx effects. Discontinuation due to adverse events occurred in 14.1% in the 380 mg and 6.7% in the 190 mg group and 6.7% in the placebo group.	Long-acting naltrexone was well tolerated and resulted in reductions in heavy drinking among treatment-seeking alcohol-dependent patients during 6 mo of therapy. These data indicate that long-acting naltrexone can be of benefit in the tx of alcohol dependence. The 25% relative reduction in the heavy drinking event rate with the 380-mg dose reflects the avg reduction in drinking events within the tx group. However, the avg reduction in events is disproportionately weighted by participants who were drinking at highest levels during the study. These pts contributed a greater number of events to the overall analysis and thus had a greater impact on the avg. Men comprised the majority (68%) of pts in this study, which is consistent with prevalence pattern of alcohol dependence in the US, and showed a substantial tx effect. Men and women in study differed on number of important variables, including prevalence of smoking and antidepressant use, weight, and commitment to abstinence. Study included pts from both public and private tx settings and also specialty and non-specialty practices. Dropouts reduce the extent to which the findings generalize to the population of all alcoholics. However, dropout rates were equivalent across the 3 tx groups.

Kane, J.M., Eerdekens, M., Lindenmayer, J.P., et al (2003). Long-acting injectable risperidone: Efficacy and safety of the first long-acting atypical antipsychotic. *American Journal of Psychiatry*, 160(6), 1125-1132.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: Zucker Hillside Hospital; Johnson & Johnson Pharmaceutical Research ad Development, Beerse, Belgium; Manhattan Psychiatric Center-New York University School of Medicine, New York; University of New Mexico School of Medicine, Albuquerque ***Design:*** 12-wk, multicenter, double-blind, randomized study assessing efficacy and safety of long-acting injectable risperidone in patients with schizophrenia ***Time frame:*** Exact months and year not specified ***Funding source and conflict of interest:*** Study was supported by Johnson & Johnson Pharmaceutical Research and Development, Titusville, NJ	400 hospital outpts or inpts 18-55 yrs of age with dx of schizophrenia according to DSM-IV criteria. Inclusion criteria included baseline Positive and Negative Syndrome Scale total scores of 60-120 and good general health, with standard lab test results within reference ranges or not clinically significant. Were excluded if had received depot antipsychotic within 120 days of start of trial, diagnosed as substance dependent, had tardive dyskinesia or hx of neuroleptic malignant syndrome, had clinically significant ECG abnormality, were pregnant or lactating, at risk of violent behavior, or current suicidal ideation. Also if had hx of severe sensitivity or allergy, including sensitivity to risperidone. Mean ages of groups were 37.7 yrs (placebo), 38.9 (25mg), 36.2 (50mg), and 38.1 (75mg). Number of previous hospitalizations was similar across the four groups (medians of 4.0, 3.5, 4.0, and 4.0) Equal proportions were hospital inpts and outpts	Pts were enrolled at 41 centers in the US. After 1-wk screening period, doses of other oral antipsychotics were reduced and then discontinued. Simultaneously, oral risperidone was started at 2mg/days and increased to 4mg/day for at least 3 days. Patients received intramuscular injections every 2 wks of placebo or long-acting risperidone (25mg, 50mg, or 75mg). The primary measure of efficacy was the change in total score on the Positive and Negative Syndrome Scale. Adverse events and vital signs assessed at baseline and every 2 wks. Pts evaluated pain at injection site wkly and before and after each injection on visual analog scale.	Of the 400 pts to enter the double-blind, 370 received at least one post-baseline assessment. Mean changes in score of -6.2, -8.5, and -7.4 on the Positive and Negative Syndrome Scale seen at endpoint for the 25-, 50-, and 75-mg risperidone groups, respectively. All three change score significantly different from that seen with placebo (+2.6). Improvements in positive and negative symptoms also significantly greater in pts receiving risperidone. Long-acting risperidone was well tolerated. Adverse events spontaneously reported by 13% of pts receiving placebo, and 10% of pts in the 25mg risperidone group, with higher rates in the 50- and 75mg groups. Severity of extrapyramidal symptoms was mild at baseline and throughout trial in each group. Mean weight changes were small in the 25, 50, and 75mg risperidone groups (0.5kg, 1.2kg, and 1.9 kg). Injection site pain rated as low by the pts.	Long-acting injectable risperidone was efficacious and well tolerated and provides both clinicians and patients with a new mode of treatment that can improve the outcome of long-term therapy. The trial was discontinued prematurely by 68% of the placebo pts and 51-52% of the pts receiving long-acting risperidone. The dropout rate was similar in the four groups during days 1-15, after which more placebo pts discontinued tx. The study results indicate that 25mg of long-acting injectable risperidone given every 2 wks appears to offer the optimum risk/benefit profile for most pts requiring maintenance tx with an antipsychotic. Over 45% of pts in the 25mg group showed a $\geq$ 20% improvement in Positive and Negative Syndrome Scale total scores. The 75mg dose, although efficacious, offered no incremental benefit over the 25mg and 50mg doses.

Krupitsky, E., Nunes, E.V., Ling, W., et al (2011). Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicenter randomized trial. *Lancet*, 377, 1506-1513.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: Bekhterev Research Psychoneurological Institute, St Petersburg State Pavlov Medical University, St Petersburg, Russia; New York State Psychiatric Institute and Dept of Psychiatry, Columbia University, New York; Dept of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles ***Design:*** Double-blind, placebo-controlled, randomized trial to assess efficacy, safety, and patient-reported outcomes ***Time frame:*** July 2008 – October 2009 ***Funding source and conflict of interest:*** The Medisorb preparation used in XR-NTX was developed w support from NIDA and NIAAA. Lead author is consultant and received research funding for study from Alkermes. Other authors are members of Alkermes advisory board or full-time employees of Alkermes.	Pts aged $\geq$ 18 years who had $\leq$ 30 days of inpt detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. Pts were voluntarily seeking tx and excluded if under justice system coercion. 335 candidates were screened, 250 of whom were randomly assigned to extended-release naltrexone (XR-NTX) or placebo. Exclusion criteria included pregnancy/breastfeeding, significant medical conditions, positive naloxone challenge, hepatic failure, hx of an AIDS-indicator disease, active hepatitis or aminotransferase more than 3x upper limit of normal, intolerance to naltrexone, psychosis, bipolar disorder, mdd with suicidal ideation, or dependence on substances other than opioids or heroin. XR-NTX Group (n=126): mean age of 29.4, 90% male, 98% White, mean 9.1 yrs opioid dependence Placebo Group (n=124): mean age of 29.7, 86% male, 100% White, mean 10 yrs opioid dependence	Pts randomly assigned to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and sex with a centralized, permuted-block method with a block size of four. System was also used to manage supply of masked study drugs. Primary endpoint was response profile for confirmed abstinence during wks 5-24, assessed by urine tests and self report of non-use. Secondary endpoints of opioid-free days, opioid craving scores, number of days of retention and relapse to physiological opioid dependence. Pts received injection of XR-NTX or placebo w/in 1 wk after detox and then every 4 wks after, for total of six injections over 24 wks. They also were offered 12 biweekly sessions of individual drug counseling, adapted for opioid dependence.	The median proportion of wks of confirmed abstinence was 90% (95% CI: 69.9-92.4) in the XR-NTX group compared with 35% (95% CI: 11.4-63.8) in the placebo group. Pts in XR-NTX group self-reported median 99.2% opioid-free days compared with 60.4% for placebo group ($p=0.0004$). Mean change in craving was -10.1 in the XR-NTX group compared with 0.7 in placebo group ($p<0.0001$). Median retention was over 168 days in the XR-NTX group compared with 96 days in placebo group ($p=0.0042$). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 pts in placebo group compared with 1 in XR-NTX group ($p<0.0001$). XR-NTX was well tolerated. Two pts in each group discontinued owing to adverse events. No XR-NTX treated pts died, overdosed, or discontinued owing to severe adverse events.	XR-NTX represents a new tx option that is distinct from opioid agonist maintenance tx. XR-NTX in conjunction with psychosocial tx might improve acceptance of opioid dependence pharmacotherapy and provide a useful tx option for many pts. A strength of the study was geographic setting in Russia-one of many countries where opioid agonist therapy is unavailable, but where there is an alarming growth in availability of heroin and the fastest-growing HIV infection rate in the world. Pts included in this study share similarities w opioid-dependent population in other countries. Nevertheless, generalizability of these results beyond Russia is a topic for further research. There was substantial clinical response to placebo; however, tx group still showed greater benefits. Retention in placebo group might have been reduced by recognition upon opioid use that one was on placebo or-among pts in placebo group who had relapsed to regular opioid use-by reluctance to return to clinical and face a withdrawal reaction from naloxone challenge test. Drug use might have been underreported on self-report; however, there was a high degree of agreement between results from urine tests and self-report and urine data was a required confirmatory element of the primary efficacy measure.

Leal, A., Rosillon, D., Mehnert, A., et al (2004). Healthcare resource utilization during 1-year treatment with long-acting, injectable risperidone. *Pharmacoepidemiology and Drug Safety*, 13, 811-816.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: SGS-Biopharma, Belgium; Janssen Pharmaceutica NV, Beerse, Belgium; Ill Klinika Psychiatryczna Instytutu, Warszawa, Poland; Center for Addiction and Mental Health, Toronto, Canada ***Design:*** 1-year, open-label study to assess healthcare resource use in pts with schizophrenia and schizoaffective disorder during tx with long-acting risperidone. Same study population used as Chue, 2005 (see above). ***Time frame:*** Exact months and year not specified ***Funding source and conflict of interest:*** Authors acknowledge conflict of interest in that a company whose product was studied provided funding to support the work on the project	Same study population as the one used in Chue, 2005 (see above). Pts with schizophrenia or schizoaffective disorder according to DSM-IV criteria, aged $\geq$ 18 years old were eligible to enter study. Pts required to be stable on current antipsychotic medication, as judged by investigator, for $\geq$ 4 wks before entering study. 249 males (63%) and 148 females participated. Mean age of 43.6 (SD = 15.2, range 18-84). 96 inpatients, 301 outpatients. 329 with schizophrenia dx and 68 with schizoaffective disorder dx. 86% on concomitant medications.	(See Chue, 2005). Before tx, pts entered 2-wk run-in where antipsychotics other than risperidone were discontinued. During run-in, all received oral risperidone, 1-6 mg/day at determined dose. Baseline levels taken at end of 2 wks. During 12-mo open-label phase, pts received long-acting risperidone injection, 25 mg, 50 mg, or 75 mg, ever 2 wks with initial dose depending on dose of oral risperidone at end of run-in period. (1-2 mg/day oral → 25 mg; 3-4 mg/day oral → 50mg; 5-6 mg/day oral → 75mg). Oral supplementation at same dose at end of run-in was mandatory for first 2-3 wks of tx with injection. Dose of injection could be increased at scheduled visits if pt experienced psychotic symptoms. Healthcare resource use in previous 12 wks was assessed at baseline and 12-weekly intervals.	Some of the results are available in Chue, 2005 (see above). The need for partial hospitalization was very low during the study and decreased significantly over the 12-mo period, from 7% during 12 wks before tx to 3% during last 12 wks ($p=0.002$). Only 41 pts (10%) were admitted to day or night clinics during the study. Mean amount of time spend in partial hospitalization was 3.8 days (SD=19.6). Need for outpt consultation decreased significantly from 70% in 12 wks before tx to 30% ($p<0.0001$) during first 12 wks of tx. Need for outpt consultation remained stable throughout the remainder of the tx period. Rate of admission to emergency room was minimal and was consistent before and during tx with long-term risperidone; 3% of pts required ER visit in 12 wks before tx, compared with 1% in final 12 wks of study. Overall, only 35 (9%) pts required ER visit during study. In 12 wks before tx, 64% of ER visits were for psychotic condition. During trial, this proportion fell to 20%.	Healthcare resource use is significantly reduced in pts with stable schizophrenia or schizoaffective disorder receiving long-acting risperidone. It is highly likely that these reductions will decrease healthcare costs in pts receiving long-acting risperidone. It is possible that reduced levels of hospitalization and outpt consultations observed in trial are result of physicians feeling more confident in managing pts using a new drug. This study looked at 'units' of resource use rather than absolute costs of healthcare. It seems likely, however, that the reductions in resource use associated with long-acting risperidone injection will lead to decreased overall healthcare costs. While switching to a long-acting injectable formulation from an oral medication may lead to some additional costs, studies comparing oral and depot formulations of conventional antipsychotics have shown that long-acting medications are associated with overall reductions in costs. Reduction in healthcare costs also reflects the decreased burden of disease for individual pt. In addition to improvements in symptoms and relapse rate, long-acting risperidone has been shown to significantly increase patients' satisfaction w tx and health-related quality of life, thus helping to reduce the burden on family members and caregivers. It seems likely, therefore, that long-acting risperidone will also reduce the indirect costs of schizophrenia and schizoaffective disorder.

Peng, X., Ascher-Svanum, H., Faries, D., et al (2011). Decline in hospitalization risk and health care cost after initiation of depot antipsychotics in the treatment of schizophrenia. *ClinicoEconomics and Outcomes Research*, 3, 9-14.

Authors, Study Design	Study Population	Treatment	Results	Conclusions/Limitations
Locations: Eli Lilly and Company, Indianapolis, IN ***Design:*** Mirror-image study aimed to assess change in hospitalization risk from 6 mo pre- to 6 month post-initiation on any depot antipsychotic among pts treated for schizophrenia in the United States. ***Time frame:*** Jan 2004 – March 2008 ***Funding source and conflict of interest:*** Work was supported by Eli Lilly and Company. All authors are full-time employees and minor shareholders of Eli Lily and Company.	Sample selection consisted of pts (< 65 years of age) who were dx with schizophrenia and who had at least 2 outpt visits or 1 inpt hospitalization associated with the schizophrenia dx. Pts diagnosed with dementia type disorder were excluded. Pts who were initiated on any depot antipsychotic, who had no depot injection in the 6 mo before this injection, and who had continuous enrollment for the 6 mo before and 6 mo after the depot initiation date ("index date") were included in the 2 outpt visits or 1 inpt hospitalization occurred within 180 days before depot initiation. Index date was date of first depot injection. From 674 pts who were initiated depot antipsychotic, data from 147 pts met inclusion criteria and were included in analysis. Mean age was 42.6; 53.7% male; 25.9% were administered risperidone, 46.9% were administered haloperidol, and 27.2% were administered fluphenazine.	Pts initiated on a depot antipsychotic were studied in a mirror-image design to assess change in hospitalization rates, mean duration hospitalized, and hospitalization cost. McNemar's test and paired t-tests compared the proportions of pts hospitalized and the mean duration. Paired t-test and bootstrapping methods compared costs.	After initiation of depot antipsychotics, pts improved medication adherence. Mean antipsychotic MPR increased from 36.8% in the 6 mo preceding depot initiation to 60% in the 6 mo after initiation ($P < 0.001$). After depot initiation, pts were less likely to be hospitalized for any reason, for any psychiatric reason, and for schizophrenia specifically. During 6 mo preceding initiation, 79 pts (53.7%) were hospitalized for any reason compared with 44 pts (29.9%) in 6 mo after initiation ($P < 0.001$). Hospitalization for any psychiatric reason decreased from 73 pts (49.7%) to 33 pts (22.4%; $P < 0.001$). Hospitalization for schizophrenia decreased from 63 pts (42.9%) to 30 pts (20.4%; $P < 0.001$). Total health care costs declined from \$11,111 to \$7,884 ($P < 0.05$), driven by reduction in costs for psychiatric hospitalizations from \$5,384 to \$2,538 ($P < 0.05$). Total outpt costs and total medication costs did not change significantly.	Initiation of depot antipsychotic therapy appeared to be associated with a decline in hospitalization rates and costs. Current findings suggest that tx with depot antipsychotics may be a cost-effective option for a subgroup of pts with schizophrenia who are at high risk of nonadherence with their oral antipsychotic medication regimen. Results need to be considered in context of study limitations. The sample size was rather small (n=147). Also, the study design is devoid of a control group. Each pt served as his or her own control. As such, observed changes from pre- to post-depot initiation may reflect regression to the mean. Findings may not be generalizable to pts with schizophrenia who lack commercial insurance, which is a large segment of the schizophrenia population in the US.

Tiihonen, J., Haukka, J., Taylor, M., et al (2011). A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*, 168(6), 603-609.

Authors, Study Design	**Study Population**	**Treatment**	**Results**	**Conclusions/Limitations**
Locations: Dept of Forensic Psychiatry, University of Eastern Finland ***Design:*** Register-based case linkage study to explore risk of rehospitalization and drug discontinuation in nationwide cohort ***Time frame:*** Pts had first hospitalization in which schizophrenia was diagnosed during period of 2000-2008. ***Funding source and conflict of interest:*** Authors have served as consultant and/or received fees from Eli Lilly, Bristol-Meyers Squibb, GlaxoSmithKline, Pfizer, etc. Supported by the Annual EVO Financing, and by Janssen-Cilag. The funders were not involved in the conduct of the study or in collection, management, analysis, or interpretation of the data.	A total of 33,318 pts had at least one hospitalization due to schizophrenia-related illness during study period. Of these, 7,434 experienced first hospitalization during that period, and 2,588 had a strictly defined schizophrenia diagnosis during first hospitalization. Mean age of study population was 37.8 yrs and 62% were male.	Authors linked nat'l databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for effects of sociodemo & clinical variables, temporal sequence of antipsychotics used, and choice of initial antipsychotic for each patient. Cohort identified from Finnish Nat'l Hospital Discharge Register, administered by the Nat'l Institute for Health and Welfare. Outcome measures of interest were 1) risk of all-cause discontinuation of initial antipsychotic medication; 2) risk of rehospitalization for schizophrenia; 3) risk of death Only those who received any antipsychotic medication within first 30 days after discharge were included in analysis of all-cause discontinuation	Of 2,588 pts with first hospitalization, 1,507 (58.2%) used antipsychotic during first 30 days after discharge, and 1,182 (45.7% of total) continued initial antipsychotic medication for 30 days or longer. Alternatively, 54.4% of cohort either did not collect an antipsychotic prescription within 30 days of hospital discharge or used their initial antipsychotic medication for less than 30 days. Risk of rehospitalization for pts receiving depot medications was about one-third of that for pts receiving oral medications. Compared with oral risperidone, clozapine and olanzapine were each associated with significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality.	This is first study of adherence and comparative effectiveness of specific antipsychotic txs in a large unselected population of pts in a real-world setting after first hospitalization with dx of schizophrenia. In Finland, only a minority of pts adhere to initial antipsychotic during first 60 days after discharge from first hospitalization for schizophrenia. Use of depot antipsychotics was associated with significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Use of defined daily dosage in study may have caused some pts continuously using unusually low doses to have been misclassified as discontinuing the medication. Those pts who are more likely to be non-adherent with oral medication, and thus more likely to receive prescriptions for depot medication, are also likely to have poorer insight than other patients. Therefore, it is unlikely that residual confounding would explain the better outcome among pts receiving depot antipsychotics. Authors were not able to assess patients' subjective quality of life during the txs.