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Cost-Effectiveness of Long-Acting Injectable Paliperidone Palmitate vs. Haloperidol Decanoate in Maintenance Treatment of Schizophrenia

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Authors Contributions

The study was funded by grants from NIMH to Drs. McEvoy and Stroup. Drs. Byerly, Buckley, McEvoy, and Lamberti collected data. Dr. Rosenheck, Ms. Li and Mr. Sint oversaw or conducted the analyses. Dr. Rosenheck wrote the first draft of the manuscript. All authors participated in the writing and editing of the manuscript.

Drs. Stroup and Rosenheck had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

Dr. McEvoy receives speaking honoraria from Eli Lilly; consultation and honorarium fees for educational lecture for staff from Hoffman LaRoche; advisory fees from Merck; honoraria for speaking and a research grant from Sunovion; and a research grant from GlaxoSmithKline. Dr. Byerly reports research support from Otsuka. Dr. Hamer has received advisory or consulting fees, has served on a data and safety monitoring board and an advisory board, or was involved in a contract between the University of North Carolina and the following: Abbott, Acadia, Allergan, Alpharma, AstraZeneca, Cenerx, Corcept, Eli Lilly, EnabledMD, Epix, Johnson and Johnson, Novartis, Pfizer, PureTech — Ventures, Schwartz, Sanofi — Aventis, Takeda, and Wyeth. Dr. Hamer has served as an expert witness in lawsuits involving Forest, Lundbeck, Sun, Caraco, Teva, Barr, Mylan, Eurand, Cephalon, and Anesta. Dr. Rosenheck has received research support from Janssen Pharmaceutica, AstraZeneca, and Wyeth Pharmaceuticals. He has been a consultant to Otsuka. He was testifying expert in *Jones ex rel the State of Texas v Janssen Phamaceutica et al*. Dr. Swartz reports having received research funding from Eli Lilly and Co. Dr. Stroup has participated in CME activities funded by Genentech and is an investigator in a clinical trial sponsored by Auspex Pharmaceuticals.

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Abstract

Objective—This study assessed the relative cost-effectiveness of a first generation and a second generation long-acting injectable antipsychotic: haloperidol decanoate (HD) and paliperidone palmitate (PP), respectively.

Methods—A multisite, double-blind, randomized 18-month clinical trial conducted at 22 clinical research U.S. sites with adults diagnosed with schizophrenia or schizoaffective disorder (n=311) clinically assessed to benefit from a LAI antipsychotic. Patients were randomly assigned to Intramuscular injections of HD 25–200 mg or PP 39–234 mg every month for up to 24 months. Quality Adjusted Life Years was measured by a schizophrenia-specific algorithm based on the Positive and Negative Syndrome Scale and side effect assessments; and total health care costs from the perspective of the health system.

Results—Mixed model analysis of QALYs showed PP with .027 greater QALYs over 18 months (p=.03) but also greater average quarterly inpatient, outpatient and medication costs of $2,100/quarter (p<.0001). Bootstrap analysis with 5,000 replications showed an Incremental Cost effectiveness ratio for PP of $508,241/QALY (95% CI of $122,390–$1,582,711). Net Health Benefits analysis showed a 0.98 probability of greater cost-effectiveness for HD over PP at an estimated valuation of health of $150,000/QALY and only 0.50 greater at $500,000/QALY.

Conclusions—HD was more cost-effective than PP suggesting that PP's slightly greater benefits do not justify its markedly higher on-patent costs.

Non-adherence to prescribed medication is a major cause of relapse, re-hospitalization, and increased health care costs in the treatment of schizophrenia. (1) Long-acting injectable (LAI) antipsychotic medications, which can be administered every two to four weeks, are used to reduce non-adherence and relapse. The use of LAI versions of first generation antipsychotics has been limited in part due to concerns about the risk of extrapyramidal side effects. The second generation antipsychotic, risperidone microspheres was introduced in 2003 but must be refrigerated before use, reconstituted with a diluent, and administered every two weeks. In 2009, paliperidone palmitate, a long-acting version of risperidone's active metabolite became available. It can be administered monthly and does not require refrigeration or reconstitution. Because of these logistical advantages, paliperidone palmitate was considered to be an important advance in LAI antipsychotics (2), although its high cost left uncertainty about whether its costs are justified by greater benefits.

Recent trials have raised some doubts about the clinical advantages of oral second generation antipsychotics (3–6). Some newer antipsychotics appear to cause significant metabolic problems (7) and randomized trials have failed to find advantages of LAI second generation antipsychotics as compared to oral antipsychotics (8, 9). However, one recent study found robust benefits for LAI as compared to oral risperidone (10) in first episode psychosis.

In view of these uncertainties, a randomized clinical trial was designed to compare LAI paliperidone palmitate (PP) and haloperidol decanoate (HD), and found no advantage for PP in preventing relapse but greater weight gain and reduced risk of akathisia (11). This study evaluates the cost-effectiveness of PP and HD to determine the relative effects of PP and HD using a measure of the health status of people diagnosed with schizophrenia that addresses both symptoms and side effects in a single measure, and whether any advantage of PP merits its greater cost.

Method

Study setting and design

A Comparison of Long-acting Injectable Medications for Schizophrenia (ACLAIMS) was a multisite, parallel-group, double-blinded randomized controlled trial (11) conducted at 22 U.S. clinical sites from 2011–2013. Each site obtained institutional review board approval to conduct the study.

Patients

Patients were adults aged 18–65 with a diagnosis of schizophrenia or schizoaffective disorder confirmed by the Structured Clinical Interview for DSM-IV (SCID). Patients were eligible if judged by a referring psychiatrist as likely to benefit from treatment with PP or HD because they were at risk of efficacy failure due to medication non-compliance and/or significant substance abuse. Entry and exclusion criteria have been presented previously (11).

Interventions

A total of 353 patients enrolled for screening; 311 were eligible and randomized to study treatment (see consort diagram in McEvoy et. al., 2014). Study treatments were long-acting injectable PP supplied in dosages of 39 mg, 78 mg, 117 mg, 156 mg and 234 mg; and HD supplied in vials of 50 mg/ml or 100 mg/ml for injection. Each participant received a blinded trial of the oral version of the assigned medication prior to receiving an injection. The first injection was given 4–7 days after the baseline visit. Subsequent visits were at weeks 1, 2, 4, 6, 8, 10, and 12, then monthly (i.e., every four weeks) for up to 24 months. Altogether 62 (43%) PP patients completed the 18 month follow-up assessment and 71 (49%) of HD patients with no significant difference between groups (chi sq= 0.77, df=6, p=0.94).

Study physicians and all other personnel were blinded to treatment condition. A clinician not otherwise involved in the trial administered the injection (11).

Outcome Measures

The primary outcomes were Quality Adjusted Life Years (QALYs) and total costs from the perspective of the healthcare system (12).

Effectiveness—Cost-effectiveness analysis depends having a single measure of health related quality of life that addresses health gains as well as losses due to side effects. It is recommended that health states be expressed as QALYs, a year of life rated on a cardinal scale from 0 (worst possible health) to 1 (perfect health), as evaluated by members of the general public (12).

A series of studies has demonstrated a method for evaluating QALYs in schizophrenia (13–15) based on the Positive and Negative Syndrome Scale (PANSS) (16) and side-effect data. The derivation of QALYs from PANSS data began with a cluster analysis of a sample of almost 400 patients which identified 8 disease-specific health states. With input from expert study clinicians, script and video materials were developed to convey impairments experienced with each schizophrenia state, and with five commonly co-occurring adverse side effects (orthostatic hypotension, weight gain, tardive dyskinesia, pseudo-parkinsonism and akathisia) (13). Using these video presentations, the states were rated by 620 members of the general public using the standard gamble, the recommended method for QALY determination (12). Responses were weighted to represent the socio-demographic characteristics of the adult US population.

Costs—The economic perspective addressed total health care costs (mental health and medical health service use plus medications at prices faced by the health care system. the perspective used in this study). Service use was assessed through detailed quarterly interviews conducted by trained research staff, documenting inpatient and outpatient psychiatric and medical health service use. Costs were then estimated by multiplying the number of units of each type of service received by the estimated unit cost of that service, and then summing the products across difference services.

Evaluation of Service Use and Costs: Monthly service use was documented every three months through a self-report questionnaire that recorded four kinds of hospital days (medical, surgical, psychiatric, and substance abuse) across six different facility types (e.g. state mental hospitals, private psychiatric hospitals, non-federal general hospitals). Nights spent in nursing homes and halfway houses were also recorded. Use of 16 types of outpatient mental health care, including psychiatric and psycho-social rehabilitation services, were documented along with 8 different types of medical or surgical outpatient visit, and emergency room services.

Unit costs of these services were estimated from published reports (33–38) and administrative data sets (38)(Medicaid, MarketScan® private claims data base, and Veterans Health Administration data).

Costs of antipsychotic medications, other psychotropic medications, and non-psychotropic medication were based on discounted prices from the Federal Supply Schedule Prices, which are the lowest non-generic prices available – the most conservative prices. The unit of

analysis for cost-evaluation is the total average health cost per quarter (average monthly costs multiplied times 3), including costs of all health service use, study medications at the prescribed doses and other prescribed drugs.

Statistical methods

The analytic sample consisted of all patients who received at least one injection and at least one post-baseline assessment.

Effectiveness, service use and cost analyses compared treatment groups on average quarterly effectiveness and service use (QALYs, hospital or residential days, outpatient visits and medications) and related costs across 18 months using a mixed model including terms representing treatment group and time (treated as a classification variable for 3, 6, 9, 12, 15, and 18 months). A random subject effect and a first-order autoregressive covariance structure were used to adjust standard errors for the correlation of observations from the same individual.

In addition to the comparison of effectiveness (improvement in QALYs from baseline) and costs between treatments, the incremental cost-effectiveness ratio was calculated as the difference in benefits divided by the difference in quarterly costs. The uncertainty of estimated differences in cost and effectiveness was estimated by non-parametric bootstrapping of 5,000 ICER regression replications with replacement (17).

The principal cost-benefit analysis was conducted using the method of net health benefits (18). In this approach, a range of estimates for the dollar value of a QALY are multiplied by the QALY estimate for each patient at each time point to estimate the monetized value of their health status at each observation. Following conventions used in policy making (19, 20), with more recent academic refinements we use estimates of $0/QALY/year to $600,000/QALY/year in this sensitivity analysis. This yielded a monetized estimate of health status for each patient at each time point.

Monthly health care costs were then subtracted from these estimated health benefits to generate an estimate of “net health benefit” for each patient for each month at each of the estimated monetary values of a QALY. Mixed model regression analyses of the type described above were used to compare mean differences between the groups using monthly estimates of net health benefits from all time points and adjusting for time, site, and other factors.

Over the past decade, it has been increasingly recognized that policy makers typically have to make decisions even when findings do not meet the usual 5% standard of uncertainly and that it is important to know the probability that one treatment will be more cost-effective than another, even when the uncertainty is greater than the conventional 5% (17). Using the method of Hoch et al. (21), we calculate the probability that HD had greater net health benefits than PP at each of the estimated monetary values of a QALY. This calculation was based on a 1-tailed test based on the p-value associated with the coefficient for the treatment variable, representing the significance of differences between the treatments calculated as HD-PP, and was computed as 1-p/2 (21). These data allow plotting of a Cost-Effectiveness

Acceptability Curve, which illustrates graphically the probability that that HD was more cost-effective than PP at each estimated monetary value of a QALY.

Analyses were performed using SAS version 9.3 (SAS Institute, Inc.).

Results

The progress of patients who were screened and randomly assigned to each group was presented previously (11). Baseline demographic and clinical characteristics of the 145 PP and 145 HD patients in the primary analysis were presented in Table 1 of that paper (11).

Dose

In the initial month of LAI treatment, which included doses on day 1 and day 8, the mean dose of PP was 325 mg and of HD 94 mg. Subsequently, the mean monthly dose of PP ranged from 129–169 mg and the mean monthly dose of HD ranged from 67–83 mg.

Summary of previously published results

In the primary analysis of the original paper (11), there was no statistically significant difference in the time to efficacy failure (49 days for PP vs. 47 days for HD; site stratified log rank p=.90; site and baseline PANSS adjusted hazard ratio 0.98, 95% CI=0.65–1.47). On average, patients taking PP gained weight progressively over time while those on HD lost weight (p<0.001).

Patients taking HD experienced greater increases in Barnes Akathisia Scale (BAS) global scores (0.45 (0.31–0.59) for PP vs. 0.73 (0.59–0.87) for HD; p=0.006). There were no statistically significant differences in changes in ratings of Parkinsonism measured by the Simpson-Angus Extrapyramidal Scale (p=0.34) and decreases in PANSS total scores from baseline were not significantly different between groups at each time point.

Quality Adjusted Life Years—Mixed model analysis of QALYs as measured by the algorithm described above showed slightly higher scores for PP than HD of .0297 QALYs over 18 months (p<.03)(Figure 1).

Costs—Antipsychotic drug costs (Table 1) were $2,213 greater per quarter for the PP group than for the HD group (p<.001). There were no significant differences in other medication costs. Nor were there any significant differences between treatments in total inpatient and outpatient, mental health and medical health services use or related service costs (excluding medications)(Table 1). Total health service costs including medications (Table 1, Figure 2) were $2,100 greater per quarter for the PP group than for the HD group (p<.001).

Cost-Effectiveness/Net Health Benefits—Dividing incremental costs by incremental benefits in the bootstrap analysis generated an incremental cost effectiveness ratio of $508,241/QALY (95% CI=$122,390–$1,582,711) for PP as compared to HD (Figure 3) with 98% of observations falling the upper right quadrant of the cost-effectiveness plane, indicating greater benefits for PP as well as greater costs.

Analysis of net health benefits expressed in dollars at each estimated value of a QALY showed HD to have a 0.95 probability of being more cost-effective than PP at QALY values less than $150,000 and 0.81 of being more cost-effective if QALYs are valued at $300,000 (Figure 4). The probability that HD is more cost-effective than PP declines steadily at values of a QALY greater than $300,000 (Figure 4), and is only 0.50 at $500,000 per QALY and . 44 at $600,000.

Discussion

This study found that, using a disease-specific method to calculate health states measured in QALYs for people diagnosed with schizophrenia, treatment with PP resulted in a statistically significant but small advantage in health status. However, because PP remains on-patent and has relatively high acquisition costs, it is not a cost-effective treatment choice under a wide range of estimates of the monetary value of a QALY. This was true even though we used the lowest available estimate for the cost of the drug. For example, 117 mg of LAI PP is priced at $758 on the Federal Supply Schedule used here, while the published average wholesale price was $889 (See website: http://pharmacyservices.utah.edu/bulletins/NDB_214.pdf. Accessed July 16, 2015) and on-line retail prices for the same dose range from $1,023 to $1,106 (See website: http://www.goodrx.com/paliperidone-palmitate#/?filterlocation=&coords=&label=Invega+Sustenna&form=syringe&strength=0.75ml+of+117mg&quantity=1.0&qty-custom= Accessed on July 16, 2015). Our findings thus would be sustained under a wide range of 2015 prices for PP although prices are likely to drop when generic versions of the drug appear after patent protection runs out in 2017.

Many studies of newer second generation antipsychotics end up with ambiguous findings showing that while some side effects are less severe with newtreatments, others are more severe. The QALY measure used in this study (13) provides a rational approach to combining data on symptoms and major side effects in a single measure. In addition, selective inclusion only of individuals judged by their clinicians to be likely to benefit from LAI treatment, and therefore most like patients prescribed LAI treatments in real-world practice, enhances the study's external validity.

There has been controversy about what monetary value should be assigned to a QALY in cost-benefit analysis. On the one hand some governments have long used a value of $50,000 as the appropriate value of a QALY for policy making (22). However, this estimate was first established in 1982 (20), and, with adjustment for inflation alone its value would have reached $117,000 by 2011 when the present study was initiated. A more recent valuation based on an empirical estimate of the cost-effectiveness of treatments available in 2003 as contrasted with care available in 1950, and on the implicit cost-effectiveness of unsubsidized insurance as compared to self-pay care, suggest a range from $183,000–$264,000 per QALY. While HD was clearly more likely to be cost-effective than PP at a QALY valuation of $50,000 (with .998 probability) and at an inflation-adjusted valuation of $117,000 (.985 probability) it also had a .94 probability of being more cost-effective at $200,000/QALY (the lower bound of the Braithwaite et al estimate) and 0.81 at $300,000/QALY (above the upper bound estimate of Braithwaite et al.). The probability that HD was more cost-effective than PP only declined at values of $500,000 and $600,000/QALY, far higher than currently

accepted values. Thus HD is substantially more likely to be cost-effective than PP at a broad range of estimates of the value of a QALY as well as of the cost of PP.

The results of this study are consistent with the one other RCT-based cost-effectiveness study of a LAI second generation antipsychotic which found no significantly greater benefit for LAI risperidone on multiple measures (8) in comparison with doctor's choice of oral medication, but did find more neurological side effects for the LAI treatment and significantly increased drug costs, although the difference in total health care cost, while 7% greater, was not statistically significant (23).

While several RCTs have found no benefit of LAI second generation antipsychotics as compared to oral antipsychotics (24–27) two studies found positive benefits for LAI risperidone (9, 28) and a recent publication found robust benefits for LAI risperidone as compared to oral risperidone in patients experiencing their first episode of psychosis (10). While evidence of the superiority of second generation antipsychotic LAIs to oral medications is mixed, the use of LAIs is still supported by systematic reviews (29, 30) and expert panels (31) but the current study is the only RCT to compare the cost-effectiveness of first and second generation LAIs.

As several newer LAI antipsychotics are now on the market in the US with high on-patent acquisition costs, expenditures on these drugs may rise rapidly. The results of this study should encourage consideration of older, less expensive drugs such as haloperidol decanoate. Used at moderate dosages in this study, HD's overall effectiveness and tolerability were only slightly worse, as reported here, to that of PP, and it had clear advantages in cost-effectiveness. When generic versions of the newer LAIs become available, the cost-effectiveness calculations will undoubtedly change. In the meantime, HD appears from trial evidence to be a cost-effective choice. A rational policy might limit use of the more expensive LAIs among patients with chronic schizophrenia to those who do not benefit from or cannot tolerate HD.

Limitations

Several methodological limitations require comment. The available QALY algorithm has not been validated beyond the initial studies and it must be acknowledged that people with serious mental illness may have difficulty responding to standard gamble choices, even when they are presented using simplified graphic displays. In addition, although the QALY responses were weighted using socio-demographic characteristics of the US population, QALY values may vary by unmeasured respondent characteristics. Imperfect as this measure may be, the results are consistent with those observed on individual measures in the original publication from this study (11) and provide a rational empirical basis for assigning monetary values to health states.

Second, utilization data were based on patient self-report estimations of service use and published estimations of unit costs (i.e. not actual unit costs or verified service use) and there were substantial missing data from the study. If, as might be expected due to memory lapses, respondents underestimated their service use, actual group differences could have been underestimated as well. Missing data was addressed with mixed models using all

available data and study drop out rates were similar to those in the NIMH CATIE study (5, 32) and others, (32) but recall biases can not be ruled out. In spite of these limitations the findings of this study appear to be robust to a number of sensitivity analyses representing alternative assumptions and methods of analysis.

Conclusion

HD was more cost-effective than PP suggesting that PP's slightly greater benefits do not justify its markedly higher on-patent costs.

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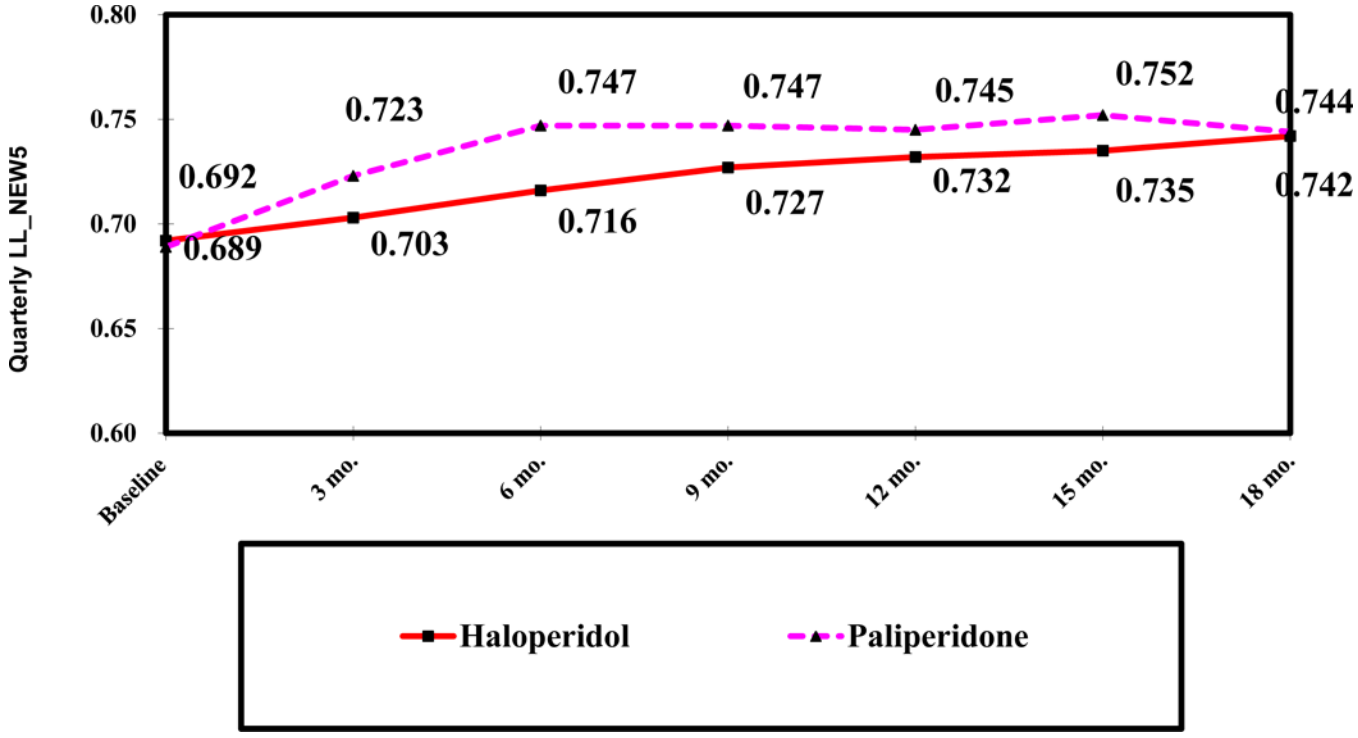

Figure 1.

Comparison of PP and HD on Quality Adjusted Life Years (QALYs)*

* Average difference = +.0297 favoring paliperidone (p<.03)

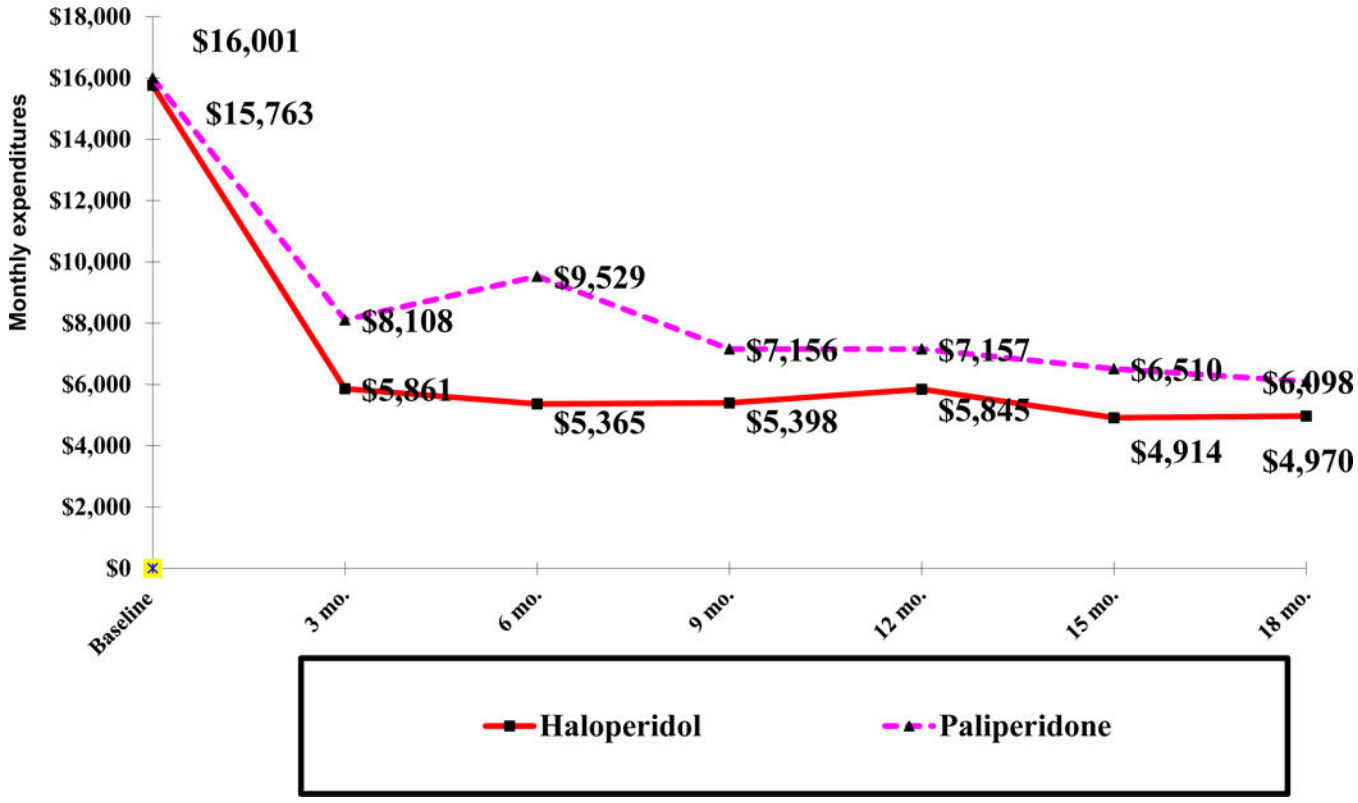

Figure 2.
Quarterly total outpatient, inpatient and drug costs (p<.003)

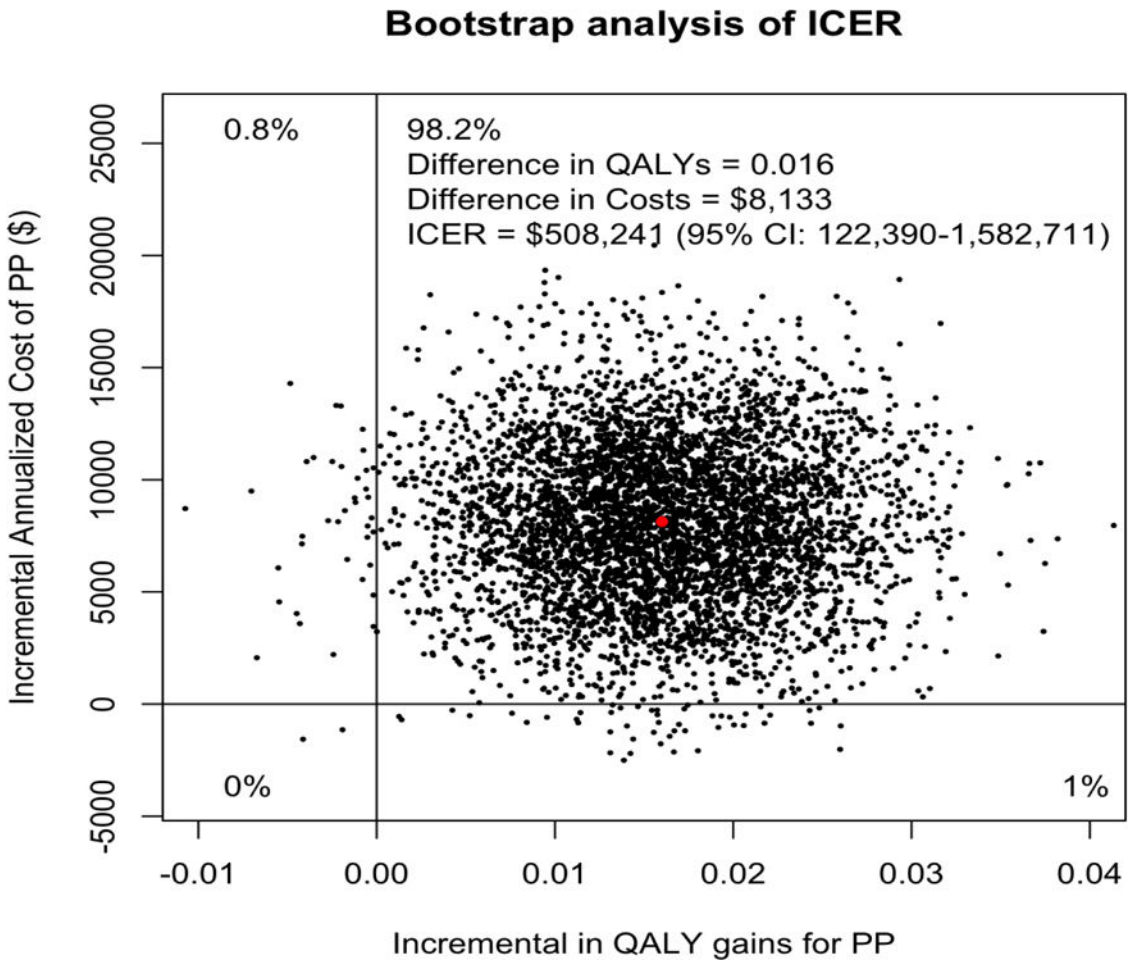

Figure 3.
Bootstrap analysis of the incremental cost effectiveness ratio (ICER): PP vs. HD

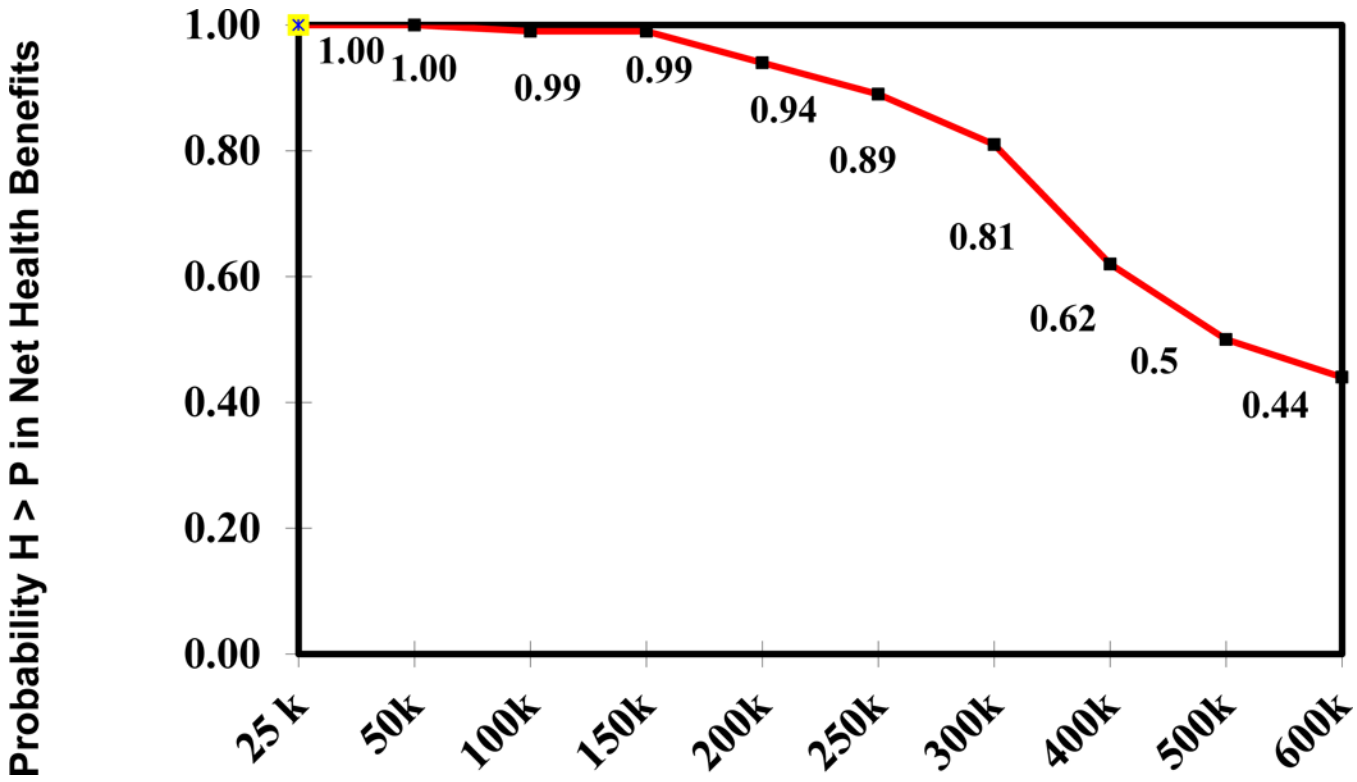

Figure 4.
Cost Effectiveness Acceptability Curve (HD>PP)

Table 1

Average quarterly service use and cost over 18 months: Paloperidone LAI vs Haloperidol LAI([1]).

	Paloperidol		Haloperidol		Difference		Z	p
	Mean	**se**	**Mean**	**se**	**Mean**	**se**		
Service Use (in inpatient or residential days per quarter or outpatient visits per quarter)								
Inpatient/residential days	4.98	.63	4.99	.63	−.01	.98	.54	.59
Mental Health Inpatient Days	.19	.04	0.26	.06	−.07	.15	.64	.52
Residential/Nursing Home Days	4.53	.64	4.69	.6	−.16	.93	.94	.35
Medical Surgical Inpatient Days	.09	.03	.07	.03	.02	.09	1.5	.13
Outpatient visits	4.0	.39	4.4	.46	−.4	.99	.41	.68
Emergency Department Visits	.1	.03	.06	.008	.04	.02	1.4	.16
Mental Health Outpatient Visits	3.48	.37	3.89	.43	−.41	.93	.72	.47
Medical Surgical Outpatient	.42	.04	0.45	.06	−.03	.11	.21	.84
Costs (quarterly costs for each service category)								
Total Service Costs (excluding medications)	$3,654	488	$3,754	428	−$100	1081	.38	.7
Inpatient/residential treatment costs	$2,367	452	$2,316	349	$51	1023	.47	.64
All Mental Health and Medical Surgical Inpatient Costs	$1,441	365	$1,470	299	−$29	956	.31	.76
Residential and Nursing Home Costs	$877	127	$860	114	$17	166	1.09	.27
Outpatient Service Costs	$1,315	138	$1,413	150	−$98	297	.15	.88
Emergency Department Costs	$40	9.6	$25	3.1	$15	9	1.44	.15
Medical Surgical Outpatient Costs	$120	12	$130	16	−$10	29	.21	.84
Mental Health Outpatient Costs	$1,157	134	$1,264	144	−$107	287	.16	.87
Total Medication Costs	$3,770	135	$1,653	112	$2,117	173	17	p<.001
Study Medication	$2,275	116	$62	3.6	$2,213	105	26.7	p<.001
Other Psychotropic medications	$591	55	$572	58	$19	70	1.26	.21
Non-Psychotropic Drugs	$934	49	$1,027	79	−$93	107	.47	.64
Total Costs (Services plus medications)	$7,545	521	$5,445	484	$2,100	1098	2.94	.003

[1]Mixed model comparison across all time points adjusting for the baseline value of the dependent variable and the interaction of time by the baseline value of the dependent variable. Subordinate categories do not add exactly to superordinate categories because of model adjustment.