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Cost analysis of risperidone long-acting injection in the treatment of schizophrenia and schizoaffective disorders in Hong Kong: An approach using generalised estimating equations

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ABSTRACT

Schizophrenia is one of the most expensive psychiatric illnesses. This study compared retrospectively health-care resources consumed 12 months before and 24 months after risperidone long-acting injection (RLAI) treatment in Hong Kong. A mirror-image analysis was conducted using data ($N = 191$) from three public hospitals in Hong Kong from 2003 to 2007. The main outcome measure was hospitalisation cost. Other secondary outcomes such as hospitalisation episodes, outpatient visits and adverse events were also compared. A predictive model was established using linear regression based on generalised estimating equations. Analysis showed that RLAI was associated with a reduction in hospitalisation cost by HK\$10,001,390 (24.7%) (HK\$40,418,694 vs. HK\$30,417,303; P-value < 0.05). Days of hospitalisation were reduced by 1538 days (10.1%) (15,271 vs. 13,733; P-value < 0.05). The predictive model estimated that the hospitalisation cost of patients using RLAI was only 11.1% (3.1–3.93%, 95% confidence interval (CI)) compared to those receiving conventional antipsychotics combined with oral risperidone. Cost of hospitalisation was significantly reduced after RLAI therapy. However, results should be considered as indicative or suggestive only, due to potential channelling bias where certain drug regimens are preferentially prescribed to patients with particular conditions. The findings from our study may be useful in health-care decision making considering treatment options for schizophrenia in resource-limited settings.

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1. Background

Schizophrenia is known to be one of the most expensive psychiatric illnesses to treat due to the associated indirect and direct costs arising from the management of the disorder (Andreasen, 1991; Glazer and Johnstone, 1997). It is a devastating mental illness that causes substantial medical, social, psychological and financial burdens on patients, their families and the community. It can result in significant costs amounting to as much as 3% of the total health-care expenditure (Knapp, 2000). The major reasons are the poor potency and adverse effects of old antipsychotic agents leading to poor compliance and therefore higher frequency of relapses (Gitlin et al., 2001).

Prior to the advent of atypical antipsychotics, conventional antipsychotic drugs such as haloperidol were used to treat this condition. However, suboptimal therapeutic efficacy and low rate of compliance were the major problems leading to relapses. Aside from this, use of these agents is also associated with an increased frequency of adverse reactions, the most disabling and disturbing of which is the occurrence of extrapyramidal symptoms (National Institute for Health and Clinical Excellence, 2011). Studies were conducted to estimate the medication compliance of patients with psychosis (Cramer and Rosenheck, 1998). It was estimated that patients taking antipsychotics only took an average of 58% of the recommended medications. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study initiated by the National Institute of Mental Health (NIMH) where a total of 1493 patients with schizophrenia were recruited and randomly assigned to receive different antipsychotic drugs, approximately 74% of patients overall discontinued the study medications before 18 months (Lieberman et al., 2005). Another study showed that the

oral route of administration can result in a higher risk of relapse than depot injections (Schooler, 2003). All the above studies have indicated a need for new pharmacotherapies which could improve patients′ compliance. Conventional antipsychotics such as haloperidol nevertheless are however still used as the first-line therapy in some jurisdictions, presumably due mainly to cost considerations.

In recent years, the presence of newer and more potent second-generation antipsychotics such as risperidone offers an alternative to the management of this illness. Their efficacy, tolerability and safety in the management of schizophrenia and other schizoaffective disorders have already been established in previous studies (Csernansky et al., 2002; Leucht et al., 2003). In addition, a study also showed that long-acting formulations of antipsychotics can offer assured delivery of medication and therefore can potentially enhance patients′ compliance, protect vulnerable patients against therapeutic lapses and hence lead to overall savings in the long run (Haycox, 2005). An earlier study also demonstrated a reduction of hospital admission by 73% and the duration of stay by 82% after patients were switched to depot injections (Denham and Adamson, 1971). The initial drug cost of such agents however seems prohibitive at the outset, thus limiting their continued use. Risperidone long-acting injection (RLAI), an atypical antipsychotic agent, has been proven to be efficacious in clinical trials (Chue et al., 2005). In a most recent observational study based on an electronic database in Australia, it was shown that RLAI had led to reduced severity in symptoms and improved mental health status using the Clinical Global Impression and the Global Assessment of Functioning (Lambert et al., 2012).

RLAI can potentially improve medication compliance compared with oral conventional antipsychotic agents and hence lead to improved treatment outcomes. In another trial, patients with psychosis treated with RLAI had maintained symptomatic control or shown improvement (Fleischhacker et al., 2003). RLAI, with these clinical benefits, hence could lead to better patient compliance with fewer relapses and hence save health-care resources in the long run. Another recent study also showed that the use of RLAI could significantly reduce the 1- and 2-year relapse rates and improve medication compliance (Lee et al., 2010). There are two recent studies in the Chinese population on RLAI. In China, a decision analytic model using a time horizon of 2 years was used to evaluate the cost-effectiveness of RLAI, olanzapine (OL) and quetiapine (QT), outcome measures being proportion of patients successfully treated and health-care costs involved. It was shown in the study that the success rate of RLAI, OL and QT was 46.7%, 39.9% and 31.3%, respectively and RLAI was proven to be more cost-effective than QT and OL (Yang et al., 2009). In Taiwan, a 1-year mirror-image study with 108 patients where each patient served as his or her own control was conducted to compare service utilisation and relapse rate of pre- and post-RLAI treatment (Chang et al., 2009). The study showed a significant reduction in re-admissions by 55%, hospital days by 48% and relapse by 54%. Current pressure on resources and, in particular, concerns on future resource implications have attracted growing attention on the role of economic evaluation of new antipsychotic drugs such as RLAI.

So far, most of the studies including those two mentioned in the previous paragraph on antipsychotic drugs were however confined to descriptive analyses. The statistical regression model applied to the mirror-image study to build a predictive model for the major outcomes such as medical cost or resource utilisation was rarely used to adjust for patients′ baseline characteristics. Due to the longitudinal nature of the mirror-image study design in which patients′ outcomes are measured repeatedly, traditional linear regression models are incapable of handling the correlated structure between repeated measurements. The generalised estimating equations (GEEs), which is a specific type of semi-parametric method, have been widely applied in the generalised linear regression model to account for longitudinal and correlated data which commonly arise in medical literature (Diggle et al. 1994; Burton et al., 1998). In this study, we attempted to use the GEE to estimate the regression coefficients of the generalised linear regression model. The GEE has the major advantage that, under mildly restricted conditions, regression coefficients estimated using the GEE method are robust even when the correlation structure of repeated measurements is unknown (Liang and Zeger, 1986). Another benefit of GEE is that standard errors of regression coefficients are accurate, which could produce a reasonable range of confidence intervals (CIs).

Currently, very few data are available in Hong Kong to substantiate the long-term cost-effectiveness of RLAI treatment. The first objective of this study was to compare the health-care utilisation and associated cost in a group of patients with schizophrenia and schizoaffective disorder before and after RLAI treatment and to build a predictive model of hospitalisation cost using the generalised linear model based on the GEE method. The second objective was to examine the pattern of resource consumption and the rate of adverse effects before and after initiation of RLA therapy.

2. Methods

We conducted a retrospective cost analysis to examine the potential benefits of RLAI in patients with schizophrenia in terms of health-care resource utilisation compared to the usual treatment options. This economic evaluation was performed from the perspective of the Government of Hong Kong.

2.1. Patients

Patients′ data were collected from three public hospitals in Hong Kong under the New Territories East Cluster of the Hong Kong Hospital Authority. Ethics approval was obtained from the Chinese University of Hong Kong ethics committee. Patients who started on antipsychotic treatment but later on switched to RLAI therapy due to adverse effects, or poor response or other reasons and remained on RLAI for a period of at least 12 months were included. Inclusion criteria included:

(1) have a diagnosis of schizophrenia or schizoaffective disorder,
(2) receive at least one dose of RLAI and 12 months of continuous monitoring record before and after the initial RLAI treatment and
(3) have complete case notes for the entire study period.

2.2. Study design

A retrospective mirror-image analysis was conducted where each patient′s data were collected for 3 years from 2003 to 2007 as shown in Fig. 1. The initial RLAI administration date served as the index date. The study period was 12 months before and 24 months after the index date. Patient′s baseline clinical data were compared to the data at the end of study. No formalised diagnostic procedures and randomisation were used in order to reflect the real-world treatment scenario.

2.3. Outcome measures

For each patient, the following baseline characteristics were recorded: sex, age, disease duration, working status, marital status, psychiatric diagnosis and previous treatment with antipsychotics. The main outcome measure used was the total cost of hospitalisation after the start of RLAI compared to the total cost of hospitalisation before the starting of RLAI treatment. Other cost variables collected were the cost of outpatient visits and the cost of an adverse event (AE). Costs of medication were used as secondary outcome measures and were also compared. The utilisation variables are number of AEs, number of outpatient clinic visits and number of hospitalisation days.

2.4. Statistical analyses

All statistical analyses were performed using STATA (StataCorp. 2007, *Stata Statistical Software: Release 10*; College Station, TX, USA: StataCorp LP). The two-tailed P-value < 0.05 was considered statistically significant. Continuous data were