ASSESSMENT OF QUALITY OF LIFE, ECONOMIC AND CLINICAL OUTCOMES AMONG PATIENTS WITH SCHIZOPHRENIA IN UNIVERSITI KEBANGSAAN MALAYSIA MEDICAL CENTRE

by

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DEDICATION

I dedicate this thesis to my children Luqman, Haziq and ‘Aina in the hope that they appreciate the commitment, courage, patience and perseverance involved in completion of this thesis and embrace these indispensable qualities in their own pursuit of knowledge.

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LIST OF ABBREVIATION

ASC-C	Approaches to Schizophrenia Communication Clinician Interview Version
CEA	Cost-effectiveness analysis
CPZeq	Chlorpromazine equivalent doses
CUA	Cost-utility analysis
CutLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CGI-SCH	Clinical Global Impressions-Schizophrenia scale
DALY	Disability-adjusted life years
EPS	Extra-pyramidal side effects
EQ-5D	EuroQoL group health-related quality of life scale
GDP	Gross domestic product per capita
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
MYR	Malaysia Ringgit
NMHR	National Mental Health Registry
QALY(s)	Quality-adjusted life year (s)
QoL	Quality of life
SQLS-R4	Schizophrenia Quality of Life Scale Revision 4
TTO	Time-trade off
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
VAS	Visual analogue scale
WHO	World Health Organization
WHO-CHOICE	World Health Organization Choosing Interventions that are Cost-Effective

LIST OF SYMBOLS

%	Percent
α	Alpha
$\|r_s\|$	Spearman rank correlations
n	Number
>	More than
<	Less than

PENILAIAN KUALITI HIDUP, EKONOMI DAN KLINIKAL DALAM KALANGAN PESAKIT SKIZOFRENIA DI PUSAT PERUBATAN UNIVERSITI KEBANGSAAN MALAYSIA

ABSTRAK

Skizofrenia merupakan penyakit mental kronik dan serius yang bermula pada awal remaja dan berterusan sepanjang hayat. Ia mendatangkan kesan ke atas aspek peribadi, sosial dan ekonomi pesakit, keluarga dan masyarakat pada amnya. Objektif kajian ini adalah bagi menentukan dan membandingkan impak kualiti hidup, ekonomi dan klinikal di kalangan pesakit skizofrenia yang menerima rawatan dengan berlainan kumpulan antipsikotik selama setahun. Kajian ini adalah kajian pengamatan dan prospektif. Pesakit dibahagikan kepada 2 kumpulan iaitu kumpulan atipikal dan tipikal antipsikotik. Pesakit dinilai pada permulaan kajian, 3, 6 dan 12 bulan. Kualiti hidup pesakit dinilai menggunakan instrumen kualiti hidup spesifik iaitu ’Schizophrenia Quality of Life Scale Revision 4’ (SQLS-R4) dan instrumen kualiti hidup generik iaitu ’EuroQoL Group EQ-5D’. Kesan klinikal dinilai menggunakan instrumen ’Clinical Global Impressions-Schizophrenia’ (CGI-SCH) untuk simptom penyakit, ’Approaches to Schizophrenia Communication Clinician Interview Version’ (ASC-C) untuk kesan sampingan antipsikotik dan rekod pengisian preskripsi untuk kepatuhan terhadap pengambilan antipsikotik. Analisis keberkesanan kos dan analisis kos utiliti dikira untuk setiap kumpulan antipsikotik. Nisbah keberkesan kos tambahan agen antipsikotik atipikal dibandingkan dengan agen antipsikotik tipikal. Terdapat 159 pesakit yang kekal dalam kajian. Pesakit dalam kumpulan antipsikotik atipikal lebih muda, kebanyakkannya bujang dan mempunyai tahap akademik yang lebih tinggi berbanding dengan pesakit dalam

kumpulan antipsikotik tipikal. ’SQLS-R4’ merupakan instrumen kualiti hidup yang sah dan konsisten (nilai ’Cronbach’s α’ adalah 0.95 untuk subskala psikososial dan 0.85 untuk subskala daya hidup; ‘item to total correlations’ dalam julat 0.45 ke 0.70). Tiada perbezaan signifikan bagi purata skor keseluruhan ’SQLS-R4’ di antara kedua-dua kumpulan. Anggaran nisbah keberkesanan kos tambahan bagi agen antipsikotik atipikal dibandingkan dengan agen antipsikotik tipikal adalah RM85, 575.44 setiap unit peningkatan skor keseluruhan ’CGI-SCH’ dan RM770 179 setiap ’QALY’ yang diperolehi. Nisbah keberkesan kos tambahan juga sensitif terhadap harga ubat antipsikotik. Tiada perbezaan dalam simptom keseluruhan penyakit di antara kedua-dua kumpulan. Keterukkan simptom menyumbang 25% kepada kualiti hidup. Kedua-dua kumpulan juga tidak berbeza dari segi kesan sampingan agen antipsikotik kecuali bagi masalah kabur penglihatan, masalah seksual dan masalah menstruasi/payudara. Pesakit dalam kumpulan ubat antipsikotik tipikal mempunyai kadar pengisian preskripsi antipsikotik yang lebih baik dan signifikan (79%) berbanding dengan pesakit dalam kumpulan ubat antipsikotik atipikal (70%). Rawatan dengan agen antipsikotik atipikal tidak menyumbang kepada perbezaan signifikan terhadap kualiti hidup, tahap simptom dan kebanyakkan kesan sampingan umum jika dibandingkan dengan agen antipsikotik tipikal. Ia juga merupakan strategi yang tidak kos efektif sekiranya tahap maksimum kesediaan untuk membayar bagi setiap ’QALY’ yang diperolehi adalah 3 kali ’Gross Domestic Product’ (GDP).

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ABSTRACT

Schizophrenia is a chronic and serious mental illness that occurs early and persists for a lifetime. It has significant personal, social & economic impact on the patients, families and society. The objective of the study was to determine and compare the impact of different types of antipsychotic maintenance treatment on humanistic, economic and clinical outcomes in routine clinical practice. The study was prospective and observational in nature. Patients were grouped into two treatment groups; atypical and typical treatment group and assessed at baseline, 3, 6 and 12 months. Health-related quality of life (HRQoL) outcomes were assessed by disease specific scale, the Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4) and generic scale, the EuroQoL Group EQ-5D. Clinical outcomes were assessed using the Clinical Global Impressions-Schizophrenia (CGI-SCH) severity scale, the Approaches to Schizophrenia Communication Clinician Interview Version (ASC-C) side-effect checklist and prescription refills for antipsychotic adherence. Cost-effectiveness analysis and cost-utility analysis were calculated for each treatment group. The incremental cost effectiveness (ICER) was determined for atypical antipsychotic relative to typical antipsychotic drug. There were 159 patients who completed the study. Patients on atypical antipsychotic treatment were younger, mainly single and tend to have higher academic qualifications than patients on typical antipsychotics. The SQLS-R4 was a valid and reliable HRQoL scale (Cronbach's α = 0.95 and 0.85 for psychosocial and vitality subscale, respectively;

item to total correlations ranged from 0.45 to 0.7). There was no significant difference in the mean SQLS-R4 overall scores between the treatment groups. The estimated adjusted ICER for atypical antipsychotics relative to typical antipsychotics was MYR85 575.44 per unit improved in CGI-SCH overall score and MYR770 179 per QALY gained. The ICER was sensitive to acquisition costs of antipsychotic drugs. Overall symptom severity was not significantly different between the 2 treatment groups. It contributed to 25% variation in the mean SQLS-R4 overall scores. There were no significant differences in side-effects between atypical and typical treatment groups except for blurred vision, sexual difficulties and menstrual irregularities/breast problem. Patients in the typical antipsychotic treatment group had significantly higher antipsychotic refills (79%) compared to atypical treatment group (70%). Treatment with atypical antipsychotics did not result in significant difference in HRQoL, symptom severity and most common-side effects compared to treatment with typical antipsychotics. It was not a cost-effective strategy than typical antipsychotic if the maximum willingness to pay for a QALY gained is 3 times the Gross Domestic Product (GDP).

CHAPTER 1

GENERAL INTRODUCTION

1.1 Epidemiology and Consequences of Schizophrenia

Schizophrenia is one of the most severe and disabling mental disorder that typically occurs in early adulthood and normally persists for a lifetime affecting patients' quality of life and imposes immense burden on the society (Voruganti et al., 2000a). The condition is characterized by a varied symptom dimensions that includes positive symptoms (hallucinations, delusions), negative symptoms (flat affect, poverty of speech, decreased motivation, emotional and social withdrawal), disorganized symptoms (inappropriate affect, disorganized speech and behaviour), mood symptoms as well as various neurocognitive deficits (Awad et al., 1997a). There is wide variability in the course of schizophrenia, but generally its course is long-term following a mixed pattern of acute episodes of psychotic aggravations and periods of relatively well-balanced condition (Tunis et al., 2004). Absolute recovery from schizophrenia is infrequent. However, with advanced pharmacotherapy and appropriate psychosocial care nearly fifty percent of the patients initially diagnosed with schizophrenia would supposedly attained sustained remission from the illness (World Health Organization, 2001a).

The incidence of schizophrenia worldwide is comparatively low (15.2 per 100,000 adults per year), but its prevalence is quite substantial (7.2 cases per 1000 adults) owing to the chronic nature of the illness (Picchioni & Murray, 2007). It has been estimated that about 1% of the world population would be affected by schizophrenia at any time in their lifetime but the prevalence and incidence rates of

schizophrenia may vary across geographical areas (Awad & Voruganti, 2004a; McGrath et al., 2008). According to a recent analysis of three systematic reviews, the incidence rates of schizophrenia were higher in men compared to women (median ratio; 1.4: 1), among individuals who took up residence in the urban areas than those from rural or mixed urban-rural settings and among migrants versus the local residents (McGrath et al., 2008). Patients with schizophrenia also have a significantly higher mortality rate with two to threefold greater risks of death than the general public and reduced life expectancy approximately by an average of 10 years (McGrath et al., 2008; Lindstrom et al., 2007a). The illness also contributes to higher risks of comorbidity with physical illness and other psychiatric syndromes (Knapp & Kavanagh, 1997).

In Malaysia, mental disorders account for 8.6% of the total disease burden and schizophrenia was the fourth highest burden among mental disorders (Chee, 2009). The National Mental Health Registry (NMHR) was established by the Ministry of Health, Malaysia in 2003 and its initial priority was the schizophrenia registry to document the epidemiological data of schizophrenia and related psychotic disorders (Gill et al., 2005). Based on the NMHR report for the year 2003 to 2004, there were 2,467 new cases of schizophrenia registered in Malaysia with the majority being male (65%) and the ethnic composition of the cases reflected those of Malaysian population with Malays constitute the majority of the cases (53%) followed by patients of Chinese and Indian ethnicity; 27% and 9%, respectively (Gill et al., 2005). Most patients were also unmarried and without a job.

The personal, social and economic impact of schizophrenia upon patients, families and the common public are enormous (Voruganti et al., 2000a). Schizophrenia is among the top contributors to the global burden of disease and has

been estimated to account for 1.1% of the total disability-adjusted life years (DALY) lost due to all diseases and injuries and 2.8% of years of life lost due to disability (YLD) worldwide (Picchioni & Murray, 2007). Schizophrenia causes sufferings, disabilities and unfavourably affects quality of life in many areas of patient's life functioning including physical and cognitive functioning as well as the ability to care for one self, maintain usual daily life activities, interact with others, establish relationships and acquire permanent employment (Knapp & Kavanagh, 1997). Families of the affected individuals also suffer a significant amount of distress in coping with their behaviours and burden in terms of productivity and time losses, and money spent on patient care (Essock et al., 2002). Additionally, it imposed costs on the society in terms of direct costs which involves monetary expenditure for therapy as well as indirect costs associated with lost productivity due to patient morbidity and mortality (Shaw, 2002).

Schizophrenia is a relatively expensive illness to treat. The lifetime prevalence of schizophrenia across populations is about 1.0%, but the resources utilized constitute 1.5 to 3.0% of the total healthcare budget (Geitona et al., 2008). As the condition occurs early in life and follows a chronic course, costs continued to be incurred for a long time leading to accumulation of direct costs from treatment and support, indirect costs of lost productivity and intangible costs of pain and sufferings due to reduced quality of life (Procyshyn et al., 2000). The direct costs of schizophrenia contributed 30-50% to overall costs with hospitalization accounting for a significant portion of direct medical costs (Rey, 2002). Indirect costs are difficult to quantify and often omitted from pharmacoeconomic analyses. Nonetheless, according to the latest studies the amount of indirect cost of schizophrenia is greater than the direct cost (Shaw, 2002). For instance, the

estimated total cost of treating schizophrenia in the United States for the year 1991 was US$65.2 billion of which 70% of costs were attributed to indirect costs (Hudson et al., 2003).

1.2 Treatment of Schizophrenia

The current modality of schizophrenia treatment involves a variety of interventions including pharmacological approach, rehabilitation and psychosocial therapy (Awad & Voruganti, 2004a). Drug treatment with antipsychotic medication however, is the principal component of clinical management of schizophrenia providing effective symptom control in acute and chronic phases of the disease (Lublin et al., 2004). Previously, the treatment of schizophrenia was non-specific and mainly physical which comprised social isolation, physical restraints, insulin coma and electroconvulsive therapy as well as a variety of occupational therapies involving agricultural work (Logan & Finley 1999; Deva, 2004). On the other hand, drug-based treatment like chloral hydrate or paraldehyde provides no antipsychotic effect but merely used to sedate and contain patients (Cancro, 2000).

The serendipitous discovery of the first antipsychotic, chlorpromazine by the French anaesthesiologist and surgeon, Henri Leborit in the 1950s was a major landmark in the contemporary treatment of patients with schizophrenia and other psychotic disorders (Edlinger et al., 2005). Chlorpromazine not only reduces agitation and controls the overt positive symptoms of schizophrenia; it also facilitates the release of patients from the asylums enabling them to function fairly well in the society (Sawa & Snyder, 2002). In the next forty years, subsequent antipsychotic medications of similar dopamine D2-receptor-blocking activities as chlorpromazine like haloperidol and perphenazine were developed and collectively

termed ‘neuroleptics’ or currently known as typical antipsychotic drugs due to linkage of its antipsychotic action and extrapyramidal symptoms (EPS) (Lauriello & Bustillo, 2001). During that period of antipsychotic development, it was hypothesized that the event of EPS was crucial to achieving the therapeutic antipsychotic effects (Weiden, 2007).

However, many patients approximately up to 60% of those treated had to endure disabling and upsetting acute extra-pyramidal side effects (EPS) including dystonic reactions (sudden onset of sustained intense muscle contraction), Parkinsonian-type symptoms, akathisia (restlessness) and at least 5% of the patients were inflicted by late-emerging tardive dyskinesia (irregular twisting or writhing movements), the most severe motor side-effects (Walker et al., 2004). The typical antipsychotics also do not relieve all symptoms, with their therapeutic properties confined mainly to the positive manifestations of the disease while being far less effective towards negative and neurocognitive symptoms (Lublin et al., 2005). Close to 60% of patients undergoing treatment with typical antipsychotics achieve full or partial remission of the positive symptoms, no less than 40% have unremitting or residual symptoms and further 20-30% of patients respond insufficiently to the medication with 15-20% relapsing each year (Singh, 2005; Gee et al., 2003).

The hypothesis that EPS was indispensable side effects of antipsychotics was re-considered when clozapine was found to have antipsychotic efficacy but negligible extra-pyramidal effects (Weiden, 2007). Clozapine was initially introduced to the European market in the 1960s but was soon withdrawn from sale following reports of rare but potentially fatal incidents of agranulocytosis (Shen, 1999). It re-emerged in the 1980s following a landmark study that provided evidence of its superior efficacy and reduced EPS against chlorpromazine, steering

the development of successive antipsychotics that have similar benefits but without the risk of agranulocytosis and EPS (Remington, 2003).

The grouping of antipsychotic medication into 'typical' or 'atypical' to a certain extent is based on their in vivo occupancy of different receptors and the term 'atypical' commonly refers to a new class of antipsychotic medication that has a lower risk of inducing severe neurological side effects known as "extrapyramidal symptoms" (Lauriello & Bustillo, 2001). Clozapine and subsequent antipsychotics including risperidone, olanzapine, quetiapine and aripiprazole were referred as 'atypical antipsychotics' as they have different pharmacological profile from the traditional antipsychotics with mostly have relatively lower affinity for dopamine D2 receptors and higher affinity for other neuroreceptors including serotonin 5-HT2 receptors that may explained for their enhanced efficacy and reduced tendency for EPS (Miyamoto et al., 2005).

Currently, in many developed nations, atypical antipsychotics other than clozapine have become the drug of choice for the treatment of schizophrenia and related disorders (Barbui et al., 2005). Clozapine on the other hand, is generally reserved for treatment-refractory patients because of its potential risk of agranulocytosis (Walker et al., 2004). Atypical antipsychotics are generally as efficacious as typical antipsychotics in reducing positive symptoms but less likely to cause extrapyramidal side-effects (Chue, 2006). In numerous studies, these newer generation of antipsychotics have also demonstrated a trend of superior efficacy in the management of a broader range of symptoms including negative, cognitive and affective symptoms (Lambert & Naber, 2004). Additionally, in a few studies involving limited number of atypical antipsychotics like clozapine, risperidone and

olanzapine, there is a tendency for patients to display improvement in quality of life (Awad, 2004a).

However, the typical antipsychotics are still the prevalent medications prescribed for the treatment of schizophrenia in many low and middle-income countries (Choong et al., 2004). For instance, according to the Malaysian National Mental Health Registry (NMHR) report 2003-2004, a mere 13.3% of schizophrenia patients were prescribed with atypical antipsychotics while the majority were treated with typical antipsychotics (Gill et al., 2005). Compared to their predecessors, atypical antipsychotics have higher acquisition costs wherein the price of a unit dose of atypical antipsychotics reaching 10-25 fold higher than those of conventional antipsychotics (Tandon, 2006). Moreover, particularly for less developed countries, the price of antipsychotic is influenced by the currency exchange rates and market forces. These partially explained the astounding 61.8 % of the overall direct costs spent on medications in a study in Nigeria compared to a lower proportion of 1.1% to 9% paid by the high income countries (Knapp et al., 2004). Under consumption of more expensive antipsychotics in these countries is also limited by the low provision of resources for mental health services as well as out-of pocket payments by individuals (Dixon et al., 2006). In Malaysia, only 3% of the yearly health budget was provided for the expenditures of mental health including the acquisition of antipsychotic medications (Chee, 2009).

Varying use of atypical antipsychotics among the nations is also affected by the uncertainties of whether the benefits of these medications are worth their additional costs (Haro et al., 2003a). Although there have been claims that atypical antipsychotics generate better health benefits which compensate for their higher acquisitions costs, there is no clear evidence to support that atypical antipsychotics

are more cost-effective than the typical antipsychotics (Polsky et al., 2006). Moreover, at least a number of atypical antipsychotics are associated with significantly greater risk for metabolic side-effects including weight gain, impaired glucose regulation, diabetes mellitus and dyslipidemia which have implications to treatment outcomes and costs (De Hert et al., 2006). Advantages of atypical antipsychotics on other outcomes like cognition, affect and quality of life also have not been extensively investigated and thus far their therapeutic benefits have been considered as modest and not substantial (Miyamoto et al., 2005).

1.3 Quality of Life and Antipsychotic Medications

An array of outcome measures have been utilised to examine the health outcomes of schizophrenia or compare pharmaceutical treatment alternatives (Burns, 2007). The Economic, Clinical and Humanistic Outcomes (ECHO) model has been proposed to describe health outcomes along three aspects; clinical consequences of medical intervention or illness such as symptom outcomes, economic impact regarding the amount spent or value for money associated with an intervention and humanistic outcomes like quality of life or functional status that captures the impact of disease or treatment on patient's daily living (Mahmoud et al., 2002).

Over the past twenty years, there has been a rise in the investigation of quality of life (QoL) in general medicine, mainly in chronic disabling disorders (McKenna, 1997). Heightened interest in the QoL concept symbolizes the expansion of therapeutic outcome criteria that extends beyond traditional, physiological or biological measures. Furthermore, it reflects the modern image of health viewed from a bio-psychosocial standpoint that emphasizes on the patient's subjective perspective of the disease or medical interventions (Naber et al., 2002). Nonetheless,

there is no universal definition of QoL while various terms such as ‘life satisfaction’, ‘health status’, ‘functional status’ and ‘well being’ have been equated to it (Chan & Yu, 2004). The term ‘health-related quality of life’ (HRQoL) has been coined by researchers in the medical discipline to differentiate their area of research from the global concept of quality of life those of other field like social science (Bungay et al., 2005). While quality of life refers to an evaluation of every components of a person’s life, HRQoL includes aspects of life that are exclusively related to personal health and activities performed to maintain or improve health (Bungay et al., 2005).

Research in the HRQoL in schizophrenia commenced with growing concerns about the predicament of the chronically mentally ill patients living among the society following the deinstitutionalization movement in the USA in the 1970s (Revicki et al., 1999). Interest in the HRQoL assessment in schizophrenia declined thereafter as research was restricted by certain factors like lack of clarity on the conceptual models, scarcity of standardized measures for schizophrenia and qualms regarding the reliability of self-report in patients with schizophrenia (Gee et al., 2003). The rapid development of new antipsychotic medications and the need to verify their therapeutic superiority in compensation for their relatively expensive acquisition costs has encouraged further interest in the use of HRQoL as an outcome measure in clinical trials (Awad et al., 1997a). Atypical antipsychotic medications collectively display greater efficacy in treating negative symptoms and cause fewer extrapyramidal effects which led to assumptions that these characteristics would translate into favourable HRQoL in patients (Montes et al., 2003).

There is no general consensus about the constituents of HRQoL, but many agreed that it is a multidimensional construct and mainly include the dimensions of physical functioning, social functioning, role functioning, mental health and general

health perceptions (Murdaugh, 1997). A few conceptual models of the interactions among the components of HRQoL in schizophrenia have been considered including the 'clinical model', the 'mediation model' and the 'distress-protection model' (Ristner et al., 2004a). Basic 'clinical model' by *Awad et al.* (1997b) defined HRQoL as one's perception of the outcome interaction between symptoms, side-effects, subjective responses to antipyschotics and psychosocial performances. On the other hand, 'mediation model' by Zissi et al. (1998) emphasized the significance of psychological processes in the HRQoL construct while 'distress/protective model' by Ritsner et al. (2002) postulated that HRQoL is an outcome of the interaction of an array of distress/clinical factors and protective factors in which HRQoL lessens if distress/clinical factors outweighed protective factors and vice versa (Ritsner et al., 2004a).

Numerous HRQoL scales has been utilised in research involving schizophrenia patients. In general, these instruments are categorised as generic or disease-specific and available as self-rated or clinician-rated scale (Awad et al., 1997a). Generic measures provide broader information on all aspects of life and permit comparisons with other diseases which are useful in facilitating health policy decisions and economic evaluations of medications and treatments (Konig et al., 2007). Alternatively, disease-specific HRQoL instruments have the potential of being sensitive to changes to treatment effects (Karow et al., 2005). There is no consensus on the best scale to assess HRQoL in patients with schizophrenia (Karow et al., 2005a). The instrument of choice for HRQoL measurement depends on the purpose of its assessment (Bobes et al., 2005). As the generic and disease-specific instruments are deemed complementary, the use of both measures is recommended whenever practical (Konig et al., 2007). Health-related quality of life instrument for

patients with schizophrenia should also incorporate life domains highly relevant to those inflicted with the disease generated via in-depth qualitative interviews with the patients (McKenna, 1997).

Schizophrenia specific questionnaires like the Heinrichs-Carpenter Quality of Life Scale (QLS), the Drug Attitude Inventory (DAI) and the Subjective Well-being under Neuroleptics (SWN-K) have been used to evaluate the effectiveness of antipsychotic medications on HRQoL, but the predominantly used scale is the QLS (Karow & Naber, 2002). Although it has historical values, the QLS is a clinician-based measure that does not include the patients' view of their quality of life and primarily designed to address negative symptoms in schizophrenia (Bobes et al., 2005). Alternatively, the Schizophrenia Quality of Life Scale (SQLS) is a self-report measure, developed by Wilkinson et al., (2000) with contents that are highly relevant to people with schizophrenia derived from in-depth interviews with schizophrenic patients. The Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4) has been translated into 52 languages including the Malay language through standardized procedures and has been validated in several East Asian countries including Japan, Korea and Taiwan (Kaneda et al., 2002; Kim et al., 2006; Kuo et al., 2007). Testing of internal consistency and construct validity has also demonstrated that SQLS-R4 is a simple and reliable scale for measuring quality of life in patients with schizophrenia (Kaneda et al., 2002; Kim et al., 2006).

A few generic instruments such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), the World Heath Organization Quality of Life Instrument (WHOQOL) and the EuroQoL Group EQ-5D have been validated in patients with schizophrenia (Bobes et al., 2005). The EQ-5D is a self-administered, straightforward and short HRQoL that could be used to describe health profile, but

also preference-based valuation of HRQoL as weights for quality-adjusted life years (QALYs) in cost-utility analysis (Konig et al., 2007). It is the instrument of choice for the calculation of QALYs and has been validly translated into no less than 30 languages including the Malay language (Konig et al., 2007). The EQ-5D has been used in population health surveys in numerous medical disorders and economic evaluation of drug or health-care interventions for a specific health condition (Willige et al., 2005).

Studies on the effects of antipsychotics on HRQoL in schizophrenia patients have generated contradictory findings. Favourable HRQoL for patients treated with atypical antipsychotics against typical antipsychotics have been documented but not consistently reproduced by other trials (Awad & Voruganti, 2004a). Although there is a likely trend for the newer generation of antipsychotics to surpass the conventional antipsychotics in improving HRQoL, comparisons across studies are complicated because different conceptual models, study designs, HRQoL instruments and time frame were applied on various clinical populations (Pinikahana et al., 2002). Moreover, not many studies include atypical antipsychotic drugs other than olanzapine, clozapine and risperidone (Awad & Voruganti, 2004a).

Socio-demographic factors and clinical conditions have also been suggested to affect HRQoL (Chan & Yu, 2004). In a few studies, young patients, married people, women and less educated individuals with schizophrenia have reported better HRQoL (Gladis et al., 1999). Alternatively, presence of intense positive and negative symptoms as well as longer duration of illness has been associated with poorer HRQoL (Chan & Yu, 2004; Konig, et al., 2007). The impact of sociodemographic and clinical factors however, varies from one study to another (Chan & Yu, 2004).

1.4 Pharmacoeconomic Evaluation of Antipsychotic Treatment

With the introduction of atypical antipsychotics into the standard practice, there is growing concern over the costs of treatment for schizophrenia (Revicki et al., 1999). Although acquisition costs of antipsychotic medications constitute a small fraction of direct treatment costs, the comparatively higher acquisition costs of atypical antipsychotics than the established therapy and its increased consumption have somewhat contributed to the rise in drug expenditure (Basu, 2004). Considering the increased use of limited health care resources, assessment of the incremental value of these novel antipsychotics is crucial for public policy decisions and other resource allocations decisions (Polsky et al., 2006). Pharmacoeconomic studies investigate the impact of different antipsychotic drugs on medical costs and health benefits providing insight in assessing the value of new antipsychotic medications and facilitating decision making for the efficient allocation of health care resources (Basu, 2004). Cost-effectiveness analysis (CEA) is the prevalent method among the several types of pharmacoeconomic analyses used in the medical literature to address such issue (Basu, 2004).

In CEA, all medical resources consumed (costs) and relevant health outcomes (consequences) are compared between different treatment alternatives to determine the average cost-effectiveness (C/E) ratio (average cost per outcome) for each treatment alternative. Incremental (ICER) ratio indicates the cost to produce a unit increase in an outcome for a new treatment relative to an existing alternative treatment (Skrepnek, 2005). Cost assessments are similar across different methods of economic analyses, but the outcome measure differs and for the CEA of antipsychotic medications, the outcome is expressed in natural units including

extrapyramidal symptom-free months, psychiatric symptoms, disability-free days and hospitalizations avoided (Polsky et al., 2006).

Given the multitude of outcome measures that were used in the cost-effectiveness studies, it is difficult to compare the efficacy of various treatments with different outcomes or measure different treatments against one another when they each perform differently with certain outcome measures (Mangalore, 2000). Considered by some as an adaptation of CEA, cost-utility analysis (CUA) was developed to address the problem of comparing treatment interventions with different health outcomes (Dernovsek et al., 2007). CUA is more appropriate when HRQoL is the important outcome, when both quantity and quality of life are affected by treatment and when interventions being compared have extensive possible health outcomes (Coons & Kaplan, 2005). In this form of economic evaluation, HRQoL outcomes are adjusted for patient preferences or utility and expressed as a single composite measure typically quality-adjusted life years (QALYs) (Proschyn et al., 2000). QALY supplies a common measure to evaluate the extent of health benefits achieved from a variety of treatments in terms of HRQoL as well as quantity of life (Neumann, 1999).

Health state preferences for the calculation of QALY may be assessed directly using a variety of techniques including standard gamble, rating scale, time-trade off or indirectly using preference-based HRQoL instruments also known as multi-attribute health status classification systems like the Quality of Well-Being Scale (QWB), the Health Utilities Index (HUI) and the EuroQol Group's EQ-5D (Coons & Kaplan, 2005). The EQ-5D is one of the commonly used instruments for assessing QALYs (Patterson et al., 1999). It provides standard HRQoL assessments and concurrently allows the assignment of patients' preferences without having

recourse directly to the standard yet complex techniques like standard gamble or time-trade off (Prieto et al., 2004).

In a recent literature review of randomized clinical trial-based cost-effectiveness studies of antipsychotics, Polsky et al. (2006) concluded that thus far there is no clear evidence to suggest that atypical antipsychotics generate cost savings or are cost-effective for schizophrenia treatment in general. These cost-effectiveness studies have limited applicability as their validity was profoundly affected by inappropriate methods of measurement, analysis and study design while only a few studies employ the cost-utility analysis approach (Polsky et al., 2006). Moreover, particularly in developing countries, there are very few economic evaluations on antipsychotic drugs to facilitate policy-makers and clinicians in the selection of the most appropriate therapy (Shah & Jenkins, 2000). Extrapolation of the economic evaluations of alternative antipsychotics in one country to another may not be feasible as differences in price levels, supply of specific services and the structure of mental health services may affect treatment effectiveness as well as service use and therefore costs (McCrone, 2007).

1.5 Clinical Outcome Domains in Schizophrenia Treatment

Symptoms of disease, treatment burden in terms of side-effects and treatment adherence are among the target outcome domains considered in the assessment of clinical effectiveness of antipsychotic medications (Naber & Vita, 2004). Positive symptoms (e.g. hallucinations, delusions) of schizophrenia were the conventional measure of effectiveness in drug investigations, but better understanding on the role of other symptom domains of negative (e.g. social withdrawal, decreased motivation), cognitive (e.g. memory impairment, attention deficits) and affective

symptoms (e.g. depression, mood swings) have positioned them as key treatment outcomes as well (Nasrallah et al., 2005). Negative, cognitive and affective symptoms have been suggested to be associated with functional outcomes of schizophrenia and their improvements were deemed important for good long-term prognosis (Naber & Vita, 2004).

In general, atypical antipsychotics were comparable to typical antipsychotics regarding their efficacies against psychotic symptoms (Lublin et al., 2005). The increasing evidence on the greater efficacy of atypical antipsychotics in the treatment of negative symptoms are limited by uncertainties of the causal relationship between atypical antipsychotics and negative symptoms as well as their modest treatment effects (Miyamoto et al., 2005). There has been a trend for atypical antipsychotics to exert improvement in cognitive functioning, but the effects of atypical antipsychotics on cognition have not been widely studied (Miyamoto et al., 2005). The Clinical Global Impression-Schizophrenia (CGI-SCH) scale; a modification of the Clinical Global Impression (CGI) scale is among the most commonly used symptom rating scales that measures various symptoms in schizophrenia and is applicable for both observational study and regular clinical practice (Mortimer & Al-Agib, 2007).

The side effects of antipsychotic medications are wide-ranging and have been associated with physical and psychological impairment in patients with schizophrenia (Ritsner et al., 2002). The presence of side effects has also been linked to reduced adherence to treatment regimens (Miyamoto et al., 2005). Atypical antipsychotics generally produce fewer extrapyramidal side-effects (EPS) than typical antipsychotics, but this newer generation of antipsychotics are associated with a different range of adverse effects including non EPS side-effects typically

weight gain, sexual difficulties, sedation and amenorrhoea (Weiden & Miller, 2001). Many scales for the assessment of antipsychotic side-effects were particularly developed to monitor EPS (for example the Barnes Akathisia Rating Scale, the Simpson-Angus Extrapyramidal Side Effects Scale and the Abnormal Involuntary Movement Scale) and their use also requires special expertise (Weiden & Miller, 2001). Alternatively, the Approaches to Schizophrenia Communication Clinician Interview Version (ASC-C) include all the common and troubling antipsychotic side-effects and check for subjective distress instead of objective severity of side-effects (Nasrallah et al., 2005).

Adherence to antipsychotic medication is pertinent to attaining effective symptom controls in schizophrenia (Dolder et al., 2002). Non-adherence to prolonged antipsychotic treatment has been linked to greater risk of relapse, frequent hospital admissions and emergency visits (Gilmer et al., 2004). In research, non-adherence to antipsychotic medications may also lessen the chance to distinguish between treatment outcomes, thus can influence the study validity by inflating the risk of false negative results (Hess et al., 2006). Since atypical antipsychotics cause minimal EPS compared to typical antipsychotics, better medication adherence behavior was anticipated among patients on atypical antipsychotics (Dolder et al., 2002). However, very few studies compared medication adherence between typical and atypical antipsychotics. Findings from these studies were also contradictory in which not all found greater medication adherence among patients receiving atypical antipsychotics (Awad, 2004).

1.6 Problem Statement

Economic evaluations of treatment interventions in mental disorders were generally limited particularly, for developing countries (WHO, 2001). In Malaysia, there is paucity of research data including economic evaluations in mental conditions necessary for policy-makers and clinicians to make informed choices (Deva, 2004). According to the Malaysian National Medicines Use Survey (NMUS) 2005, psycholeptics (a group of medications that produces calming effects on patients including antipsychotics) were among the 30 widely utilized medications, but there is inadequate information on the epidemiology and the treatment of the medical condition for which these medications are indicated (Sarojini et al., 2008).

This observational study with prospective design will examine and compare the effectiveness, cost-effectiveness and cost-utility of typical and atypical antipsychotic drugs in schizophrenia patients receiving outpatient treatment in a teaching hospital in Kuala Lumpur, Malaysia. This research will obtain data on the outcomes of different types of antipsychotics in terms of clinical effectiveness, HRQoL and economic consequences by cost-effectiveness and cost-utility analyses to determine the relative benefits of atypical antipsychotics in regular clinical practice to facilitate clinical decision makings and prudent allocations of scarce healthcare resources (Basu, 2004).

1.7 Purpose Statement

The purpose of this study was to determine whether there is a significant difference between schizophrenia outpatients undergoing treatment with typical antipsychotics and those on treatment with atypical antipsychotic adjusted for any difference in demographics, illness and treatment related factors in the areas of:

(i) HRQoL scores as measured by the disease-specific Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4),

(ii) HRQoL scores as measured by generic instrument, the EQ-5D,

(iii) Cost-effectiveness from a societal perspective,

(iv) Cost-utility from a societal perspective,

(v) Clinical outcomes in terms of symptom severity as measured by the Clinical Global Impressions-Schizophrenia (CGI-SCH) severity scale, side-effects as measured by the Approaches to Schizophrenia Communication Clinician Interview Version (ASC-C) side-effect checklist and antipsychotic adherence as measured by prescription refills.

(vi) The study also intended to examine the relationships between HRQoL and clinical outcomes of symptom severity, side-effects and treatment adherence.

1.8 Rationale of Study

The concept of 'health' has been historically viewed as freedom from disease. However, in 1948 its meaning was expanded by the World Health Organization (WHO) to include complete physical, mental and social well-being (Bungay et al., 2005). Over the past two decades the therapeutic goal for many chronic and disabling medical conditions like diabetes and arthritis has been broadened to include maintaining or restoring quality life. Likewise in psychiatry,

the concept of outcome has been extended beyond symptom improvement to incorporate HRQoL, an important measure of therapeutic effectiveness and thus has become an important element in the economic evaluations (Bobes et al., 2005).

In schizophrenia, antipsychotics are significant contributors to HRQoL. A study on clinically stabilized schizophrenic patients demonstrated that 50% of the variance in patient ratings of HRQoL was explained by severity of clinical symptoms and subjective distress by adverse effects of antipsychotics such as akathasia and neuroleptic dysphoria (Revicki et al., 1999). Hence with the introduction of new antipsychotics, there is a need to evaluate the impact of different antipsychotics on HRQoL.

Schizophrenia also imposes a great economic burden on society as a result of its prevalence, early onset and chronicity (Procyshyn et al., 2000). In a recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in the United States, much of the costs of treatment of chronic schizophrenia are driven by the costs of drugs (Freedman et al., 2006). Thus cost-outcome evaluations are particularly important as they allow comparisons of the potential costs and consequences of various treatments to allow judicious use of scarce resources (Shah & Jenkins, 2000).

Cost-utility analysis is based on values that people place on different health outcomes and captures in single measure, improvements in HRQoL and increases in life expectancy. It is the most informative type of economic analysis that provides the necessary data for comparing alternative medical treatments within and across different disease categories. It is also the approach to economic evaluation recommended by the Panel on Cost-Effectiveness in Health and Medicine of the United States Public Health Service (USPHS), the committee which provide

recommendations for conducting standard cost-effectiveness studies (Singh et al., 2001, Coons & Kaplan, 2005).

Most HRQoL outcome studies of antipsychotic drugs have been performed on Caucasian populations and their application to Asian community may be limited as subjective HRQoL are influenced by the cultural background of individuals (Kongsakon et al., 2006). Very few studies have explored the efficacy of antipsychotic medications using utility or preference based measures of HRQoL (Patterson et al., 1999). Economic studies in psychiatric conditions were rare in developing countries and the very few available studies were mainly cost-of-illness and cost-effectiveness studies (Shah & Jenkins, 2000). The application of economic analysis from one country to another is not always possible considering that many factors including local health and social service characteristics, culture, family lifestyles, religion, stigma attached to mental illness, local demography and local epidemiology of mental disorders may affect the use and efficacy of any new interventions (Shah & Jenkins, 2000).

In Malaysia, the few available documented quality of life studies in patients with schizophrenia centred on the impact of demographic profiles and community-based mental health programmes on the general quality of life (Mubarak et al., 2003; Mubarak, 2005; Mubarak, 2006). There is little documentation on the cost-effectiveness or cost-utility studies of different types of antipsychotics among schizophrenia patients undergoing regular out-patient care. Only two local studies were identified; a study by Chee (2009) that compared the HRQoL outcomes between typical and atypical antipsychotics in schizophrenic outpatients and Hatim et al. (2009) that evaluated the costs involved in switching treatment from typical antipsychotic to the atypical antipsychotic, risperidone. Thus, more studies need to

be conducted in Malaysia to determine the value of the newer generations of antipsychotics in terms of HRQoL, clinical and economic outcomes to add to the existing scarce data.

1.9 Potential Contribution of the Study Findings

According to the National Mental Health Registry (2005), only 13% of registered schizophrenia cases from 28 Ministry of Health hospitals and 4 University hospitals were started on atypical antipsychotics. A study of drug utilization in Malaysia, the Malaysian Statistics on Medicine (2006) also found similar prescribing pattern. Low utilization of this newer generation of antipsychotic was attributed to its higher price. Public health sector is heavily subsidized by the government but escalating costs of health care including procurement of pharmaceuticals has to a certain extent limited access to medicines (Babar et al., 2007).

In order to ensure sustainability of Malaysian healthcare system, a new mechanism of health care financing known as The National Health Financing Scheme was considered during the Fourth Malaysian Plan (1981-1985) and in view of ever-increasing health care costs was further highlighted in the Ninth Malaysian Plan 2006-2010 (WHO, 2008). For this proposed scheme, the provision of pharmaceuticals will be managed through a drug procurement system where patients have to pay a certain amount in order to obtain prescribed medicines (Choe & Damis, 2010).

Local research on the HRQoL, clinical and economic outcomes of different types of antipsychotics thus, will provide information on both costs and outcomes of alternative antipsychotics to aid drug regulatory authorities in making decisions on

the availability and access of different antipsychotic alternatives for the imminent drug delivery system. Clinical, humanistic and economic outcomes of antipsychotic treatment which include the interest of patients also facilitate understanding among patients and their payers on ‘value for money’ of alternative antipsychotics as well as improve clinicians’ appreciation of antipsychotic consequences on patient’s psychosocial well-being to plan for individual clinical care and improve the existing practice of care.

CHAPTER 2

GENERAL METHODOLOGY

2.1 Study Objectives

2.1.1 General Objectives

The objectives of the study were to determine and compare the impact of different types of antipsychotic maintenance treatment on comprehensive measurement parameters; clinical, humanistic and economic outcomes in routine clinical practice over a period of time adjusted for socio-demographic, clinical or treatment differences.

2.1.2 Specific Objectives

(i) To evaluate and compare HRQoL outcomes of atypical versus typical antipsychotic drugs using schizophrenia specific HRQoL instrument, the SQLS- R4 and generic HRQoL instrument, the EQ-5D.

(ii) To evaluate and compare the clinical outcomes of symptom severity using the CGI-SCH, side-effects by the ASC-C and treatment adherence using prescription refills of atypical versus typical antipsychotic drugs.

(iii) To estimate the cost-effectiveness and cost-utility ratios of atypical antipsychotics and typical antipsychotics from the perspective of society.

(iv) To determine the incremental cost-effectiveness ratios for atypical antipsychotics to typical antipsychotic drugs.