

**ECONOMIC EVALUATION
OF SCHIZOPHRENIA IN PENANG GENERAL
HOSPITAL, MALAYSIA**

ALOTAIBI FUAD FADHEL A

UNIVERSITI SAINS MALAYSIA

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**ECONOMIC EVALUATION
OF SCHIZOPHRENIA IN PENANG GENERAL
HOSPITAL, MALAYSIA**

by

ALOTAIBI FUAD FADHEL A

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Life is a journey from the first breath until the last one. During that journey, we come to know and learn from the experiences and people around us. Therefore, I would like to share my appreciation for those who assisted me during the journey to finish my dissertation.

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LIST OF SYMBOLS

n	Required sample size
$Z_{1-\alpha/2}$	Confidence interval
P	The expected prevalence or proportion in the population
d	The degree of accuracy

LIST OF ABBREVIATIONS

BID	Two times a day dose
CBA	Cost-Benefit Analysis
CMA	Cost Minimization Analysis
COI	Cost of Illness
CUA	Cost-utility Analysis
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ECT	Electroconvulsive Treatment
FBC	Full Blood Count
FBG	Fasting Blood Glucose
FLP	Fasting Lipid Panel
FSGs	First-Generation Antipsychotics
GDP	Gross Domestic Product
GLM	Generalized Linear Model
HICs	High-Income Countries
HPP	Hospital Pulau Pinang
ICD-10	International Classification of Diseases
inj	Injection
IQR	Interquartile range
LFT	Liver Function Test
LMICs	Low- and Middle-Income Countries
MOH	Ministry of Health
MREC	Medical Research and Ethics Committee
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Clinical Excellence

NSAID	Non-Steroidal Anti-Inflammatory Drug
OPD	Outpatient Department
PSC	Psychiatric Service Centers
q.m.t	once a month dose
rCBF	Regional Cerebral Blood Flow
RP	Renal Profile
SCZ	Schizophrenia
SD	Standard deviation
SGAs	Second-Generation Antipsychotics
SSRIs	Selective Serotonin Reuptake Inhibitors
Tab	Tablet
TAM	Time and Motion
TDM	Therapeutic Drug Monitoring Test
TFT	Thyroid Function Tests
TMAP	Texas Medication Algorithm Project
UDS	Urine Drug Screening
WBC	White Blood Cell

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**PENILAIAN EKONOMI SKIZOFRENIA DI HOSPITAL
PULAU PINANG, MALAYSIA**

ABSTRAK

Skizofrenia (SCZ) merupakan penyakit mental yang serius yang memberi kesan kepada sebahagian besar populasi dan meletakkan beban kewangan yang besar kepada sistem kesihatan. Di Malaysia, terdapat kajian yang terhad berkenaan kos perubatan langsung yang berkaitan dengan SCZ. Selain itu, kajian tersebut tidak memberikan pandangan semasa dan menyeluruh mengenai beban ekonomi SCZ, terutamanya sejak tahun 2015, yang belum ditangani dengan memadai. Secara khusus, terdapat kekurangan maklumat terkini mengenai kos perubatan langsung dan perbezaan dalam penggunaan sumber antara pesakit inpatient dan outpatient. Selain itu, faktor penentu kos SCZ dan impak bajet SCZ ke atas sistem kesihatan tidak pernah dinilai. Oleh itu, kajian ini bertujuan untuk menilai kos perubatan langsung bagi individu yang disahkan mengidap skizofrenia di Hospital Pulau Pinang, Malaysia. Selain itu, kajian ini bertujuan untuk mengenal pasti ciri-ciri yang berkaitan dengan kos inpatient dan outpatient dan untuk menilai impak potensi ke atas bajet negara bagi Kementerian Kesihatan Malaysia, hasil daripada pengenalan dan penambahan lumateperone dalam campuran rawatan standard semasa untuk SCZ di Malaysia. Reka bentuk kajian retrospektif, bukan intervensi, dan bottom-up digunakan untuk menjalankan kajian ini. Populasi kajian merangkumi semua pesakit skizofrenia dewasa (SCZ) yang menerima ubat di Hospital Pulau Pinang yang menjalani rawatan perubatan dari 1 Januari 2019 hingga 27 April 2021. Saiz sampel 120 pesakit SCZ outpatient (20 di antaranya mengalami hospitalisasi) dari pangkalan data rekod perubatan hospital dipilih berdasarkan kriteria penyertaan (diagnosis SCZ disahkan,

berumur 18 tahun ke atas, dan data lengkap untuk follow-up setahun). Pesakit-pesakit ini dikesan ke hadapan selama satu tahun dari tarikh indeks perekrutan. Apabila kos gabungan untuk semua pesakit (n=120) dipertimbangkan, kos perubatan langsung keseluruhan mencapai MYR 436,308 (USD 97,826.90) dengan purata keseluruhan $\pm$ SD kos SCZ setiap pesakit setahun (PPPY) sebanyak MYR 10,705.4 $\pm$ MYR 4,839.1. Daripada 120 pesakit outpatient yang dikaji, 54.2% adalah perempuan, dengan purata $\pm$ sisihan piawai (SD) umur 39.5 $\pm$ 10.4 tahun. Kos perubatan langsung keseluruhan untuk pesakit outpatient (n=120) berjumlah MYR 266,640 (USD 59,784.75). Bagi pesakit inpatient (n=20), purata umur adalah 39.4 $\pm$ 10.4 tahun, dengan kos perubatan langsung keseluruhan sebanyak MYR 169,668 (USD 38,042.15), dengan purata MYR 8,483.4 $\pm$ MYR 7,070.1, mewakili 79.2% daripada kos keseluruhan. Hospitalisasi sahaja menyumbang 62% daripada kos keseluruhan, dengan purata MYR 6,643 $\pm$ MYR 7,104.6. Walau bagaimanapun, purata kos outpatient setiap pesakit setahun membentuk MYR 2,222 $\pm$ MYR 2,571.9, membentuk 20.8% daripada kos keseluruhan. Beberapa pembolehubah mempengaruhi secara signifikan kos purata keseluruhan SCZ setiap pesakit setahun (PPPY). Etnis memainkan peranan, dengan etnik India (p = 0.004, nisbah kos = 0.67, 95% CI: 0.53-0.73) dan kategori etnik lain (p = 0.001, nisbah kos = 0.31, 95% CI: 0.26-0.44) berkaitan secara signifikan dengan pengurangan kos penjagaan kesihatan. Selain itu, keparahan SCZ berdasarkan DSM5 menunjukkan hubungan yang signifikan, dengan nisbah kos yang lebih tinggi sebanyak 1.77 (95% CI: 1.25-1.89, p = 0.003) untuk kes yang sederhana berbanding kes yang ringan. Tambahan pula, jenis ubat antipsikotik juga signifikan, dengan nisbah kos 0.42 (95% CI: 0.34-0.63, p = 0.021) untuk ubat jenis typical, menunjukkan kos penjagaan kesihatan yang lebih rendah. Juga, analisis impak bajet dilakukan. Model kami terdiri daripada dua senario: senario semasa (tanpa lumateperone 42mg) dan

senario baru (dengan lumateperone 42mg). Data bahagian pasaran diperoleh dari carian literatur dan pendapat pakar. Kos ubat diperoleh daripada unit pengadaan kerajaan. Tiada modifikasi, pengurangan, atau penangguhan dos dianggap; kos ubat dan sumber yang digunakan (ujian makmal, prosedur, dan ubat-ubatan) diasumsikan untuk kekal konstan selama tiga tahun. Model senario semasa menunjukkan kos pengurusan SCZ sebanyak MYR841,895,112.30 selama tiga tahun di Malaysia. Kos keseluruhan meningkat kepada MYR1,376,635,545.43 selepas pengenalan lumateperone, menimbulkan kos bajet bersih sebanyak MYR534,740,433.11. Analisis impak bajet menunjukkan bahawa menyertakan lumateperone dalam rawatan SCZ dapat meningkatkan secara besar-besaran bajet farmaseutikal keseluruhan, berkisar dari 2.50% hingga 17.79%. Berdasarkan dapatan, jelas bahawa kos rawatan SCZ tinggi, dengan kos tertinggi diperhatikan dalam pengaturan inpatient. Ini menunjukkan kepentingan untuk menyediakan perkhidmatan outpatient yang menyeluruh dan berkesan untuk menyokong individu dengan skizofrenia dan mengurangkan keperluan untuk hospitalisasi, yang boleh menjadi kos tinggi. Juga, ini menuntut pihak berkuasa kesihatan dan pembuat dasar untuk memberi keutamaan dan mengagihkan lebih banyak sumber untuk mengurus SCZ, khususnya dengan menumpukan pemandu kos seperti harga ubat dan tempoh penginapan hospital. Mempunyai impak yang besar ke atas keseluruhan bajet farmaseutikal. Selain itu, terdapat keperluan untuk melabur dalam penyelidikan lanjut untuk mengenal pasti rawatan dan intervensi yang lebih kos efektif untuk SCZ, seperti program intervensi awal, dengan mempertimbangkan penambahan Lumateperone dalam pengurusan pesakit SCZ, dan meningkatkan penjagaan pesakit untuk mengurangkan keperluan untuk rawatan hospital, yang dapat membantu mengurangkan beban kewangan keseluruhan.

ECONOMIC EVALUATION OF SCHIZOPHRENIA IN PENANG GENERAL HOSPITAL, MALAYSIA

ABSTRACT

Schizophrenia (SCZ) is a serious mental illness that affects a significant portion of the population and places a substantial financial burden on healthcare systems. In Malaysia, there is limited research regarding the direct medical costs associated with SCZ. Furthermore, the research lacks current and comprehensive insights into the economic burden of SCZ, particularly since 2015, which has not been adequately addressed. Specifically, there is a lack of recent information regarding the direct medical costs and distinctions in resource utilization between inpatients and outpatients. Furthermore, predictors of SCZ costs and the budget impact of SCZ on the healthcare system have not been assessed. Therefore, this study aimed to assess the direct medical costs for individuals diagnosed with SCZ at the Hospital Pulau Pinang in Malaysia. In addition, the study aimed to identify the characteristics linked to inpatient and outpatient costs and to assess the potential impact on the national budget for the Ministry of Health in Malaysia, resulting from introducing and adding lumateperone within the current standard care treatment mix for SCZ in Malaysia. A retrospective, non-interventional, and bottom-up study design was employed to conduct this study. The study population comprises all adult schizophrenic (SCZ) patients receiving medication at Hospital Pulau Pinang who underwent medical treatment from 1 January 2019 to 27 April 2021. A sample size of 120 SCZ outpatients (20 of whom had hospitalizations) from the medical records database of the hospital was selected based on the inclusion criteria (a confirmed diagnosis of SCZ, aged 18 and above, and complete data for the 1-year follow-up). The patients were tracked

forward for one year from the index date of recruitment. When considering the combined cost for all patients (n=120), the total direct medical cost reached MYR 436,308 (USD 97,826.90) with an overall mean $\pm$ SD cost of SCZ per patient per year (PPPY) of MYR 10,705.4 $\pm$ MYR 4,839.1. Of the 120 outpatients examined, 54.2% were female, with a mean $\pm$ standard deviation (SD) age of 39.5 $\pm$ 10.4 years. The total direct medical cost for outpatients (n=120) amounted to MYR 266,640 (USD 59,784.75). For inpatients (n=20), the average age was 39.4 $\pm$ 10.4 years, with a total direct medical cost of MYR 169,668 (USD 38,042.15), with a mean of MYR 8,483.4 $\pm$ MYR 7,070.1, representing 79.2% of the total cost. Hospitalization alone constituted 62% of the total cost, with a mean of MYR 6,643 $\pm$ MYR 7,104.6. However, outpatient mean cost per patient per year accounted for MYR 2,222 $\pm$ MYR 2,571.9, comprising 20.8% of the total cost. Several variables significantly influence the mean total cost of SCZ per patient per year (PPPY). Ethnicity played a role, with Indian ethnicity (p = 0.004, cost ratio = 0.67, 95% CI: 0.53-0.73) and the other ethnicities category (p = 0.001, cost ratio = 0.31, 95% CI: 0.26-0.44) were significantly associated with reduced healthcare expenses. Moreover, the severity of SCZ based on the DSM-5 showed a significant association, with a higher cost ratio of 1.77 (95% CI: 1.25-1.89, p = 0.003) for moderate cases compared to mild cases. Furthermore, the type of antipsychotic medication prescribed was also significant, with a cost ratio of 0.42 (95% CI: 0.34-0.63, p = 0.021) for typical medications, indicating lower healthcare costs. Also, a budget impact analysis was conducted. Our model consisted of two scenarios: the current scenario (without lumateperone 42mg) and the new scenario (with lumateperone 42mg). The data for the market share was obtained from the literature search and experts' opinions. The cost of medications was obtained from the government procurement unit. No dose modification, reduction, or delay was considered; the cost

of drugs and the resources used (lab tests, procedures, and medications) were assumed to remain constant over three years. The current scenario model demonstrated that SCZ management costs MYR841,895,112.30 over three years in Malaysia. The overall cost climbed to MYR1,376,635,545.43 following the introduction of lumateperone, incurring a net budget cost of MYR534,740,433.11. The budget impact analysis model estimated that including lumateperone in SCZ treatment could substantially increase the overall pharmaceutical budget, ranging from 2.50% to 17.79%. Based on the findings, it is evident that the cost of treating SCZ is high, with the greatest cost observed in the inpatient setting. This suggests the importance of providing comprehensive and effective outpatient services to support individuals with SCZ and reduce the need for hospitalization, which can be costly. Also, this necessitates health authorities and policymakers to prioritize and allocate more resources for managing SCZ, specifically by targeting cost drivers like medication prices and hospital stay lengths. had a high impact on the overall pharmaceutical budget. Moreover, there is a need to invest in further research to identify more costeffective treatments and interventions for SCZ, such as early intervention programs, considering the addition of Lumateperone in the management of SCZ patients, and improving patient care to reduce the need for hospital admission, which could help reduce the overall financial burden.

CHAPTER 1

INTRODUCTION

This chapter provides an in-depth understanding of the context and scope of the study. Initially, it offers a background for the study. It then presents the specific problem statement that the research aims to address. After that, the aim and objectives of the research, including specific objectives, are outlined, along with the research questions that guide the investigation. Finally, the chapter articulates the significance of the study from various perspectives (clinicians, healthcare policymakers, patients' families and caregivers, and the literature).

1.1 Background

Schizophrenia, often abbreviated as SCZ, is a chronic mental illness characterized by hallucinations (perceiving unreal sensory experiences), delusions (false beliefs despite the contrary evidence), and other symptoms that significantly impair the individual's ability to function in both social and professional environments (Miller & Buckley, 2021). For instance, people with SCZ may experience a unique range of symptoms that can affect their lives differently (Schultze-Lutter et al., 2019). They may begin to act differently, often showing decreased personal performance, such as losing interest in their usual activities or neglecting personal hygiene. They might also withdraw from social circles, display unusual behaviour, or have difficulty staying focused (WHO, 2022). Family members and close friends may notice these behavioural changes, impacting the person's ability to hold a job, continue their studies, or maintain relationships (Szczotka & Majchrowicz, 2018).

Sometimes, the first sign of illness is impulsive behaviour (especially in adolescents), such as running away from home, a suicide attempt, and aggressive or violent crimes (Hodgins & Klein, 2019). Also, SCZ behaviour is marked by hesitation and contradiction. Generally, patients with SCZ tend to oppose everything from the outside world, reject, for example, the hand that extends to them, or show passivity by cynicism (Carrà et al., 2019).

SCZ is a significant health concern due to the extent of the disability it can impose, its chronic nature, and its profound effect on the patient's family (Chen et al., 2019). The substantial financial burdens associated with providing care and the fact that it leads to enduring, long-term disability in more than half of those afflicted further underscore its importance (Huhn et al., 2019). Moreover, the societal setting is often challenging for individuals with SCZ, as they often face lower expectations from the general public and healthcare professionals (WHO, 2022).

SCZ, a significant mental illness altering behaviour, thoughts, and feelings, is proposed to be debilitating Volkan (2020). Patients often exhibit unstable convictions, engaging in irrational or destructive behaviour. Schultz et al. (2007) estimate SCZ's impact on around 1% of the UK population, equivalent to 0.1 or 0.2 incidence per 1000, with varying prevalence reported by McGrath et al. (2008) and Simeone et al. (2015).

Moreno-Küstner et al. (2018) and Subramaniam et al. (2021) reported a lifetime median prevalence of 7.5 per 1000 individuals. Li et al. (2022) highlighted a male-to-female ratio of 1.4 to 1. Ayano et al. (2019) noted higher SCZ incidence rates in developing countries.

The onset of SCZ appears 3.2 to 4.1 years earlier in males than in females (Fernando et al., 2020). A Finnish study (Sommer et al., 2020) found men diagnosed at a mean age of 34.4, compared to 38.2 for women, with a peak incidence around age 22. Despite earlier onset, both genders exhibit high re-hospitalization rates (69.5%) over a ten-year follow-up, slightly higher for women.

The Finnish study observed a lower mortality rate in women with SCZ (HR=0.54), attributed to fewer suicides and cardiovascular deaths, yet raised concerns about diagnostic delays and undertreatment for women (Sommer et al., 2020). Immonen et al. (2017) found that a younger age at onset in SCZ correlated with increased hospitalizations, severe negative symptoms, more relapses, and poorer overall outcomes (combined occupational, social, and clinical course).

SCZ carries a doubled mortality rate for both genders, with cardiovascular disease often the leading cause of death related to SCZ medications (Howell et al., 2019; Stoner, 2017). The interplay of birth circumstances and socioeconomic status elevates the risk of SCZ. Lower socioeconomic background, father's occupational status, and residence in an area with lower socioeconomic status contribute to this risk (Cantor-Graae, 2007) (Werner et al., 2007). These findings suggest that social factors intertwine with genetic, biological, and environmental influences in SCZ development (Wahbeh & Avramopoulos, 2021).

SCZ exhibits positive symptoms like disorganized thinking and negative symptoms such as social withdrawal and lack of motivation (Farah (2018). Carrà et al. (2019) emphasized that socially disruptive behavior linked to SCZ poses the most significant challenge for families. Negative symptoms often misattributed to personality flaws disrupt familial bonds Correll and Schooler (2020).

Expanding on the narrative, Qureshi et al. (2013) emphasized the dehumanization of individuals with mental illness, reducing them to objects. Embodiment, as described by (Tschacher et al., 2017), contributes to this dehumanization process. Stigmatization, highlighted by Shahwan et al. (2022), leads to societal judgments that view individuals with mental illness as unworthy of full social acceptance. This judgmental perspective categorizes them as irrational, deviant, or dangerous, projecting perceptions of inferiority and contempt.

Tesfaw et al. (2020) questioned societal biases in judging individuals with SCZ, particularly in societies where irrationality prevails. Koenig et al. (2014) pointed out historical stigmatization, with mentally ill individuals often secluded or neglected. The presence of mental illness within a family may evoke shame and imply an insufficient support system, impacting the entire family.

1.2 Schizophrenia Symptoms

Acute psychotic episodes typically start abruptly and have uncommon clinical symptoms, such as the patient losing the sense of reality (Farah, 2018). The primary distinctions between cognitive, negative, and positive symptoms are indicated in Figure 1.1. SCZ symptoms are also sometimes referred to as SCZ syndrome.

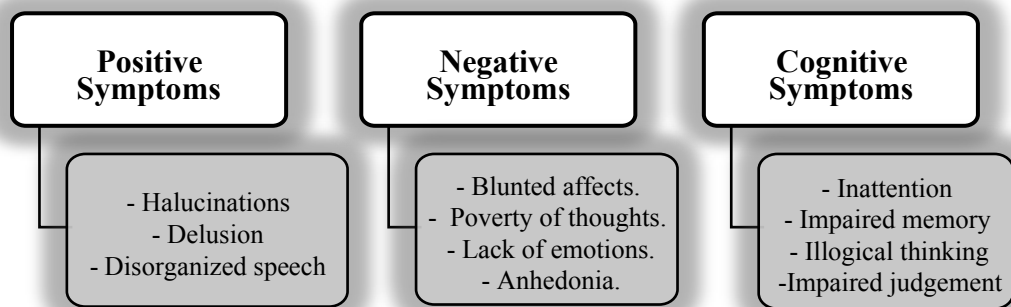


Figure 1.1 SCZ's symptoms

1.2.1 Positive Symptoms

Positive symptoms in SCZ, such as hallucinations and delusions, are effectively managed by standard antipsychotic medications. The dopamine hypothesis suggests that these symptoms result from dopamine overactivity, supported by postmortem findings of abundant dopamine receptor D2 cells in the nucleus accumbens (Farah, 2018; Yang & Tsai, 2017).

1.2.2 Negative Symptoms

Negative symptoms, including alogia and emotional flattening, are characterized by diminished abilities and social withdrawal. CT scans suggest enlarged brain lining in individuals with negative SCZ symptoms, leading to cognitive decline from a young age (Carrà et al., 2019; Malla et al., 2002).

1.2.3 Cognitive Symptoms

Cognitive symptoms of SCZ, such as poor memory and unstructured thinking, are linked to prefrontal lobe abnormalities. Positive emotions are associated with transient malfunction, while negative symptoms and cognitive impairment are directly tied to prefrontal lobe abnormalities (Martínez et al. (2021)

1.3 Pathophysiology of Schizophrenia

The fundamental pathology of SCZ involves anatomical brain modifications and neurochemical imbalances (Deng & Dean, 2013). Magnetic resonance imaging (MRI) studies indicate brain size increase, overall decline in brain mass, and cortex reduction in SCZ. Anatomical alterations include hippocampus, cerebral cortex, and

superior temporal gyrus changes linked to hallucinations. Regional cerebral blood flow (rCBF) variations have also been observed (Yang & Tsai, 2017).

Postmortem investigations reveal neuro-pathological changes in the hippocampus and frontal cortex in SCZ patients, including increased D2 receptors in subcortical and limbic regions. Dysfunctions in dopaminergic, glutamatergic, serotonergic, and GABA signaling systems may lead to abnormal interneuronal activities, manifesting as cognitive, behavioral, and social dysfunction (Plavén-Sigra et al., 2022; Yang & Tsai, 2017). The surge in serotonin levels beneath the cortex is hypothesized to contribute to positive symptoms in SCZ.

1.4 Course and Prognosis of Schizophrenia

SCZ, a chronic brain condition, is often misdiagnosed due to varied symptoms and its overlap with other conditions (Bae et al., 2021). Treatment reduces symptom intensity, especially in acute cases. However, relapses, frequent hospital stays, and treatment resistance are common, increasing the overall cost of care. The SCZ pathway comprises pre-disease, early (prodromal), active, and residual phases (Eske (2022), as depicted in Figure 1.2: pre-disease, early phase (prodromal phase), active, and residual phases.

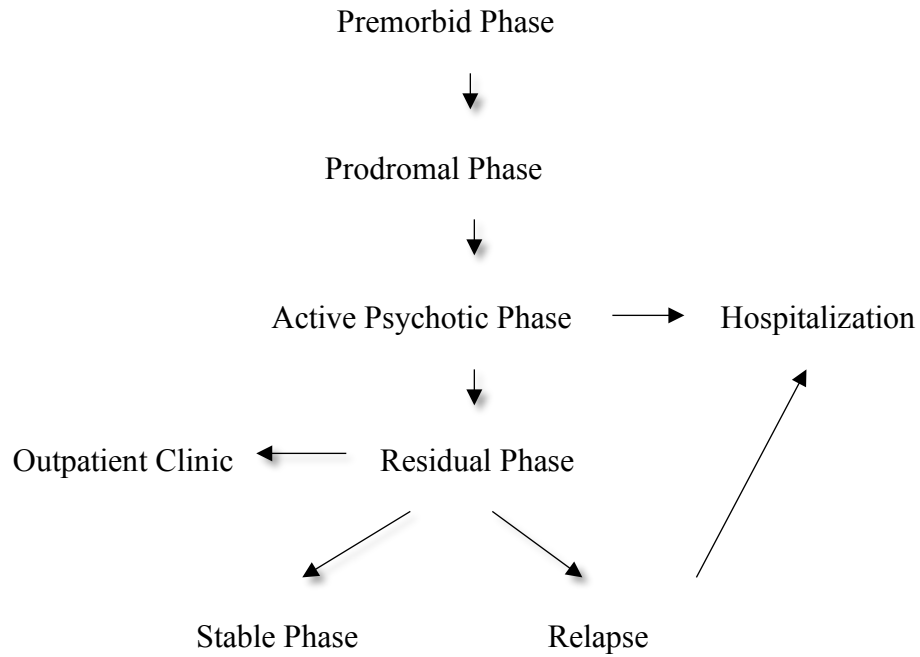


Figure 1.2 SCZ's Course and Prognosis

1.4.1 Pre-morbid Phase

Pre-morbid symptoms in SCZ appear before diagnosis, encompassing subtle cognitive, behavioral, and emotional aberrations. Early signs include social disengagement, mood changes, and language delay in childhood Davidson (2001).

1.4.2 Prodrome Phase

The prodrome phase precedes psychosis, marked by a functional and behavioral decline. Characteristics include poor attention, low energy, sadness, and isolation Eske (2022).

1.4.3 Active Psychotic Phase

Initiation of psychotic symptoms defines the active phase, featuring hallucinations, delusions, and erratic behavior. Multiple episodes signal cognitive and mental state changes, often leading to job loss Eske (2022).

1.4.4 Residual Phase

Post-severe psychosis, residual symptoms emerge, varying but commonly involving worry, poor judgment, lack of insight, and social isolation, hindering daily tasks Eske (2022).

1.5 Diagnosis of Schizophrenia

If SCZ is suspected in individuals experiencing hallucinations and delusions, considering their symptoms is crucial. Diagnosis involves assessing general behavior, appearance, mood, speech, mental content, hallucinations, aberrant beliefs, and abnormal ideas (Bahn & Guest, 2012). While physical examination provides limited information, it aids in excluding physical disease and guiding antipsychotic choice. Self-mutilation may signal potential risks, guiding decisions on admission or outpatient psychiatric therapy.

Diagnosing SCZ, per DSM-5 criteria, requires at least two symptoms (delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms) for a significant portion of one month. One symptom must be delusions, hallucinations, or disorganized speech. Continuous disturbance signs should persist for six months, causing significant distress or impairment in functioning (Regier et al., 2013; Tandon et al., 2013). Patient interviews and diagnostic tools like PANSS and BPRS aid in accurate assessments.

1.6 Historical Treatments and Antipsychotics Development

Historically, SCZ treatments involved trial and error, ranging from castor oil to sleep therapy. Camphor-induced seizures and electroconvulsive therapy were attempted, eventually supplanted by chlorpromazine in the 1950s. Atypical antipsychotics like clozapine emerged, with initial setbacks but eventual recognition for treatment-resistant cases. The late 20th century introduced various atypical antipsychotics, improving efficacy and reducing side effects. Holistic SCZ treatment involves a multidisciplinary approach with pharmacological, psychological, and social interventions (Huhn et al., 2019; Stępnicki et al., 2018).

1.6.1 Psychosocial Support

Psychosocial support enhances life skills, stress management, and drug adherence in SCZ patients (Mueser & Bond, 2000). Psychotherapy includes individual and group sessions to aid in addressing patients' challenges, fostering mutual support, and reducing stigma. Family education is vital upon patient discharge, empowering them to manage potential issues and enhance medication adherence, improving overall treatment effectiveness (Ganguly et al., 2018).

1.6.2 Pharmacotherapy of Schizophrenia

Effectively managing acute SCZ involves early detection, diagnosis, and appropriate pharmacotherapy. During acute episodes, antipsychotic medication initiation or adjustment is crucial. Guidelines recommend starting at the lower end of the therapeutic dose range and adjusting based on effectiveness and tolerance. Maintenance treatment post-acute episode management is emphasized, with the

optimal duration varying (Correll et al., 2022; Salisbury-Afshar, 2021). First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are used,

1.6.2(a) First Generation Antipsychotics

FGAs, though effective, have declined in use due to side effects. SGAs are often considered the first line of treatment due to their lower adverse effect profile and efficacy in managing negative, cognitive, and emotional symptoms (Leucht et al., 2009).

1.6.2(b) Second Generation Antipsychotics

SGAs, including clozapine, have improved perceptions of SCZ treatment and exhibit promising outcomes in drug-resistant cases (Cohen et al., 2012). Current research focuses on finding safer and more efficient therapies (Rubio & Kane, 2022)

1.6.2(c) Lumateperone

Lumateperone (LUM), also known as Caplyta, is a novel drug developed by Intra-Cellular Therapies to treat SCZ and other neuropsychiatric and neurological disorders (Blair, 2020). It is a first-in-class agent that modulates serotonin, dopamine, and glutamate neurotransmission (Syed & Brašić, 2021). It is a potent 5-hydroxytryptamine (serotonin) 2A (5-HT_{2A}) receptor antagonist and also binds to dopamine (D₁, D₂) receptors. Additionally, preclinical data confirmed that LUM exclusively acts as an indirect modulator of glutamatergic phosphoprotein with D₁-dependent augmentation of both NMDA and AMPA activity via the mammalian target of rapamycin (mTOR) pathway, mechanisms thought to predict potent and rapid antidepressant effects (Kumar & Kuhad, 2018). This unique mechanism of action

makes it a potential treatment for a range of mood disorders, including bipolar depression (Kumar & Kuhad, 2018). It has also shown promise in the treatment of other psychiatric and neurological diseases, such as behavioral symptoms of dementia or Alzheimer's disease and sleep disturbances (Mohamed).

Furthermore, it has a favorable safety profile, making it a potential option for personalized treatments (Mazza et al., 2020). New studies concluded that LUM significantly improves symptom severity in adults with SCZ and exhibits a favorable tolerability and safety profile with placebo-level rates of weight gain, metabolic disruption, akathisia, extrapyramidal side effects (excluding akathisia), and prolactin elevation. They recommended conceptualizing LUM as a first-line treatment strategy for adults with SCZ (Greenwood et al., 2021; Jawad et al., 2022).

1.6.3 Antipsychotic Treatment Algorithms

When administering antipsychotics for SCZ, the Texas Drug Algorithm (TMAP) suggests six distinct phases (Moore & Buchanan, 2007). The first three phases involve SGA or FGA monotherapy, with the possibility of introducing clozapine if needed. The subsequent phases may include combinations of antipsychotics, electroconvulsive therapy (ECT), or mood stabilizers based on the patient's response. The choice between oral or injectable combinations depends on the individual's condition, adverse effects, and medication compliance (Takeuchi et al., 2021).

1.6.4 Augmentation Therapy

Combination treatments using more than one antipsychotic are common in SCZ management. Augmentation therapy involves supplementing antipsychotics with medications other than antipsychotics to enhance effectiveness. Combining Divalproex with Olanzapine or Risperidone has shown greater symptom reduction. Additionally, using FGAs with selective serotonin reuptake inhibitors (SSRIs) and adding antidepressants to antipsychotic treatment can help manage aggressive symptoms and improve negative symptoms Casey et al. (2009) (Baandrup, 2020).

1.6.5 Electroconvulsive Therapy

Electroconvulsive therapy (ECT) involves inducing seizures through periodic electrical pulses and is effective in managing severe and sustained phases of SCZ. ECT, when used in conjunction with antipsychotic drugs, can reduce positive and affective symptoms, enhance social functioning, and improve life quality. Studies indicate that ECT helps patients leave the hospital sooner and reduces the recurrence of symptoms, alleviating economic strain on patients' families and healthcare systems (Chan et al., 2019; Grover et al., 2019); Sinclair et al. (2019).

1.7 Social Indications Toward Mental Health

Over the years, approaches to mental illness have been categorized into three main areas: etiological research, categorization of mental illnesses, and the development and application of psychoactive medications Thoits (1999). However, these approaches lack sufficient scientific substantiation, leading to debates about the validity of the biomedical model in psychiatry. Scholars like Scheff (2013) and Deacon (2013) question the biomedical approach, emphasizing the role of interpersonal

relationships in mental health and the need to consider people's experiences. Van Zelst (2009) highlights how psychiatric diagnoses can lead to stigma and its associated consequences, including isolation and discrimination.

The biomedical approach in psychiatry often involves the objectification of individuals and prioritizes medical intervention over other therapeutic practices. Psychiatric diagnoses might be assigned even when a person is healthy, raising concerns about medicalizing expected behaviors (Taiminen et al., 2001). Rössler (2016) discusses the power imbalance in the doctor-patient relationship and the tendency of clinicians to find symptoms consistent with a diagnosis, potentially nudging individuals into the "patient role." Ahmedani (2011) explores society's influence on our understanding of typical behaviors and the predefined roles associated with mental illness trajectories.

1.8 Schizophrenia Globally

Around the globe, SCZ affects an estimated 24 million individuals, translating to roughly one out of every 300 people, or 0.32% of the global population. The rate is slightly higher among adults, affecting about one in every 222 people or 0.45% (WHO, 2022). SCZ onset is often in the late teenage years through the twenties, with the initial occurrence tending to be earlier in males than females (Eranti et al., 2013; WHO, 2022). Interestingly, the disparity in the age of onset between genders remains fairly consistent, irrespective of whether the country is developed or developing (Eranti et al., 2013). Although SCZ is not as prevalent as several other mental health conditions, it is a highly debilitating disease and has ranked 11th as the leading cause of disability worldwide in the past few years (Teoh et al., 2017).

The annual global economic burden linked to SCZ ranges between USD 94 million and USD 102 billion (Chong et al., 2016). Research that evaluates the economic burden of SCZ in relation to the Gross Domestic Product (GDP) of various nations reveals that the costs vary from 0.02% of the GDP in the UK to as high as 1.65% of the GDP in Sweden (Kowalec et al., 2021; Ride et al., 2020). A significant proportion of these costs primarily stems from indirect costs, including productivity loss and the cost of informal care. The extensive variation in estimated global costs can be ascribed to several factors. These include differences in healthcare systems, patterns of resource use, the scope of cost components, the diversity of the sampled populations, and the varied data sources utilized (Chong et al., 2016).

1.9 Schizophrenia in Malaysia

Establishing the National Mental Health Registry in 2003 by the Malaysian Ministry of Health marked a significant step forward in local research on SCZ. This initiative has significantly enhanced psychiatric practices, research, and services related to SCZ (Chee & Salina, 2014). For instance, in its clinical practice guideline for SCZ management, the Ministry of Health Malaysia reported an incidence rate of 15.2 per 100,000 individuals (Aziz et al., 2008; CPGs, 2009). These studies showed that most patients with SCZ were between 20-40 years and higher in males, urban, and migrant populations. A recent study disclosed that the peak age for the patient's presentation was 30, the incidence was higher among urban residents; males constitute more than 60% of SCZ cases, and there were 42.4% Malay, 46% Chinese, 9.3% Indians, and 2.4% others (Suarn et al., 2019).

In Malaysia, the management process for individuals with severe mental disorders such as SCZ may require a tandem approach with comprehensive management. An example of this is the implementation of community psychiatric care practices in mainstream clinics across Malaysia. This involved mental health professionals conducting rehabilitative activities in the patients' homes, fostering closer ties between hospital-based community teams and primary mental health caregivers, who are readily accessible to the patient's families. Similarly, this strengthened the enhancement of rehabilitation exercises at hospital-based Psychiatric Service Centers (PSC) (Ramli et al., 2010).

The Hospital-based Psychiatric Service Centers (PSC) initiative is a developing intervention that has a vision for PSCs to become integrated centers of excellence for mental health care, providing a comprehensive range of services in a well-coordinated and patient-centered environment aimed at reducing rehospitalization rates among patients with severe mental illnesses, such as SCZ, in Malaysia (Dahlan et al., 2013). These centers provide various services, including psychosocial first aid and individual self-help techniques, often administered by nonprofessionals (Riessman & HALLOWITZ, 1967). The administration of these services has evolved rapidly in recent years, focusing on integrating various programs and services (Woolston, 2002).

These PSCs serve a diverse patient population, including adults, adolescents, and children. There are 410 registered psychiatrists in Malaysia, with a significant disparity in their distribution across the country (Guan et al., 2018; Midin et al., 2018). However, there is a shortage of mental health professionals, including clinical psychologists and social workers (Parameshvara Deva, 2004). The available literature does not provide the exact number of Psychiatric Service Centers (PSCs) in Malaysia.

Moreover, the psychosocial counseling manual was developed recently, and mental health staff was trained at the primary health care level. Activities at these PSC centers have focused on assisting patients through occupational and psychosocial techniques. PSC activities generally went hand in hand with developing psychiatric services in Malaysia. It commenced in an institutionalized mental setting and moved to public hospitals and primary health care centers. It has evolved into communitylevel initiatives by local community mental health teams, family members of patients, and community members (Ramli et al., 2010).

Following the evolution of mental health services in Malaysia, new challenges have emerged. Despite an increase in the prescription of multiple antipsychotic medications, the management of SCZ remains inadequate in many instances (Teoh et al., 2017). This predicament has multiple facets. Firstly, SCZ-related costs in Malaysia are rising, signaling a potential area for intervention and cost-saving. Further, the prices of the different antipsychotic medication classes used to treat SCZ must also be supported by data on direct medical expenses.

Additionally, observational data were going to be used in this investigation. Official statistics reflect what indeed occurs in day-to-day medical practice. This information is crucial for making informed choices about health care policy and has the benefit of helping to comprehend treatment results that are not governed by trial protocols or clinical practice standards.

1.10 Costs of Schizophrenia and Medication Treatments

McKenna (2021) pointed out that SCZ significantly contributes to the global disease burden. However, measuring the costs associated with SCZ presents a complex challenge, as Zhu et al. (2008) and Barbosa et al. (2018) asserted. They reported that

his complexity arises due to the variety of services utilized by SCZ patients and the intricacy involved in determining which costs ought to be included in the calculations and which ones to exclude. To illustrate, Ride et al. (2020) revealed that the cost burden of SCZ surpasses that of any other mental disorder, accounting for a substantial 5% of the UK's national health budget. Although the prevalence of SCZ in the UK was estimated at around 6% in 1978 (M. A. Taylor & Abrams, 1978), more recent studies have suggested a lower figure. A global study found the age-standardized point prevalence of SCZ in 2016 to be 0.28% (Charlson et al., 2018), with no significant variation across countries. Ride et al. (2020) study estimated the annual cost of SCZ to the UK economy at a staggering 11.8 billion pounds. However, it's important to note that this estimate doesn't include some indirect costs. Indirect costs, such as loss of employment and familial caregiving, are often several times higher than the direct costs related to healthcare and social services, further exacerbating the financial impact of SCZ. (Ride et al., 2020). In managing these costs by choosing cost-effective medications, Taylor et al. (2021) underscores the advantages of atypical secondgeneration antipsychotic medications (SGAs). These researchers argue for a more extensive application of such drugs, given that they result in fewer side effects compared to traditional antipsychotic medications while maintaining comparable efficacy.

In Indonesia, Puspitasari et al. (2020) showed that the average annual cost for each person with SCZ was approximately USD 236 in 2016-2018. According to Keepers et al. (2020), most individuals with SCZ refused access to antipsychotics due to cost. Relapses in SCZ are predicted to cost USD 155.7 billion on average for 3.5 million registered patients in the USA (Wander, 2020); USD 117.3 billion accounted for indirect expenditures, as it made up 76% of the overall financial impact. In

Malaysia, 15,104 cases of SCZ were reported to have been treated in 2015, with a total economic burden of USD 100 million, equivalent to 0.04% of the nation's GDP (Teoh et al., 2017). With this scale of economic burden, it becomes increasingly clear that making suitable therapies accessible to individuals with SCZ is necessary. This is especially pertinent considering the mounting evidence that novel medication treatments can enhance clinical functioning and enable release from the hospital in circumstances where treatment has previously failed.

The economic burden of SCZ involves both direct and indirect costs. Direct medical costs, which include hospitalization, outpatient services, and medications, contribute a significant portion but are not the majority of the overall economic burden. Indirect costs, such as loss of productivity due to high unemployment rates and caregiver burden, make up a larger share. For instance, a U.S. study found that only 24% of the total cost of SCZ was attributed to direct healthcare costs, with inpatient visits and medications being the largest contributors to these costs, accounting for 10% and 6% of the total cost, respectively. The rest was due to indirect costs, contributing to 76% of the total economic cost (Wander, 2020). The situation was similar in Malaysia in 2015, where only 26% of the total economic burden of SCZ was attributed to direct medical costs, and a much larger portion, 72%, was attributed to indirect costs (Teoh et al., 2017). According to Ride et al. (2020), the expenditures associated with inpatient care can account for more than 75% of the costs associated with SCZ in the UK, while pharmacological prices are still relatively modest at 4%. There are still questions about whether the therapy is the best option considering the significant recurrence expenses.

Pharmacological therapies continue to be the cornerstone for the management of individuals with SCZ. Psychiatric approaches like family therapy and cognitive behavioural therapy are adjuvants rather than replacements for medication therapy (Keepers et al., 2020). For medical professionals, the focus on SGAs is more crucial. Such evidence stems from the point that typical antipsychotics have undesirable side effects. Antipsychotic medication potency should also be considered, and modern antipsychotics should be considered as a viable therapy choice. Several researchers have even gone as far as to state that medication choices must be made following consultation with the patient and the medical professionals in charge of their care. Ackenheil and Weber (2022) claimed that some individuals with SCZ seemed reluctant to take medications on a cost basis to support the case for prescribing new, non-standard medications. Even though there is growing evidence that modern antipsychotics are most effective for treating SCZ, many patients quit using them due to the adverse side effects, which eventually increase symptoms and lead to relapses. This phenomenon underscores the need to address not only the effectiveness but also the tolerability of these medications. As a result, interventions aimed at reducing the overall cost of SCZ and enhancing patient adherence become crucial components of comprehensive treatment strategies.

Several strategies can mitigate the economic burden associated with SCZ. These encompass early intervention and treatment, medication adherence programs, supported employment initiatives, and social interventions, including housing assistance and case management. However, evaluating the financial implications of these interventions requires a systematic approach beyond traditional analysis.

Budget Impact Analysis (BIA) is an economic tool that evaluates and estimates the financial consequences of adopting new interventions (Sullivan et al., 2014). BIA studies incorporate medication costs, hospitalization expenses, side effects, and acute exacerbation costs. This approach offers insights into an intervention's short- and medium-term financial effects and facilitates comparisons between different interventions to identify the impact of the new intervention on the healthcare budget (Garattini & van de Vooren, 2011). Furthermore, BIAs enable informed decisions about resource allocation in the context of treatment adoption (de Mello Vianna et al., 2020).

Nonetheless, BIAs come with their share of limitations. Factors such as the accuracy of estimates, time horizons, and the analysis's perspective can influence its outcomes (Chugh et al., 2021; Garattini & van de Vooren, 2011). Accurate data availability can also pose a challenge, and certain non-monetary benefits may be overlooked (Rueda et al., 2020). Assumptions made during the analysis can significantly impact results and accuracy. However, despite these limitations, BIAs remain valuable tools for decision-makers grappling with the potential implementation of novel SCZ treatments (Chugh et al., 2021; Garattini & van de Vooren, 2011).

1.11 Statement of Problem

Diagnosing SCZ at its inception is challenging due to polymorphic and nonspecific first manifestations (Westhoff et al., 2022). As healthcare costs rise, there is a growing interest in evaluating the economic burden, as reflected in recent studies on the economics of medicine (Le et al., 2021). Understanding the economic consequences of SCZ is crucial, with cost-of-illness studies emerging as essential tools

to measure and compare economic burdens, guide decision-makers, and inform policy (Jo et al., 2020)(C. Jo, 2014).

While economic burden studies on SCZ are prevalent in high-income countries (HICs), there's a notable gap in understanding the economic burden in low- and middle-income countries (LMICs) like Malaysia (Chong et al., 2016). Despite a prior study in Malaysia by Teoh et al. (2017), there's a need for a new study to address gaps. Teoh's study employed a unique combination of a societal perspective, retrospective analysis, and micro-costing with a bottom-up approach, assessing the economic burden of SCZ in Malaysia. They leveraged patient data to estimate key cost parameters, such as healthcare utilization rate, per-patient medical costs, and national SCZ prevalence. However, being conducted about ten years ago, Teoh et al.'s study lacks current context. The study also lacked a detailed breakdown of direct medical costs, and recommendations based on recent data. Therefore, a new study is essential to provide more recent, comprehensive, and detailed insights into the economic burden of SCZ in Malaysia.

Moreover, the economic effects of SCZ on Malaysian society, particularly in Penang State, are not quantified. The impact of the growing utilization of care resources, SCZ medical expenditures, and the absence of statistics on SCZ direct costs in Malaysia pose challenges to healthcare reform and effective SCZ management. Additionally, despite available medications for SCZ, therapeutic outcomes remain burdensome and challenging, necessitating pharmacoeconomic evidence to reconcile outcomes with resources used.

1.12 Research Questions

The research is performed to answer the following questions:

- i) What are the direct medical costs of SCZ patients from every component, such as clinical visits, medications, diagnostic tests, hospitalizations, physical interventions, and home medical visits?
- ii) How do medication costs, diagnostic tests, and physical interventions differ between inpatients and outpatients diagnosed with SCZ?
- iii) What is the potential impact on the national budget for the Ministry of Health in Malaysia, resulting from introducing and adding lumateperone into the standard care treatment regimen for SCZ?

1.13 Aim and Objectives

The general objective is to evaluate the direct medical costs of SCZ management in Hospital Pulau Pinang (HPP), Penang, Malaysia, from the Ministry of Health's (MOH) perspective.

1.13.1 Specific Objectives

- i) To estimate the direct medical costs of SCZ patients from every component, such as clinical visits, medications, diagnostic tests, hospitalizations, physical interventions, and home medical visits.
- ii) To compare the costs of medication, diagnostic tests, and physical intervention for inpatients and outpatients with SCZ.
- iii) To assess the potential impact on the national budget for the Ministry of Health in Malaysia, resulting from introducing and adding

lumateperone within the current standard care treatment mix for SCZ in Malaysia.

1.14 Significance of the Study

This study is valuable and important from various perspectives. For instance, it offers valuable insights for healthcare professionals, policymakers, family members, and caregivers of patients and also contributes to existing scholarly work. The scarcity of healthcare resources, coupled with the significant financial burden chronic illnesses like SCZ impose on the community, make it imperative to bring awareness to the financial impacts of these diseases and to aid in the selection of disease prevention and management tactics.

Firstly, the study is relevant for clinicians working on the front lines. Unveiling the actual cost of treating SCZ is crucial in orienting medical practice toward cost-effective treatments. By relying on scientific evidence-based practices, clinicians can help allocate some of the limited resources that SCZ patients utilize more efficiently and save SCZ patients from going through the acute stages of illness or acquiring costly consequences (Jo et al., 2020; Suarn et al., 2019).

Secondly, the implications of this study for healthcare policymakers are notable, especially within the context of Malaysia's healthcare system. A significant issue in Malaysia's delivery of healthcare is the high prevalence of SCZ, long-term medication needs, and high costs of medical therapy. Budgets for healthcare will be distributed more effectively and wisely if useful and practical statistics are provided to Malaysian decision-makers. It has become common practice to provide health officials with information by analyzing the economics of medicine. By providing health

authorities with financial information on SCZ, they can ascertain how much SCZ is allotted in Malaysia and establish standards for its prudent and effective management.

The study's significance extends to patients' families and caregivers, offering valuable information about the economic evaluation of SCZ. By evaluating the economic impact of SCZ, this study can provide valuable insights into the financial burden of the illness on patients, families, and caregivers, which can help them better plan and manage their finances. Additionally, the study can provide insights into the cost analysis of different treatment options for SCZ, which can help patients and families make informed treatment decisions and choose the most effective and affordable options. The study can also shed light on the barriers to accessing healthcare services for individuals with SCZ, including financial barriers, which can help patients and families advocate for better access to care. Moreover, the study's findings can help identify the need for additional support services for individuals with SCZ and their families, including financial assistance programs and other forms of support.

Finally, the contribution of this study to literature is immense, such as bridging the knowledge gap, comparative analyses, and guiding future research. In this light, the study will bridge the current gap in the literature concerning the direct medical costs associated with SCZ in Malaysia. Moreover, the findings could provide a unique opportunity for comparative analyses with other countries and regions. This comparison can inform global understandings of the financial burdens associated with SCZ, facilitating international cooperation and shared learning in managing the disease and its economic implications. Furthermore, by providing a comprehensive overview of the direct medical costs of SCZ in Malaysia, this study will set a benchmark for future research. It will stimulate additional inquiries and research into the indirect costs, social implications, and potential interventions for SCZ. In this way, the study