

# Schizophrenia, Metabolic Syndrome and the Opportunity for developing Pharmacist-led Toolkit for Education and Metabolic Syndrome Screening (EMESYS): A Review

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**Review Article**

# Schizophrenia, Metabolic Syndrome and the Opportunity for developing Pharmacist-led Toolkit for Education and Metabolic Syndrome Screening (EMESYS): A Review

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**ABSTRACT**

The use of Second-Generation Antipsychotic (SGA) medications has been common for patients with Schizophrenia. However, this comes with an increased risk of metabolic syndrome event. Such condition has been a concern given the long-term period for therapy. This highlights an untapped opportunity for pharmacists in preventing metabolic syndrome events and educating patients about the risk of their treatment. A toolkit for supporting such an extended pharmacist's role is essential due to the paucity of a practical tool. This study provides a review about the use of SGAs, the potential of metabolic syndrome events, and the development of a toolkit supporting the pharmacist's role in treating the patient with mental health issues, including Schizophrenia. Treatment of Schizophrenia and metabolic syndrome is indeed challenging. Nevertheless, the toolkit might facilitate the interaction between pharmacist and patient, implying better outcomes might be achieved in the long-term treatment.

**Keywords:** Schizophrenia, Antipsychotics, Metabolic Syndrome, Pharmacist, Mental Health**INTRODUCTION**

Severe mental disorders, mainly Schizophrenia, are responsible for significant disease burden on healthcare than HIV/AIDS, transportation injuries, tuberculosis, and diabetes (Whiteford et al., 2013). Such burden can be alleviated through effective management of Schizophrenia which includes both pharmacological treatment and psychological intervention (Panesar, 2012). However, it is important to note that patients with Schizophrenia might need to use antipsychotic medications in the long term (Kishimoto et al., 2013).

Second Generation Antipsychotics (SGAs) are currently recommended as the first choice in the schizophrenia treatment as they may improve compliance and patient's quality of life than the First-Generation Antipsychotics (Panesar, 2012; Julaeha et al., 2019). Unfortunately, this comes with an increased risk for Metabolic Syndrome (MetS), such as weight gain, hypertension, dyslipidemia, and hyperglycemia (Church et al., 2010).

Several studies in a number of countries, namely in the United States (Valenstein et al., 2011;

Schneiderhan et al., 2014; Hinds et al., 2015), Japan (Hashimoto, 2016; Hashimoto and Tensho, 2016; Ishida et al., 2018), Australia (Ally and Stallman, 2016), Ireland (Ni Dhubhlaing et al., 2017), Turkey (Yalcin et al., 2019) and Montenegro (Ilicovic et al., 2015) demonstrated that better health outcomes in patients with Schizophrenia could be achieved by improving patients' knowledge, conducting regular monitoring of the therapy, initiating early screening of side effects, and improving communication between health care professionals and patients. Interestingly, these studies were led by pharmacists highlighting pharmacist potential to involve in the management of Schizophrenia.

The element of education and health screening combined with active interaction between the pharmacist and the patient can be a nexus for reducing the prevalence of MetS in the case of Schizophrenia. Pharmacists are well-positioned as the custodian of medicine, enabling them to identify, resolve, and prevent drug therapy problems, including MetS, which is the adverse effect of the SGAs (Cipolle et al., 2012). Such position is critical to improving therapy for patients

receiving SGAs, particularly in developing countries such as Indonesia. The primary healthcare provider highly relies on physicians, highlighting pharmacists as another potential resource for treating patients with Schizophrenia. In Indonesia, Schizophrenia is included as the top nine chronic diseases covered by national health insurance due to its high prevalence (Social Insurance Administration Organization, 2014). Therefore, there is a demand for implementing pharmacist-led education and screening services for MetS.

The Ministry of Health of Indonesia in 2007 has issued the standard of pharmaceutical care for patients with mental depression (Ministry of Health RI, 2007). However, the scope of the standard has been broad and not specific to Schizophrenia. In addition, the standard was much focused on the use of pharmaceuticals and disregarded the potential for MetS in the patient. Unfortunately, almost 15 years after the standard was published, there is a paucity of information that highlights the interrelation between MetS and pharmaceutical care in Schizophrenia, which becomes the objective for this narrative review. Accordingly, this review aims to stimulate a discourse on pharmacist involvement by shining a light on using a toolkit for pharmacist which focuses on the Education and Metabolic Syndrome Screening (EMESYS) services.

#### Antipsychotics induced Metabolic Syndromes

Metabolic Syndromes (MetS) are common antipsychotic adverse effects marked by increased weight gain, glucose abnormalities, and lipid abnormalities (Hasan et al., 2013). Such effect is highly prevalent in the long-term use of antipsychotics (McEvoy et al., 2005). McEvoy et al. (2005) also investigated that patients receiving SGAs are likely to experience the metabolic syndrome. Patients with Schizophrenia have been identified to have higher morbidity and mortality as compared to the general population. These patients have a significantly shorter life expectancy of 20% than healthy people (Compton et al., 2011). This condition is even exacerbated by metabolic syndrome, which is one of the major leading causes of morbidity and mortality among patients with Schizophrenia. MetS leads to a high risk of cardiovascular diseases in such patients (Brown et al., 1999; Trevisan et al., 1998).

Atypical antipsychotics work by blocking the dopamine type 2 (D2) receptors in the brain's mesolimbic and mesocortical dopamine tract. D2 receptor blockade contributes to treating hallucination and delusion symptoms (Church et al., 2010). All SGAs, except aripiprazole, are characterized by complete antagonism and strong affinity for the 5-HT<sub>2A</sub> receptor (Church et al.,

2010). The influence of SGAs on the 5-HT<sub>2A</sub> receptor can negatively affect cardiovascular function and is associated with weight gain and other metabolic adverse effects. Most SGAs, especially clozapine and olanzapine, are potent 5-HT<sub>2A</sub> antagonists (Manu et al., 2015). The adverse effect is more significant with clozapine and olanzapine; moderate with paliperidone, risperidone, and quetiapine; no risk or less risk with aripiprazole and ziprasidone (Hassan et al., 2013). Aripiprazole is a unique SGA that acts as a partial agonist on the D<sub>2</sub> receptor and antagonist on the 5HT<sub>2A</sub> receptor (Church et al., 2010).

Metabolic syndromes demonstrate a cluster of conditions that occur together, such as weight gain, blood glucose abnormalities, and lipid abnormalities. This condition raises the risk for heart disease and other health problems such as stroke, hypertension, and diabetes mellitus. Weight gain due to the use of SGAs often happens between four and twelve weeks of therapy. The blockade on the 5-HT<sub>2</sub> receptor has been associated with appetite increasing leading to increased weight (Tschoner et al., 2007). Clozapine and olanzapine appear to have the strongest affinity for the 5HT<sub>2</sub>. These medicines significantly increase weight (Reynolds et al., 2010). Therefore, weight management strategies including weight monitoring, physical activity, healthy life modification, healthy dietary intake are recommended, and options to use other antipsychotics with less weight gain impact (Iqbal et al., 2016).

The use of SGAs also induced glucose abnormalities with hyperglycemia often appears six weeks after the initial use of SGAs. Three indicative mechanisms trigger the increase of blood glucose level: 1) Antipsychotics induced insulin resistance, 2) Weight gain induced insulin resistance, and 3) Antipsychotics induced  $\beta$ -cell abnormal function, which leads to apoptosis (Chen et al., 2017). A study showed that clozapine and olanzapine contribute to the significant risk of diabetes in patients undertaking SGAs (Tahir, 2007).

Dyslipidemia has been associated with patients using SGAs, with less impact was found on patients using aripiprazole. Nasrallah (2008) highlighted that dyslipidemia occurs due to weight gain. Prevalence of dyslipidemia, hypertension, and type 2 diabetes is approximately 1.5 to 2 times higher in individuals with schizophrenia than in the general population (Riordan et al., 2011). A sedentary lifestyle and other risk factors such as smoking, alcohol consumption, and low nutrition might affect lipid metabolism and lead to abnormalities (Riordan et al., 2011). Antipsychotics exacerbated dyslipidemia by inducing oxidative stress due to

disrupted activities of enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione (Baig et al., 2010). Other studies indicated the harmful effects of antipsychotic medication on mitochondrial dysfunction, leading to fatty acid oxidation and lipid accumulation (Scharauwen et al., 2010).

### Pharmaceutical Care in Schizophrenia

Pharmaceutical care embraces the responsibility of pharmacists in managing drug therapy to achieve specific outcomes and quality of life improvement (Cipolle et al., 2012; Joel, 2014). Comprehensive care for patients with Schizophrenia is better tailored in the context of interprofessional collaboration through comprehensive disease management consisting of psychosocial services and pharmacological therapy (NICE, 2019; Dipiro et al., 2020). Pharmaceutical care in Schizophrenia upholds a patient-centered approach from data collection, assessment, planning, implementation to follow-up monitoring and evaluation (figure 1).



Fig.1: Patient-centered-care process (Dipiro et al., 2020).

**Data Collection:** Patient characteristics (age, race, gender, social status, marital status, dwelling condition, and pregnant status); Patient history (history of mental status or disorder, medical history, medication adherence, family mental history, diet, tobacco use, alcohol, and substance use); Mental status exam; Medication (past and current); Objective data (positive and negative symptoms measurement; blood pressure; heart rate; height; weight, Body Mass Index); Laboratory testing (Hemoglobin A1c, glucose plasma, lipids, and another testing if indicated).

**Assessment:** Patient's concern and attitudes toward treatment and medication adherence; Symptoms' severity and treatment goals have achieved; Presence of any other mental disorders, medical diseases, and illicit substance use; Patients' need for psychosocial intervention; Medication side effects; Appropriateness and effectiveness of current psychotropic treatment regimen (Dipiro et al., 2020).

**Planning:** Actively engage with the patient; Drug therapy regimen, Specify the continuation and discontinuation of existing therapies; Monitor

parameters including efficacy and time frame; Patient education (medication and lifestyle management); Referral to other providers if necessary such as a physician and psychologist.

**Implementation:** Provide patient education about treatment plan; Use motivational (patient empowerment) and interviewing strategies; Interprofessional collaboration (Dipiro et al., 2020).

**Follow-up:** Monitor and evaluate the goal of pharmaceutical care intervention (Dipiro et al., 2020).

As part of the health care team in the management of Schizophrenia, pharmacists have a vital leadership role in identifying, resolving, and preventing drug therapy problems. Most importantly, the pharmacist can assist patients with Schizophrenia by showing empathy and encouragement, supporting patient medication adherence, providing education and counseling for side effects (Rickles et al., 2005; Rickles et al., 2006).

This review shows a significant untapped opportunity for pharmacist involvement in the management of Schizophrenia to reduce MetS for patients receiving SGAs. Pharmacists are well-positioned to provide a number of services, as the following:

1. Counsel patient about the use of antipsychotics.
2. Counsel patient about Schizophrenia and its progressivity.
3. Screening metabolic syndrome effects. For instance, measuring Body Mass Index, waist circumference, blood pressure, lipid profile, and plasma glucose results.
4. Conducting health promotion mainly stops smoking services, promotes a healthy lifestyle, balanced-diet, alcohol restriction, and increasing physical activity.
5. Monitor appropriate and effective treatment regimen, risk of metabolic syndrome effects (American Diabetes Association, 2004; Maayan et al., 2010; Hermes et al., 2011; Correl et al., 2013).

### Pharmacist-led Toolkit for Education and Metabolic Syndrome Screening (EMESYS) Services

The growing prevalence of Schizophrenia and its associated life-long physical, psychological, social, and financial impacts in individual patients and communities are of concern. In addition, the long-term healthcare utilization for treating patients with Schizophrenia implied the need for an investment and quality improvement of care, especially pharmaceutical care in contemporary real-world settings. Pharmacists are in a favorable position as aforementioned. However, they may

not consistently adapt and translate the actual implementation of the intervention due to multiple factors related to the content of the intervention, the context in which pharmacists are working, and the competencies of a pharmacist. The use of a toolkit can be the answer to support the implementation. A toolkit may include adaptable resources such as educational material, timelines, guidelines, and assessment tools to bridge the gap between the need and practice. Therefore, this study developed a pharmacist-led toolkit for Education and Metabolic Syndrome Screening (EMESYS) services.

The toolkit provides a structured process for education and screening for metabolic syndrome in patients taking SGAs by the pharmacist. The toolkit can be a valuable resource for the pharmacist to guide both clinical intervention and implementation activities. The toolkit's content focused on one-on-one education between the pharmacist and the patient and subsequently followed by screening services to identify the presence of the metabolic syndrome.

The toolkit was developed in two phases. Phase 1 included the synthesis of existing literature and preparation of the draft toolkit, and Phase 2 included content validation of the draft toolkit with experts.

The toolkit development's first phase focused on reviewing guidelines, models, prior research studies, and available existing toolkits involving pharmacists or management of metabolic syndrome, which are relevant to mental health and/or Schizophrenia. These are clinical practice guideline for Schizophrenia in Indonesia (Indonesian Psychiatric Association, 2011), prevention and management of psychosis and Schizophrenia in (NICE, 2019), the guideline

<sup>31</sup> for biological treatment of Schizophrenia, the maintenance medication of schizophrenia, and antipsychotic adverse effects handling (Hasan et al., 2013), risk assessment and reduction in cardiovascular disease (National Institute for Health and Care Excellence, 2020), standard management of dyslipidemia in Indonesia (Indonesian Association of Clinical Endocrinologists, 2015), and standard management of diabetes mellitus in Indonesia (Indonesian Association of Clinical Endocrinologists, 2015).

Investigators subsequently created a draft of the toolkit structured as the following: definition, goals of therapy, timelines, screening procedures and instruments, educational materials, outcome measurements, and follow-up sheets. The toolkit draft was printed on an A4 page (Figure 2) supplemented with practical educational materials for patients printed in a folding calendar model (Figure 3).



Fig.2: Printed EMESYS Toolkit



Fig.3: Printed educational materials for patient

The second phase focused on content validation of the draft toolkit. Investigators distributed the toolkit to the four experts: two experts of intervention study design and two pharmacists in mental health. Investigators demonstrated the use of the toolkit to these experts, highlighting the potential of one-on-one education between pharmacist and

patient in identifying and resolving metabolic syndrome and preventing through non-pharmacological intervention such as weight management, smoking, dietary change, and behavior modification (Table 1). Moreover, the toolkit was also supplemented with measurement

of outcomes and targeted outcomes should be achieved by patients (Table 2).

**Table 1: One-on-one education model between pharmacist and patient**

<b>Education about the use of antipsychotic medications including:</b>
1. Informing the patients of any changes in their medication
2. Ensuring the patients on how to use the medicines safely and effectively
3. Explaining the patients about potential side effects and how to handle them
4. Discussing the importance of medication adherence to achieve goals of treatment
<b>Education about schizophrenia disorder including:</b>
1. Encouraging the patients on how to identify symptoms of Schizophrenia, namely negative symptoms, positive symptoms, and cognitive impairment
2. Providing moral supports for patients
3. Explaining the patients about possibilities for relapse and its concomitant factors
4. Warning the patients to avoid substance addiction, e.g., drugs and alcoholism
<b>Education about the presence of the metabolic syndrome</b>
1. Explaining the patients about metabolic syndrome and its risk factors
2. Explaining to the patients how to prevent metabolic syndrome through physical activity, dietary program, and lifestyle modification.
3. Discussing quit smoking strategies with the patients
4. Discussing the risk and strategies to decrease alcohol intake

**Table 2: Outcome Measurements**

No	Outcome measurement	Instrument	Parameter
1	Medication adherence	Medication Adherence Rating Scale (MARS)	Total score < 5= poor adherence, total score 5-7 = partial adherence, total score ≥ 8 = good adherence (Yalcin et al., 2019).
2	Quality of life	Subjective Well Being Under Neuroleptic (SWN)	Total score ≥ 80 = good quality of life, or increased 20% (10 points) from total score baseline (Lambert et al., 2008).
3	Metabolic Syndrome effects	Laboratory testing	Body mass index ≥ 25 Kg/M <sup>2</sup> or waist circumference ≥ 90 cm for men and ≥ 80 cm for women; High Density Lipoprotein (HDL) < 40 mg/dL for men and < 50 mg/dL for women or Triglyceride ≥ 150 mg/dL or total lipid ≥ 200 mg/dL; Fasting plasma glucose ≥ 110 mg/dL, or random glucose level between 140-199 mg/dL (if fasting plasma glucose is not possible due to patient condition); Blood pressure ≥ 130/85 mmHg.
4	Risk of cardiovascular disease	Framingham Risk Score	Risk level < 10% = low risk, risk level 10-19% = moderate risk, risk level ≥ 20% = high risk (National Institutes of Health, 2001).

### CONCLUSION

This review presents evidence about the mechanism of Metabolic Syndrome effects in patients receiving Second-Generation Antipsychotics, which to some extent will provide an avenue for pharmacist involvement. A pharmacist is in an ideal position to educate patients and provide screening in these patients. Toolkit for Education and Metabolic Syndrome Screening (EMESYS), as promoted in this review, may help pharmacists better manage patients with Schizophrenia.

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PAGE 1

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PAGE 2

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PAGE 3

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PAGE 4

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PAGE 5

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PAGE 6

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PAGE 7

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