SPECIAL REPORT

PROCEEDINGS FROM A SYMPOSIUM IN THE 2018 AFPA CONVENTION IN THE PHILIPPINES: RETHINKING THE ROLE OF LONG-ACTING ANTIPSYCHOTIC INJECTABLES (LAIS) IN A COMPREHENSIVE, RECOVERY-ORIENTED TREATMENT APPROACH AMONG PATIENTS WITH SCHIZOPHRENIA

Erwin G. Benedicto, MD, MPH[1], Kristine Joy L. Tomanan, RN[2], Marvin P. Angeles, RN[1], Carl Abelardo T. Antonio, MD, MPH[3]

KEYWORDS: *Long acting antipsychotic injectables, schizophrenia*

INTRODUCTION

Schizophrenia is a chronic, debilitating illness affecting around 21 million people globally. It is a severe form of mental health problem, affecting more individuals aged 15-35 years (late adolescence to early adulthood) and commonly found among males[1]. It is thought to result from a combination of genetic, environmental and psychosocial factors.

In the Philippines, schizophrenia is the leading cause for mental health consultation and treatment in hospitals[2]. Based from the Philippine Health Information System on Mental Health data gathered from 2014 to 2015 in 14 health facilities, around 42% out of 2,562 patients on record were diagnosed with schizophrenia. From this data, it is estimated that 1% or around 1 million of the country's total population are affected by this disorder.

Poor adherence to medication is a major cause of poor outcomes in patients with schizophrenia, with non-adherence as high as 50-74% in the initial phase of treatment[3-5]. Non-adherence is associated with relapse, re-hospitalization and poor quality of life among individuals with the illness[3].

While remission and ultimately, recovery, is the goal, the foundation of successful treatment is appropriate medication prescription and good adherence. The use of new generation, long-acting injectable (LAI) antipsychotic medications is one of the ways to improve patient's adherence to treatment by reducing frequency of administration and improving the consistency of drug delivery as well as bioavailability in the circulation[6].

On January 25, 2018, Johnson and Johnson Philippines organized a symposium on LAI treatment during the 2018 International Congress of the Asian Federation of Psychiatric Associations (AFPA) and 44th Philippine Psychiatric Association Annual Convention at the Philippine International Convention Center, Pasay City. The purpose of the symposium was to discuss the role of long-acting antipsychotic medications in a comprehensive treatment approach for schizophrenia. A total of almost 300 psychiatrists and psychologists attended the activity.

The aim of this special report is to present the discussion of the guest speaker Dr. Allan Tasman, and weigh the pros and cons of using long-acting injectable (LAI) antipsychotics as part of treatment for Filipino patients with schizophrenia. Dr. Tasman is an internationally known psychiatrist and advocate of integrative biopsychosocial treatment model within a comprehensive, collaborative system of care and innovation for psychiatric education and clinical services. He is currently professor and emeritus chairman of the Department of Psychiatry and Behavioral Sciences at the University of Louisville, and Schwab Endowed Chair in Social and Community Psychiatry.

The primary objectives of Dr. Tasman's presentation were to: (1) review comprehensive treatment approaches in schizophrenia, keeping in mind up-to-date medication management as the foundation of treatment; and (2) use evidence-based practice in maximizing the likelihood of recovery in patients with schizophrenia.

Importance of Therapeutic Alliance in Schizophrenia & its Role in Medication Management

The therapeutic alliance is important in treating patients with

[1]*Johnson and Johnson (Philippines), Inc.*
[2]*Department of Community Development, College of Social Work and Community Development, UP Diliman*
[3]*Corresponding author Department of Health Policy and Administration, College of Public Health, UP Manila*
Tel# +63 2 3428932; email add: ctantonio@up.edu.ph

antipsychotic medications. Attention to the alliance and the doctor-patient relationship enhance adherence to medication treatment. In particular, a trusting and collaborative relationship must be fostered between the patient, physician, other members of the treatment team, family and support groups. To maximize the alliance, practitioners should consider the following: (1) patient variables, (2) treatment characteristics, (3) family issues, and (4) culture and social issues.

It is vital to note that medication prescription is given meaning by both patient and doctor. There are at least two forms of meaning: (1) from the "illness belief system" or the nature of the theoretical explanation of the illness and (2) unique meaning attributed to the medication itself. Meanings influence how patients perceive their medication, the prescriber (doctor) and themselves. This is especially a problem in psychotic disorders such as schizophrenia and personality disorders, where positive or negative meanings are ascribed. Misuse or overuse of prescription can occur when a patient is in a grandiose state while non-adherence is possible when a patient is in a delusional state (usually) brought about by paranoia or pessimism). Also, side or adverse effects from medications may be interpreted more negatively.

To address this issue, a thorough history of the patient is essential, which should include history of significant relationships and usual patterns of interaction, as well as assessing potential difficulties in the therapeutic alliance related to transference. Transference and counter-transference are frequently part of the transaction between the patient and doctor during medication and are of special concern in patients with psychosis. Table 1 shows positive and negative factors when evaluating possible transference reactions, while Table 2 presents possible diagnoses for consideration when dealing with counter transference feelings. Paying attention to the patient is critical. Specifically, patients with schizophrenia are remarkably sensitive to reactions of people around them. A doctor that shows heartfelt interest to the patient as a person not as a disease will positively affect adherence to medication and overall treatment.

TABLE 1. Evaluating possible transference reactions[7]

EXTERNAL ISSUES		TRANSFERENCE
Positive Factors		
Psychiatrist	Professional appearance Observance of social conventions Empathic listening Patient education Patient involvement in decision making Adherence to scheduled appointment times Prompt, focused response to telephone calls Courteous, efficient support staff	Confidence & trust Validation of symptoms & distress Nurtured Cared for Educated
Medication	Highly effective Favorable side-effect profile Easy to use Rapid response	Benevolent gift Healing remedy Useful tool Validation of suffering Source of hope Transitional object
Negative Factors		
Psychiatrist	Disorganized Odd behavior, grooming, dress Rude interactions Uninterested in patient Careless Dismissive of complaints Authoritarian	Distrust Lack of confidence Rejected Disregarded Demeaned Confused
Medication	Limited effectiveness Unfavorable side effects Difficult to remember Gradual response	Crutch Artificial treatment Poison Deny or avoid real issues Minimize interaction with therapist

Recovery after an Initial Schizophrenia Episode Study (RAISE)

In 2008, the United States National Institute of Mental Health (NIMH) launched the Recovery after an Initial Schizophrenia Episode (RAISE) project, a large-scale research that began with 2 studies examining different aspects of coordinated specialty care (CSC) treatments for patients experiencing first-episode psychosis. Overall, RAISE aimed to develop, test and implement person-centered, integrative treatment approaches that promote symptomatic and functional recovery[8].

Under RAISE-Early Treatment Program, the experimental treatment NAVIGATE included 4 core interventions: 1) personalized medication management (assisted by a web-based decision support system); 2) family psychoeducation; 3) resilience-focused individual therapy; and 4) supported employment and education (SEE). Thirty-four community mental health centers in 21 states participated in comparing the impact of NAVIGATE compared to usual community care on patients' quality of life[8].

NAVIGATE is a comprehensive, multidisciplinary, collaborative treatment approach that embodies the philosophy of the recovery model. Results showed that NAVIGATE improved patient outcomes for 24 months—patients stayed in treatment longer, experienced greater improvement in quality of life and symptoms, as well as greater involvement in work and school. Benefits were more significant in patients with shorter duration of untreated psychosis (<74 weeks), while there was no significant

difference found in hospitalization between groups[8].

Results of the RAISE study demonstrated the critical importance of increasing patients' access to comprehensive treatment programs, where recovery was more possible within a patient-centered, shared-decision making, coordinated specialty care model. The collaborative approach employed respect, which was more effective in establishing positive therapeutic alliance and maintaining engagement with patients and their family members over time[9]. The RAISE research project showed that therapeutic alliance was indeed crucial in influencing treatment outcomes.

TABLE 2. Diagnostic possibilities in response to counter-transference[7]

COUNTER TRANSFERENCE	PATIENT SYMPTOM
Anger	Manipulation
Boredom	Personal disconnection
Defensiveness	Anger, hostility
Fear	Paranoia, aggression
Hopelessness	Hopelessness
Narcissism	Idealization
Rescue fantasies	Dependencies
Sexual arousal	Seductiveness

The Recovery Model and its importance in comprehensive schizophrenia treatment

The recovery model traces its origins to the 1970's during the rise of the health consumer movement in the United States. Dr. William Anthony and Dr. Anthony Lehman were identified as pioneers of the recovery approach, both of whom worked in community settings. Current successor approaches include "medicine for the person" in the United Kingdom and "psychiatry for the person" in the World Psychiatric Association (WPA).

The recovery approach to treating schizophrenia asserted that understanding "who is the person with the illness" was as important as understanding "what is the illness". This was required to strengthen patient's self-monitoring, self-awareness and self-regulation abilities in personal activities and relationships with others in social and work settings.

In the United States, the goal of recovery is defined as overcoming or managing one's disease and symptoms in a way that patients make informed choices that support physical and emotional well-being, in the context of having stable living arrangements and meaningful life activities within supportive relationships and social networks[10-11].

The recovery model has 10 guiding principles, with hope as the catalyst of the recovery process. Table 3 shows the description for each principle as outlined by Substance Abuse and Mental Health Services Administration (SAMHSA). It was developed when the etiology of schizophrenia was widely believed to be due to biological vulnerabilities (medical or disease model). However, despite advances in genetics and neuroscience, these have not changed the human capacity to respond to trauma, developmental conflict or deficit. Understanding the complexity of genetic-developmental interactions support the significance of therapeutic relationship as an agent of change, which underpinned the work of Dr. Eric Kandel, a Nobel Prize winner in psychiatry.

TABLE 3. Ten Guiding Principles for Recovery[11]

PRINCIPLE	DESCRIPTION
Hope	Catalyst of recovery process
Holistic	Encompasses all aspects of life—mind, body, spirit & community
Responsibility	Personal responsibility for self-care & process of recovery
Self-direction	Individual defines own life goals
Individualized & person-centered	Multiple pathways to recovery based on individual strengths, resiliencies & needs
Empowerment	Authority to choose from a range of options & decision-making
Nonlinear	Envisions continual growth, setbacks & learning from experience
Strengths-based	Focuses on valuing & building individual characteristics
Peer support	Mutual support integral to recovery
Respect	Self-acceptance & self-respect fostered by external respectful relations

The neurotoxicity of psychosis in schizophrenia & the effect of antipsychotic medications

In 1979, Weinberger found enlarged lateral cerebral ventricles in patients with schizophrenia. Subsequent studies have demonstrated volume loss in hippocampus[12] and cortical gray matter[13,14]. Results from these studies led to the hypothesis that pathophysiology of schizophrenia may be related to neurotoxicity by unknown mechanisms.

In response to the controversy about medication toxicity producing loss of brain tissue, Lieberman, principal investigator of the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found that gray matter volume decrease was greater with first generation antipsychotics (FGA) than second-generation antipsychotics (SGA) and volume decrease was greater in the first 12 weeks of study[15].

Lieberman believed that this effect was more likely due to the acuity of the illness rather than medication and suggested that SGA medications might have antagonistic effect on neurotoxic processes in psychosis[15]. Subsequent meta-analysis done by Vitaand Van Haren supported the view of psychosis as a neurotoxic disease process[13,14]. A review by Arango and Kahn concluded that volume loss may be the result of both early and late neurodevelopmental abnormalities in schizophrenia, leading to progressive loss of volume, with severity of loss related to the number of psychotic episodes and loss of gray matter reduced with SGA versus FGA medications[16].

In a lecture at the13th Scientific Meeting of the Pacific Rim College of Psychiatrists in 2008 held in Tokyo, Japan, Kahn presented the summary of these findings: 1) gray matter loss was neuro-developmentally mediated; 2) degree of loss correlated with total duration of psychosis over time; 3) SGA and New Generation Antipsychotic (NGA) medications serve neuroprotective functions rather than neurotoxic; and 4) rapid intervention was essential when psychosis occurred to minimize days of psychosis over time following a first episode. With these results, medication management and vigilance in treatment adherence are crucial practices in reducing symptoms and facilitating patient recovery.

Adherence to Pharmacotherapy &Therapeutic Promise of Long Acting Injectable (LAI) Antipsychotic Medications

Poor adherence to medication is a major cause of poor treatment outcomes in schizophrenia. Non-adherence can be as high as 50%. In the CATIE study, non-adherence was noted at more than 70% in the first phase of treatment. Contributors to non-adherence included: 1) nature of the illness, e.g. delusional thinking, hallucinations, cognitive and behavioral disorganization; 2) unpleasant side effects and actual effects; as well as 3) familial, cultural and social influences.

After the introduction of oral antipsychotic medications in the 1950s, poor adherence to oral formulation was identified as a critical issue leading to the development of the first long-acting injectable (LAI), fluphenazine, in the United States. Fluphenazine, however, was not widely used. Haloperidol, was more popular but eventually became less prescribed due to problematic side effects. The entry of SGA and NGA LAI medications brought much lower rates of acute and chronic extrapyramidal side effects, with greater tolerability and smaller risk of decreased safety or effectiveness e.g. Risperidone LAI showed very low level of developing tardive dyskinesia and low rate of medication discontinue due to adverse events.In the United States, clinicians have begun more widespread use of SGA and NGA LAI medications in situations where adherence is a concern.

Nevertheless, even with one-month LAI medications, adherence could still be a problem, which led to the development of three-month LAIs like paliperidone palmitate, which is currently available in the US and increasingly around the world. Savitz et al compared one- and three-month paliperidone palmitate formulations in 1000 patients and found that both had similar tolerability[17]. No new safety concerns were noted. Other reports comparing one-month paliperidone palmitate to placebo, risperidone or tablet form had similar findings regarding effectiveness, adverse effects and safety. As for the three-month formulation, there were fewer studies due to its shorter period of availability. Further research will determine whether three-month paliperidone palmitate will indeed lead to greater adherence; however, less frequent administration (four versus 12 injections/ year) would logically result to improved adherence since adverse effects would be low and side effects similar to other formulations.

On the other hand, consensus on the most effective medications or method of administration has been inhibited by variability of research methods. Also, controversy still exists regarding potential dose reduction during maintenance treatment in the absence of emerging side effects such as significant weight gain; thus, the optimal medical treatment for individual patients is still unpredictable. More research is required to bring the promise of personalized medicine to schizophrenia treatment, especially on refining diagnostic nosology and sophisticated diagnostic tools e.g. genetics, neuroimaging, neurocognitive, blood or tissue-based biomarkers. At present, major priority lies in improving adherence with medication and the use of LAIs as a standard first-line treatment should be considered (Figure 1).

Rethinking the Role of LAIs in Comprehensive Recovery-Oriented Treatment

The development of novel pharmacological treatments since the second half of the 20th century has led to dramatic improvements in the treatment and management of schizophrenia. However, non-adherence to antipsychotic medications is common among individuals with the illness and is linked to relapse, re-hospitalization and poor quality of life[3].

To address the issue of non-adherence, long-acting injectable (LAI) antipsychotics were developed to reduce the frequency of administration to once every 2-4 weeks compared to oral antipsychotic medications taken every day[6,19]. LAIs are particularly useful for patients with adherence problems and those with a history of severe relapse upon discontinuation of medication[20]. Monitoring of treatment compliance is also simpler as non-compliance is quickly recognized if patients do not show up for their scheduled injections[20,21].

LAIs are also referred to as "depot" injections, administered as intramuscular (IM) injections via the gluteus or deltoid muscle[19]. LAI medications however, did not gain positive acceptance in its early stages because of fears of increased side effects and lack of efficacy[22]. It was also perceived as an attempt by psychiatrists to impose treatment upon patients without due respect for their rights or feelings, with potential for medicolegal issues or repercussions[22,23]. In time, with more studies showing significant benefits and advantages over oral antipsychotics, LAIs became more widely accepted.

In terms of bioavailability, LAI medications avoid first-pass metabolism in the liver compared to oral antipsychotics[24,25], which increases the proportion of the drug that is available centrally[26] and subsequently allows the use of the lowest effective dose[27]. However, the slow dose titration, longer time to reach steady state and persistent side effects (if required to be suspended for safety)usually limit the use of LAIs[6]. Newer long-acting injectables such as paliperidone palmitate can address these issues, as rapid therapeutic levels can be achieved through a "loading dose regimen", which allows its usage for patients with moderate symptoms[28]. The resulting rapid onset of action no longer requires supplementation by oral antipsychotics[5].

Paliperidone palmitate LAI is a palmitate salt ester of paliperidone (9-hydroxyrisperidone) and the active metabolite of risperidone[29,30]. It is provided as a nanocrystal suspension in an aqueous vehicle. The once-monthly formulation was approved by the US Food and Drug Administration (FDA) in 2009 and marketed as Invega® Sustenna® (Janssen Pharmaceutica NV, Belgium) in several countries (in the Philippines, it was registered in 2011).A three-monthly formulation was recently approved in 2015 in Europe and United States[29,31].

Proposed therapeutic activity in schizophrenia and schizoaffective disorder is mediated through combined dopamine type 2 (D2) and serotonin type 2 (5HT2A) receptor antagonism. Antagonism at receptors other than D2 and 5HT2A could account for other effects of paliperidone[30].

Recommended initiation of paliperidone LAI is with a 150 mg dose on day 1 and 100 mg one week later, both administered in the deltoid muscle to achieve faster therapeutic concentrations. After the second initiation dose, monthly maintenance doses can be administered in either deltoid or gluteal muscle.

Recommended monthly maintenance dose is 75 mg and may range from 25-150 mg based on individual tolerability and/or efficacy[30].

In terms of safety and tolerability, several clinical trials have showed paliperidone palmitate was generally well-tolerated. Extrapyramidal symptoms (EPS), injection-site reactions, dizziness, somnolence/sedation, insomnia, worsening of schizophrenia, nasopharyngitis, headache, weight gain and increased prolactin levels were listed as common adverse effects experienced by patients, mild to moderate in severity[30,32]. However, the drug should be used with caution in patients with history of cardiac arrhythmias, congenital long QT syndrome or when used with drugs that prolong QT interval[30]. It should also be used with caution when patients have known cardiovascular disease e.g. heart failure, myocardial infarction or ischemia, cerebrovascular disease or conditions that predispose patients to hypotension e.g. dehydration, hypovolemia, antihypertensive medication treatment; as well as in patients with history of seizures or other conditions that potentially lower the seizure threshold[30]. Hyperglycemia, diabetes mellitus and exacerbation of pre-existing diabetes have also been reported during treatment with paliperidone LAI, which warrant vigilant monitoring of symptoms[30]. For patients with renal impairment, dosage should be reduced but for patients with moderate to severe renal impairment, paliperidone palmitate is no longer recommended. The only contraindication to the drug is known hypersensitivity to the product i.e. main drug or excipients[30].

In terms of costs, schizophrenia treatment is expensive. In the Philippines, a 2015 study of adult patients with schizophrenia admitted in a tertiary hospital found that the estimated cost of treatment ranged from Php 2,332.00-Php 44,861.00 (USD 50.88-USD 978.86) in the service (charity) ward, while for pay or private patients, costs ranged from Php 15,347.00-Php 246,831.00 (USD 334.87-USD 5,385.80)[33]. On the other hand, annual cost for outpatient care ranged from Php 2,892.00-Php 213,612.00 (USD 63.10-USD 4,660.96) for service patients and Php 17,292.00-Php 1,125,600.00 (USD 377.31-USD 25,681.04) for pay or private patients[33]. Choice of medication was identified as the major factor influencing cost of treatment[33]. For patients and their families from the lower socioeconomic classes, both inpatient and outpatient treatment costs could be catastrophic with price of oral medications as high as Php 200.00 or more (USD 4.36 or more) per tablet, to be taken daily.

While LAI medications are costlier compared to oral antipsychotics, studies in several countries such as the United States, France, Germany, Japan, Sweden, Norway and South Korea evaluated the overall cost-effectiveness of paliperidone LAI and noted that it was more cost-effective in general and compared to other LAIs in the long run[34-42].

The chronic, debilitating nature of schizophrenia not only provides considerable financial burden but also imposes

substantial burden on caregivers, with patient dependency as high as 70% in Asian countries[43].

A recent pooled analysis of two double-blind, randomized, phase 3 studies in 27 countries that evaluated improvement or worsening of schizophrenia-related caregiver burden following paliperidone palmitate LAI (1-monthly and 3-monthly treatment) in 1,498 caregivers showed that there was significant overall lessening of caregiver burden among patients on prior oral antipsychotics after switching to LAI and in the urging and worrying domain[44].

With considerable advantages of new-generation antipsychotic LAIs such as paliperidone palmitate in terms of safety and tolerability, convenience of administration as well as long-term cost-effectiveness, there is a need to rethink LAIs as first-line choices in acute and maintenance treatment of schizophrenia. With newer LAIs and a patient-centered, multidisciplinary and holistic treatment plan, symptom remission and recovery is possible for Filipino patients. The passage of the Philippine Comprehensive Mental Health Act (Republic Act No. 11036) is expected to dramatically improve the delivery of integrated mental health services, promote mental health, protect the rights and freedom of individuals with mental health needs and reduce the burden and impact of mental illness, brain disorders and disabilities[45].

DISCLOSURE

Dr. Tasman provided consent for documentation and publication of his lecture. Primary Author and Co Author are employees of Johnson and Johnson (Philippines), other Co Authors received professional fees from Johnson and Johnson (Philippines). Funding support for documentation of the symposium was provided by Johnson and Johnson (Philippines), Inc.

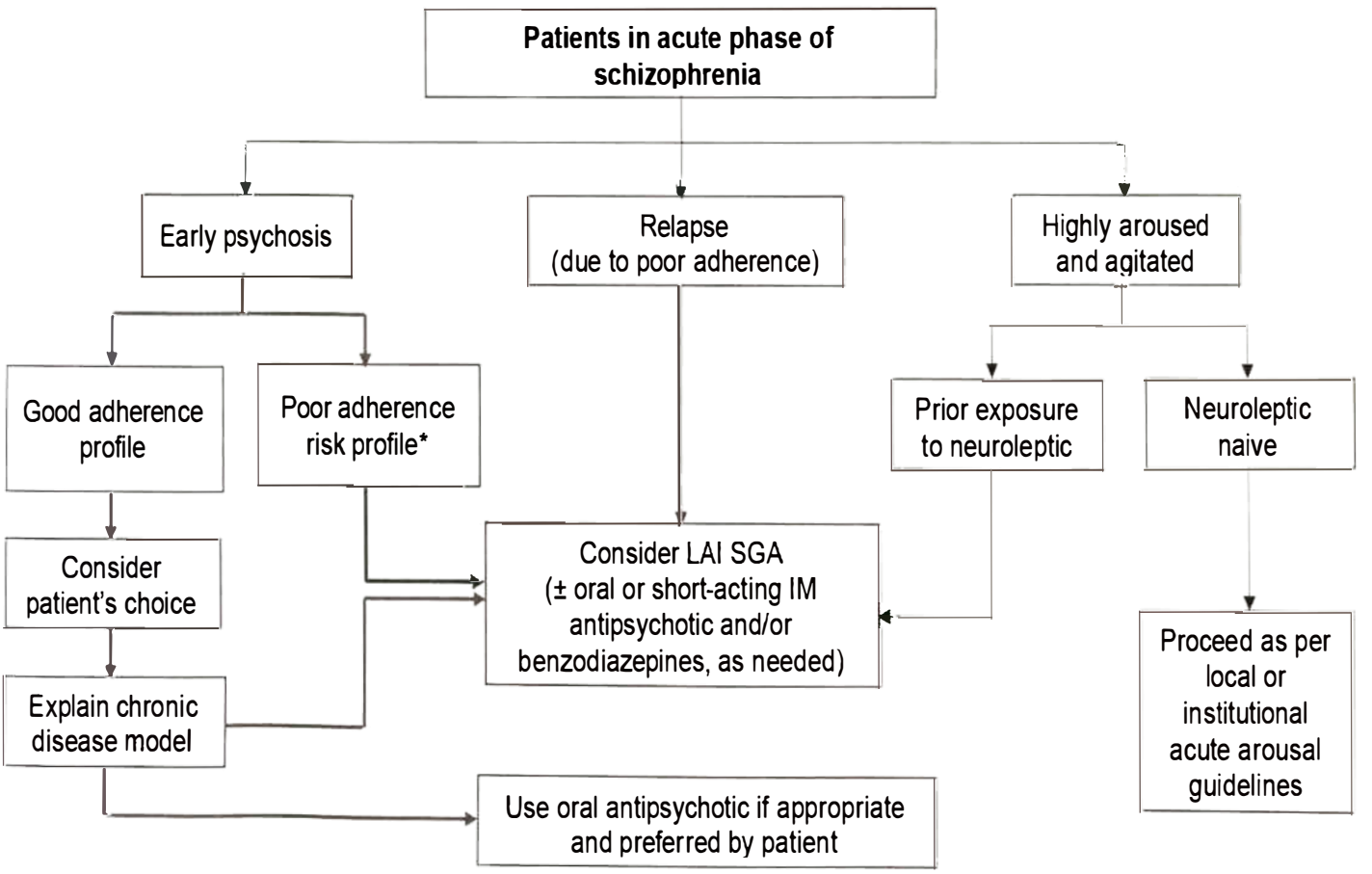

Figure 1. Treatment algorithm for schizophrenia: Potential role of LAI- SGA medications[18]

REFERENCES

1. WHO: Media centre [Internet]. World Health Organization; c2016-2018. Schizophrenia; April 2016. Available from http://www.who.int/mediacentre/factsheets/fs397/en/
2. Uy J. Schizophrenia top mental disorder afflicting Filipinos who seek help, says study [Internet].08 June 2015. Philippine Daily Inquirer. Available from http://newsinfo.inquirer.net/696823/schizophrenia-top-mental-disorder-afflicting-filipinos-who-seek-help-says-study
3. McCabe R, Bullenkamp J, Hansson L, Lauber C, Martinez-Leal R, Rossler W, et al. The therapeutic relationship and adherence to antipsychotic medication in schizophrenia. PLoS ONE. 2012;7(4) e36080.
4. Lieberman J, Stroup S, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209-23.
5. Brissos S, Ruiz Veguilla M, Taylor D, Balanza-Martinez V. Ther Adv Psychopharmacol. 2014; 4(5):198-219.
6. Sacchetti E, Grunze H, Leucht ST, Vita A. Long-acting injection antipsychotic medications in the management of schizophrenia. Evidence-based Psychiatry Care.2015;1:27-36.
7. Tasman A. The role of long-acting antipsychotic medications in a comprehensive treatment approach for schizophrenia. Lecture presented at: 2018 International Congress of Asian Federation of Psychiatric Associations (AFPA) and 44th Philippine Psychiatric Association Annual Convention; 2018 Jan 25; Pasay City, Philippines.
8. Kane JM, Robinson DG, Schooler NR, Mueser KM, Penn DL, Rosenheck RA, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. Am J Psychiatry.2016;173:362-72.
9. Heinssen RK, Goldstein AB, Azrin ST. Evidence-based treatments for first episode psychosis: Components of Coordinated Specialty Care [Internet]. Available from https://www.nimh.nih.gov/health/topics/schizophrenia/raise/nimh-white-paper-csc-for-fep_147096.pdf
10. Frese FJ, Knight EL, Saks E. Recovery from schizophrenia: with views of psychiatrists, psychologists, and others diagnosed with this disorder. Schiz Bulletin. 2009;35(2):370-80. Available from https://academic.oup.com/schizophreniabulletin/article-abstract/35/2/370/1908368
11. Substance Abuse and Mental Health Services Administration (SAMHSA). Working definition of recovery [Internet]. 2012. Available from https://academic.oup.com/schizophreniabulletin/article-abstract/35/2/370/1908368
12. Koolschijn PCM, van Haren NEM, Cahn W, Schnack HG, Janssen J, Klumpers F, et al. Hippocampal volume change in schizophrenia. J Clin Psychiatry. 2010;71(6):737-44.
13. Vita A, de Peri L, Deste G, Barlati S, Sachetti E. The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: Does the class matter? a meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. Biol Psychiat 2015;78(6):403-12.
14. Van Haren NEM, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RCW, Collins DL, et al. Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharm.2007;32:2057-66.
15. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry. 2005;62(4):361-70.
16. Arango C, Kahn R. Progressive brain changes in schizophrenia. Schizophr Bull. 2008;34(2):310-11.
17. Savitz AJ, Xu H, Gopal S, Nuamah I, Ravenstijn P, Janik A, et al. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, non inferiority study. Int J Neuropsychopharmacol. 2016;19(7):1-14.
18. Newton R, Hustig H, Lakshmana R, Lee J, Motamarri B, Norrie P, et al. Practical guidelines on the use of paliperidone palmitate in schizophrenia. Curr Med Res Opin 2012;28(4):559-67.
19. Morris MT, Tarpada SP. Long-acting injectable paliperidone palmitate: a review of efficacy and safety. Psychopharmacol Bull.2017;47(2):42-52.
20. Fleischhacker WW, Miyamoto S. Pharmacological treatment of schizophrenia: current issues and future perspectives. Clinical Neuropsychopharmacology and Therapeutics.2016;7:1-8.
21. Fleischhacker WW. Second-generation antipsychotic long-acting injections: systematic review. Br J Psychiatry Suppl. 2009;52:S29-36.
22. Johnson D. Historical perspective on antipsychotic long-acting injections. Br J Psychiatry. 2009;195:S7-S12.
23. Glazer W, Kane J. Depot neuroleptictherapy: an underutilized treatment option. J Clin Psychiatry.1992; 53:426-433.
24. Dencker S. The risk/benefit ratio of depot neuroleptics: a Scandinavian perspective. J Clin Psychiatry.1984;45:22-27.
25. Marder S, Hubbard J, Van Putten T, Midha K. Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications. Psychopharmacology.1989; 98:433-439.
26. McEvoy J. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry. 2006;67(Suppl. 5):15-18.
27. Gerlach J. Depot neuroleptics in relapse prevention: advantages and disadvantages. Int Clin Psychopharmacol.

1995; 9(Suppl. 5):17-20.
28. Gilday E, Nasrallah H. Clinical pharmacology of paliperidone palmitate a parenteral long-acting formulation for the treatment of schizophrenia. Rev Recent Clin Trials.2012;7:2-9.
29. Emsley R, Kilian S. Efficacy and safety profile of paliperidone palmitate injections in the management of patients with schizophrenia: an evidence-based review. Neuropsy D Treatment.2018;14:205-223.
30. Paliperidone palmitate [Invega ® Sustenna ®]. Proposed package insert. 02 February 2017 version. Johnson and Johnson (Philippines), Inc
31. Carpiniello B, Pinna F. Critical appraisal of 3-monthly paliperidone depot injections in the treatment of schizophrenia. Drug Des Devel Ther.2016;10:1731-42.
32. Kim S, Solari H, Weiden PJ, Bishop JR. Paliperidone palmitate injection for the acute and maintenance treatment of schizophrenia in adults. Patient Prefer Adherence.2012;6:533-45.
33. Abala AT, Bautista T. Estimate range of cost of treatment of adult schizophrenia patients at a tertiary hospital as of October 2015. Value in Health. 2016;19 (7):A841.
34. Druais S, Doutriax A, Cognet M, Godet A, Lancon C, Levy P et al. Cost effectiveness of paliperidone long-acting injectable versus other antipsychotics for the maintenance treatment of schizophrenia in France. PharmaEconomics.2016;34:363-91.
35. Zeidler J, Mahlich J, Greiner W, Heres S. Cost-effectiveness of paliperidone palmitate for the treatment of schizophrenia in Germany. Appl Health Econ Health Policy. 2013;11(5):509-21.
36. Mahlich J, Nishi M, Saito Y. Modeling the budget impact of long-acting injectable paliperidone palmitate in the treatment of schizophrenia in Japan. Clinicoeconomics Outcomes Res 2015;7:267-72.
37. Mehnert A, Nicholl D, Pudas H, Martin M, McGuire A. Cost-effectiveness of paliperidone palmitate versus risperidone long-acting injectable and olanzapine pamoate for the treatment of patients with schizophrenia in Sweden. J Med Econ. 2012;15(5):844-61.
38. Einarson TR, Vicente C, Zilbershtein R, Piwko C, Bo CN, Pudas H, et al. Pharmacoeconomic analysis of paliperidone palmitate versus olanzapine pamoate for chronic schizophrenia in Norway. Acta Neuropsychiatr. 2013;25(2):85-94.
39. Kim B, Lee TJ, Woo JM, et al. Cost-utility analysis of paliperidone palmitate long acting injection (PLAI) vs oral atypical antipsychotics in non-adherent schizophrenia patients. Korean J Psychopharmacol.2012;23:17-27.
40. Joshi K, Lin J, Lingohr-Smith M, Fu DJ. Estimated medical cost reductions for paliperidone palmitate versus placebo in a randomized, double-blind relapse-prevention trial of patients with schizoaffective disorder. J Med Econ.2015;23:1-22.
41. Lafeuille MH, Grittner AM, Fortier J, Muser E, Fasteneau J, Duh MS, et al. Comparison of rehospital¬ization rates and associated costs among patients with schizophrenia receiving paliperidone palmitate or oral antipsychotics. Am J Health Syst Pharm. 2015 Mar 1; 72(5):378–389.
42. Pilon D, Muser E, Lefebvre P, Kamstra R, Emond B, Joshi K. Adherence, healthcare resource utilization and Medicaid spending associated with once-monthly paliperidone palmitate versus oral atypical antipsychotic treatment among adults recently diagnosed with schizophrenia. BMC Psychiatry. 2017;17(1):207.
43. Chan SW. Global perspective of caregiver burden of family for person with schizophrenia. Arch Psychiatr Nurs.2011;25:339-49.
44. Gopal S, Xu H, McQuarrie K, Savitz A, Nuamah I, Woodruff K, et al. Caregiver burden in schizophrenia following paliperidone palmitate long acting injectables treatment: pooled analysis of two double-blind randomized phase three studies. NPJ Schizophrenia. 2017 Jul 27; 3(23):1-6.
45. Mental Health Act. Republic Act No. 11036 (June 20, 2018). Available from https://www.pllo.gov.ph/images/Documents/Downloads/RepublicActs-JointResolutions/RA.11036_mental.health.act.pdf